Improving somatic health for outpatients with severe mental illness

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Plenary Lectures

Monday 4 June 2012

PL-01. Course, causes and developments in drug treatment of schizophrenia

PL-01-001 **Course, causes and developments in the treatment of schizophrenia**

H.-J. Möller. *Ludwig-Maximilians-University, Deptartment of Psychiatry, Munich, Germany*

According to recent long-term studies is schizophrenia a chronic disorder with a high risk of poor outcome in terms of symptoms and social functioning and possibly also progressive brain alterations. The relapse rate is high and each relapse can induce further aggravations, both in psychosocial as well as in neurobiological terms. Thus acute and long-term treatment with the highest degree of effectiveness should be provided to the patients in acute and long-term treatment. It is of special interest that some schizophrenia susceptibility genes and chromosomal abnormalities, particularly examined for early onset populations, are associated with premorbid neurodevelopmental abnormalities. Recent MRI imaging studies on patients at risk for schizophrenia showed a specific pattern of brain alterations which is predictive for the development of a full-blown psychosis. In addition to neurodevelopmental disorder, a neuroprogressive brain disorder is increasingly being hypothesized to explain a further decline especially in the poor outcome subgroup of schizophrenic patients. Results from genetic research, especially recently from the genome-wide association studies hint at disturbances of neurodevelopment/neuroplasticity as well as immunological and glutamatergic processes as part of the complex aetiopathogenesis. The relevance of immunological processes is especially supported by results indicating immunological parameter alterations in patients suffering from schizophrenia and especially by the positive outcome of double-blind, randomised add-on studies using the COX-2 inhibitor Celecoxib as add-on to neuroleptic treatment (risperidone, amisulpride). Support for the glutamatergic hypothesis comes primarily from animal models and recently also from the positive outcome of double-blind, randomised trials on new dopaminergic compounds. This glutamatergic approach in the drug treatment seems to be a very promising one, although it currently seems that these compounds are more effective in the treatment of negative symptoms/cognitive symptoms and not so much in positive symptoms.

PL-02. Addiction: From molecules to neuronal circuits

PL-02-001 **Addiction: From molecules to neuronal circuits**

N. Volkow. *National Inst. on Drug Abuse, National Institutes of Health, Bethesda, USA*

Addiction is a disorder that involves complex interactions between genes, development and the social environment. Studies employing neuroimaging technology paired with behavioral measurements, and more recently genetics, have led to remarkable progress in elucidating neurochemical and functional changes that occur in the brains of addicted subjects. Although large and rapid increases in dopamine have been linked with the rewarding properties of drugs, the addicted state, in striking contrast, is marked by significant decreases in brain dopamine D2 receptor mediated signaling. Such decreases are associated with dysfunction of prefrontal regions including orbitofrontal cortex, cingulate gyrus and dorsolateral prefrontal cortex and impaired striato frontal connectivity. In addiction, disturbances in salience attribution result in enhanced value given to drugs and drug-related stimuli at the expense of other reinforcers and promote inflexible behaviors. Dysfunction in inhibitory control systems, by decreasing the addict's ability to refrain from seeking and consuming drugs, ultimately results in the compulsive drug intake that characterizes the disease. Discovery of such disruptions in the fine balance that normally exists between brain circuits underling reward, motivation, memory and self-control have important implications for designing multi-pronged interventions for the prevention and treatment of addictive disorders.

Tuesday 5 June 2012

PL-03. Depressing tales of adult neurogenesis: A hard look at the evidence

PL-03-001 **Depressing tales of adult neurogenesis: A hard look at the evidence**

P. Rakic. *Yale University School of Medicine, Department of Neurobiology, New Haven, USA*

The idea that the beneficial effect of antidepressants in humans acts by enhancing neurogenesis of granule cells in the dentate gyrus of the hippocampus was based on the work in young adult mice, where neurogenesis is robust and is increased by antidepressant treatment. However, it is not clear if this correlation in mice can be extrapolated to humans. I will present evidence, from our and many other laboratories, that the effect of various drugs including antidepressants on the turnover (e.g. genesis and death) of granule cells in control mice and in models of depression such as ''forced helplessness'' is a side effect that is unlikely related to the depression and its treatment in humans. Our strategy has been to compare neurogenesis in developing, young, adult and aged rodents, non-human primates and humans, to learn not only from their similarities, but also from their differences. These differences include how changes in the timing and sequence of gene expression affect molecular and cellular events to produce both quantitative and qualitative changes. Use of various proliferation markers, indicates that the magnitude and timing of neurogenesis in non-human primates is very different from the high neuronal turnover in various vertebrates including rodents. More specifically, division of neural stem cells in primates last almost two days and maturation of the newborn granule cells requires a minimum of 6 months, which is incompatible with the pharmacodynamics of antidepressants in humans, some of which can act within hours or days after exposure. I will also discuss possible molecular pathways implicated in limiting neurogenesis in adult primates and discuss the advantages of this limitation. It is hoped that a better understanding of the evolutionary differences, such as genetically controlled decrease in adult neurogenesis, will allow for insight into its role on brain homeostasis, as well as potential of neural stem cells in replacement therapy of human-specific neuropsychiatric disorders.

PL-04. Psychopharmacology and Cognition

PL-04-001 **Psychopharmacology and cognition**

B.J. Sahakian. *University of Cambridge, School of Clinical Medicine, United Kingdom*

Psychiatric disorders are disorders of neurocognition. Many psychiatric disorders, such as schizophrenia and attention deficit hyperactivity disorder, are of neurodevelopmental origin with an onset or prodromal stage in childhood or adolescence. Cognitive manifestations include: attentional biases; aberrant learning; dysfunctional reward systems; and lack of top down cognitive control by prefrontal

cortex. Recent neuroscience and mental health policy has emphasized the importance of successful and resilient neurodevelopment. (Beddington et al., 2008; Sahakian et al., 2010; Collins et al., 2011). Therefore biomarkers, including cognitive, genetic and neuroimaging ones, are needed for prevention, early detection and for assessing the efficacy of treatments. Policy has also emphasized the importance of novel approaches to drug development for psychiatric disorders. For instance, targets for treatment may become closely related to genetics and neurobiology (e.g. impulsivity, episodic memory) rather than diagnostic categories (e.g. schizophrenia, ADHD) (see Sahakian et al., 2010; Sahakian 2011, Insel and Cuthbert 2010). A treatment which reduces impulsive behaviour, for example, might also do so whether an individual has a diagnosis of mania, ADHD or substance abuse, and treatment of episodic memory problems might prove useful for improving cognition and functional outcome in both mild Alzheimer's disease and first-episode schizophrenia (Sahakian et al., 2010; Sahakian 2011). It is now recognised that cognitive problems may impair performance of everyday functioning of patients with mental health disorders and prove the biggest barrier to rehabilitation and return to paid employment (Beddington et al., 2008). Therefore cognitive enhancing drugs are needed to treat cognitive impairment associated with debilitating neuropsychiatric disorders. Such treatments will improve the quality of life and wellbeing for patients and their families and reduce the financial burden on society (Beddington et al., 2008). Pharmacological treatments may prove most effective when used in combination with cognitive ones, such as cognitive behavioural therapy or cognitive training.

Policy of full disclosure: Beddington J, Cooper CL, Field J, Goswami U, Huppert FA, Jenkins R, Jones HS, Kirkwood TBL, Sahakian BJ, & Thomas SM (2008). The mental wealth of nations. Nature, 455, 1057–1060 Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Bordin IA, Costello EJ, Durkin M., Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo M-M, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ, Anderson W, Dhansay MA, Ewart W, Phillips A, Shurin S, & Walport M (2011) Grand challenges in global mental health. Nature, 475, 27–30. Insel T & Cuthbert B (2010) Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. Am J Psychiatry 167:7 Sahakian BJ, Malloch G, Kennard C (2010) A UK strategy for mental health and wellbeing. Lancet, 375, 1854–1855. Sahakian BJ (2011) Benefits and Opportunities In Brain Waves Module 1: Neuroscience, society and policy. The Royal Society. http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/publications/2011/4294974932.pdf Professor Barbara Sahakian consults for Cambridge Cognition. She has consulted for Novartis, Shire, GlaxoSmithKline, Lilly, Boehringer-Ingelheim and Hoffmann-La Roche. She holds a grant funded by Johnson and Johnson. She has also received honoraria for Grand Rounds in Psychiatry at Massachusetts General Hospital (CME credits) (Boston, 27 April 2007) and Grand Rounds in Psychiatry at the UT Health Science Center at San Antonio (CME credits) (2011) and for speaking at the International Conference on Cognitive Dysfunction in Schizophrenia and Mood Disorders: clinical aspects, mechanisms and therapy (Brescia, 17–19 January 2007). She was on the Medical Research Council Neurosciences and Mental Health Board (2010) and on the Science Co-ordination Team for the Foresight Project on Mental Capital and Wellbeing, 2008 (Office of Science, The Department of Innovation, Universities and Skills). She was on Panel LS5 for the European Research Council. As an Associate Editor, she also receives an honorarium from the Journal of Psychological Medicine.

Wednesday 6 June 2012

PL-05. CNS Drug development at present

PL-05-001 A role for academic institutions in CNS drug discovery

J. Conn. *Vanderbilt Center for Neuroscience, Drug Discovery, Nashville, USA*

Despite tremendous progress in furthering our understanding in biology, chemistry, and related disciplines, academic scientists often fail to perform studies needed to more fully validate potential new drug targets and allow basic science discoveries to be most useful in supporting full drug discovery efforts in industry settings. Likewise, fiscal pressures make it increasingly difficult for companies to invest significant resources in early exploratory basic science projects where potential therapeutic utility and drugability of a new target remains highly speculative. This is especially true for CNS disorders and many companies have deprioritized CNS drug discovery in recent years. For the CNS drug discovery and development to be maximally effective in translating new basic science discoveries into breakthrough new therapeutic agents, it will be important for scientists in academic and other non profit settings to increase efforts to critically evaluate novel hypotheses related to new drug targets and provide data needed to allow translation of advances in basic science to drug discovery programs. The Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) represents a new model in which fully integrated drug discovery research has been implemented in an academic setting. These efforts are now yielding a steady pipeline of drug candidates that are advancing into clinical development. These include new approaches for schizophrenia, Fragile X syndrome, Parkinson's disease, and depression. Importantly, each of these efforts represents a novel approach that has potential to fundamentally impact the standard of patient care. Also, in each case, these efforts have provided critical validation of the druggability of new targets and have provided the data sets that have enabled multiple companies to invest in independent efforts focused on innovative targets that have emerged from basic research.

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PL-06. Rational pharmacotherapies of major depressive disorder

PL-06-001 Rational pharmacotherapies of major depressive disorder

S. Kasper. *Medical University of Vienna, Department of Psychiatry and P, Austria*

Depression is one of the most thoroughly evaluated diseases in psychiatry with regard to diagnosis and treatment possibilities. Early treatment should be achieved and watchful waiting, which is for instance not done in the treatment of high blood pressure or diabetes, has not demonstrated to be a rational approach based on neurobiological considerations. Like in other diseases, it is apparent that an untreated illness may result in biological damage i.e. in depression in a reduced volume size of the hippocampus. Interestingly, the course of illness shows that life events are less important in the later stages of the illness, which can be interpreted that the disease has approached a specific neurobiologically determined course. The introduction of the group of selective serotonin reuptake inhibitors (SSRI) marked a revolution in the treatment of depression, since it was possible to treat patients effectively with a considerably lower side effect profile than compared to tricyclic antidepressants. More patients could be reached with this approach and a possible association between usage of SSRIs and the reduction of the suicide rates in countries like Sweden, Austria and Hungary have been discussed. Dual reuptake inhibitors effecting both the serotonergic and the noradrenergic pathways and the dopaminergic noradrenergic medication bupropion have been introduced in the field with specific characteristics of treatment goals like pain, somatic symptoms or drive. The recently introduced antidepressant agomelatin demonstrates a novel and unique mechanism of action with a combination of melatonergic agonistic and serotonergic antagonistic activity exhibiting a more distinct influence on the circadian rhythm compared to other currently available antidepressants. Deep brain stimulation and vagus nerve stimulation for treatment refractory depressed patients yield promising first results, although need further substantiation. More thorough characterisation of the underlying pathophysiology of depression including molecular biological variables and brain imaging characterizations will hopefully result in further insight

into of the understanding of the illness and yield rational decisions for the treatment of depression.

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PL-07. Drugs for Alzheimer's disease

PL-07-001 Drugs for Alzheimer's disease

B. Winblad. *Stockholm, Sweden*

Alzheimer disease (AD) is the most common cause of dementia in advanced age. Currently available medications improve AD symptoms, and development of disease-modifying drugs is a very active area of research, which includes cholinergic, glutamate inhibitor (NMDA receptor antagonist), anti-amyloid compounds, drugs targeting tau-protein or mitochondria, neurotrophins, and other therapeutic approaches. The amyloid cascade hypothesis dominates current drug development strategies. Identification of effective disease-modifying drugs will benefit from understanding the interplay between mechanisms causing neurodegeneration in AD. Combined therapy could me a more effective strategy to halt AD progression. Solving methodological problems in clinical trials on AD – including use of standardized diagnostic criteria able to identify homogeneous group of patients, appropriate treatment duration and measures of disease-modifying effects – will help finding a cure for AD. The lecture will summarize current treatment possibilities for AD, as well as the main findings for new, and less new drugs with novel therapeutic use in AD, focusing mainly on compounds in the human testing phase.

Thursday 7 June 2012

PL-08. The crisis in drug discovery. What can we do to get it right?

PL-08-001 The crisis in drug discovery. What can we do to get it right?

A. Carlsson. *Göteborg, Sweden*

In Sweden we have recently been reminded of the serious waning of the drug R&D by the closing down of one of the main research units of AstraZeneca in Södertälje, only a few years following upon the closing down of its subsidiary Draco in Lund, Sweden. Less than a decade ago Pharmacia, the other Swedish Big Pharma, was devoured by Pfizer. Thus the drug R&D debacle has hit Sweden probably more than any other country. Nevertheless, the global aspect needs to be considered in the first place, and work to identify its causes is underway. Perhaps especially illuminating is an article by Swimney and Anthony (Nature Reviews, Drug Discovery, Vol. 10, July 2011, p. 507), who examined the discovery process behind all drugs approved by FDA during 1999 through 2008. It is concluded that the pharmaceutical industry has unfortunately concentrated its resources on in-vitro strategies full of pitfalls, i.e. High-Throughput Screening and the like, resulting in a fatally high attrition rate. This shocking outcome needs to be examined further. Should we place most of the blame on the pharmaceutical industry? This is by no means certain. If we look back on the golden half-century of drug R&D starting in the 1940s, preclinical academic research as well as important clinical feedback seem to have been the main driving forces. How come that they apparently have stopped working? The present wave-trough in drug R&D is most unfortunate for millions of sick people as well as for biomedical research as a whole. Moreover, it is paradoxical, given the enormous technical and other scientific advances made during the past century. There is an urgent need for the identification of its causes and for further action. Presumably reversal to a balanced and well integrated use of in-vivo and in-vitro techniques will be required.

Monday 4 June 2012

S-01. Dopamine receptors, noradrenergic mechanisms and D2 containing heteromers as targets for antipsychotic drugs

S-01-001 Antipsychotics – are we targeting the right system but the wrong end

S. Kapur. *Institute of Psychiatry, London, United Kingdom*

Objective: Antipsychotics were discovered by serendipity nearly 60 years ago. Since then efforts to make antispychotics that avoid the dopamine system entirely have not been successful. This raises the question why dopamine blockade is essential for antipsychotic action. Despite several studies looking for an increase in dopamine D2 receptors – the data remains equivocal.

Methods: We have recently completed a meta-analysis of all the available neuroimaging studies (44 studies with 618 patients) of the dopamine system and find only weak evidence for an increase in D2 receptor numbers – a finding that was driven by a few studies using butyrophenone tracers in previously treated patients.

Results: This raises the possibility of whether an increase in D2 receptors is missed as this increase is restricted to the High states of the D2 receptor, a state that can be missed by the standard antagonist radioligands. Therefore, using 11C-PHNO, a ligand that can image the high states of the D2 receptor and D3 receptors we have examined patients with schizophrenia – and find no evidence of an increase in D2/3 receptors – though treatment seems to induce an upregulation of the D3 subtype. The most striking finding in the meta-analysis is an increase in the presynaptic uptake of 18F-Dopa, suggestive of increased synthesis capacity (effect size 0.79). More recent data suggests that it is not the level of D2 blockade (provided it is in the sufficient range) that determines antipsychotic response – but, the level of presynaptic DA synthesis capacity.

Conclusion: Thus, it seems, that for the last sixty years the antipsychotics have been blocking dopamine transmission by focussing on the wrong end of the DA synapse. The implications of this view for further antipsychotic development will be presented.

S-01-002 Dopamine, D1 receptors and noradrenergic mechanisms in the modes of action of antipsychotic drugs

T. Svensson[1], C. Björkholm[2], K. Jardemark[2], M. Marcus[2], S. Nyberg[3], B. Schilström[2]. [1]*Karolinska Institutet, Physiology and Pharmacology, Stockholm, Sweden;* [2]*Karolinska Institutet, Stockholm, Sweden;* [3]*AstraZeneca R&D, Södertälje, Sweden*

Objective: Recent clinical data show, using in vivo imaging techniques, a reduced cortical DA release in schizophrenia (SZ), contrasting the previously observed enhanced striatal DA release that correlates with psychosis. The reduced prefrontal DA release is thought to generate impaired cognition by means of insufficient D1-R signaling, as e.g. D1-R stimulation can reverse the working memory deficit induced by ketamine, a psychotomimetic NMDA-R antagonist. Both clozapine and quetiapine, which are effective atypical antipsychotics at low D2-R occupancies, may improve working memory in SZ. The present work aimed to elucidate the role of noradrenergic mechanisms and D1-Rs in their mode of action.

Methods: Experiments were performed in rats using electrophysiological intracellular recording in pyramidal cells in a prefrontal cortical slice preparation to assess NMDA-R function, microdialysis in freely moving animals to assess regional monoamine efflux in brain, and behavioral methodologies, including the conditioned avoidance response (CAR) test to assess antipsychotic activity, the 8-arm radial maze to study working memory (WM) and a catalepsy test to assess extrapyramidal side effects (EPS).

Results: Since the clinical effects of quetiapine are partly mediated by its metabolite norquetiapine, which is not formed in rodents and qualitatively differs from quetiapine only by its potent NET inhibitory action, we compared the behavioral and neurobiological effects of clozapine and a combination of quetiapine and the selective NET inhibitor reboxetine with those of raclopride, a typical D2-R antagonist. In contrast to raclopride, both clozapine and the combination of quetiapine and reboxetine effectively suppressed CAR at low D2 occupancy levels, markedly and selectively enhanced DA outflow in the medial prefrontal cortex (mPFC) and, via D1-R activation, facilitated NMDA-R mediated transmission in this region, an effect that was able to reverse the WM impairment induced by the selective NMDA-R antagonist MK-801. The effects of clozapine could largely be mimicked by a combination of raclopride with idazoxan, an alpha2R antagonist, and those of quetiapine plus NET inhibition by a combination of raclopride and the NET inhibitor reboxetine.

Conclusion: The results clearly implicate brain noradrenergic mechanisms in the modes of action of clozapine and quetiapine. Blockage of presynaptic alpha2-R on NE terminals may release both NE and its precursor DA and, moreover, the increased extracellular NE concentration may elevate cortical DA levels as both transmitters compete for the same transporter, thus producing D1-R activation in the mPFC. A recent meta-analysis (Hecht & Landy 2011) provides further support for he utility of noradrenergic targets in antipsychotic therapy.

S-01-003 Putative D2 receptor containing heteromers in the ventral striatum and their relevance for treatment of schizophrenia

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Objective: Our working hypothesis is that one or several of the potential D2R containing heteromers in the ventral striatum especially A2AR-D2R, D2R-5-HT2AR and NTS1-D2R heteromers may be targets for typical and atypical antipsychotic drugs. The activation of the A2AR, 5-HT2AR and NTS1 protomers of the respective heteromers should result in anti-schizophrenic actions in view of their antagonistic receptor-receptor interactions within ventral striatal D2R heteromers.

Methods: We have used in situ PLA, FRET/BRET, coimmunoprecipitation, biochemical binding, receptor autoradiography, dual-probe microdialysis and behavioural measurements.

Results: The A2AR-D2R heteromer has been indicated through biochemical-biophysical methods. On the basis of the existence of the antagonistic A2AR–D2R interactions, A2AR agonists were proposed to be atypical antipsychotic drugs. A2AR agonists counteract the D2R-induced reduction of the glutamate drive from the mediodorsal thalamic nucleus to the prefrontal cortex via their reduction of D2R signaling in the nucleus accumbens. There may also exist extrasynaptic A2AR–D2R–mGluR5 receptor mosaics located on the dendritic spines of the local circuits of the ventral and dorsal striato-pallidal GABA neurons. Behavioral evidence indicates that the A2AR agonist CGS21680 and the mGluR5 agonist CHPG synergize in counteracting phencylidine-induced motor activity. Furthermore, we demonstrated that the D2LR and the 5-HT2AR form stable and specific heteromers in mammalian cells. Costimulation of D2LR and 5-HT2AR within the heteromer led to inhibition of the D2LR functioning, thus suggesting the existence of a 5-HT2AR-mediated D2LR trans-inhibition

phenomenon. Also, antagonistic NTS1-D2 receptor interactions in postulated NTS1–D2R heteromers in the ventral striatum have been repeatedly proposed to be the molecular mechanism involved in the postulated antipsychotic effects of neurotensin.

Conclusion: D2R heteromers may be disrupted or dysfunctional in schizophrenia leading to removal of the brake on D2R signaling in the striato-pallidal GABA circuits.Receptor-receptor interaction between cortical NA and DA receptors in potential heteromers should also be considered as targets for antipsychotics.

S-01-004 The DA receptor-transporter complexes and increased D2 receptor dimerization: Relevance for schizophrenia

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Objective: All antipsychotics work via dopamine D2 receptors (D2Rs), suggesting a critical role for D2Rs in psychosis; however, there is little evidence for a change in receptor number or pharmacological nature of D2Rs. Recent data suggest that D2Rs form dimers in-vitro and in-vivo, and we hypothesized that schizophrenia, as well as preclinical models of schizophrenia, would demonstrate altered dimerization of D2Rs, even though the overall number of D2Rs was unaltered.

Methods: We measured the expression of D2Rs dimers and monomers in patients with schizophrenia using Western blots, and then in striatal tissue from rats exhibiting the amphetamine-induced sensitized state (AISS). We further examined the interaction between D2Rs and the dopamine transporter (DAT) by co-immunoprecipitation, and measured the expression of dopamine D2High receptors with ligand binding assays in rat striatum slices with or without acute amphetamine pre-treatment.

Results: We observed significantly enhanced expression of D2Rs dimers (277.7 ± 33.6%) and decreased expression of D2Rs monomers in post-mortem striatal tissue of schizophrenia patients. We found that amphetamine facilitated D2Rs dimerization in both the striatum of AISS rats and in rat striatal neurons. Furthermore, amphetamine-induced D2Rs dimerization may be associated with the D2R-DAT protein-protein interaction as an interfering peptide that disrupts the D2R-DAT coupling, blocked amphetamine-induced up-regulation of D2Rs dimerization.

Conclusion: Given the fact that amphetamine induces psychosis and that the AISS rat is a widely accepted animal model of psychosis, our data suggest that D2R dimerization may be important in the pathophysiology of schizophrenia and may be a promising new target for novel antipsychotic drugs.

S-02. Management of treatment-resistant major depression

S-02-001 TRD: Pharmacotherapeutic strategies for adults with major depressive disorder

G.I. Papakostas. *Massachusetts General Hospital, Boston, Ma, USA*

Objective: Major depressive disorder can, often, be chronic, recurrent, and associated with significant disability, morbidity, and mortality. Numerous pharmacologic and non-pharmacologic treatment options exist for the treatment of major depressive disorder, with full and sustained symptomatic remission being the goal of treatment. However, it has been estimated than as many as half of all patients may not experience a remission of their depressive episode despite a treatment trial of adequate dose (in the case of drug therapy) and duration, while a significant burden of (subsyndromal) depressive symptoms may persist among those patients who do achieve remission of their depression. Thus, in most cases, subsequent treatment approaches are required to help achieve full and sustained symptomatic remission. The progressive increase in recognition of the prevalence and burden of TRD, has sparked a rapid growth of research in this treatment area, with a number of novel therapeutic options emerging. Ultimately, these approaches combined may help improve the standard of care for major depressive disorder. The goal of the symposium is to review the prevalence and burden of treatment-resistant major depressive disorder (TRD), and to review novel as well as established therapeutic strategies for TRD.

Methods: Literature will be searched for randomized, double-blind, placebo-controlled trials of pharmacologic interventions for TRD.

Results: Numerous studies are found and discussed.

Conclusion: Numerous studies support the use of various interventions for TRD. Their evidence-base, relative efficacy, tolerability, and safety are discussed.

Policy of full disclosure: Dr. Papakostas has served as a consultant for Abbott Laboratories, AstraZeneca PLC, Brainsway Ltd, Bristol-Myers Squibb Company, Cephalon Inc., Dey Pharma, L.P., Eli Lilly Co., GlaxoSmithKline, Evotec AG, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire Pharmaceuticals, Theracos, Inc., and Wyeth, Inc. Dr. Papakostas has received honoraria from Abbott Laboratories, Astra Zeneca PLC, Bristol-Myers Squibb Company, Brainsway Ltd, Cephalon Inc., Dey Pharma, L.P., Eli Lilly Co., Evotec AG, GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Lundbeck, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer, Pierre Fabre Laboratories, Ridge Diagnostics, Shire Pharmaceuticals, Theracos, Inc., Titan Pharmaceuticals, and Wyeth Inc. Dr. Papakostas has received research support from AstraZeneca PLC, Bristol-Myers Squibb Company, Forest Pharmaceuticals, the National Institute of Mental Health, PAMLAB LLC, Pfizer Inc., and Ridge Diagnostics (formerly known as Precision Human Biolaboratories). Dr. Papakostas has served (not currently) on the speaker's bureau for BristolMyersSquibb Co and Pfizer, Inc.

S-02-002 Pharmacotherapeutic strategies for adults with bipolar depression

M. Bauer. *Univ. Hosp. Carl Gustav Carus, Technische Universität Dresden, Germany*

Objective: The burden of depression represents the most debilitating dimension for the majority of patients with bipolar disorder and dominates the long-term course of the illness. The purpose of this presentation is to review the evidence base of the available treatment options for bipolar depression assigned to two frequent clinical scenarios A and B.

Methods: The evidence is largely based on a systematic literature search. All relevant randomized controlled trials were critically evaluated.

Results: Scenario A: if a patient with bipolar depression is currently not being treated with a mood stabilizing agent (de novo depression), then quetiapine or alternatively olanzapine are an option, carbamazepine and lamotrigine can be considered. Antidepressants are an option for short-term use, but whether they are administered as mono- or combination treatment with mood stabilizing agents is still controversial. Most clinicians prefer to use antidepressants in combination with an antimanic substance. Scenario B: If a patient is already treated with a mood stabilizing agent (breakthrough depression) once adherence has been confirmed and the dose has been adjusted, lamotrigine is an option in patients on lithium. There is no evidence for further effects of antidepressants in cases where a patient is already receiving a mood stabilizer, however, an additional antidepressant is preferred by most clinicians.

Conclusion: Overall, the evidence from treatment trials in bipolar depression is relatively sparse compared with the number of controlled trials in unipolar depression and as such the choice of treatment is governed by a multitude of factors. While clinical trials provide evidence on the efficacy of a certain intervention in a specific population, they cannot necessarily determine which intervention will be optimal for a given patient in a given specific situation. They can however inform the choice of intervention and in particular prevent clinicians from choosing interventions that have been shown to be ineffective.

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S-02-003 Somatic therapies – Brain stimulation methods

M.S. George. *Medical Universiry of South Carolina, Charleston, SC, USA*

Objective: This talk overviews recent advances using Brain Stimulation therapies for treating medication or treatment resistant depression.

Methods: A literature review shows that these methods range from relatively non-invasive (e.g. transcranial direct current stimulation (tDCS) and prefrontal transcranial magnetic stimulation (TMS)), to more invasive (electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS)) to very invasive (deep brain stimulation (DBS) and epidural cortical stimulation (EPCS)).

Results: To date, tDCS studies in acute depression are mixed. TMS is now US FDA approved and a recent NIH pivotal study (OPT-TMS) provides class I level of evidence in treating acute depression. The level of treatment resistance affects TMS response rates. New work involves accelerated TMS over 3 days, or for use in suicidal crisis. ECT continues to be the most effective treatment for acute depression. New advances in ECT pulse width (ultrabrief unilateral ECT) are showing promise with similar efficacy but less toxicity than older methods. We will show data on 17 patients treated with a new directional form of ECT called FEAST. VNS does not have class I level evidence of effectiveness in acute depression but two longitudinal studies in either Europe or the US showed similar long-term benefit in TRD patients followed over several years. The onset of action is slow (months) but appears durable. DBS controlled trials are underway with preliminary promise in patients who have failed to respond to many of the above interventions. There are at least 4 different brain regions being targeted by different groups. While preliminary results are promising, DBS remains an investigational technique without convincing class I evidence of either acute or chronic effects.

Conclusion: Clinicians are now beginning to offer the brain stimulation methods in a staged approach, similar to cancer management, starting with less invasive methods and then gradually advancing.

S-02-004 Treatment of adolescent depression: Some substantive issues

J.K. Buitelaar. *St. Radboud and Karakter Child and Adolescent Psychiatry, Nijmegen, Netherlands*

Objective: The objective of this presentation is to discuss the challenges in treating pediatric depression, and balance medication and psychological approaches to treatment.

Methods: Narrative review of the results of key clinical trials with medication and psychological interventions in child and adolescent depression, based on PubMed search and consultation of authoritative reviews.

Results: More severe depressive episodes will generally require treatment with antidepressants. Depressed children and adolescents treated with SSRIs have a relatively good response rate (40%–70%), but the placebo response rate is also high (30%–60%). With the exception of the fluoxetine studies (e.g., Emslie et al., 1997), significant differences between SSRIs and placebo were, due to the high placebo response, only found in depressed adolescents but not in depressed children (Bridge et al., 2007). The TADS compared fluoxetine, cognitive behaviour therapy (CBT), and their combination (TADS, 2004). In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT to medication also enhances the safety of medication. Taking benefits and harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents (TADS, 2007). Results of the TORDIA studyshow that depressed adolescents who have failed to respond to an adequate trial with a SSRI, a switch to another antidepressant plus CBT resulted in a better response than a switch to another antidepressant without additional psychotherapy (Brent et al., 2007). Fluoxetine was shown to normalize brain activity in multiple brain regions, including the frontal, temporal, and limbic cortices after 8 weeks of treatment (Tao et al., 2012).

Conclusion: Though a reasonable percentage of depressed adolescents respond to treatment, remission rates are rather low in short-term trials. Treatment should be continued after remission for at least 6–9 months. Most patients recover after 2–4 years, but in the meantime, another 50% of these show already recurrence.

Policy of full disclosure: Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

S-03. Cocaine-induced changes in glutamate neuroplasticity in developing and mature neuronal circuits

S-03-001 Cocaine-induced changes in glutamate neuroplasticity in developing and mature mesolimbic circuits

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Objective: As in many parts of the central nervous system of the mouse, glutamatergic synapses onto dopamine (DA) neurons in the ventral tegmental area (VTA) mature postnatally. We have recently demonstrated that at birth many AMPARs lack GluA2 and most NMDARs contain the GluN2B subunit. Within two weeks these receptors are replaced with GluA2- and GluN2A- containing AMPARs and NMDARs respectively. Here we now show that a single injection of cocaine triggers not only the redistribution of AMPARs, but also rearrange NMDARs.

Methods: In order to test our hypothesis, we use in vitro whole-cell patch-clamp recording in VTA acute slices from neonatal and juvenile mice.

Results: After the drug exposure the synapses express GluN2B containing NMDARs along with GluA2-lacking AMPARs, as if addictive drugs reopen a developmentally critical period. Both during the development and after single cocaine exposure, mGluR1 activation drives the insertion of NMDARs (mGluR1-LTPNMDA). This is associated with an overall increase in NMDAR-EPSCs (mGluR1-LTPNMDA) and involves PLC, Ca^{2+} release from the internal stores as well as PKC activity. Moreover, we identify the Shank3/Homer interaction as an important player in the mGluR1-LTPNMDA.

Conclusion: While we are only beginning to understand the repercussions of drug-evoked receptor redistribution, the striking resemblance with the processes occurring during early postnatal development brings a new, exciting perspective that may help us to understand both normal development and the development of addiction.

S-03-002 Cocaine experience modulates synaptic transmission in the habenula complex

M. Mameli[1], M. Maroteaux[1]. [1]*Institut du Fer a Moulin, Batiment INSERM, 75005 Paris, France*

Objective: Goal directed actions, aimed to obtain a reward, motivate our behaviors and influence our decisions. Midbrain dopamine neurons activity and therefore dopamine release are enhanced by external cues predicting a reward. Lateral habenula (LHb) neurons play a central role in this regulation since they instruct dopamine neurons during reward learning. Addictive subtances induce an abnormal increase in dopamine neurons and recent theories posit that addiction develops by hijacking the reward system promoting strong association between drug and context. Given the critical importance of LHb neurons in tuning dopamine neurons firing and participating to cue-reward association we tested whether synaptic trasnmission and plasticity at glutamatergic synapses in this nuclei are sensitive to drug exposure.

Results: We have used patch clamp recordings and identify peculiar biophysical properties of AMPA receptors that suggest that such proteins lack the subunit GluA2. Cocaine experience strenghtens excitatory transmission and alters synaptic plasticity in treated animals compared to saline injected ones.

Conclusion: These result suggest that cocaine exposure alters the synaptic inputs onto LHb neurons, which in turn could explain some of the mechanisms during drug-context association occurring in the reward circuit.

S-03-003 Neuroplastic changes following repeated exposure to cocaine during adolescence: Focus on the glutamatergic system

F. Fumagalli[1], L. Caffino[2], G. Giannotti[2], G. Racagni[2]. [1]*University of Milan, Dept of Antidrug Policies, Italy;* [2]*University of Milan, Italy*

Objective: To investigate changes in glutamate receptors expression and phosphorylation following repeated exposure to cocaine during adolescence.

Methods: We therefore treated male rats from post-natal day (PND) 28 to PND 42 with saline or cocaine (20 mg/kg). Animals were sacrificed 3 days (PND 45) after the end of treatment or at adulthood (PND 90) and the brain regions of interest (prefrontal cortex and nucleus accumbens) were removed. Analyses were carried out by Western blots.

Results: No major changes were found in the phosphorylation or expression of the main subunits of NMDA receptors in the prefrontal cortex of PND 45-old rats with only a slight reduction in the major AMPA subunit, i.e. GluR1; conversely, in nucleus accumbens, we found increased phosphorylation, but not expression, of NR1, NR2B and GluR1. At adulthood, we primarily found a significant reduction in GluR1 expression and phosphorylation in the prefrontal cortex with no major changes in the nucleus accumbens. Additionally, when we challenged the animals with an acute stress to evaluate whether exposure to cocaine during adolescence had altered the response of the glutamatergic system to the stress itself, we found a dysregulated response in the phosphorylation of the main glutamatergic subunits, i.e. the NR-1 NMDA subunit and the GluR-1 AMPA subunit.

Conclusion: Our results suggest 1) an early activation of the glutamate system in nucleus accumbens; 2) a persistent effect of the exposure to cocaine during adolescence on GluR-1 subunit, which persists into adulthood 3) a dynamic role of glutamatergic receptors following adolescential exposure to cocaine which is not limited to changes at the steady state level of these receptors.

S-03-004 Corticostriatal glutamate dysregulation in an animal model of cocaine addiction and relapse

R. See. *University of South Carolina, Department of Neurosciences, Charleston, South Carolina, USA*

Objective: Cocaine-induced changes in corticostriatal glutamate regulation have been implicated in cocaine seeking after prolonged cocaine self-administration in rats. Here, we examined changes in striatal glutamate release in rats with a history of daily cocaine intake. Based on evidence for normalization of glutamatergic function by the cysteine prodrug, N-acetylcysteine (NAC), further experiments tested whether repeated NAC administration would produce lasting reductions in cocaine-seeking.

Methods: Male rats self-administered intravenous cocaine during daily sessions, followed by daily extinction (no reinforcement) or abstinence (alternate environment) sessions. To assess glutamate release in the dorsal striatum, in vivo microdialysis procedures were used in awake animals to collect samples that were then analyzed by HPLC-EC. For assessment of chronic NAC effects, rats received daily injections of saline, 60, or 100 mg/kg NAC (IP). Subsequently, rats were tested for cocaine-seeking via conditioned cue-induced, cue + cocaine-primed, and context induced cocaine seeking.

Results: Rats with a history of chronic cocaine self-administration showed enhanced striatal glutamate efflux under both context induced conditions and after acute injection of cocaine. Chronic NAC administration blunted cocaine-seeking under multiple experimental protocols. Specifically, NAC attenuated responding during cue and cue + cocaine-primed reinstatement tests following extinction, and context, cue, and cue + cocaine tests of drug seeking following abstinence. Reduction of cocaine seeking by NAC persisted well after treatment was discontinued, particularly when the high dose was combined with extinction trials.

Conclusion: Dysregulation of striatal glutamate release likely plays a key role in persistent cocaine seeking following abstinence. The finding that NAC reduced cocaine-seeking after treatment was discontinued supports recent preclinical and clinical evidence that NAC may serve as an effective treatment for inhibiting relapse in cocaine addicts.

S-04. Insights for personalized medicine in psychiatry

S-04-001 Complex regulation of gene expression in brain

C. Wahlestedt. *The Scripps Research Institute, Jupiter, USA*

Objective: This lecture will present our view on how gene expression is dynamically regulated by protein and RNA mechanisms in contexts of different epigenetic states and psychiatric disorders.

Methods: We have conducted a wide variety of transcriptomic and epigenetic experiments over a number of years.

Results: Rather than a fixed hierarchy with one or very few master regulators at the top, the picture that emerges is that of a recurrent network in which multiple transcription factors mutually coordinate their activity in conjunction with the actions of regulatory RNAs. Much of the mammalian genome is transcribed into small or long non-coding RNAs of different categories and different modes of function. MicroRNAs as well as long noncoding RNAs appear to control the expression and function of most conventional genes and pathways.

Conclusion: In the decade since the first publications on the entire human genome, the number and general architecture of conventional genes has remained remarkably stable. By contrast, surprising changes have come from noncoding regions and from studies on epigenetic phenomena, and their interplay with known gene function, which have created an entirely new paradigm for all aspects of genome-related research.

S-04-002 Gene x environment interactions in the prediction of response to antidepressant treatment

E. Binder. *Max-Planck Inst of Psychiatry, Munich, Germany*

Objective: High hopes have been held for the field of pharmacogenetics in the prediction of antidepressant response, but so far no associations could be consistently replicated. As for the development of psychiatric disorders per se, treatment response is likely not only moderated by main genetic effects but also environmental factors and gene x environment interactions.

Methods: This presentation will focus on early life trauma and present molecular genetic data, including gene x environment interaction data, epigenetic data and gene expression data in human pharmacogenetic trials.

Results: Several lines of evidence are presented suggesting the importance of gene x environment interactions in predicting response to antidepressant treatments. First, a number of genetic polymorphisms, including polymorphisms within the serotonin transporter gene and the stress hormone system genes CRHR1 and FKBP5, have been shown to interact with early trauma to predict mood disorders. The same polymorphisms have also been shown to predict response to antidepressant treatment. Second, gene x environment interactions lead to highly different biological disturbances in mood disorders. This will be illustrated with FKBP5 polymorphisms as an example, for which we could show allele-specific epigenetic changes following exposure to early trauma. These are accompanied by distinct system-wide molecular changes, suggesting that different pathways need to be targeted to elicit antidepressant response depending on both, the FKBP5 genotype and exposure to early trauma. Finally, preliminary data supporting the importance of early trauma x gene interaction in the overall and differential prediction of response antidepressant to current antidepressant treatments (medication vs. cognitive behavioral therapy) will be presented.

Conclusion: Different combinations of environmental and genetic risk factors likely lead to biologically distinct subsets of mood disorders that could show preferentially response to certain treatment types. This can be related to the prediction of response to currently used antidepressant therapies but may also aid in the identification of novel antidepressant targets.

S-04-003 Personalized medicine and the management of TRD

C. Nemeroff. *University of Miami, USA*

Although there are several effective pharmacotherapeutic and psychotherapeutic treatments for major depression, a large majority of patients do not obtain remission after an adequate monotherapy trial with one of these modalities. There is increasing evidence that biologically distinct subtypes of major depression, so-called endophenotypes, are to a large extent responsible for this current unfortunate state of treatment outcomes in depression and related mood and anxiety disorders. One subtype of depression that has repeatedly been shown to exhibit a lower than expected rate of treatment response to antidepressants is patients with major depression and a history of child abuse and neglect. This presentation will summarize the evidence that such patients represent a neurobiologically distinct subgroup as revealed by structural magnetic resonance imaging (MRI) and functional brain imaging (PET and fMRI) findings, alterations in neuroendocrine and immune function and a distinct pattern of distribution of several genetic polymorphisms (CRHR1, FKBP5, PAC1, BDNF) that mediate gene-environment interaction. In addition, unique symptom profiles of this patient group including cognitive impairment will be described. Taken together these data support the development of novel treatment strategies based on this subgroup-specific pathophysiology for optimal personalized management of a sizeable percentage of the treatment refractory depressed population.

Policy of full disclosure: Research/Grants: National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ) Speakers Bureau: None Consulting: Xhale, Takeda, SK Pharma, Shire, Roche, Lilly Stockholder: CeNeRx BioPharma, NovaDel Pharma, Inc., PharmaNeuroBoost, Revaax Pharma, Xhale Other Financial Interests: CeNeRx BioPharma, PharmaNeuroBoost Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1) Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2) Compounds, Compositions, Methods of Synthesis and Methods of Treatment Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), NovaDel Pharma (2012), Inc., Xhale, PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail, AstraZeneca Pharmaceuticals (2009) Board of Directors: AFSP, NovaDel Pharma (1/12/2012), Inc., Mt. Cook Pharma (2010), Skyland Trail Income sources or equity of $10,000 or more: AstraZeneca Pharmaceuticals, PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, Xhale.

S-04-004 Pharmacogenetics of alcohol reward and therapeutic response to naltrexone

M. Heilig[1], A. Thorsell[1]. [1]*Linköping Health Univ, Linköping, Sweden*

Objective: Mu-opioid (OPRM1) receptors are key to rewarding properties of alcohol, and the target for the approved alcoholism medication naltrexone. Functional 118A→G variation at the OPRM1 locus was suggested to represent a genetic vulnerability factor for alcohol and heroin addiction, and to moderate therapeutic efficacy of naltrexone, but these findings remain controversial.

Methods: We first examined alcohol responses, consumption and efficacy of naltexone in a functionally equivalent rhesus OPRM1 77C→G model. Next, DA release in response to alcohol was examined using PET and [11C]raclopride displacement in social drinkers recruited by OPRM1 118 genotype. Finally, the causal role of the human OPRM1 118A→G SNP was isolated from other polymorphisms using humanized mouse lines carrying the respective OPRM1 118 variant.

Results: In rhesus macaques, male OPRM1 77G carriers displayed markedly elevated psychomotor stimulation in response to alcohol, accompanied by increased alcohol consumption and preference. These observations suggested an enhanced dopamine (DA) response to alcohol in minor allele carriers. Accordingly, in male social drinkers, striatal DA response to alcohol was restricted to carriers of the OPRM1 118G allele. In humanized mice, alcohol-induced DA-release in the Nc Accumbens in response to alcohol was markedly greater in male 118GG than male 118AA mice. Male, but not female 118GG mice also consumed higher amounts of alcohol than 118AA mice of the corresponding sex, in particular at higher alcohol concentrations.

Conclusion: These studies collectively establish that the functional OPRM1 118G variant is sufficient to confer greater alcohol-induced DA-release and consumption. These findings are consistent with a role of this variant to predispose human carriers to endorphin-dependent alcoholism, but also to render patients more responsive to opiod antagonist treatment.

S-05. Mechanism of PTSD: From genes and epigenetics to neurocircuits and endophenotype

S-05-001 Searching for epigenetic biomarkers in PTSD

S. Morinobu[1], M. Fuchikami[2], S. Okada[1], S. Yamawaki[1], I. Liberzon[3], A. King[3], J. Seng[3]. [1]*Hiroshima University, Japan;* [2]*Yale University, New Haven, USA;* [3]*University of Michigan, Ann Arbor, USA*

Objective: The development of posttraumatic stress disorder (PTSD), follows exposure to a traumatic/highly stressful event. Since it is well known that stress exposure changes the mRNA levels of genes in the rodent brain, it is conceivable that changes in gene expression mediated by alterations in the DNA methylation in the brain are involved in the pathophysiology of PTSD. In this context, it is hypothesized that the DNA methylation status may be a potent diagnostic biomarker in PTSD.

Methods: We examined the methylation profile of 35 CpGs located in one CpG island (799 bp), covering the exon 1 of the serotonin transporter (5-HTT) gene using genomic DNA from peripheral blood of 173 patients with PTSD and48 healthy controls. Methylation rate at each CpG unit was measured using a MassARRY® system (SEQUENOM).

Results: Two-dimensional hierarchical cluster analysis (diagnosis × methylation rate) of all CpG units did not yield correct diagnostic classification to healthy controls and patients groups. The methylation rates of 6 CpG units out of 35 CpG units were significantly different in patients having current PTSD diagnosis and the methylation rates of 5 CpG units were significantly different in patients with having lifetime PTSD diagnosis as compared to healthy controls. Among these, two CpGs units were common to the lifetime and the current PTSD diagnosis groups. In addition, we will present the results from the analyses of the methylation status of one CpG island at the promoter of the exon 1 of the brain-derived neurotrophic factor gene.

Conclusion: These findings suggest the possibility that the methylation rate of a certain CpG at the promoter of the 5-HTT gene may be a diagnostic biomarker in PTSD.

S-05-002 Genetic approaches to understanding posttraumatic stress disorder

K. Ressler. *Emory University, Atlanta, USA*

Objective: Posttraumatic Stress Disorder (PTSD) is an anxiety disorder which can develop as a result of exposure to a traumatic event and is associated with significant functional impairment. Family and twin studies have found that risk for PTSD is associated with an underlying genetic vulnerability and that more than 30% of the variance associated with PTSD is related to a heritable component.

Results: Using a fear conditioning model to conceptualize the neurobiology of PTSD, three primary neuronal systems have been investigated – the hypothalamic-pituitary-adrenal axis, the locus coeruleus-noradrenergic system, and neurocircuitry interconnecting the limbic system and frontal cortex. The majority of the initial investigations into main effects of candidate genes hypothesized to be associated with PTSD risk have been negative, but studies examining the interaction of genetic polymorphisms with specific environments in predicting PTSD have produced several positive results which have increased our understanding of the determinants of risk and resilience in the aftermath of trauma. Promising avenues of inquiry into the role of epigenetic modification have also been proposed to explain the enduring impact of environmental exposures which occur during key, often early, developmental periods on gene expression. Studies of PTSD endophenotypes, which are heritable biomarkers associated

with a circumscribed trait within the more complex psychiatric disorder, may be more directly amenable to analysis of the underlying genetics and neural pathways and have provided promising targets for elucidating the neurobiology of PTSD.

Conclusion: Knowledge of the genetic underpinnings and neuronal pathways involved in the etiology and maintenance of PTSD will allow for improved targeting of primary prevention amongst vulnerable individuals or populations, as well as timely, targeted treatment interventions. This article is part of a Special Issue entitled 'PTSD'.

S-05-003 Stress, emotion and cognition: Lessons from studying PTSD neurocircuitry

I. Liberzon. *University of Michigan, Ann Arbor, USA*

Objective: Functional neuroimaging studies identified abnormalities in amygdala, Anterior Cingulate Cortex, Medial Prefrontal Cortex and insula in Post-traumatic stress disorder. Our presentation will describe recent studies and state of the art knowledge of neurocircuitry involved in PTSD vulnerability, neurophysiology and symptom formation.

Methods: The original conceptualization linked Amygdala and mPFC abnormalities to abnormal fear learning and expression, however more recent models examine the potential contribution of these regions to processes of emotional regulation, memory recall and reinstatement and contextual modulation. fMRI studies using these methods in PTSD will be discussed.

Results: In addition, novel analytical approaches to fMRI data allow for study of connectivity among various brain regions both during resting state and during specific tasks, providing additional information about the status of functional networks of brain regions. Initial findings of functional network abnormalities in PTSD are emerging, and they offer additional insights into abnormal brain processes potentially contributing to PTSD pathophysiology and symptom formation.

Conclusion: Together, these novel and more complex models of information processing in PTSD allow for more nuanced understanding of PTSD pathophysiology and symptom formation, as well identifying potentially more sensitive endophenotypic endpoints for treatment studies. Finally, recent integration of genetic and neuroimaging approaches offers a new and powerful tool to further describe intermediate phenotype (endophenotype) in PTSD, and to better identify the specific contribution of genetic vulnerability or resilience in PTSD development.

S-05-004 Intrinsic network abnormalities in PTSD

R. Lanius[1], J. Daniels[1], P.C. Williamson[1], A.C. McFarlane[1], K.A. Moores[2], C.R. Clark[3], M. Shaw[4]. *[1]London, Canada; [2]Millswood, Australia; [3]Adelaide, South Australia, Australia; [4]Heidelberg, Germany*

Objective: Previous neuroimaging studies in healthy controls have shown the existence of a ''default mode network'' of correlated brain regions active during rest. These regions include the posterior cingulate, anterior cingulate and medial prefrontal cortex, and lateral parietal areas. The current studies examined (1) the nature of the abnormalities in the default network in chronic PTSD related to early life trauma; (2) whether default network connectivity could predict PTSD symptomatology in an acutely traumatized sample; and (3) the pattern of default network connectivity during rest versus a working memory task in PTSD.

Methods: Patients with acute and chronic posttraumatic stress disorder (PTSD) related to early-life trauma and healthy controls underwent a 5.5-minute functional magnetic resonance imaging scan with their eyes closed. Areas of the brain whose activity positively and negatively correlated with that of the PCC/precuneus were assessed in both groups. In addition, a working memory task and psychophysiologic interaction analyses with the posterior cingulate cortex and the medial prefrontal cortex as seed regions during fixation in patients with chronic PTSD and healthy controls were conducted.

Results: In healthy controls, activity in the posterior cingulate seed region was found to positively correlate with other regions of the default network. This correlation was significantly altered in the chronic PTSD group. Altered connectivity between the posterior cingulate and brain regions associated with the task positive network were observed in chronic PTSD during a working memory task. Results in the acutely traumatized sample suggest that resting state connectivity of the PCC with the right amygdala predicts future PTSD symptoms.

Conclusion: These results suggest that the integrity of the default network is compromised in acute and chronic PTSD and that the extent of the deficit reflects clinical measures of PTSD.

Track: Basic

S-06. The glutamate synapse and its regulation: An opportunity for novel pharmacologic approaches in mood/anxiety disorders

S-06-001 Targeting glutamate clearance in the development of treatments anxiety and depression: Focus on EAATS

G. Sanacora. *Yale University, Nerw Haven, USA*

Objective: There is increasing evidence suggesting altered regulation of glutamate neurotransmission contributes to the pathophysiology of major mood and anxiety disorders. Recent reports demonstrating the antidepressant-like effects of several glutamatergic agents has further spurred interest in gaining a greater understanding of the role of glutamate in mood disorders. In a parallel line of research several postmortem studies have demonstrated marked glial cell pathology and altered levels of excitatory amino acid transport (EAAT) expression associated with several neuropsychiatric disorders. As glial cells are primarily responsible for the clearance and metabolism of glutamate in the brain there is strong motivation to understand the interaction between glial cells, glutamate neurotransmission and psychiatric disorders.

Methods: The rodent chronic unpredictable stress (CUS) model was employed to investigate the effects of stress on glial cell function and glutamate cycling. Additional studies using drugs such as riluzole and ceftriaxone, shown to alter glial cell clearance of glutamate were used to investigate potential antidepressant-like effects in the CUS model. Molecular, cellular and physiological measures were made to determine the effects of stress and the drugs on glial cell markers, metabolism and glutamate/glutamine cycling. Dihydrokainic acid (DHK) an EAAT blocker, was used to specifically investigate the role of glutamate uptake in relation to the effects of stress and antidepressant actions. Lastly, studies using GLT-1 (EAAT2) knockout mice were performed to further evaluate the effects of glutamate clearance. Clinical trials evaluating the efficacy of these drugs will be discussed.

Results: CUS resulted in reduced levels of GLT-1 protein in the pre-and infra-limbic brain regions and reduced levels of glutamate/glutamine cycling. Riluzole and ceftriaxone both produced antidepressant-like effects in several rodent models that could be attenuated with DHK. The drugs also had a reduced antidepressant-like effect in heterozygous GLT-1 knockout mice.

Conclusion: Similar to previous findings form postmortem studies of depressed patients the findings suggest CUS produces changes in glial cells and glutamate transporters. Drugs targeting glutamate transporter activity appear to have antidepressant-like effects in rodent models and possibly in clinical trials.

S-06-002 Modulating the NMDA receptor complex in developing therapeutics for bipolar disorder and major depressive disorder

C. Zarate. *NIH/NIMH, Bethesda, USA*

Objective: Current treatments are generally unsuccessful for a number of patients with severe and recurrent mood disorders. Reasons for this lack of better therapeutics include our limited understanding of the neurobiological basis of mood disorders, and of the mechanism of action of existing effective medications. A key limitation of existing therapeutics is that they are associated with a significant lag of onset of action. Pharmacological strategies that

rapidly reverse depressive symptoms including suicidal ideation would have an enormous impact on public health. Several converging lines of evidence suggest that dysfunction of the glutamatergic system—particularly the N-methyl-D-aspartate (NMDA) receptor complex—may play an important role in the pathophysiology of major depression. Therefore, testing the efficacy of NMDA receptor modulators and subunit modulators could yield an improved knowledge of the neurobiological processes involved in these complex illnesses, and lead to the development of radically improved treatments.

Methods: Several trials examining drugs that affect the NMDA receptor complex have been conducted to date at NIH in major depressive disorder (MDD) and bipolar depression (1 double-blind placebo-controlled study with memantine, 1 with ketamine followed by continuation therapy with riluzole, 3 controlled studies with the NMDA antagonist ketamine, and 1 with a selective NR2B antagonist). In addition, we have obtained biomarker data with including peripheral and electrophysiological and neuroimaging measures such as magnetoencephalography (MEG), neuroimaging (positron emission tomography [PET], magnetic resonance spectroscopy [MRS]) looking for peripheral and neural signals of antidepressant response to NMDA antagonists.

Results: In the three controlled studies with ketamine, a rapid antidepressant response was found. In the first study in MDD, we found an onset of antidepressant action within 110 minutes. The effect size for the drug difference was very large (d = 1.46) after 24 hours and large (d = 0.68) after 1 week. In two BPD studies, we found an antidepressant response within 40 minutes; this improvement remained significant through most of the week for up to 3–5 days. In the latter controlled study, we found significant anti-suicidal effects within 4 minutes lasting 3 days. An antidepressant signal was also found with an oral selective NR2B antagonist in TRD. The use-dependent NMDA antagonist memantine was not found to have significant antidepressant effects. With regards to biomarkers predicting antidepressant response, we found that increases in slow wave activity (SWA, a putative marker of synaptic plasticity) and gamma power cortical activity correlated with decreases in depressive symptoms following ketamine infusion. Furthermore, pregenual anterior cingulate cortical activity in response to an emotional and cognitive task predicted antidepressant improvement to ketamine.

Conclusion: Modulating the glutamatergic system, particularly at the NMDA receptor complex appears to be important to the mechanism of immediate antidepressant and anti-suicidal response. Electrophysiological and neuroimaging studies are yielding important insights into the neural correlates of rapid antidepressant action.

S-06-003 Targeting glutamate release as a testing ground for compounds with antidepressant/anxiolytic action

M. Popoli. *University Milano, Italy*

Objective: Stressful life events impact on memory and cognition and are known to precipitate mood/anxiety disorders. It is increasingly recognized that stress and its neurochemical and endocrine mediators induce changes in glutamate synapses morphology and transmission.

Methods: We showed previously that unpredictable footshock (FS)-stress induces enhancement of depolarization-dependent glutamate release from synaptosomes of prefrontal and frontal cortex (P/FC), due to a rapid increase of corticosterone (CORT) levels, activation of glucocorticoid receptor and presynaptic SNARE complexes accumulation. Intriguingly, chronic pretreatments with several antidepressants, with distinct primary mechanisms, completely abolish the increase of glutamate release induced by FS-stress. Patch-clamp recordings of prefrontal cortex pyramidal neurons revealed that FS-stress induces changes in paired-pulse facilitation (PPF) and its calcium-dependence consistent with an increase in glutamate release. Chronic desipramine, as observed for glutamate release, completely prevented the changes in PPF and calcium-dependence. However, desipramine does not block the increase of the size of the readily releasable pool (RRP) of vesicles induced by FS-stress (measured as hypertonic sucrose-induced glutamate release), suggesting that the dampening action of the antidepressant does not affect the RRP size.

Results: Overall, our results show a novel effect of antidepressants that could be related to their therapeutic action in mood/anxiety disorders. Chronic treatments with benzodiazepines and antipsychotic drugs have been performed before the stress protocol, to understand whether this dampening effect of antidepressants is shared by other psychiatric drugs.

Conclusion: We are currently testing if measurement of stress-induced glutamate release can be used as a test to assay the preventing action of antidepresants in stress response. Understanding the action of traditional drugs on glutamate transmission could be of great help in developing compounds that may work directly at this level.

S-06-004 Metabotropic glutamate receptors as therapeutic targets for anxiety and depression: Focus on mGluR7

J. Cryan. *University College Cork, Ireland*

Growing evidence suggests that the glutamatergic system may be a relevant therapeutic target for stress-related disorders such as depression, anxiety, and cognitive dysfunction. Metabotropic glutamate (mGlu) receptors are poised to participate in a wide variety of functions of the CNS. The presynaptic mGlu(7) receptor shows the highest evolutionary conservation within the family and it is thought to regulate neurotransmitter release. The mGlu(7) receptor is also the most widely distributed of the presynaptic mGlu receptors and is present at a broad range of synapses that are postulated to be critical for both normal CNS function and a range of psychiatric and neurological disorders. A growing body of evidence suggests that the mGlu(7) receptor is a key player in shaping synaptic responses at glutamatergic synapses as well as being a key regulator of inhibitory GABAergic transmission. The development of selective pharmacological and genetic tools has allowed for the unravelling of mGlu(7) receptor function in a host of physiological and behavioural processes. Knockout mice and siRNA knockdown has pointed to a role of the mGlu(7) receptor in anxiety, extinction of fear and aversion learning, spatial memory and the hormonal response to stress. In addition, these studies are largely supported by pharmacological manipulation of mGlu(7) receptor although controversies exist and better in vivo selective ligands are necessary. Finally, selective antidepressant drugs and models of depression have alterations in hippocampal mGlu(7) expression which may contribute to their behavioural effects. Together, these data suggest that the mGlu(7) receptor is an important regulator of glutamatergic function and modelates behaviours relevant to depression, anxiety and cognition. Thus this receptor represents an innovative therapeutic target for stress-related disorders at the interface of cognition and emotion.

Policy of full disclosure: None.

S-07. Suicide: Pathophysiology, psychopharmacology and biomarkers

S-07-001 Suicide: Social, psychological, biological and genetic risk factors

W. Bunney. *Univ of California, Irvine, USA*

Objective: Suicide represents a major public health problem with an estimated 1 million deaths per year worldwide. The international magnitude of the problem of suicide, including social, psychological, biological and genetic risk factors will be reviewed. The critical component of psychological pain in suicide will be discussed. Specific biological markers that could predict suicide will be reviewed. Protective factors for suicide will be presented.

Methods: Postmortem brain tissue from depressed patients who died from suicide compared to depressed patients who died from other causes was analyzed by microarrays and findings were confirmed by qPCR.

Results: The expression of a family of genes, metallothioneins (M1, M2), was significantly decreased in brains of depressed patients who died from suicide in contrast to depressed patients who died from other causes.

Conclusion: Metallothioneins are modulated by cortisol and provide neuroprotection against the high cortisol levels consistently reported in mood disorders. Thus, neuroprotection may be significantly decreased in suicide victims. Metallothioneins are highly expressed in blood and could serve as biomarkers of suicide.

S-07-002 Genetic associations and gene-environment interactions between candidate genes related to stress-response and stressful life events, in severe suicide attempts.

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Objective: Suicidal behavior (SB) is a major burden in most nations world-wide and a major public health concern, as ~1 million people commit suicide (SC) each year and 10–20 times more perform suicide attempts (SA). The causes of why certain people engage in SB are complex, involving both environmental and genetic factors, and interactions in-between. The aim of this study is to elucidate the interaction of certain genes with exposure to physical and sexual abuse amongst the young (G × E).

Methods: We performed G × E studies taking into consideration life timing of trauma and gender concerning the corticotrophin releasing hormone receptor 1 (CRHR1) gene, a major and systemic stress-modulator of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis. We assessed exposures to rape and/or physical assault (PA, below or over age of 18) or other lifetime stressful life events (SLEs) in male and females, by using a family-based design (n = 660 trios) complemented by case-control analysis, in relation to the outcome of severe lifetime SA in the offspring.

Results: We observed CRHR1 G × E among predominantly female SA between 5-SNP rs7209436 and PA below 18 years of age and a male-specific G × E between 3′-SNP rs16940665 and adulthood PA exposure, both sharing the SA characteristic of aggression. A third male-specific CRHR1 G × E was among depressed SA, between SNP rs4792887 and cumulative lifetime SLEs. Furthermore, excessive stress has the potential to induce unfavorable side-effects in a variety of brain-functions, by interactions of the HPA axis with other neurosystems, and we will further report about the results from our ongoing studies concerning such aspects as well.

Conclusion: We conclude that SA showed differences in their G × Es, concordant with a complex SB-aetiology, and that knowledge of specific G × Es might become helpful for focused prevention and intervention efforts in the future.

S-07-003 The pharmacogenetics of suicidal adverse reactions to SSRI medications in children and adolescents

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Objective: Depression is a common disorder in adolescents with serious morbidity and even mortality if not treated. SSRI medications are commonly used for such treatment but only about 55–60% of depressed subjects respond to treatment and 5% show severe side effects in including suicidal behavior and ideation.

Methods: Consecutive admissions (n = 121) to a Child and Adolescent Psychiatry outpatient were assessed and diagnosed by DSM-IV-TR criteria. The following assessment instruments were used: The Schedule for Affective Disorders and Schizophrenia for school aged children, Present and Lifetime, Screen for Child Anxiety and Related Emotional Disorders, Children s Depression Inventory; Suicidal Ideation Questionnaire, Clinical Global Impression Scale, SSRI Side Effect Profile Inventory. Genetic polymorphisms of several genes relevant to the pharmacokinetic and dynamic properties of SSRI were determined-5HTT, MAO-A, BDNF, TPH2, 5HT2c, 5HT2a, 5HT1b, FKBP5, CHHR1, CRHR2, GR, TBX19, CYP2C19, CYP2D6.

Results: 5HTT: Children with the ll allele responded in 75% of cases, ls in 56% of cases and ss in 40% ($p < 0.05$). TPH2 gg allele together with ll showed and 80% response whereas tg/tt together with ll had an 80% response ($p = .01$); 5-HTR1B Children with cc had a 57.1% incidence of motor activation vs. 15.9% with gg ($p < 0.05$); Children with cc had 28.5% psychological activation vs. 4.5% with gg ($p < 0.05$) FKBP5 rs 136070 cc showed 82.1% remission vs. 33.3% remission with tt. CRHR1 rs4792887 ct vs. Ct showed significant increase suicidal ideation after treatment.

Conclusion: These preliminary findings are encouraging and provide the basis for further investigations in the field.

S-07-004 Noradrenergic and serotonergic pathways and the stress diathesis model of suicidal behavior

J. Mann[1], V. Arango[1], R. Parsey[1], M. Oquendo[1], H. Glafalvy[1]. [1]*Columbia University, NY State Psychiatric Institute, New York, USA*

Objective: To map the state of the noradrenergic and serotonergic neurotransmitter systems in suicide and nonfatal suicide attempts and link to identified components of psychopathology associated with suicidal behavior.

Methods: Postmortem brain autoreadiography was employed to map changes in pre and post-synaptic receptors in the serotonergic and noradreneregic neurotransmitter systems in suicides. PET in vivo imaging was used to map serotonin receptors and the transporter in brain in nonfatal suicide attempters with major depression compared with nonattempter major depression and healthy volunteers. Findings are related to clinical components of the stress diathesis model we have proposed for suicidal behavior.

Results: Noradrenergic deficiencies are related to lethality and probability of suicidal behavior and to its lethality. These deficits are correlated with hopelessness and depression. Serotonergic deficits are found in suicides in the brainstem nuclei, ventromedical prefrontal cortex and anterior cingulate. More recently we have conformed some of these findings in living survivors of suicide attempts. Genetic and epigenetic causal factors have been identified for some of these findings.

Conclusion: The identification in nonfatal suicide attempters of biological abnormalities also found in suicides suggests that brain scanning may be a potential screening tool for those at risk for suicide. Treatment and prevention strategies using these findings as biomarkers of risk offer an alternative method for outcome indices in medication and psychotherapy trials.

Policy of full disclosure: Dr. Mann has past unrelated imaging grants from GSK and Novartis.

S-08. The neurobiology of compulsivity and OCD: From basic science to clinical practice

S-08-001 Symptomatology and pharmacotherapy of obsessive-compulsive disorder

D. Stein. *University of Cape Town, Department of Psychiatry, Capetown, South Africa*

Objective: Obsessive-compulsive disorder is an important neuropsychiatric disorder associated with significant morbidity. This presentation aims to review key questions about the symptomatology and nosology of obsessive-compulsive disorder, as well as current work on the pharmacotherapy of this disorder.

Methods: A number of systematic reviews have recently been undertaken of both diagnostic issues and pharmacotherapy approaches in obsessive-compulsive disorder; this presentation draws from this work, highlighting key questions for the field, and summarizing relevant data.

Results: There is growing acceptance in the field of the construct of ''obsessive-compulsive related disorders'', although there continues to be debate about its optimal boundaries. There is good evidence for the efficacy of serotonin reuptake inhibitors (SRIs) as first line agents, some evidence for the efficacy of antipsychotic agents as augmenting agents in individuals refractory to SRIs, and ongoing interest in a range of other drug classes.

Conclusion: While there have been advances in diagnosis and treatment of obsessive-compulsive disorder, further work to delineate the underlying psychobiology of this disorder is needed to continue to progress the field.

Policy of full disclosure: Dr. Stein has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth.

S-08-002 Unraveling neural mechanisms of compulsivity using the signal attenuation rat model

D. Joel. *Tel Aviv University, Department of Psychology, Israel*

Objective: Obsessive-compulsive disorder (OCD) is a psychiatric disorder affecting 1–3% of the population. The orbitofrontal cortex, the striatum and the dopaminergic and serotonergic systems have been implicated in the pathophysiology of OCD, yet the ways in which these neural systems interact to produce obsessions and compulsions in patients is currently unknown. Data obtained using pharmacological manipulations, lesions, inactivation and electrical stimulation in the signal attenuation rat model of OCD suggest specific ways in which these neural systems interact to produce compulsive behaviors.

Methods: The signal attenuation model is a theory-driven rodent model of OCD which builds on the assumption that compulsive behaviors result from a deficient signaling that a response was effective in producing an outcome.

Results: Work in this model found that lesions to the orbitofrontal cortex decrease striatal serotonin and dopamine content and increase compulsive lever-pressing, and that this increase is blocked by intrastriatal administration of a selective serotonin reuptake inhibitor. Lesions to the subthalamic nucleus similarly decrease striatal serotonin and dopamine and increase compulsive lever-pressing. Consistent with these findings, high frequency stimulation of the subthalamic nucleus, which exerts an anti-compulsive effect in OCD patients and in the signal attenuation model, increases dopamine content in the striatum.

Conclusion: Taken together, these results suggest that alterations in striatal serotonin and/or dopamine may provide a final common pathway by which different brain pathologies may lead to compulsive behaviors.

S-08-003 The translational neuroscience of OCD

T. Robbins. *University of Cambridge, Dept. Experimental Psychology, United Kingdom*

Objective: Obsessive-compulsive disorder entails a tendency compulsively to perform repetitive acts and has traditionally been associated with anxiety states and obsessions, putatively reflecting pathology in the orbitofrontal cortex, striatum and amygdala. We have been searching for endophenotypic markers in the disorder that can also be related to these brain systems on the basis of studies with human neuroimaging and animal models.

Methods: A major candidate has been cognitive inflexibility, for example, in reversal learning and extra-dimensional set-shifting (a core component of the Wisconsin Card Sorting Test), previously shown in studies with monkeys and rodents to depend on distinct cortico-striatal loops involving the orbitofrontal and lateral prefrontal cortex. We used a human fMRI paradigm previously shown to separate these regions according to the BOLD responses during reversal and extra-dimensional set-shifting as well as parallel behavioural paradigms in rodents and monkeys.

Results: We demonstrated hypoactivity of the orbitofrontal network during reversal learning in an obsessive-compulsive group and in their first degree relatives without clinical symptoms. Parallel work with marmoset monkeys showed reversal learning to depend on 5-HT modulated functions of the orbitofrontal cortex and dopamine-modulated functions of the ventromedial striatum. Stop-signal reaction time performance was similarly impaired in patients with obsessive-compulsive disorder and their first-degree relatives, and was also shown to involve orbitofrontal and lateral frontal-striatal circuits in rodents. Finally, the balance of competing neural systems mediating action-outcome learning and stimulus-response habit learning was shifted towards the latter in obsessive-compulsive disorder, based on performance of a human associative learning paradigm inspired by neuropsychological experiments on associative learning in rodents.

Conclusion: These results (obtained with appetitive paradigms that do not elicit anxiety) are discussed in terms of contributory neurobehavioural mechanisms underlying obsessive-compulsive disorder. They may also be relevant to changing perceptions of its aetiology and nosological status.

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S-08-004 Animal models of obsessive-compulsive disorder: What deep brain stimulation may tell us about pathophysiology

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Objective: OCD patients exhibit hyperactivity in the orbitofrontal cortex (OFC), and effective treatments normalize OFC activity. Moreover, intractable OCD is responsive to deep brain stimulation (DBS) of the ventral striatum (VS). Therefore, we evaluated animal models of OCD, and examined the neuronal alterations produced by continuous DBS of the VS target used in OCD treatment in humans.

Methods: Two models of OCD were evaluated; the clomipramine model (15 mg/kg twice/day between postnatal days 9 and 16) and the quinpirole model (0.5 mg/kg twice/week for 7 weeks). Rats were evaluated for compulsive behavior and VTA DA neuron activity. DBS was administered to the VS site for 5 days continuously (130 Hz, 100 usec and 100 uA bilaterally), and local field potentials recorded.

Results: In our hands, the clomipramine model failed to show results consistent with OCD. Quinpirole treated rats showed significant perseveration and compulsive lever pressing, and increased VTA DA neuron population activity. DBS in control rats increased gamma power bilaterally in the VS, but decreased coherence between the VS and the prelimbic PFC, and between the VS and the thalamus. In contrast, there was an increase in coherence between the OFC and the thalamus, and the OFC bilaterally.

Conclusion: These data suggest that DBS induces acute increases in power in cortical regions, but over time this change undergoes compensation and is replaced with changes in coherence. Changes in coherence is likely to reflect alterations in information processing. Thus increased coherence between the OFC and its afferent structures would improve signal processing, potentially enabling the OFC to effectively devalue stimuli that are no longer relevant for behavior; a function impaired in OCD. In contrast, decreased coherence in the prelimbic PFC and ventral striatum may reflect improved extinction. Whether DBS has different effects on power and coherence in animal models of OCD is currently being evaluated.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Pfizer, GalaxoSmithKlein, Merk, Takeda, Dainippon Sumitomo, Otsuka.

S-09. Neuropeptides and mental diseases

S-09-001 Role of orexin/hypocretin in panic and other stress disorders

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Objective: Panic disorder (PD) is a severe anxiety disorder characterized by recurrent panic attacks affecting about 2–5% of the population and resulting in severe disability in about a third of those subjects. We recently identified that orexin (hypocretin) neurons are one of the key regulators of a coordinated panic response and that patients with panic but not depression symptoms do indeed have high levels of orexin in their cerebrospinal fluid. Panic patients also have enhanced vulnerability to conditioned fears, avoidance and phobias. The present study was conducted to elucidate the mechanisms of these long term consequence of panic disorder utilizing preclinical model system.

Methods: Utilizing chronic disinhibition of orexinergic neurons in the perifornical/dorsomedial hypothalamus (PeF/DMH, we tested the effects on disrupted network functions on induction of 1) chronic anxiety states; 2) enhanced fear conditioning; and 3) delayed extinction of conditioned fear. We measured behavioral, molecular and electrophysiological endpoints, utilizing pharmacological and gene silencing experiments in both whole animal and slice preparations.

Results: Chronic disinhibition of ORX neurons in the DMH/PeF inducing molecular and network changes in the bed nucleus of the stria terminalis (BNST) to decrease GABAergic and to enhance glutamatergic neurotransmission in order to induce a chronic anxiety-like phenotype. Hyperactivation of orexin system enhanced acquisition and expression of conditioned fears seen in panic-prone rats, and resulted in excitation and reduced inhibition in the central nucleus of the amygdala (CeA), thus facilitating neuronal plasticity in the CeA.

Conclusion: These results provide a mechanistic model to understand the pathophysiology of PD and its disabling consequences and provide insight into the functional network electrophysiology as well as basic cellular and molecular changes within key limbic circuits. Finally, at the translational level, these results provide novel insights into the persistent and hard to extinguish nature of agoraphobia and anticipatory anxiety in patients with panic disorder.

Policy of full disclosure: Supported by the US National Institute of Mental Health grant, R01 MH052619.

S-09-002 CRH1 Receptor antagonists – Back on the map

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Objective: Strong evidence emerged from basic and clinical research that many of the signs and symptoms prevalent in depression are mediated by CRH via CRHR1 receptors. Key findings were behavioral changes in animals that were chronically stressed, received centrally CRH or were overexpressing transgenically CRH. The CRHR1 subtype was among other techniques identified by conditional CRHR1 gene deletions. Clinical support for targeting the CRH/CRHR1 system came from enhanced CRH concentrations in the brains and cerebral spinal fluids of depressed patients, neuroendocrine and sleep-EEG studies and a first open label trial with R121919, a nonpeptide CRHR1 antagonist. All major pharmaceutical companies developed CRHR1 antagonists and compared them with current standard compounds and placebo. Without exception all so far reported controlled trials yielded negative results, i.e. the test drugs were equal to placebo and comparators were superior. The reason was that in the absence of laboratory tests identifying patient subgroups where CRH hyperactivity accounts for the clinical condition, a specific intervention such as CRHR1 blockade will be inferior to a current unspecific antidepressant.

Methods: We developed a genetest allowing to accumulate potential CRH hypersecretors. In addition, we observed in transgenic mice overexpressing CRH a disinhibiton of REM-like sleep. REM-disinhibition was associated with beneficial response to CRHR1 antagonist treatment among severely depressed patients. Therefore we argue that a genetest combined with sleep-EEG analysis will identify potential CRHR1 antagonist responders.

S-09-003 Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia

J. Sebat. *Chief, Beyster Center for Genomics of Neuropsychiatric, La Jolla, USA*

Rare copy number variants (CNVs) have a prominent role in the aetiology of schizophrenia and other neuropsychiatric disorders. Substantial risk for schizophrenia is conferred by large (>500-kilobase) CNVs at several loci, including microdeletions at 1q21.1 (ref. 2), 3q29 (ref. 3), 15q13.3 (ref. 2) and 22q11.2 (ref. 4) and microduplication at 16p11.2 (ref. 5). However, these CNVs collectively account for a small fraction (2–4%) of cases, and the relevant genes and neurobiological mechanisms are not well understood. Here we performed a large two-stage genome-wide scan of rare CNVs and report the significant association of copy number gains at chromosome 7q36.3 with schizophrenia. Microduplications with variable breakpoints occurred within a 362-kilobase region and were detected in 29 of 8,290 (0.35%) patients versus 2 of 7,431 (0.03%) controls in the combined sample. All duplications overlapped or were located within 89 kilobases upstream of the vasoactive intestinal peptide receptor gene VIPR2. VIPR2 transcription and cyclic-AMP signalling were significantly increased in cultured lymphocytes from patients with microduplications of 7q36.3. These findings implicate altered vasoactive intestinal peptide signalling in the pathogenesis of schizophrenia and indicate the VPAC2 receptor as a potential target for the development of new antipsychotic drugs.

S-09-004 Galanin and galanin receptors in depression – focus on the human brain

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Objective: Galanin is a 29 (30 in humans) neuropeptide that is expressed in many regions of the rodent brain, including locus coeruleus (LC) and dorsal raphe nucleus (DRN), where it in rat coexists with noradrenaline and serotonin, respectively. There is evidence from animal experiments that galanin is involved in mood regulation, in fact also from human genetic studies. Animal experiments suggest that a galanin antagonist should have antidepressant actions. The aim of this work is to reveal to what extent distribution of the galanin system in the human brain is similar to that reported in rodents.

Methods: We have used riboprobes and in situ hybridization to localize galanin and its receptor (GalR1–3) mRNAs in LC and DRN. Some other markers like transcripts for tyrosine hydroxylase, tryptophan hydroxylase 2, vesicular glutamate transporters and nitric oxide synthase were also analysed.

Results: In the human post mortem brain LC galanin and GalR3, but not GalR1 and -R2 could be detected. In the DRN galanin was not found in areas harbouring serotonin neurons, but GalR3-positive and serotonin neurons overlapped.

Conclusion: These findings indicate that the galanin system exhibits considerable species differences, which should be taken into account in work aiming at development of novel antidepressants. Our results based on analysis of the human post mortem brain, and on animal experiments, suggest that antagonists at the GalR3, but not the GalR1, receptor would be potential antidepressants. In fact, such antagonists have been generated.

S-10. Putative abnormalities in Orexin and GABA metabolism in panic disorder

S-10-001 Orexin and psychiatric symptoms in suicide attempters

L. Brundin[1], L. Träskman-Bendz[2]. [1]*Lund University, Psychoimmunology Unit, Sweden;* [2]*Lund University, Sweden*

Objective: The orexins (hypocretins) are hypothalamic peptides initially discovered to be involved in the regulation of sleep, appetite and state of arousal. We analyzed orexin levels in the cerebrospinal fluid (CSF) of patients who were hospitalized after a suicide attempt.

Methods: At the day of the lumbar puncture, psychiatric symptoms were carefully rated using the Comprehensive Psychopathological Rating Scale (CPRS) as well as the Suicide Assessment Scale (SUAS), and the patients underwent a thorough diagnostic interview.

Results: We found that suicide attempters with a diagnosis of Major Depressive Disorder had significantly lower levels of orexin in the CSF than patients with adjustment disorder and dysthymia. Furthermore, we found that orexin levels increased significantly during the first year after the suicide attempt, together with an improvement of the scores on the SUAS. We also found that low CSF-orexin levels were related to pronounced symptoms of inertia and reduced motor activity in suicidal patients.

Conclusion: The lower the orexin levels, the higher were ratings of overall illness, as observed by a specialist in psychiatry. Interestingly, depressed patients with anxiety display significantly higher orexin levels than patients without such symptoms. Thus, high vs. low levels of orexin might be coupled to different spectrums of psychiatric symptoms.

S-10-002 GABA imaging findings in panic disorder measured by ^{1}H MRS

U. Dydak[1], Z. Long[2], Y.-W. Shin[3], M. Dzemidzic[4], A. Goddard[4]. [1]*Purdue University, West Lafayette, USA;* [2]*School of Health Sciences, West Lafayette, USA;* [3]*Department of Psychiatry, Seoul, Republic of Korea;* [4]*Indiana Univ. School of Med., Indianapolis, USA*

Objective: Several 1H Magnetic Resonance Spectroscopy (MRS) studies found decreased levels of the inhibitory neurotransmitter

y-aminobutyric acid (GABA) in cortical regions of unmedicated patients with panic disorder (PD). Furthermore it has been suggested that a positive family history of PD may play a role in cortical GABA changes in PD patients. This talk will review published 1H-MRS GABA findings in PD and present data from a recent study investigating the influence of family history on GABA levels in unmedicated PD patients.

Methods: A GABA-editing MRS technique was used for GABA detection in anterior cingulate cortex (ACC) and occipital cortex (OCC) in five family history-positive (FHP) patients, six family history-negative (FHN) patients and 11 matched controls.

Results: While no significant difference in GABA levels, expressed as the ratio of GABA over total Creatine (tCr), were found between the groups in either brain region, ACC GABA/tCr levels had a numerical trend to be lower in FHP patients versus controls. A significant correlation was found between OCC GABA/tCr levels and the trails B test scores (a test of visual attention) ($r = 0.8$, $p < 0.05$) in this patient group. Interestingly, the correlations between prescan state anxiety scores and GABA/tCr levels seem to be opposite for ACC and OCC, as well as for FHP and FHN patient groups: a positive correlation is found for FHN patients in ACC ($r = 0.95$, $p < 0.01$) and for FHP patients in OCC ($r = 0.52$, trend only); however, a negative correlation was seen for FHN patients in OCC ($r = -0.88$, $p < 0.01$) and for FHP patients in ACC ($r = -0.62$, trend only).

Conclusion: Our results agree with previous reports on GABA deficits in PD patients. Decreased GABA in family history-positive patients suggests a unique GABAergic mechanism in these patients.

S-10-003 Resting-state functional connectivity in panic disorder

Y.-W. Shin[1], M. Dzemidzic[2], U. Dydak[3], A. Goddard[4], Z. Long[5]. [1]*Ulsan University, Seoul, Republic of Korea;* [2]*Department of Neurology, Indianapolis, USA;* [3]*Department of Radiology, Indianapolis, USA;* [4]*Department of Psychiatry, Indianapolis, USA;* [5]*School of Health Sciences, West Lafayette, USA*

Objective: Decreased GABA concentration in the anterior cingulate cortex (ACC) has been reported in panic disorder. A recent study showing the increased GABA concentration in the ACC was positively correlated with negative blood oxygen level dependent response in the area has made it necessary to investigate a resting-state functional connectivity of the ACC in panic disorder.

Methods: The functional connectivity maps with seed ROI located in the ACC were identified in the patients with panic disorder ($N = 11$) and age- and sex- matched normal control subjects ($N = 11$). The correlation was investigated between the index of functional connectivity in the area showing group differences and the GABA concentration around the seed ROI volume.

Results: The patients with panic disorder showed increased functional connectivity between ACC and precuneus compared to control subjects with family-wise error corrected at $q < 0.05$. The functional connectivity between the ACC and precuneus had a negative correlation with GABA concentration in the ACC.

Conclusion: Increased functional connectivity in the resting-state default mode network including the ACC and precuneus might play an important role in the pathophysiology of panic disorder.

S-10-004 Clinical studies of Orexin (ORX) and GABA function in panic anxiety: Translational implications.

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Objective: PD is a significant public health problem as it is a common psychiatric condition with a lifetime prevalence of up to 4% in the general community. It is a chronic illness, which can profoundly affect functioning and quality of life. Despite improvements in diagnosis and treatment over the last few decades, the pathophysiology of PD and mechanisms of effective treatments remain unclear. The present work evaluates the role of GABA-ORX interaction in human panic.

Methods: As mentioned by other symposium speakers, perturbations in GABA (MRS measures) and neuropeptide/ORX function (CSF ORX) may contribute to a panic vulnerability state, which may be reflected in variations in resting-state fcMRI parameters. A series of recent preclinical and clinical studies (Johnson, Truitt et al., 2010), has led us to hypothesize that PD is associated with specific cortical and subcortical GABA deficits that result in disruption of normal inhibitory regulation of ORX neurons. This disruption promotes excessive ORX release, sympathetic activation, and vulnerability to spontaneous or lactate-induced panic.

Results: Follow-up animal and human work within our anxiety research team has identified evidence of ORX neuronal hyperactivity in association with CO2-induced anxiety. Furthermore, other investigators have reported ORX metabolic abnormalities at rest in patients with chronic PTSD, another anxiety disorder with pathophysiologic similarities to PD (Strawn et al., 2010).

Conclusion: Our collaborative research effort has implications for elucidating key ORX-GABA interactions that contribute to human panic states, as well as for defining the therapeutic mechanisms of actions of known effective antipanic therapies (e.g. benzodiazepines, SSRIs, CBT), and novel panicolytics (e.g. ORX1 receptors antagonists).

Policy of full disclosure: Pfizer-Consultant, Janssen-Independent grant awardee, Astra-Zeneca-Independent grant awardee.

RS-01. Neuroimaging applications in neuropsychopharmacologyCINP Asia Regional Committee

RS-01-001 Imaging evaluation of drug target molecule: translational perspective from animal model and human brain

T. Suhara. *National Institute of Japan, Radiological Sciences, Chiba, Japan*

Positron emission tomography (PET) techniques have enabled the visualization of transporter protein and functions. In the field of neuropsychopharmacology, monoamine transporters such as serotonin transporter and norepinephrine transporter (NET) are the major target of antidepressants and efflux transporters such as P-glycoprotein is a major component of blood brain barrier. The serotonin transporter occupancy has been used as a reliable index for therapeutic drug monitoring. Previous PET studies on antidepressants have suggested over that 80% of occupancy provides the desired therapeutic effects. On the other hand, the NET occupancy by antidepressants in human brain has not been reported because of a lack of suitable radioligands for NET. (S,S)-[18F]FMeNER-D2 was recently developed as a radioligand for the measurement of NET binding with PET. The mean NET occupancies by nortriptyline doses were 16.4% at 10 mg, 33.2% at 25 mg, and 41.1% at 75 mg, respectively. The mean plasma concentration of nortriptyline was 0 ng/ml at 10 mg, 23.7 ng/ml at 25 mg, and 50.5 ng/ml at 75 mg. Estimated ED50 (50% effective dose) was 76.8 mg of administration dose and 59.8 ng/ml of plasma concentration.

RS-01-002 Drug-receptor occupancy study in predicting proper dose of psychotropic drugs with PK-PD modeling

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Objective: To predict proper dose of antipsychotic drugs in terms of receptor occupancy, it is necessary to determine the relationship between plasma drug concentration and receptor occupancy. Typically, most studies of antipsychotic drugs have applied the Emax model alone to characterize the relationship. However, a limitation of this approach is that it does not account for the discrepancy between the time courses of plasma drug concentration and receptor occupancy by antipsychotic drugs. This prompts the necessity of combined pharmacokinetic-pharmacodynamic (PK-PD) modeling for the reliable analysis of the concentration-occupancy relationship. We will introduce PK-PD modeling in the concentration-occupancy analysis and compare it with conventional approach (Emax model alone).

Methods: We measured dopamine receptor occupancy using [11C]raclopride PET and plasma concentration of aripiprazole at a number of time points after the administration of aripiprazole. We built the PK-PD model and simulated the time effect on the concentration-occupancy relationship.

Results: The hysteresis characteristics were observed in the concentration-occupancy relationship and the value of EC50 was different according to the analysis approach (EC50 = 11.1 ng/ml (95%CI = 10.1 ~ 12.1) from Emax model alone; EC50 = 8.63 ng/ml (95%CI = 7.75 ~ 9.51) from PK-PD model).

Conclusion: This finding suggests that PK-PD modeling is required to obtain reliable results in study about the antipsychotic concentration-occupancy relationship.

RS-01-003 Association of brain serotonin transporter (SERT) availability and brain-derived neurotrophic factor in models of SERT genotypes in human subjects: a new insight for the development of antidepressant

Y.-H. Chou. *Taipei Veterans General Hospit, Taiwan*

Objective: The S-allele of functional polymorphisms of the serotonin transporter (SERT) gene has been demonstrated to have lower transcriptional activity compared with the L-allele, which shows low expression of SERT in the brain. However, this finding cannot be consistently replicated in vivo. Importantly, the frequency of polymorphism is different from Asian and Caucasian. The aim of this study was to determine the availability of SERT based on SERT genotype in an Asian population. We also examined the relationship between brain-derived neurotrophic factor (BDNF) and the availability of SERT.

Methods: Sixty-two healthy subjects were recruited. Each subject underwent single photon emission computed tomography (SPECT) with 123I-ADAM for imaging SERT in the brain. The specific uptake ratio (SUR) was measured and venous blood was drawn when the subject underwent SPECT to evaluate plasma BDNF levels and SERT genotype. All subjects expressed SERT genotypes that were consistent with a bi-allelic model, and 26 subjects had SERT genotypes that were consistent with a tri-allelic model.

Results: No differences in SUR were detected in the midbrain, putamen, caudate and thalamus based on the SERT genotype using the bi-allelic and tri-allelic models. Interestingly, linear regression revealed a positive correlation between plasma BDNF and SERT availability. In particular, this relationship was observed in homozygous S-allele expression and a genotype with low functional expression (SaSa/SaLg) in the bi-allelic and tri-allelic models of SERT genotypes, respectively.

Conclusion: This finding might explain why the SS genotype of SERT did not increase the risk of MDD in Asian populations and implicate an important role of BDNF in the patients, who has the SS genotype of the SERT gene.

RS-01-004 A two-year follow-up study on the functional connectivity abnormality in first-episode drug-naive schizophrenia in a Chinese population

T. Li. *Chengdu, China*

Objective: By first episode of illness and prior to treatment, diffusion tensor imaging (DTI) studies confirm patients with schizophrenia have lower regional white matter fractional anisotropy (FA) measures than typically developing controls. However, it is not clear whether antipsychotic drugs ameliorate or worsen microstructural changes in white matter systems during the very early phase of treatment. To explore longitudinal alterations in white matter (WM) microstructure in antipsychotic-naïve patients with first-episode schizophrenia during the very early phase of treatment.

Methods: High-resolution diffusion tensor imaging (DTI) was obtained from 35 first-episode drug-naïve patients with schizophrenia and 22 controls at baseline and 6 weeks later, respectively. The patients received standard antipsychotic treatment during the 6-week period. The differences in Positive and Negative Syndrome Scale (PANSS) scores and Global Assessment of Functioning (GAF) scores between baseline and 6 weeks later were evaluated and expressed as a 6-week/baseline ratio. In addition a 6 week 'difference map' was generated from the follow-up image minus the baseline DTI image. The FA difference maps in cases and controls were compared and potential correlations between FA changes and changes in PANSS, outcome scores and antipsychotic drug dosages were explored.

Results: Compared to healthy controls, there was a significant decrease in absolute FA in WM around the bilateral anterior cingulate gyrus and right anterior corona radiata of frontal lobe in first episode drug-naive patients with schizophrenia following 6 weeks treatment. The change in FA did not correlate with change in clinical symptoms or the dosages of antipsychotic medication.

Conclusion: During the early phase of treatment, there is an acute reduction in white matter FA which may due to the effects of antipsychotic medications. However, it is not possible to entirely exclude the effects of underlying progression of illness.

Tuesday 5 June 2012

S-11. Mental health and the immune system

S-11-001 Antidepressants as anti-inflammatory agents in the treatment of depression: Fact or fiction?

B. Leonard. *National University of Ireland, Galway, Ireland*

Objective: There is substantial evidence that chronic low grade inflammation plays a vital role in the psychopathology of depression. As antidepressants attenuate depressive symptoms, do they do so by attenuating the inflammatory status?

Methods: A search of the published literature clearly indicates that the pro-inflammatory cytokines, IL-6 and TNF-alpha are consistently raised in the sera of depressed patients. The response of these markers to effective antidepressant treatment was assessed.

Results: The effects of antidepressants on the pro-inflammatory cytokines in the sera was inconsistent, dual action antidepressants being most effective. Evidence from some studies show that the cytokine concentration in the frontal cortex increases despite the reduction in the sera associated with the therapeutic response. Concurrent administration of ibruprofen was shown to block the antidepressant response but to reduce the cortical inflammatory cytokines.

Conclusion: The hypothesis that effective antidepressant treatment is associated with a reduction in brain inflammation requires further evaluation. The previously reported enhancement of the antidepressant response by NSAID's also needs reconsideration.

S-11-002 The role of tryptophan catabolites in the pathogenesis of depression: Lessons from interferon-alpha

C. Raison. *Emory University, Atlanta, USA*

Objective: To assess the possibility that activation of the body's inflammatory response system promotes depression and related behavioral symptoms in part via indoleamine 2,3-dioxygenase (IDO) induced production of kynurenine and its metabolites.

Methods: Recent data are reviewed that support a role for IDO in the development of depression in response to chronic immune activation provided by treatment with the cytokine interferon (IFN)-alpha.

Results: While it has long been known that inflammatory stimuli activate IDO, it was presumed that IDO contributed to depression primarily by reducing the availability of serotonin precursors. More recent findings suggest that marked increases in CNS levels of kynurenine and its metabolites quinolinic acid and kynurenic acid may be more directly involved in depressive pathogenesis.

Conclusion: Recent findings using IFN-alpha as a model system support long-forgotten findings from early psychiatric research that kynurenine and its metabolites may be relevant to the pathogenesis of depression. Agents that impact kynurenine production and/or metabolism may hold therapeutic promise for the treatment of depression.

Policy of full disclosure: Work presented here was funded by the National Institute of Mental Health. In the previous 12 months

Dr. Raison has served as a consultant to Brystol Myers Squibb and Pamlab and has developed and presented disease state promotional material for Pamlab.

S-11-003 The immune system and the kynurenine pathway in schizophrenia: Pathophysiological and therapeutic aspects

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Objective: The paradigm of a disturbed dopaminergic neurotransmission being a key-feature in the neurobiology of schizophrenia has more and more been replaced by more complex hypotheses including the interaction between distinct neurotransmitter systems and the immune system. One highly intriguing functional link is represented by the kynurenine pathway of the tryptophan metabolism.

Methods: This presentation will sum up results of several studies.

Results: The immune response in schizophrenia seems to be a two-sided sword: There are data clearly indicating an enhanced activation of the T-helper2-like immune system associated with more pronounced positive symptoms, which fit with the findings of an enhanced production of the NMDA and alpha7nACh receptor antagonist kynurenic acid. On the other hand there are data showing that the immune system is clearly activated, characterised by an enhanced production of pro-inflammatory cytokines. This pro-inflammatory state is associated with the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) resulting in an increased production of neurotoxic kynurenine metabolites including 3-hydroxykynurenine. The immunological effects of antipsychotics partly reverse the immune imbalance and there is evidence for their modulating effect on the kynurenine pathway as well.

Conclusion: Substances acting directly on the kynurenine metabolism, are still in early stages of development, while anti-inflammatory drugs acting indirectly on this metabolism are discussed as therapeutic or preventive agents in schizophrenia. Most of the current data are related to COX-2 inhibitors, which have been tested in animal experiments and in clinical trials, pointing to favourable effects in schizophrenia.

Policy of full disclosure: The author is involved in two patents on kynurenine metabolites as biomarkers for psychiatric disorders.

S-11-004 Oxidative and immune biomarkers as targets for the development of novel therapies

M. Berk. *University of Melbourne, Swanston Centre, Geelong, Australia*

Objective: There is abundant evidence that inflammatory and oxidative processes play a role in mood disorders. There is evidence of increased inflammatory activity in mood disorders, including elevations in cytokines.

Methods: The brain is the most metabolically active tissue, and disruptions in mitochondrial energy generation are now well described in mood disorders. Administration of pro-inflammatory cytokines is amongst the best models of depression. The consequences of inflammatory and oxidative stress include lipid peroxidation, DNA fragmentation protein carbonylation and an increased vulnerability to apoptosis. Inflammatory and oxidative stress leads to decreased BDNF and other trophic factors. Established antidepressants and mood stabilisers including lithium and valproate have a role in ameliorating oxidative stress, and additionally alter immune markers. N-acetyl cysteine (NAC) is a precursor of glutathione, has anti-inflammatory properties and has been shown to reverse animal models of oxidative stress.

Results: Clinical data shows a significant benefit of NAC on measures of depression, quality of life and functioning Equally, inflammation provide some novel therapeutic targets, which are clinically accessible, including statins, aspirin and NSAIDS.

Conclusion: There is data that these agents may reduce risk for mood disorders. Such biomarker data have the potential to lead to the development of novel therapies for mood disorders outside of traditional monoamine targets.

Policy of full disclosure: Grant/Research support: Stanley Medical Research Foundation, MBF, NHMRC, BeyondBlue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier. Speaker: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Servier, Solvay, Wyeth. Consultant: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Servier.

S-12. Oxidative stress, and the development of mental disorders

S-12-001 Mood disorders and mitochondrial dysfunction

T. Young. *University of Toronto, Canada*

Mood disorders present an enormous burden of illness and many patients do not respond to available treatments. While we continue to focus on neurocognitive changes and cellular loss and damage in specific brain regions, the exact etiology remains uncertain. Genome wide association studies support multiple genes of small effect which confer increased for these illnesses. Continued progress on studying post-mortem brain tissue and blood cells from patients have demonstrated new possibilities for biological causes of these disorders. Evidence from a number of investigators has shown that oxidative stress and damage is increased in patients with bipolar disorder which may be related to abnormalities within the electron transport chain. Build up of oxidative metabolites may lead to cellular damage and loss. Studies from animal models and patients suggest that treatment with mood stabilizers may reduce oxidative damage and ultimately prevent cellular damage and loss. Oxidative stress has long been held as a mechanism in other neurodegenerative disorders including Parkinsonism. Of particular interest is the relation of oxidization to dopamine metabolism which may be important in the mechanism of action of mood stabilizing drugs. These findings help to broaden yet focus the search for the specific causes of mood disorders, lead to the development of biomarkers and make way for novel effective treatments.

S-12-002 Long term consequences of brain oxidative-stress during early postnatal life

M. Behrens. *Salk Institute, La Jolla, CA, USA*

Objective: Through its involvement in the generation of gamma oscillatory activity, the fast-spiking parvalbumin-positive (PV+) neuronal system is essential for shaping neuronal circuits during postnatal brain development. Discrete functional disruptions in this GABAergic system are expected to alter the excitatory/inhibitory balance in brain and to produce cognitive deficiencies, as those observed in schizophrenia. We have studied the postnatal developmental periods in which a redox imbalance produced by NMDA receptor antagonists leads to a permanent alteration of the PV+ neuronal system in the rodent cortex.

Methods: Our studies encompass molecular determinations, slice electrophysiological recordings, and in vivo EEG recordings of mice exposed to ketamine during the perinatal period. These data is then used in computer simulation studies of prefrontal cortex function.

Results: Our work has shown that repetitive exposure of rodents to ketamine during the perinatal period increases brain levels of IL-6 and activates the superoxide-producing enzyme NADPH oxidase (Nox2). This, in turn, produces a lasting redox imbalance that leads a permanent loss of PV and GAD67 expression in PV+ neurons, to a decreased response of the interneurons to excitatory transmission and to a diminished inhibitory drive to pyramidal neurons. At the systems level, it leads to pronounced alterations in auditory evoked related potentials, with decreased stimulus-induced gamma oscillatory activity, and a shift in the evoked gamma/beta ratio. Computational simulations that incorporate the reductions in PV and GAD67 observed in the mouse model lead to networks showing a diminished gamma-band oscillatory activity in response to stimuli, and to a reduced evoked gamma/beta ratio as observed in vivo.

Conclusion: Our data suggest that a period of oxidative-stress, caused by activation of the IL-6/Nox2 pathway during early life, may alter the normal development of PV+ neurons leading to the alterations in gamma oscillatory activity observed in schizophrenia patients.

S-12-003 Oxidative stress in prefrontal cortical parvalbumin interneurons in the neonatal ventral hippocampal lesion model of schizophrenia

P. O'Donnell[1], P. Piantadosi[1], J.H. Cabungcal[2], K. Do[2]. [1]*University of Maryland, Baltimore, Md, USA*; [2]*University of Lausanne, Switzerland*

Objective: Prefrontal cortical interneurons are affected in a variety of rodent models of schizophrenia, including the neonatal ventral hippocampal lesion (NVHL) and genetic models. Together with post-mortem studies showing altered markers related to GABA transmission in the prefrontal cortex (PFC) of schizophrenia patients, these findings suggest inhibitory interneurons in the PFC may become affected by many genetic and environmental factors during development. As there is increasing evidence of redox dysregulation in schizophrenia, we tested whether NVHL rats exhibit signs of oxidative stress in PFC interneurons and whether antioxidant treatment improves outcome.

Methods: Sprague-Dawley rats received a bilateral injection of ibotenic acid (lesion) or vehicle (sham) in the ventral hippocampus at postnatal day (P) 6–7. Some rats received the antioxidant N-acetyl-cysteine (NAC) between P5 and P56. Rats were euthanized and parvalbumin (PV) cell counts were assessed with unbiased stereology; additional rats were tested for prepulse inhibition deficits and electrophysiological measures.

Results: Juvenile rats with a NVHL, but not sham controls, exhibited high levels of the oxidative stress marker 8-oxo-DG but no differences in PV staining. Most PV neurons exhibited 8-oxo-DG staining, indicating this cell type is susceptible to oxidative damage. At P61, we observed a marked reduction in parvalbumin labeling in untreated NVHL PFC. NAC treatment reversed the deficit in PV cells as well as the PPI deficits in NVHL rats.

Conclusion: The data indicate that a neonatal hippocampal lesion has deleterious effects on PFC development, yielding PV interneurons with oxidative damage during the pre-pubertal stage and a loss of PV labeling and behavioral deficits in the adult stage, which are reversed with antioxidant treatment. This suggests that PFC interneurons can present oxidative stress in rodent models of schizophrenia, and this could be the mechanism that renders them into a reduced level of activity, eventually causing cognitive and other deficits associated with the disease.

S-12-004 Redox dysregulation, inhibitory-excitatory imbalance and myelination impairment in schizophrenia

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Objective: Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in chronic schizophrenia (SZ) patients. Polymorphisms of key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic and modifier (GCLM) subunits, are associated with SZ. GSH dysregulation was investigated now in early psychosis patients (EP). Impaired GSH synthesis of genetic origin, when combined with environmental risk factors generating oxidative stress, may play a critical role in inducing connectivity anomalies, a hypothesis tested in GCLM-/- mice (70% lower GSH).

Methods: In EP, GSH genes were genotyped and their expression assessed in fibroblasts. In GCLM-/- mice hippocampus (HP) and anterior cingulate cortex (ACC), morphology (oxidative stress, parvalbumin immunohistochemistry of inhibitory interneurons [PVI], myelin), electrophysiology (oscillations and synchronization), neurochemical profile (1H-MRS at 14.1Tesla) were assessed, as well as behavior. A dopamine uptake inhibitor was used to model the impact of environmental factors.

Results: In EP fibroblast, mRNA decrease of GSH genes, observed in chronic SZ, is confirmed in EP, demonstrating that redox dysregulation is not due to chronicity or treatment. Moreover, mRNA decrease of xCT, the exchanger Glu/Cyt, absent in chronic SZ, appears in EP. GCLM-/- mice show morphological, physiological and behavioral phenotypes similar to patients, including elevated oxidative stress, impairment of PVI and β/γ-oscillations in ventral HP. In ACC, PVI formation is delayed. PVI are vulnerable to insults applied during development but not in adulthood. Myelination is impaired. Neurochemical profile reveals increased Gln, Glu, Gln/Glu at peri-pubertal age, as in EP. N-acetyl-cysteine, a GSH precursor and antioxidant, reverses PVI and neurochemical anomalies.

Conclusion: Redox dysregulation is a critical SZ risk factor. In GSH deficit models, it leads to region and time selective oxidative stress, Glu anomalies and impairment of structural and functional integrity.

S-13. Molecular mechanisms and prophylaxis in PTSD, contributions from prospective and longitudinal studies

S-13-001 Biological correlates of PTSD: From endocrinology to molecular biology

R. Yehuda. *New York, USA*

Objective: Many endocrine and glucocorticoid alterations have been examined with PTSD, prompting an interest in molecular biology. Epigenetic and molecular mechanisms that may influence glucocorticoid alteration in PTSD. This study examined cytosine methylation of the 1F exon on the human GR gene (NR3C1) and gene expression of the GR related genes in order to determine the relevance of these measures to PTSD risk, pathophysiology, or recovery.

Methods: Cytosine methylation of the GR gene along with other neuroendocrine measures (cortisol, glucocorticoid receptor sensitivity, and neuropeptide Y) were measured over time in association with symptom change following prolonged exposure psychotherapy. We will present data from 16 patients, all combat veterans, obtained prior to treatment, at treatment end, and at follow-up.

Results: At treatment end, 50% of patients no longer met diagnostic critieria for PTSD. Treatment response was significantly predicted by cytosine methylation of the GR gene. Cytosine methylation, in turn, predicted neuroendocrine changes in urinary cortisol excretion (which was significantly elevated) and plasma neuropeptide Y (also elevated) in responders compared to non-responders.

Conclusion: This is the first study examining gene methylation and expression cross-sectionally in PTSD in association with treatment. It is also the first to provide an indication that molecular mechanisms associated with GR activity are involved in PTSD risk, pathophysiology, and resilience. We conclude that the molecular biology of the GR should be further examined as it may be a potential target for PTSD prevention and treatment.

S-13-002 True prospective studies in military cohorts; central and peripheral regulation of combat stress

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Objective: The course of central and peripheral regulation of severe stress can provide information on preexisting vulnerability factors as well as neuronal responsivity to severe stress. Prospective studies can be informative in understanding trajectories of resiliency as well as disease.

Methods: We conducted a large epidemiological study in which functional stress-related biological parameters were used in association with predicting PTSD symptoms prior to and on two separate time points within the first year after deployment. We also looked at neural responsivity to salient stimuli with fMRI in similar time course.

Results: Before military deployment, GR number in PBMCs was significantly higher in a group that, after deployment, developed PTSD symptoms relative to matched comparison subjects. This was maintained at 1 and 6 months after deployment. Also FKBP5 and GILZ mRNA expression contributed as a predictor for PTSD symptoms in the total cohort. Amygdala reactivity to salient stimuli was correlated to high threat perception during deployment, in comparison to a group that was not deployed during the same time period.

This normalized in the first year after deployment. Yet, we observed persistent changes in amygdala-dACC connectivity.

Conclusion: The results from this study have enhanced our ability to understand biological concomitants of vulnerability and resilience. Preexisting high GR number in PBMCs as well as FKBP5 and GILZ mRNA expression are vulnerability factors for subsequent development of PTSD symptoms. Central regulation of combat stress at the level of the amygdala appeared highly plastic and adaptive to environmental demands. We speculate that a normalization failure may underlie the pathophysiology of PTSD which is presumably related to preexisting vulnerabilities.

S-13-003 Hydrocortisone in the golden hours and PTSD trajectory – Clinical and animal studies

J. Zohar. *Tel Hashomer, Israel*

Objective: Animal studies and anecdotal human case reports point out the importance of adaptive response of the HPA axis in response to traumatic events. Along these lines, it is possible that the administration of cortisol immediately after exposure (in the ''golden hours'') to a trauma might alter the trajectory of trauma exposure by promoting recovery. A series of studies using a well-validated animal model for PTSD demonstrated a greater susceptibility to experimentally induced PTSD-like behavioral changes in rats with hypoactive/reactive vs. hyperactive/reactive HPA axis, i.e., Lewis strain vs. Fischer strain. Exogenous administration of cortisol to Lewis rats prior to the stressor significantly reduced this difference. Further animal studies examined the effect of a single intervention with high-dose corticosterone immediately after exposure to a stressor. A significant reduction in the incidence of PTSD-like behaviors and improved resilience to subsequent trauma was observed.

Methods: We conducted a double blind, placebo-controlled clinical pilot study, in which patients were randomly assigned to one of two treatment groups: placebo or hydrocortisone treatment (100–140 mg iv, injected 1.5–5.5 hours following the traumatic event).

Results: Results based on 2-week and 3-month follow-up support a potential therapeutic role for administration of hydrocortisone in the ''golden hours''.

Conclusion: Potential interventions, once explored in a systematic way in an animal model can then, via a process of translational research, be implemented into the clinical arena. Early intervention after psychological trauma is an area which may specifically benefit from translational research. Changing the focus from treatment once PTSD is already established to secondary prevention of PTSD in the ''window of opportunity'' – the first few hours after exposure to a traumatic event – has opened the door to new exciting possibilities in PTSD research and treatment.

Policy of full disclosure: Prof. Zohar has received research funding from Lundbeck, Servier and Pfizer, and has been a speaker/consultant for Lundbeck, Servier, Pfizer, Abbott, Pierre Fabre, BMS and Roche.

S-13-004 Prospective study of risk and resilience factors for posttraumatic stress in police officers

C. Marmar. *New York, USA*

Objective: Results will be presented on a prospective longitudinal study of risk and resilience for PTSD symptoms in 400 police academy recruits, assessed during academy training and followed during the first 7 years of police service.

Methods: Utilizing Latent Growth Mixture Modeling (LGMM) we have established three symptom trajectories, highly resilient, initially distressed with gradual improvement and increasing distress.

Results: We will present findings on the relations of the following predictors ascertained during academy training to the three PTSD symptom trajectories: I.Q., family histories of anxiety, depression, alcohol and drug abuse, neuroticism, personal histories of childhood or adolescent traumatic exposure, levels of awakening cortisol, fear-potentiated acoustic startle, MHPG and cortisol responses to a critical incident video challenge, sleep quality as measured by actigraphy, and candidate polymorphisms including serotonin transporter (SLC6A4), adrenergic pathway genes, (ADRB1, ADRB2, ADRA2C), brain derived neurotrophic factor gene (BDNF), genes for several critical components of the HPA axis such as the glucocorticoid receptor (NR3C1), CRH receptor 1 (CRHR1), and FK506 binding protein 5 (FKBP5) and Catechol-O-methyltransferase (COMT). Mulivariate models of risk and resilience will be presented utilizing a multinomial logistic regression nested in the unconditional LGMM.

S-14. Pharmacogenomics and personalised medicine in psychiatry: Prospects for clinical implementation

S-14-001 Genomics of response and side effects of antipsychotics

D. Rujescu. *University of Munich, Dept. of Psychiatry, Germany*

Objective: A major drawback of the therapy with antipsychotics is the lack of efficacy and the occurrence of extrapyramidal symptoms (EPS) in some patients that can both limit therapy and compliance. Thus, the availability of a predictive tool for response to antipsychotics is desirable.

Methods: To search for genes associated with response to antipsychotics or EPS, a hypothesis free approach was used including animal models, neuronal cell cultures, and differential gene expression analyses. Immunohistochemical analyses were performed in rats that received an agent mimicking aspects of psychosis (MK-801), haloperidol, a combination of these agents, or saline. Genes differentially expressed between the different groups had been genotyped in one hundred four patients with acute psychosis (schizophrenia, schizoaffective, brief psychotic, and substance-induced psychotic disorder) treated with haloperidol for up to 28 days. Diagnosis was established by applying the SCID I and II interview. Patients were assessed at baseline and on days 3, 7, 14, 21 and 28. Improvement and response were measured by using the Positive and Negative Syndrome Scale.

Results: Furthermore, genome wide studies were performed for parkinsonism, dyskinesia and akathisia.

Conclusion: Dan Rujescu will present novel data on this ongoing genetic study on response to haloperidol and discuss that in the context of the literatur.

S-14-002 Pharmacogenetics of antidepressant therapies

A. Serretti. *University of Bologna, Italy*

Objective: The response to antidepressant treatment is still unsatisfactory: about 40–50% of depressed patients do not respond to first antidepressant and about 60% do not reach remission at all. Evidence suggests that genetic factors contribute for about 50% of the antidepressant response therefore the knowledge of the patient genetic profile may lead to an individualized therapy in the next years.

Results: Several gene variants have been reported in association with short term antidepressant response. A growing number of evidence has been reported for the functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), particularly l allele has been associated with a better response in Caucasian. A significant number of replication findings are present in literature also for 5-HT2a, 5-HT1a, BDNF, COMT, MAOA, NET, Gbeta3, FKBP5, Pgp, TPH, ACE and GSK-3β variants, although an high number of failure of replication is reported for these genes. Furthermore new candidate genes have been recently identify through the genome-wide scan approach and multi-sites projects like STAR*D and GENDEP. Among these the more promising are GRIK4, GRIK2 and DTNBP1. A pathway analysis performed by us on the large STAR*D and STEPBD databases yielded promising results.

Conclusion: Until now genetics was not able to predict the overall response to antidepressant. However there are increasing evidences of a genetic modulation on treatment response, both directly and through a modulation or an interaction with clinical variables that could influence the response to antidepressant, like personality and social modulators.

Policy of full disclosure: Dr. Serretti is or has been consultant/speaker for: Abbott, Astra Zeneca, Clinical Data, Boheringer, Bristol

Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi, Servier.

S-14-003 Pharmacogenomics of nicotine addiction

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Nicotine dependence (ND) is a complex, multifactorial phenotype, in which both genetic and environmental factors are involved. The heritability of ND is estimated at more than 50%. Due to their prominent biological relevance, brain nicotinic acetylcholine receptor (nAChR) – encoding genes are among the most widely studied candidate genes for ND. Traditionally, much attention has been paid to two nAChR genes, encoding the alpha4- and beta2-subunits respectively. However, the focus has shifted substantially in the last few years with the discovery of the major contribution of the chromosome 15q24 nAChR gene loci, CHRNA5-CHRNA3-CHRNB4, to several smoking phenotypes as well as to substance abuse in general. At least three common independent ND risk variants located within these loci are associated with several ND-related phenotypes, each with a small effect size. The association results are robustly supported by multiple replications in various populations. Less clear, however, is their association with smoking cessation in pharmacogenetic trials. One of the ND associated SNPs, rs16969968, changes an amino acid in the CHRNA5 protein, and thus alters the electrophysiological properties of the nicotinic receptor. Other associated SNPs may influence receptor expression level. Many interesting questions are currently emerging, such as the possible influence of rare variants within the loci on the phenotype, relation of ND genetic risk variants to lung cancer susceptibility and interaction with other genes and environmental factors. On the other hand, functional biological understanding of the novel genetics findings is relatively limited and translational approaches are needed (for example, in transgenic mouse models), exploration of the interaction of these gene variants with environmental factors and their role in cognitive processes influenced by nicotine. Findings may have important implications for the neurobiological understanding of addiction, as well as for the development of pharmaceutical agents to aid in nicotine withdrawal.

S-14-004 The role of leptin in the pharmacogenomics of obesity

M.-L. Wong. *John Curtin Institute, ANU, Canberra, Australia*

Objective: Pharmacogenomics is based on the premise that genomic heterogeneity will be reflected in treatment heterogeneity. Common and complex disorders such as obesity are the outcome of genetic and environmental factors. Each person has different contributions of genetics and environmental to their body weight. In obesity, 3 to 5% of cases are due to genes of major effect. In those situations the effect of a genetic mutation overrides environmental effects. Such is the case with functional mutations of the leptin gene. Leptin is an adipokine that is synthesized principally by white fat and for which there are receptors in the brain. It send a satiety signal to the central nervous system by activating anorectic pathways, mediated by POMC and MC4-R, and by suppressing oxeregenic pathways, mediated by NPY and AgRP. Leptin is also a trophic factor for the maturation of the reproductive system.

Methods: We have studied a Turkish family with a Mendelian recessive missense mutation in the leptin gene that results in the same truncated and non-functional molecule as that found in the ob/ob mouse. Those patients were morbidly obese and hypogonadic, with a body mass index (BMI) of 50.

Results: Treatment with recombinant human leptin, while not generally effective for obesity, had a major effect in those patients and drastically reduced their weight and brought about normalization of reproductive function.

Conclusion: Our results show that indeed genetic heterogeneity is the basis of treatment heterogeneity in the therapeutics of obesity.

S-15. Oxytocin in normal and abnormal psychology: Promises and caveats

S-15-001 Oxytocin increases the salience of social agents: Evidence from psychopathology

S. Shamay-Tsoory. *University of Haifa, Israel*

Objective: Recent classes of theories explaining the role of oxytocin in social behavior have focused mainly on prosocial positive behaviors such as trust, generosity and empathy. A plausible hypothesis suggested here is that oxytocin has a general effect on increasing the salience of social agents, and therefore administration of oxytocin may provoke a wide range of emotions and behaviors related to social behavior. To show that oxytocin is involved mainly in increasing the salience of social agents we conducted two experiments that examined the effects of oxytocin on competitive as well as collaborative behaviors.

Methods: In the first experiment we investigated the influence of a single intranasal administration of oxytocin on cooperative behavior. Cooperation was assessed using a computerized drawing task (a coordinated Etch a Sketch game) which required participants to work together in coordination with each other. In the second experiment participants played a game of chance with another (fake) participant who won more money (envy manipulation), lost more money (schadenfreude manipulation) or won/lost equal amounts of money.

Results: In the first experiment we demonstrate that the administration of oxytocin improves subject's accuracy in the cooperation task when completing the task in the couple condition, as compared to the performance of the same subjects subsequent to the administration of placebo. In the second experiment, oxytocin, compared with placebo, had an effect of increasing envy ratings during unequal monetary gains conditions involving relative loss and increased ratings of gloating during relative gain conditions.

Conclusion: It is concluded that rather than being involved solely in positive prosocial behaviors (as believed so far), the oxytocinergic system probably plays a key role in a wider range of social emotion-related behaviors.

S-15-002 Oxytocin modulates cooperation and competition within and between groups

C. de Dreu. *University of Amsterdam, Netherlands*

Objective: Examines the possibility that hypothalamic release (or infusion) of the neuropeptide oxytocin modulates the regulation of cooperation and conflict among humans.

Methods: Reviews research programs focusing on effects of intranasal administration of oxytocin (v.s placebo) in healthy volunteers.

Results: First, oxytocin enables social categorization of others into in-group versus out-group. Second, oxytocin dampens amygdala activity and enables the development of trust. Third, and finally, oxytocin up-regulates neural circuitries (e.g., inferior frontal gyrus, ventromedial prefrontal cortex, caudate nucleus) involved in empathy and other-concern.

Conclusion: Consistent with an evolutionary perspective on the functionality of cooperation, oxytocin-motivated cooperation is mostly parochial—it motivates (i) in-group favoritism, (ii) cooperation towards in-group but not out-group members, and (iii) defense-motivated non-cooperation towards threatening outsiders. In addition to its well-known role in reproduction and pair-bond formation, oxytocin's primary functions include in-group ''tend-and-defend.''

S-15-003 Oxytocin treatment in schizophrenia reduces psychotic symptoms and improves theory of mind and social perception

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Objective: Because oxytocin (OT) has prosocial and antipsychotic-like effects in animals and recent human studies, we hypothesized that a trial of OT treatment would reduce social cognition deficits as well as psychotic symptoms in schizophrenia.

Methods: A double blind study compared twice daily intranasal OT (24 IU/dose, N = 14) vs. placebo (N = 11) for 14 days on social cognition tests, PANSS scores and Paranoia Scale self-ratings. Subjects' symptoms (PANSS > 60) and psychotropic medications were stable for > 1 month prior to starting the treatment trial and medications were unchanged during the trial.

Results: From baseline to treatment day 14, the OT group: 1) significantly increased accuracy in recognition of 2nd and 3rd order false belief on the Brüne Theory of Mind Task; 2) trended toward greater accuracy in recognizing deception on the Brüne Task and more trustworthy ratings of faces on the Trustworthiness Task. Also, mean scores on PANSS social items (suspiciousness, hostility, social withdrawal [passive/apathetic, active], uncooperativeness) declined dramatically. There were significant reductions in PANSS total, positive, negative and general subscale scores, the individual suspiciousness and anxiety item scores as well as Paranoia Scale scores. In the placebo group, only PANSS suspiciousness and anxiety item scores declined significantly. ANCOVAs controlling for baseline revealed that the OT group vs. placebo group had significantly greater declines in PANSS total scores and trends toward greater declines in PANSS mean social item and positive subscale scores.

Conclusion: Enhancement of social cognition suggests that OT treatment may improve social dysfunction, which responds poorly to antipsychotic medications and is the major cause of disability in schizophrenia. OT may augment antipsychotic efficacy and should be tested as a monotherapy for schizophrenia. Our results indicate that OT may play an important role in the pathophysiology of psychotic symptoms in schizophrenia and associated social cognition and social function deficits.

S-15-004 Does oxytocin have a role in borderline personality disorder?

M. Brüne[1], A. Ebert[1]. [1] *Ruhr-University Bochum, Germany*

Objective: Oxytocin (OT) is an evolutionarily conserved nonapeptide which attenuates fear responses, improves empathy, exerts major effects on pair-bonding and attachment, and has the potential to improve trust and reciprocity. With regard to borderline personality disorder (BPD), a recent study reported that stress reactivity improved upon administration of OT, whereas another study demonstrated that trust and cooperation decreased in patients with BPD as a function of anxious-ambivalent attachment. Accordingly, we sought to examine interpersonal perception and the processing of threat in BPD under OT compared to placebo.

Methods: Twenty patients with BPD and 20 matched healthy controls received OT versus placebo in a randomized controlled double-blind trial. Threat processing was examined using a dot probe task. Interpersonal perception was assessed using the Interpersonal Perception Task.

Results: Preliminary analyses show that patients with BPD process social stimuli diffferently compared to controls.

Conclusion: OT may have differential effects depending onn personality variable, and does not unequivocally act in a ''prosocial'' manner.

S-16. Alpha7 nicotinic acetylcholine receptors in dementia and other brain disorders: From bench to bedside

S-16-001 Alpha 7 nicotinic acetylcholine receptor crosstalk with the lipid microenvironment in health and disease

F. Barrantes. *National Science & Technology, Res. Council (CONICET), Bahía Blanca, Argentina*

The homomeric alpha7-subtype of nicotinic acetylcholine receptors (AChR) is one of the pentameric ligand-gated ion channels that mediate fast synaptic transmission. It is broadly distributed in the central nervous system, where it plays important roles in synaptic signaling, neurite outgrowth, synaptic plasticity, learning, memory formation and neuroprotection, and constitutes an important target for the treatment of cognitive deficits in schizophrenia and Alzheimer's disease (AD). The alpha7 AChR is highly expressed in brain regions relevant to cognitive and memory processing. The alpha7 AChR subunit gene (CHRNA7) is located in the highly duplicated 15q13–q14 region implicated in several neuropsychiatric diseases, including schizophrenia and bipolar affective disorder. Postmortem brains show decreased amounts of AChRs in AD patients; the most vulnerable neurons appear to be those expressing high levels of alpha7 AChR. In cortical neurons, alpha7 AChRs are expressed postsynaptically at over 70% of synapses, where they may regulate glutamate receptor trafficking. There is increasing evidence showing a misregulation of lipid, and in particular cholesterol metabolism in the development of AD. Since cholesterol affects the AChR protein at multiple levels (distribution in the membrane, degree of aggregation, endocytosis, association with the cytoskeleton, trafficking, single-channel conductance) we have speculated that some of the neurological correlates of AD might be partly associated with abnormal crosstalk between the receptor protein and the sterol in this synaptopathy (see e.g. Barrantes, Valles and Borroni, FEBS Lett. 584 (2010) 1856–1863).

S-16-002 Alpha7 nicotinic receptors as important targets for neuroprotective mechanisms in new drug targets for Alzheimer's disease

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Objective: The neuronal acetylcholine receptors (nAChRs) play an important role in cognitive processes in brain regulating and modulating several neurotransmitters. The nAChRs also seem to be involved in pathological processes as amyloid (Aβ) toxicity in Alzheimeŕs disease (AD).

Methods: Fibrillar Aβ was measured using 3H-PIB binding, astrocytes using 3H-Deprenyl and 131-I-Bungarotoxin in AD autopsy brain tissue.Fibrillar and oligomeric and its interactions with Aβ and with α7 nAChRs and α7 nicotinic agonists were characterized in PC cells.

Results: Binding studies showed a significant negative correlation between regional 3H-nicotine binding (α4β2 nAChRs) and deposition of fibrillar (Aβ (3H-PIB binding) in autopsy AD brains (Kadir et al., 2011). Fibrillar Aβ may at least partly exert its toxic effect by forming a complex and blockade of α7 nAChRs while oligomeric Aβ may instead act as ligand activating α7 nAChRs (Lilja et al., 2011). The α7 nAChR agonist JN403 as well as the partial α7 nAChR agonist varenicline but not the α4 nAChR agonist cytosine induced an increase in the 3H-PIB binding in AD autopsy brain tissue homogenates as a sign for interaction and release of Aβ from preformed complex Aβ/nAChR compex (Ni et al., submitted). The α7 nAChRs are also found in astrocytes and thereby also related to neuroinflammatory processes in AD.

Conclusion: Activation of α7nAChRs might be a promising strategy to prevent Aβ toxicty and obtain neuroprotective effects in early stages of AD. Kadir A et al., Brain 2011;134: 301–317. Lilja AM et al., J Alzheimers Dis 2011;23: 335–347.

S-16-003 Neuronal circuits and mechanisms involved in the cognitive enhancing properties of α7 nicotinic acetylcholine receptor (nAChR) modulators

J. Mikkelsen[1], M.S. Thomsen[2], K. Alexander[3], M. Pershing[4], D. Bortz[4], R. Schwarcz[5], J.P. Bruno[4]. [1] *Center Integrated Molecular, Brain Imaging, Copenhagen, Denmark*; [2] *Neurobiology Research Unit, University Hospital Copenhagen, Copenhagen O, Denmark*; [3] *Dept Psych Neuroscience, The Ohio State University, Columbus, USA*; [4] *Dept Psychol Neurosci, The Ohio State University, Columbus, USA*; [5] *Maryland Psych Res Ctr, University of Maryland, Baltimore, USA*

Objective: Alpha7 nicotinic acetylcholine receptor (nAChR) selective agonists have been reported to exhibit pro-cognitive effects in patients with schizophrenia (SCZ). We have carried out behavioural, biochemical and neuroanatomical studies in the rat to investigate the neuronal systems and mechanisms involved in this effect.

Methods: Systemic administration of kynurenine (KYN, 100 mg/kg, ip), the precursor of kynurenic acid (KYNA, an endogenous, astrocyte-derived, antagonist of α7nAChR whose levels are increased in the brains of schizophrenics), produced selective deficits in the initial

reversal and extra-dimensional shift stages of an attentional set-shifting task. These deficits mirror the performance of patients with SCZ in such tasks.

Results: Pre-treatment with the α7nAChR agonist SSR180711 (3 mg/kg, ip) returned the performance of KYN-treated rats back to control levels. Performance in this task is highly dependent on increases in glutamatergic and cholinergic transmission within the prefrontal cortex (PFC). However, the mechanisms within the PFC through which these α7nAChR modulators work to enhance performance are poorly defined. Systemic administrations of a number of α7 nAChR agonists produce an increase in c-Fos activation in the prelimbic region of the PFC as well as in cholinergic cells of the basal forebrain projecting directly to the PFC. This increase in gene expression is mediated via the cholinergic neurons in the basal forebrain, because a selective lesion of the cholinergic input to the PFC eliminates c-Fos induction after administration of an α7nAChR agonist. Furthermore, intra-PFC infusion of SSR180771 led to a dose-dependent increase in local extracellular glutamate as measured by a microelectrode array.

Conclusion: The α7 nAChR-dependent increases in prefrontal acetylcholine and glutamate may be critical components of the pro-cognitive effects of SSR180711 in KYN-treated rats. These data further support the potential value of the α7nAChR as a therapeutic target for the development of drugs to treat the cognitive deficits associated with SCZ.

S-16-004 Alpha7 nicotinic acetylcholine receptors as a potential target for imaging of brain disorders with positron emission tomography

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S-17. Neurodevelopmental bases for progress in pharmacotherapy in autism spectrum disorders

S-17-001 Neurophysiological biomarker of impaired social interaction in ASD

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Objective: The core symptoms of Autism spectrum disorders (ASD) (i.e., impaired social interactions; communication, and restricted and repetitive patterns of interests and behavior) can be attributed to the impaired delivery of afferent signals To understand neuropathological underpinnings of ASD, it is important to specify clear biomarkers of neurobiological abnormalities. Our original integrated multivariate analysis of the neuropsychological cues may be useful in diagnosis for ASD. Furthermore, we tried arachidonic acid as supplementation since this has neuronal signal transduction effect.

Methods: The core symptoms of Autism spectrum disorders (ASD) (i.e., impaired social interactions; communication, and restricted and repetitive patterns of interests and behavior) can be attributed to the impaired delivery of afferent signals To understand neuropathological underpinnings of ASD, it is important to specify clear biomarkers of neurobiological abnormalities. Our original integrated multivariate analysis of the neuropsychological cues may be useful in diagnosis for ASD. Furthermore, we tried arachidonic acid as supplementation since this has neuronal signal transduction effect.

Results: The 7 individuals with ASD exhibited increases of prefrontal EEG β spectrum power and the standard deviation of the head surface temperature based on IRS in response to unfamiliar male approach, which reflect heightened central nervous system arousal. While, plasma prolactin and cortisol levels didn't increase. Our supplementation regimen improved the repetitive and stereotyped interests and behavior, and the impaired communication (Yui K). Improvement of neurophysiological function by ARA remains to be clarified.

Conclusion: The neurophysiological responses to unfamiliar adults may reflect functional vulnerability of the limbic system relevant to relevant to social cognition. Altered signal transduction might contribute to pathophysiology of impaired social interaction in individuals with ASD.

S-17-002 The predictive value of multiparameter image of whole-brain structures in autism spectrum disorders

C. Ecker. *Section of Brain Maturation, Institute of Psychiatry, London, United Kingdom*

Objective: The objective of this research was therefore to characterize the complex and subtle structural pattern of gray matter abnormalities in adults with ASD on the basis of multiple morphometric parameters, and to disentangle spatially distributed patterns of regional differences with potentially different neuropathological underpinning. Furthermore, we aimed to examine the predictive value of individual morphometric parameters for group membership (i.e. diagnostic value).

Methods: Structural MRI data was collected on 20 well-characterized male adults with ASD, and 20 age/IQ matched healthy controls. All individuals with ASD met algorithm cut-offs for ASD on both the ADI & ADOS. For each participant, a set of 5 morphological parameters including both volumetric and geometric features were obtained at each spatial location on the cortical surface (i.e. vertex) was obtained using FreeSurfer software. This set of measures was then used to (1) discriminate between individuals with ASD and controls using a Support Vector Machine analytical approach, and to (2) find a spatially distributed pattern of regions with maximal discriminative power.

Results: SVM achieved good separation between ASD and control group and was able to identify individuals with ASD at a sensitivity and specificity of up to 90% and 80% respectively using cortical thickness. In addition, SVM revealed spatially distributed, independent patterns of regions with maximal discriminative power for each of the five morphometric features describing brain volume and geometry. For all parameters, the left hemisphere provided higher classification values than the right hemisphere.

Conclusion: Our results confirm the hypothesis that the neuroanatomy of ASD is truly multi-dimensional. These differences also provided significant predictive power for group membership, and could thus be used as a potential biomarker for ASD. The spatial patterns detected using SVM may also help further exploration of the specific genetic and neuropathological underpinnings of ASD, and provide new insights into the most likely multi-factorial aetiology of the condition.

S-17-003 Neurobiological marker in ASD

R.L. Davis. *Neuroinflammation Research, Laboratory, Tulsa, USA*

Objective: We are particularly interested in mercury-induced effects on neuroimmune signaling given that mercury exposure and neuroinflammation are both implicated in autism. Thus, our studies are focused on the hypothesis that environmental triggers of autism are mediated through disruption of neuroimmune signaling.

Methods: We utilized the prairie vole as an animal model. Prairie voles have been used extensively to study the physiological and neurochemical underpinnings of social behaviors. Prairie voles are highly social and there social behaviors are remarkably similar to those of humans. However, their preference for social proximity is quite sensitive to exposure to environmental toxins. Adult prairie voles were chronically exposed to 60 ppm HgCl2 in drinking water for 10 weeks. Mercury was therefore used as a tool to induce a male-specific change in social behavior as a model for autism-like behavior. Following mercury exposure, social behavior was assessed; then brain tissue was collected and cytokine/chemokine protein expression measured in select brain regions by ELISA.

Results: Following chronic mercury exposure, these normally highly social animals avoided strangers and displayed social withdrawal. Importantly, these social deficits were more prevalent in male voles than they were in females. Additionally, chronic mercury exposure resulted in a male-specific, increase in TNFβ protein expression in the cerebellum and hippocampus; whereas, chemokine (CCL2 and CXCL10) expression was not affected by mercury exposure.

Conclusion: Further investigation is expected to more fully define the brain regions, cell types and immune factors involved in the altered neuroimmune signaling. Together, these findings are expected to lend insight into the role of altered neuroimmune signaling in autism.

S-17-004 Disrupted Cortical Connectivity as a Neural Signature of Autism Spectrum Disorders

R.K. Kana. *UAB Civitan International Research, Center, CIRC 235G, Birmingham, USA*

Objective: The main objective of this set of studies is to characterize the brain structure, function, and connectivity in autism spectrum disorders.

Methods: Functional MRI and Diffusion Tensor data were collected from several participants (adults and children) with autism spectrum disorders. The tasks mainly focused on theory-of-mind, emotion recognition, action understanding, and resting state.

Results: In addition to decreased engagement of critical brain areas in autism, such as the mirror neuron system, theory-of-mind network, and cortical midline structures, we found disrupted connectivity across several brain areas. Functional and anatomical underconnectivity were found primarily in long-distance connections, and overconnectivity was found in short-distance or local connections, especially in frontal and in relatively posterior brain areas.

Conclusion: Overall, the results of these studies point to disrupted cortical connectivity as a characteristic feature of the brain in autism.

S-18. Fatigue syndrome in psychiatry. Novel understanding and treatments

S-18-001 The psychiatrist confronted with a chronic fatigue/ fibromyalgia patient

S. Kasper. *Medical University of Vienna, Department of Psychiatry, Austria*

Objective: Fibromyalgia/chronic fatigue patients are usually treated by rheumatologists and/or neurologists but since there is frequently comorbid depression and anxiety, psychiatrists are likely to be confronted with patients suffering from fibromyalgia. However, the patients do not want to be a ''psychiatric case'' and therefore a neurobiological approach has been reported to be most successful. The symptoms associated with fibromyalgia/chronic fatigue vary from person to person but there is one common syndrome – they ache all over, demonstrate fatigue and have difficulties concentrating. The pain can be a deep ache, a stabbing or burning pain or a tingling sensation. Pain can be mild at times but in other moments so severe that it becomes unbearable. In addition to pain, patients report fatigue, headaches, poor sleep, depressed mood, and irregular bowel habits, which are all also symptoms of depression.

Methods: For a formal diagnosis of fibromyalgia the ACR (American College of Rheumatology) criteria require the patient to have widespread pain for at least 3 months together with tenderness in at least 11 of 18 specific tender points.Treatment of fibromyalgia requires a comprehensive approach involving education, aerobic exercise, physiotherapy and cognitive behavioural therapy in addition to pharmacotherapy.

Results: The most effective drugs available (or will shortly be available) for the treatment for fibromyalgia are amitriptyline, the selective serotonin-noraepinephrine reuptake inhibitors (SNRIs), milnacipran and duloxetine and the anti-epileptic, pregabalin, are all well known to psychiatrists.

Conclusion: Improvement in pain severity is a key element of response to a treatment programme but reduction of other symptoms of the Fibromyalgia Inventory Questionnaire including fatigue, poor concentration, stiffness, anxiety and depression are also essential indicators of the patient's improvement.

Policy of full disclosure: Siegfried Kasper received grants/ research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, CSC, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pierre Fabre, Pfizer, Schwabe, Sepracor, Servier, Wyeth.

S-18-002 Treating CFS – it may not be rocket science, but at least it works

S. Wessely. *Academic Department of Psychological Medicine, London, United Kingdom*

Chronic fatigue syndrome (CFS) has an undeserved reputation for being difficult or impossible to treat, which allows a wide variety of unorthodox and sometimes unscrupulous treatments to flourish at the literal and metaphorical expense of patients. However, a long programme of work over two decades, culminating in the recent Lancet multi centre large PACE trial, now provides compelling evidence that neither nihilism nor opportunism is necessary. There are now two rehabilitative treatments that are both safe and effective. Neither are perfect, but then not much in medicine is. Both can be recommended now to patients as the best currently available options. I shall review the evidence for both, and show how non expert practitioners can use basic CBT principles in clinical practice.

S-18-003 The concept of 'Mental Fatigue' in a broader dimensional context

C. Tamminga. *USA*

Psychiatric nosology is being encouraged these days to become dimensional in its organization and to consider cognitive and affective disease symptoms as altered and pathological dimensions of normal brain functions. The NIMH has designed and discussed a system call the RDoCs approach, a system that will encourage a biological connection and formulation for all diseases of the brain. The RDoCs approach has already generated a set of dimensions of function, along with a unique anatomy, physiology and potential pharmacology for the dimensions. Along this continuum of function and dysfunction, the task for any single syndrome is to fit its primary symptoms into the defined dimensions. For a syndrome like ''Mental Fatigue'' this is a most useful and clarifying exercise. In this talk, I will suggest a framework for defining the intermediate phenotypes of mental fatigue in dimensional constructs. It will suggest its relationships to other psychiatric disease constructs and to behavioral aspects of medical disease diagnoses. These relationships might suggest new formulations for pathophysiology and certainly for treatments.

S-18-004 Effect of the dopamine stabilizer OSU 6162 on mental fatigue in neurological patients

A. Carlsson. *Göteborg, Sweden*

Objective: The (-)-enantiomer of OSU6162 is a phenylpiperidine derivative characterized as a dopamine stabilizer, given its affinity for dopamine D2 receptors leading to mixed activating and inhibitory effects on behavior. More recently this compound has also been found to be a partial agonist on a number of serotonergic receptors, which further contributes to its behaviorally stabilizing properties. Early clinical studies have shown beneficial actions in patients with Parkinson's disease, Huntington's disease, schizophrenia, and metal fantigue. The present report deals with the actions of this agent in patients with mental fatigue of long duration following upon stroke or traumatic brain injury (TBI).

Methods: OSU6162 was given orally for four weeks in doses increasing from 15 to 45 mg b.i.d. to twelve patients suffering from mental fatigue, following upon stroke (N = 6) or TBI (N = 6). OSU6162 was compared with placebo using a double-blind, randomized crossover design. Patients included were well rehabilitated physically with no gross impairment in cognitive functions other than those related to the mental fatigue.

Results: OSU6162 caused a remarkable improvement in mental stamina, as evaluated by a self assessment scale on mental fatigue. Statistical significance was reached on the primary end-point (Mental Fatigue Scale). Principal component analysis demonstrated an overall positive treatment effect in seven of 12 patients. Beneficial responses were seen already during the first few days of active drug treatment. Increasing dosage caused no further improvement. Side effects

consisted of short-lasting mild nausea and attenuated appetite. These side effects disappeared upon dose reduction.

Conclusion: OSU6162 offers promise as a candidate for treatment of mental fatigue after a stroke or TBI and deserves to be tested in other brain disorders accompanied by fatigue.

Policy of full disclosure: A.C. is a co-inventor in patent applications for OSU6162

S-19. Recent advances in research on serotonergic hallucinogens: Implications for treatment of schizophrenia

S-19-001 Hallucinogenic signaling in a GPCR heterocomplex

J. González Maeso. *Mount Sinai School of Medicine, Department of Psychiatry, New York, USA*

Objective: Traditionally, G protein-coupled receptors (GPCRs) were thought to function as monomeric units. However, over the past few years, GPCRs have been shown to be located in close molecular proximity at the plasma membrane in living mammalian cells, implying the existence of dimers or even higher-order oligomers. The neurotransmitters serotonin and glutamate both have been the target of considerable attention regarding psychosis and antipsychotic drug development. Atypical antipsychotics, such as clozapine, olanzapine and risperidone, all have in common a high affinity to block the function of the 5-HT2A receptor. The psychoactive effects of hallucinogenic 5-HT2A receptor agonists, such as lysergic acid diethylamide (LSD) and psilocybin, share several features with schizophrenia, including perceptual disturbances and alterations in cognition and mood. A new class of potential antipsychotic drugs acting as agonists at metabotropic glutamate 2/3 (mGlu2/3) receptors has recently received attention in preclinical and clinical studies.

Methods: We used biophysical assays to characterize the oligomerization of 5-HT2A and mGlu2 receptors, and mouse behavior models to determine the molecular mechanisms contributing to antipsychotic efficacy.

Results: We found that 5-HT2A and mGlu2 receptors form a GPCR heterocomplex in tissue culture and mouse frontal cortex. Our results suggest that the 5-HT2A-mGlu2 receptor heterocomplex is necessary for the cellular and behavioral responses induced by hallucinogenic and antipsychotic drugs.

Conclusion: These observations provide a mechanistic insight into antipsychotic action.

S-19-002 Comparing serotonergic and glutamatergic hallucinogens in animal and human models related to psychotic disorders

M. Geyer. *University California San Diego, La Jolla, CA, USA*

Objective: Both glutamatergic and serotonergic hallucinogens are used as model psychoses in humans and animals. Recent studies suggest that both drug classes increase levels of synaptic glutamate, suggesting some overlap in their pharmacological effects despite differing primary mechanisms of action. Here we compare the behavioral profiles of these drug classes in measures related to psychotic disorders.

Methods: Startle habituation and prepulse inhibition (PPI) have been measured in both schizophrenia and psychotic bipolar patients and in parallel animal models after administration of hallucinogens. Similarly, these psychiatric groups have been examined in terms of patterns of exploratory locomotor responses to a novel environment using methods that parallel rodent studies of the effects of glutamatergic and serotonergic hallucinogens.

Results: First-break, never-medicated schizophrenic patients have deficient PPI and habituation of startle, operational measures of the gating abnormalities related to cognitive disorganization in psychoses. Similarly, manic bipolar disorder patients exhibit deficient gating. Both hallucinogenic serotonergic agonists and psychotomimetic glutamatergic antagonists disrupt homologous measures of PPI and habituation of startle in rodents. These effects are insensitive to dopamine antagonists, but are blocked by 5-HT2A antagonists and some atypical antipsychotics. In motor activity paradigms, manic bipolar patients exhibit hyperactivity in a novel environment, while schizophrenia patients instead exhibit normal initial levels of activity but reduced rates of habituation over time. In rodents similarly tested for locomotor activity, serotonergic hallucinogens produce an exaggerated neophobia response characterized by initial reductions in exploratory behavior only in novel environments, while glutamatergic antagonists exhibit motor hyperactivity in both novel.

Conclusion: Thus, across behavioral paradigms in rodents, there are both similarities and differences in the profiles exhibited by serotonergic and glutamatergic hallucinogens. Further explication of the neurobiological substrates of these similarities and differences are likely to help elucidate the domains of overlap and differentiation between the syndromes of schizophrenia and bipolar mania.

Policy of full disclosure: Work supported by the U.S. National Institute on Drug Abuse and the National Institute of Mental Health.

S-19-003 Suppression of slow cortical oscillations by hallucinogens: Relationship to schizophrenia

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Objective: Psychotomimetic drugs, such as non-competitive NMDA receptor antagonists and serotonergic hallucinogens are used as animal models of schizophrenia. However, their neurobiological basis of action is poorly known. Our objectives are 1) to characterize the actions of hallucinogenic drugs (the NMDA receptor antagonist phencyclidine –PCP- and 5-HT2A receptor agonists) on neuronal activity in prefrotnal cortex, and 2) to examine the potential reversal of these actions by antipsychotic drugs.

Methods: Electrophysiological recordings in the medial prefrontal cortex of anesthetized rats and mice: single unit extracellular recordings of identified pyramidal neurons and local field potential recordings.

Results: The non-competitve NMDA receptor antagonist phencyclidine (PCP) and the preferential 5-HT2A agonist DOI share the ability to disrupt prefrontal cortex (PFC) activity in anesthetized rodents. These drugs markedly increase the discharge of ~40% of pyramidal neurons and decrease that of ~30%, reducing also slow cortical oscillations (SCO; <4 Hz) to which neuronal discharge is temporally coupled. Interestingly, these effects are reversed by the subsequent treatment with haloperidol and clozapine, acting also via different pharmacological mechanisms. In line with these observations, the 5-HT1A/2A receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), natural component of the Amazonian beverage Ayahuasca, evokes similar changes in PFC and other cortical areas (V1 and S1). The reduction of SCO induced by 5-MeO-DMT is also reversed by antipsychotic drugs (haloperidol, risperidone, clozapine) and by the mGluR2/3 agonist LY379268.

Conclusion: The disruption of PFC function is a common action of hallucinogens, irrespectively of their primary site of action (NMDA or 5-HT receptors). These drugs evoke a chaotic PFC activity, characterized by a randomly occurring discharge imbalance, which may account for the perceptual and cognitive changes induced by these drugs. The reversal by antipsychotic drugs with different mechanisms of action reinforces their relationship with schizophrenia symptoms.

S-19-004 Neurophysiological studies of psilocybin-induced hallucinations: role of 5-HT2A receptors

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Objective: Serotonergic hallucinogens such as psilocybin produce positive-like symptoms and perceptual disturbances including visual hallucinations and deficits in visual contour processing that are reminiscent to that observed in some patients in early or acute stages of schizophrenia. However, the neurophysiological mechanisms and 5-HT receptor sites that mediate these visual perceptual alterations remain largely unknown.

Methods: To further elucidate the role of 5-HT2A receptors in visual processing, we performed a double-blind placebo-controlled randomized trial in healthy human subjects (n = 20) to assess the effects of psilocybin (215 µg/kg p.o.), on prestimulus and subsequent visual stimulus-induced parieto-occipital alpha oscillations and

early visual-evoked potentials and to determine whether these psilocybin-induced effects are (II) reversed by the preferential 5-HT2A antagonist ketanserin (50 mg p.o.) or the partial 5-HT1A agonist buspirone.

Results: Analysis of the visual-evoked potentials revealed that psilocybin selectively increased the medial P1 potential, whereas ketanserin selectively decreased the medial P1 potential. The subsequent N170 potential was strongly decreased over the lateral occipital cortex by psilocybin and associated with the appearance of visual hallucinations and audiovisual synesthesia, both of which were completely blocked by the 5-HT2A antagonist ketanserin. A correlational analysis showed that the decease the N170 potential correlated with the intensity of psilocybin-induced subjective alterations in visual perceptions. In contrast to this, the partial 5-HT1A agonist buspirone did only moderately reduced psilocybin-induced visual disturbances and partially reversed the reduction in the N170 potential.

Conclusion: The present results show that 5-HT2A rather than 5-HT1A receptor stimulation is the key mechanism for the generation of visual hallucinations and audiovisual synesthesia in psilocybin states and suggests that such a mechanism may also be responsible for the visual disturbances observed in early schizophrenia and/or Parkinson's disease.

S-20. The translocator protein (18 KDa) as a novel target in neurology and psychiatry

S-20-001 Translocator protein 18 KDa ligands as novel anxiolytics without benzodiazepine like side effects

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Objective: The translocator protein 18 KDa (TSPO) mediates the transport of cholesterol from the outer to the inner side of the mitochondrial membrane. TSPO ligands offer a broad spectrum of diagnostic and therapeutic possibilities.

Methods: We assessed GABAergic neurotransmission by means of slice studies with the selective TSPO ligand XBD173. Moreover, we studied the effects of XBD173 on behavioral anxiety paradigms in rats and humans.

Results: XBD173 stimulated neurosteroidogenesis and enhanced GABAergic neurotransmission in slices of the mouse prefrontal cortex. Moreover, XBD173 displayed antipanic activity in rats and in humans employing the CCK-4 challenge paradigm. In contrast to alprazolam there was no sedation and no induction of withdrawal symptoms.

Conclusion: TSPO ligans may offer therapeutic potential as anxiolytics but also for other indications such as pain and neurodegenerative disorders.

Policy of full disclosure: The studies with XBD173 were sponsered by Novartis, Switherland. Rainer Rupprecht has been a consultant for Novartis and Grünenthal.

S-20-002 Structure and function of the translocator protein (18-kDa) in steroid and neurosteroid biosynthesis

V. Papadopoulos. *Montreal, Canada*

Objective: Translocator protein (18-kDa; TSPO) is the product of a gene family that is evolutionarily conserved from bacteria to humans and expressed in most mammalian tissues. Among all tissues TSPO is expressed at the highest levels in those with the ability to synthesize steroids. Subsequently, TSPO was shown to be primarily localized to mitochondria and to be associated with cholesterol import into mitochondria, a key function in steroidogenesis. Indeed, cholesterol transfer from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM) is the rate-limiting and hormone-sensitive step in the regulation of steroid biosynthesis.

Methods: Using cellular, molecular, biochemical, biophysical and genetic methods we demonstrated that TSPO binds with high affinity to cholesterol, identified a cholesterol recognition amino acid consensus and investigated the mechanism underlying TSPO-mediated cholesterol import.

Results: Our studied demonstrated that the transfer of cholesterol into OMM occurs through a protein complex termed the transduceosome which is composed both of cytosolic proteins and the OMM proteins TSPO and voltage-dependent anion channel (VDAC). Steroid production is proposed to be initiated at this complex by the mitochondrial-targeted Steroidogenic Acute Regulatory protein (STAR) which acts on the OMM to facilitate cholesterol transfer to the IMM through the assistance of TSPO. Further studies demonstrated photoactivatable cholesterol binding to two native cholesterol binding-protein mitochondrial complexes of 66- and 800-kDa. STAR was found to mobilize cholesterol from the 800-kDa complex and induce cholesterol metabolism to pregnenolone, the precursor of all steroids. Immunoblot and mass spectrometry analyses revealed that this complex contains the OMM TSPO and VDAC and IMM proteins, including CYP11A1, the enzyme metabolizing cholesterol to pregnenolone. We then demonstrated that the 800-kDa complex contains CYP11A1 activity.

Conclusion: These results identify a bioactive, TSPO-anchored multimeric protein complex spanning the OMM and IMM that is responsible for the cholesterol import, segregation, targeting, and metabolism to steroids and neurosteroids.

S-20-003 Using PET to explore the role of the translocator pattern in human brain diseases

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Objective: The TSPO is a cholesterol transporter located in the outer membrane of the mitochondrion. When activated it enhances cholesterol conversion to pregnenolone and then on to allopregnenolone and other neurosteroids. The original ligands for this site were Ro5–4864 and PK11195, both of which were available in tritiated versions.

Methods: Subsequently PK11195 was labeled with C-11 and used in a number of PET studies revealing, for instance, increased binding in the brains of patients with MS and in brain stem nuclei with neuritis. However PK11195 has limitations as a tracer due to high non-specific binding and poor modeling characteristics. For these reasons, more specific and selective tracers have been developed including the PBR series such as PBR28 and PBR111, which are amenable to C-11 and F-18 radiolabeling, respectively, and may provide the ability for more widespread use.

Results: Recent research on these compounds has revealed intriguing differences in binding of the PBR radiotracers in humans, where humans are able to be distinguished into three sub-populations, (1) those exhibiting high affinity binding, (2) those exhibiting low affinity binding and (3) those exhibiting both binding characteristics, i.e. high and low affinity. This polymorphism shows marked differences in frequency between those of Caucasian and Chinese origins, and these turned out to be due to genetic variants produced by a single amino-acid mutation within the TSPO, which can now be measured in peripheral white cells.

Conclusion: Measuring individual genotypes may offer a way to optimize the use of PET TSPO tracers for diagnostic purposes, enable patient stratification and may also explain why it may be difficult to demonstrate efficacy of drugs targeted at the TSPO binding site, since in Caucasians many patients will have low levels of drug binding.

S-20-004 Peripheral nerve regeneration: Therapeutic perspectives for TSPO ligands

M. Schumacher. *Paris, France*

Objective: We investigate the potential therapeutic benefits of translocator protein (TSPO) drug ligands for neuroprotection, axonal regeneration, neuroinflammatory responses and neuropathic pain symptoms. TSPO expression is strongly upregulated in response to nerve injury, primarily in Schwann cells and macrophages, but also in neurons. Importantly, TSPO levels only return to low control values when nerve regeneration is completed, strongly supporting a role in regenerative processes. The mechanisms of action of TSPO ligands involve the regulation of mitochondrial activity and function and the stimulation of steroid biosynthesis.

Methods: Experimental models: freeze injury or transection of the rat sciatic nerve, crush injury of the rat facial nerve, neuropathic pain symptoms induced by the chemotherapeutic agent vincristine. Treatment: chronic treatment with etifoxine. Efficacy endpoint measures: axonal regeneration, inflammatory responses, functional recovery, neuropathic pain symptoms, analysis of steroids in nervous tissues by gas chromatography/mass spectrometry.

Results: Treatment with the benzoxazine etifoxine, which binds to TSPO and GABAA receptors, resulted in a 2-fold acceleration in axonal regeneration after sciatic nerve injury and in a marked improvement of both the rate and quality of functional recovery. Walking track test, automated grid walk assay and nerve pinch test showed that the recovery of both motor and sensory functions was accelerated and improved. Treatment with etifoxine also strongly reduced the number of macrophages and blunted the production of inflammatory cytokines. This effect appeared earlier in the proximal stump than in the part of the injured nerve distal to the lesion site. Importantly, etifoxine has been shown to reduce mechanical and thermal pain induced by the chemotherapeutic agent vincristine. Thus, TSPO ligands are also promising agents for reducing neuropathic pain symptoms.

Conclusion: Etifoxine, an already clinically approved drug for the treatment of anxiety disorders, and TSPO ligands in general, offers promise for the treatment of peripheral nerve injuries and axonal neuropathies.

S-21. From gene to drug response: Multi-method approach to the pharmacogenomics of response to antidepressants

S-21-001 Multi-method approaches to pharmacogenomics in animal models

M. Popoli. *University Milano, Italy*

Objective: Preclinical research in rodent models may contribute to the identification of genomic determinants of response to drugs. Different techniques, from transcriptomics and proteomics to the more recent epigenetic methods can be employed to reach this objective. Aim of this presentation will be to draw from different animal studies a number of converging, validated genes and pathways that may inform human pharmacogenetic studies.

Methods: Results from a number of different studies will be discussed: (1) Transcriptomics of the Flinders Sensitive Line (FSL) genetic model of depression (2) Synaptoproteomics of FSL subjected to early-life stress (gene x environment model) (3) Synaptoproteomics of the Learned Helplessness (LH) model (4) Epigenetic analysis of transgenic mice carrying the BDNF Val66Met human mutation (5) Analysis of microRNAs (miRs) involved in the action of antidepressants.

Results: A common finding of the FSL and LH models studies was that energy metabolism and cellular remodeling pathways are involved in both the depressive-like phenotype and in the response to antidepressants. A number of interesting biomarkers was regulated in opposite directions by stress and antidepressants in both models. Results with the BDNF Val66Met mice have been obtained both from candidate gene studies and from a genome-wide ChIP-Seq study. Bioinformatic analysis of genes with epigenetic changes in their promoters revealed the involvement of networks related to lipid metabolism, small molecule biochemistry, cell death, cellular development functions, among others. In addition, consistent changes in epigenetic tags and in expression have been found in select splice variants of BDNF transcripts.

Conclusion: Overall, the results obtained in the different rodent studies allowed to select a number of genes and pathways that may be involved in pathophysiology as well as in response to drug treatments. Converging results from different studies and models will be implemented to inform human pharmacogenetic research.

S-21-002 Transcriptomic and epigenetic correlates of antidepressant response

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Objective: There is significant variability in antidepressant treatment outcome, with approximately 30–40% of patients with major depressive disorder (MDD) not presenting with adequate response even following several trials. To identify potential gene expression and epigenetic biomarkers of response we investigated peripheral gene expression patterns of response to antidepressant treatment in MDD.

Methods: We used Affymetrix HG-U133 Plus2 microarrays in blood samples from untreated individuals with MDD (N = 63) ascertained at a community outpatient clinic, pre- and post eight-week treatment with citalopram and used a regression model to assess the impact of gene expression differences on antidepressant response. We carried out technical validation of significant probesets by qRT-PCR and conducted CNS follow-up of the most significant result in post-mortem brain samples from MDD and control individuals. We investigated epigenetic mechanisms that could explain differential expression of selected genes.

Results: A total of 32 probesests were differentially expressed according to response to citalopram treatment following FDR correction. Interferon Regulatory Factor 7 (IRF7) was the most significant differentially expressed gene and its expression was upregulated by citalopram treatment in individuals who responded to treatment. Consistent results were found in postmortem brain tissue of MDD subjects and epigenetic mechanisms seem to play a relevant role.

Conclusion: These findings are promising and support studies investigating genomic factors associated with antidepressant response.

S-21-003 Antidepressants and emotional processing

C. Harmer. *University of Oxford, Psychiatry, United Kingdom*

Objective: The neurochemical actions of antidepressant drug treatment are relatively well understood but there has been little work on how these changes become translated into the clinical effects on mood and psychological processes seen in the treatment of depression.

Methods: A recent series of studies suggests that antidepressants affect key psychological processes important in depression early in treatment and before therapeutic effects are seen. This has been investigated using behavioural and fMRI test batteries in healthy volunteers and acutely depressed patients.

Results: Antidepressant treatments have been observed to bias emotional processing towards positive vs. negative valenced information. This increase in positive bias could therefore provide a platform for subsequent cognitive restructuring and learning which contributes to later improvements in depression. Consistent with this, we have also found that changes in emotional bias in depressed patients with a single dose of an antidepressant predicted therapeutic response after 6 weeks of treatment. fMRI studies further suggest modulation of amygdala and extra-striate responses to emotional stimuli, indicating drug-modulation of attentional processing.

Conclusion: These results challenge long held assumptions that the delay in antidepressant drug action results solely from the need for neurophysiological processes to be completed. Rather, the role of psychological mechanisms may be important in antidepressant drug response as patients learn to re-evaluate themselves and their emotional context in the light of new processing biases. Such an approach may therefore help us to understand how drug treatments are working, how we might be able to improve treatment approaches and also may provide biomarkers for early candidate selection.

Policy of full disclosure: Advisory board and shareholder in P1vital Ltd. Received consultancy from Eli-Lilly, Servier and P1vital. Company director of Oxford Psychologists Ltd. Research work has been funded by the Medical Research Council.

S-21-004 Genomic search for predictors of antidepressant response: a NEWMEDS consortium study.

K. Tansey. *King's College London, United Kingdom*

Objective: Major depressive disorder is a severe debilitating disorder with antidepressants established as the initial step in treatment; however the effectiveness of any particular antidepressant in an individual is not predictable. The current study is the largest antidepressant pharmacogenomic study to date investigating genetic predictors of response to treatment with antidepressants.

Methods: The academic and industrial partners of the NEWMEDS consortium compiled a sample of over 2000 cases of moderate to severe depression with prospective outcome data for up to 12 weeks treatment. Individuals were given either a serotonin reuptake inhibiting (SRI) or norepinephrine reuptake inhibiting (NRI) antidepressant. The primary aim of the study was to obtain genetic predictors of antidepressant response thus power analyses and interpretation of results focused on detecting clinically significant effect for genetic markers. In 1790 individuals with high quality genotyping information, four genome-wide linear regressions tested the associations of half million genetic markers with percentage change in depression severity overall, with SRI, with NRI and with differential response to SRI and NRI.

Results: None of the more than half million genetic markers significantly predicted response to antidepressants overall, SRI, NRI or differential response to SRI and NRI. Pathway analysis in ALIGATOR revealed no biological pathways that were significantly overrepresented in the results. A meta-analysis undertaken with another large sample (STAR*D) detected no significant associations. Polygenic scoring found no convergence among multiple associations in NEWMEDS and STAR*D. Machine learning algorithms suggest that genetic information can meaningfully contribute to prediction of treatment outcome and predict approximately 3% of the variance in outcome.

Conclusion: The absence of pharmacogenetic associations with clinically meaningful effect suggests that genetic information is not ready to inform personalization of treatment for depression in the near future. Complex prediction algorithms allowing for non-additive effects may be able in the future to aid in the prediction of antidepressant response.

S-22. ECT: Research and practice update

S-22-001 What we now know about ECT mechanisms of action

T. Bolwig. *Copenhagen University Hospital, Denmark*

Objective: To review the existing literature in search of a hypothesis for the working action of ECT.

Methods: The presentation has focused on hypotheses based on reproducible empirical data, and attemps to link clinical and paraclinical findings with the wealth of findings relevant for ECT emerging from animal studies conducted primarily during the last four decades.

Results: Especially three hypotheses have proven useful from a heuristic point of view: The Generalized Seizure Theory points to therapeutic efficacy being toally dependent on the elicitation of brain ctivity corresponding to a grand mal seizure. The neuroendocrine theory enounces that ECT works by restoring neuroendocrine dysfunction associated with melancholic depression. The Combined Anatomical-Ictal Theory enounces thar seizure activity in th limbic system induces neurotrophic effects crucial for the therapeutic efficacy of ECT.

Conclusion: Generalization of seizures (grand mal) is necessary for therapeutic effect of ECT. Among the theories to explain this effect the neuroendocrine theory, at the present time has the strongest foundation among the existing theories to explain the working action of ECT.

S-22-002 Latest NIMH supported ECT data – efficacy and safety

C. Kellner. *Mount Sinai School of Medicine, New York, USA*

Objective: To review recent efficacy and safety data from recent NIMH-supported multicenter clinical trials.

Methods: In this presentation, we review data from multicenter ECT clinical trials conducted under the auspices of the National Institute of Mental health (NIMH) in the USA in recent years.

Results: Studies from the Consortium for Research in ECT (CORE) and Columbia group (Opt-ECT trial) will be presented. Topics covered will include efficacy of acute ECT, efficacy of continuation ECT, comparative efficacy of electrode placements (BT, BF, RUL) and efficacy/safety of antidepressant-augmented ECT, in adult and geriatric cohorts.

Conclusion: ECT remains the most effective treatment modality for severe depression; refinements in treatment technique have made ECT even safer and more tolerable for patients.

S-22-003 Impact of ECTAS on UK ECT

C. Freeman. *Royal Edinburgh Hospital, Department of Psychiatry, Edingburg, United Kingdom*

Objective: To improve the practice, training and outcomes for ECT in England Wales and Eire.

Methods: Repeated cycles of audit and accreditation of ECT clinics in all 3 countries over a 10 year period rating clinics and staff practice on 3 levels of standards: Type 1, type 2 and type 3. Regular training courses for Psychiatrists, anaesthetists and nurses and an active email list serve and advice network. the development of competencies for all types and level of staff.

Results: Over 80% of clinics have enrolled. The most mature clinics have now been through 3 three year cycles. Results show a steady increase in the number of standards met and a progression from type 3 to 2 and type 2 to one. In other words clinics are doing better even when standards have regularly been raised.

Conclusion: Detailed and regular accreditation is possible, welcomed by staff, and has improved standards and outcomes. The status of ECT has improved and in particular ECT nursing staff are now seen as highly skilled and specialized nurses.

S-22-004 Cognitive effects of ECT

D. McLoughlin[1], M. Semkovska[1], R. Dunne[1], M. Noone[1]. [1]*Trinity College Dublin, Ireland*

Objective: Concerns about cognitive side-effects following ECT for depression limit its use. We sought to quantify ECT-associated cognitive changes, specify their pattern and progression and explore the effects of electrode placement.

Methods: We performed a series of meta-analyses to quantify changes in cognitive performance as measured using standardised tests after completing a course of ECT.

Results: Cognitive deficits were mainly limited to the first three days after completing an ECT course. During this period right unilateral (RUL) ECT was associated with significantly smaller deficits than bitemporal (BT) ECT. However, after three days there were no significant differences between BT and RUL ECT and after 15 days all levels of functioning were restored to at least baseline with many significantly improving beyond this. Meta-analyses of trials comparing bifrontal (BF) ECT to BT or RUL ECT found BF ECT to be no more effective than BT or RUL ECT with only modest benefits on visual recall compared to RUL ECT. It was not possible to meta-analyse autobiographical amnesia outcomes due to lack of use of standardised measures; and significant publication bias was found, favouring reporting of larger percentage loss. To address this we have validated a new scoring system for the Columbia Autobiographical Memory Interview – Short Form (CAMI-SF), the most commonly used such instrument in ECT studies, and have obtained normative data for retrieval consistency of its semantic, episodic-extended and episodic-specific components for both healthy controls and depressed persons. On initial assessment, depressed patients produced less episodic-specific memories than controls. Both groups showed equivalent amounts of consistency loss over a two-month interval on all components.

Conclusion: The majority of cognitive abnormalities associated with ECT appear to be transient and function improves over time. Research quantifying retrograde amnesia following ECT for depression needs to control for normal loss in consistency over time and contribution of persisting depressive symptoms.

Policy of full disclosure: Our work is funded by grants from the Health Research Board, Ireland.

Wednesday 6 June 2012

S-23. Defining the neurobiological basis of cognitive impairment in schizophrenia through translational research

S-23-001 Serotonergic-glutamateric-dopaminergic interactions: The basis for the cognitive enhancing effects of atypical antipsychotic drugs in schizoprenia and NMDA receptor antagonist animal models

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Objective: to identify contribution of various serotonin (5-HT), dopamine (DA) and glutamate (Glu) receptors to the ability of atypical antipsychotic drugs APD) to reverse or prevent the enduring deficit in novel object recognition (NOR) in female rats treated with phencyclidine (PCP), an NMDA receptor non-competitive antagonist, which has been considered to provide the best model of the cognitive deficit in SCH.

Methods: The administration of PCP, 2 mg/kg ip for 7 days, followed by a 7 day washout period, to groups of 8 rats produced a deficit in NOR that lasted for many months. Various APDs, specific 5-HT, DA and Glu receptor agonists and antagonists were given along with PCP, or acutely or for 7 days following the PCP washout period. The effect of treatments on the discrimination index (novel-familiar/novel + familiar) during the retention period, which is 0.4–0.5 in control rats was assessed.

Results: Atypical APDs which are potent 5-HT2A inverse agonists with less potency for D2 receptors, e.g. lurasidone, as well as amisulpride, a D2/D3/.5-HT7 antagonist reversed the deficit in NOR produced by subchronic PCP. Stepholidine A, a putative atypical APD, with D1 and 5-HT1A agonist properties was also effective. Haloperidol (HAL), a D2 antagonist, did not. By means of selective agonists and antagonists, it was possible to establish that D1 agonism, 5-HT1A partial agonism, 5-HT2A inverse agonism, 5-HT7 antagonism, and mGluR2/3 agonism can positively impact the effects of subchronic PCP. Some, but not all of these mechanisms, also prevented the effect of subchronic PCP to impair NOR or produce an enduring reversal of the effects of PCP.

Conclusion: A variety of 5-HT, DA and glutamate mechanisms can be shown to ameliorate the deficit in a behavior analogous to declarative memory in PCP-treated rodents. The translational value of these findings will be discussed.

Policy of full disclosure: Grant support from Dainippon Sumitomo; Masakuni Horiguchi is an employee of Dainippon Sumitomo.

S-23-002 Effects of antipsychotic and antidepressant drugs, alone and in combination, on cortical dopaminergic and glutamatergic transmission and cognitive impairment in schizophrenia

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Objective: Clinical studies indicate that both atypical antipsychotic drugs and a combination of conventional antipsychotic and antidepressant drugs may enhance neurocognition in schizophrenia. A reduced cortical dopamine release as well as impaired glutamatergic transmission in prefrontal cortical areas have also been proposed in this disease, which may underlie certain aspects of the cognitive impairment.The present studies aimed to elucidate the effects of atypical antipsychotic drugs such as clozapine as well as a combination of moderate doses of other antipsychotic drugs and conventional antidepressants on cortical dopaminergic and glutamatergic transmission, including both NMDA- and AMPA receptor functioning.

Methods: Experiments were performed in rats, using electrophysiological intracellular recording in pyramidal cells in a prefrontal cortical slice preparation, microdialysis in freely moving animals to assess regional monoamine efflux in brain, and behavioral methodologies, including the conditioned avoidance response (CAR) test to assess antipsychotic activity, the 8-arm radial maze to study working memory function and a sensitive catalepsy test to estimate extrapyramidal side effect liability.

Results: Clozapine and a combination of suboptimal doses/concentrations of other antipsychotic drugs and conventional antidepressants, i.e. reboxetine or SSRI:s, that caused a sufficient suppression of CAR to indicate an effective antipsychotic action, in parallel markedly increased prefrontal cortical dopamine outflow and also generated a significant potentiation of NMDA receptor-mediated transmission in this region. In the case of clozapine these effects were found to be associated with a reversal of impaired working memory induced by MK-801, a selective NMDA receptor antagonist, and to be mediated via dopamine D1 receptors which are coupled to the NMDA receptors. None of the drugs except clozapine was able to achieve these ends when given alone in the same doses/concentrations. Importantly, the combination of low concentrations of antipsychotic and antidepressant drugs also facilitated prefrontal cortical AMPA receptor-induced currents in pyramidal neurons.

Conclusion: These results propose that clozapine as well as a combination of antidepressants and other antipsychotic drugs may improve neurocognition in schizophrenia by means of activation of prefrontal dopamine release, D1 receptors and an associated potentiation of glutamatergic NMDA receptor-mediated transmission in this brain region. The concomitant AMPA receptor facilitation may indicate a relatively rapid onset antidepressant effect as well.

S-23-003 Translational biomarkers of NMDA dysfunction in schizophrenia: Mechanisms and opportunities

D.C. Javitt. *New York University Sch Med, Nashville, USA*

Objective: Deficits in NMDA receptor function represent a core feature of schizophrenia and a primary target for new drug development. A key challenge is development of compounds to augment NMDA neurotransmission, and development of measures that can be used in preclinical studies to guide translational drug development. Deficits in auditory sensory event-related potentials (ERP) including N1, mismatch negativity (MMN) and auditory steady-state response (ASSR) have become increasingly well documented over recent years. These studies evaluate generators of auditory ERP in animal models, and their relation to underlying NMDA function.

Methods: ERP were recording in both primates and rodents. In primates, ERP were recorded using multichannel electrodes implanted into primary auditory cortex. Laminar profile of response was analyzed as well as response to the NMDAR antagonist ketamine. In rodents, effects were measured both of NMDA receptor antagonists and genetic manipulations relative to NMDA function.

Results: In primates, generators of N1, MMN, and ASSR were localized to discrete layers of primary auditory cortex, reflecting differential function. Moreover, ketamine decreased N1 generation, while increasing ASSR, suggesting differential underlying circuit mechanisms. In rodents, serine racemase and selective PV/NMDA KO led to selective modulations of N1 and ASSR generation, and increased sensitivity to ketamine.

Conclusion: These findings validate neurophysiological measures, including N1, MMN and ASSR as indices of NMDA receptor dysfunction in both schizophrenia and in underlying primate and rodent models, and suggest their use as translational measures in early stage drug development processes.

Policy of full disclosure: Funded by NIMH, NIDA.

S-23-004 Effect of clozapine and ketanserin on S-ketamine-induced brain activation and psychotic symptoms in healthy humans

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Objective: NMDR antagonist such S-ketamine induces positive-like symptoms and cognitive impairments of schizophrenia in healthy

subjects. In animals, NMDAR antagonists disrupt sensory gating (PPI) comparable to that observed in schizophrenia, a finding that is reversed by atypical 5-HT2A/D2/3 and 5-HT2A antagonists, but not by typical antipsychotics. Similarly, previous work in humans suggests that clozapine but not haloperidol partially ameliorates ketamine-induced symptoms. Here, we examined the functional network underlying S-ketamine-induced psychotic symptoms and whether clozapine and ketanserin reverse such symptoms, and if so, where these changes would be expressed.

Methods: S-ketamine-induced psychotic symptoms (OAV) and alterations in regional brain activity were assessed using H215O-PET. Twenty male subjects were tested (double-blind, randomized): 10 receiving placebo, S-ketamine (0.006 mg/kg/min), clozapine (30 mg po), and S-ketamine plus clozapine; the other 10 receiving ketanserin (50 mg po) as pretreatment.

Results: S-ketamine produced positive symptoms and cognitive disturbances that were differentially associated with increased brain activity in an extended neural network including prefrontal regions, anterior cingultate, putamen, thalamus and the temporomedial and insular cortex. Reduced activity was found in parietal and occipital cortex regions, and cerebellum ($p < 0.00001$). Pretreatment with clozapine (30 mg) moderately reduced some of the S-ketamine induced symptoms and partially reversed the S-ketamine-induced alterations in anterior cingulate, insula, temporomedial cortex, and cerebelllum. Moreover, clozapine reduced brain activity in left hippocampus and bilaterally in parahippocampus and increased the activity in pons and orbitofrontal cortex. Pretreatment with ketanserin (50 mg) partially reversed S-ketamine-induced mania-like symptoms and alterations the left insula, putamen, anterior cingulate, cerebellum, and pons.

Conclusion: The present findings suggest that a disruption of NMDAR- but not of 5-HT2AR- mediated neurotransmission within fronto-temporal-striato-thalamic pathways mainly contributes to ketamine-induced psychotic symptoms.

S-24. Cytokines and psychiatric illness

S-24-001 Inflammation-induced depression: Evidence and mechanisms

R. Dantzer. *MD Anderson Cancer Center, Department of Symptom Research, Houston, Texas, USA*

Exposure to pathogenic micro-organisms triggers an episode of sickness behavior. The development of sickness behavior is triggered by the proinflammatory cytokines that are produced by activated cells of the innate immune system when they sense specific pathogen-associated molecular patterns via toll-like receptors. These cytokines include mainly interleukin (IL)-1 (IL-1α and IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α). The same cytokines are produced in the brain by macrophage-like cells including microglia in response to peripherally produced cytokines. Brain cytokines ultimately act on neurons to alter body metabolism and behavior. In the same way as inflammation normally resolves and leaves room for repair mechanisms, sickness behavior is normally followed by recovery. However, when the peripheral immune responses is too intense or lasts too long, the behavioral response to cytokines can become maladaptive and culminate in an episode of depression. The mechanisms of transition from sickness to depression have been studied both in the clinics in patients receiving chronic cytokine immunotherapy for the treatment of chemotherapy-resistant tumors or hepatitis C virus, and at the bench, in animal models of inflammation-induced depression. The transition from sickness to depression is mediated by activation of the tryptophan-degrading enzyme, indoleamine 2,3 dioxygenase (IDO), which is the first and rate-limiting enzyme of the kynurenine metabolic pathway. Kynurenine is further metabolized in neurotoxic compounds including 3-hydroxy kynurenine and quinolinic acid. Inhibition of IDO by pharmacological or genetic means abrogates the development of depression but does not affect sickness in response to inflammation. In contrast inhibition of the cytokine response abrogates both sickness and depression. The way this research ultimately impacts on our understanding of the occurrence and treatment of non-specific symptoms in physically ill patients will be discussed.

Policy of full disclosure: Funded by NIH Honorarium from Janssen Consultancy with Lundbeck Laboratories.

S-24-002 Inflammation as a cause of suicidality?

L. Brundin[1], S. Erhardt[2], L. Träskman-Bendz[2]. [1]*Lund University, Psychoimmunology Unit, Sweden*; [2]*Lund University, Sweden*

Objective: There is accumulating evidence that the immune system is involved in the pathophysiology of depression. Depressed patients display elevated levels of proinflammatory cytokines in the blood, and patients treated with interferons for other disorders often develop depression. It is currently not known whether inflammation gives rise to specific psychiatric symptoms. Suicidality is a comparatively well-defined phenomenon, present in some depressive patients but not others, which we hypothesized to be associated with inflammation.

Methods: In 2009, we found increased IL-6 in the cerebrospinal fluid (CSF) of suicide attempters, and that cytokine levels were related to severity of depression. In a subsequent study, we compared suicide attempters to non-suicidal depressive patients as well as healthy controls. We found that suicide attempters displayed higher plasma levels of IL-6 and TNF-α, than both depressed- and healthy controls.

Results: In a recent study we measured quinolinic acid (QUIN), a metabolite produced when the kynurenine pathway is induced by inflammation, in the CSF of suicide attempters. QUIN is an agonist of the NMDA receptor and thus an interesting link between the immune system and glutamate neurotransmission. We found increased QUIN in suicide attempters compared to healthy controls, and there was a correlation with the degree of suicidal intent as well as with IL-6 levels in CSF.

Conclusion: Our studies provide evidence of both central and peripheral inflammation in suicide attempters. There were positive correlations between inflammatory factors and both depressive and suicidal symptoms. QUIN, affecting glutamate neurotransmission might be a key player in the symptom generation.

S-24-003 Neuroinflammation in psychotic disorders

G. Engberg. *Karolinska Institutet, Stockholm, Sweden*

Objective: Accumulating evidence suggests that psychotic disorders are associated with brain inflammatory processes. However, direct evidence for a central immune activation in schizophrenia is relatively sparse. Several studies have shown that brain kynurenic acid (KYNA), a neuroactive compound blocking the glycine site of the NMDA receptor and the alpha7nicotinic receptor, is elevated in schizophrenia. In the past few years it has become evident that CSF KYNA serves as a biological marker of brain immune activation. The present study was undertaken in order to investigate concentrations of cytokines in the CSF of psychotic patients.

Methods: Cytokines were analyzed by an electrochemiluminescence biosensor assay (Meso Scale Discovery, Gaithersburg, MD, USA). Also the relationship between cytokines and KYNA was studied in in vitro settings.

Results: The pro-inflammatory cytokine interleukin (IL)-1beta is markedly elevated in the CSF of first-episode patients with schizophrenia (mean 6.5 ± 0.7 pg/ml) as compared to healthy volunteers (0.8 ± 0.04 pg/ml). Furthermore, in olanzapine-medicated patients with chronic schizophrenia we found that CSF IL-6 is elevated (3.2 ± 0.4 pg/ml $\pm$) compared to healthy volunteers (1.8 ± 0.2 pg/ml). Also in patients with bipolar disorder CSF KYNA and IL-1beta are elevated. In this regard, levels of KYNA correlate to life-time occurrence of psychotic episode, while CSF IL-1beta levels correlate to the occurrence of recent symptoms of mania. In vitro studies utilizing human astrocytes show that the rate limiting enzymes of the kynurenine pathway of tryptophan degradation, IDO and TDO, are induced by administration of IL-1beta, resulting in increased KYNA formation. These findings may rationally link together the elevation of KYNA and IL-1beta seen in patients with schizophrenia or bipolar disorder.

Conclusion: Present results provide direct evidence for brain immune activation in these disorders.

S-24-004 Cytokines in psychiatric disorders: Therapeutic approaches

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Proinflammatory cytokines, such as IL-6, IL-1 and TNF- appear to be elevated at least in the peripheral blood of depressed patients. Thus

the activity of IDO, a key enzyme of the tryptophane/kynurenine metabolism, may be enhanced in depressed patients through these cytokines. Although IL-6 does not directly act on IDO, its elevated levels in serum may contribute to IDO activation within the CNS by the stimulatory effect on PGE2, which acts as cofactor in the activation of IDO. This fits with a report on the correlation of increased in vitro IL-6 production with decreased tryptophan levels in depressed patients. In schizophrenia, however, a role for an inflammatory process has been postulated. A prenatal immune challenge during the second trimenon of pregnancy might be crucial. Due to the increase of proinflammatory cytokines and PGE2 in at least a subgroup of psychiatric patients, antiinflammatory treatment would be expected to show advantagous effects. Cyclo-oxygenase-2 inhibitors have been evaluated in major depression. We were able to demonstrate a statistically significant therapeutic effect of the COX-2 inhibitor on depressive symptoms in a randomized double blind pilot add-on study using the selective COX-2 inhibitor celecoxib in MD. Another randomized double-blind study in fifty depressed patients suffering from MD also showed an statistically significant better outcome of the COX-2 inhibitor celecoxib plus fluoxetine compared to fluoxetine alone. Further therapeutic strategies based on immune-modulatory effects will be discussed, too. Due to the signs of inflammation and the increase of PGE2 in some schizophrenic patients, antiinflammatory treatment would be expected to show also advantagous effects in schizophrenia. COX-2 inhibition reduces not only the levels of proinflammatory cytokines, COX-2 inhibition has also an impact to the glutamatergic neurotransmission and influences the tryptophan/kynurenine metabolism: all three components seem to be involved in the pathophysiology of schizophrenia. In the meantime, several studies with the COX-2 inhibitor celecoxib have been performed in schizophrenia. Short term studies of the COX-2 inhibitor celecoxib show a therapeutic effect mainly in early stages of schizophrenia, the pertaining studies will be discussed. However, other immune-based therapeutic approaches including the use of antibiotics and antiviral agents have been studied and will be outlined. Further therapeutic strategies based on immune-modulatory effects will be discussed, too.

S-25. Genetic and non-genetic risk factors in translational models of psychiatric disorders

S-25-001 Mice mutant for genes associated with schizophrenia: Effects of exposure to biological and psychosocial adversities over developmental trajectory

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Objective: As molecular genetic findings in schizophrenia advance, they are now being complemented by a new generation of epidemiological studies that implicate also both biological and psychosocial adversities acting across its developmental trajectory. This highlights a need for more incisive models of gene environment interactions that are rooted in these genetic and environmental findings. Thus, we have studied a series of such environmental adversities in mice mutant for two genes bearing different relationships to schizophrenia: neuregulin-1 (NRG1) and catechol-O-methyltransferase (COMT).

Methods: Mice mutant for NRG1 were subjected to one of three environmental adversities: intrauterine compromise via maternal immune activation with Poly I:C; adolescent psychosocial stress via repeated social defeat; and adult, subchronic exposure to the psychotomimetic phencyclidine (PCP). COMT mutants were subjected to adolescent vs. adult, subchronic exposure to the psychotomimetic Δ9-tetrahydrocannabinol (THC). Phenotypic evaluations included ethological assesment, exploratory activity, prepulse inhibition, cognition, social behaviour and magnetic resonance imaging.

Results: Effects of genetic mutation on the functional consequences of each environmental adversity were characterised. For example, effects of maternal immune activation with Poly I:C were altered in NRG1 mutants effects of acute PCP were attenuated in NRG1 mutants given subchronic vehicle but heightened in NRG1 mutants given subchronic PCP; the effects of adolescent THC were heightened in COMT mutants while no such effects of adult THC were evident.

Conclusion: The present findings indicate that for a series of both biological and psychosocial environmental factors, resultant phenotype may be determined by their interaction with psychosis-related genes operating across the developmental trajectory of schizophrenia at critical time points.

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S-25-002 Infectious and immune factors modulate neurobehavioral abnormalities in DISC1 mice

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Objective: Although infections contribute to schizophrenia, the mechanisms whereby microbes affect neurodevelopment remain unclear. Interaction between microbial and genetic factors may be responsible for the disease in predisposed individuals. We studied the neurobehavioral effects of prenatal immune activation or early postnatal parasitic infection in control and mutant DISC1 mice to model human conditions of gene-environment interactions in schizophrenia.

Methods: We evaluated neurobehavioral schizophrenia-like alterations in mice exposed to early or late postnatal infection with *Toxoplasma gondii* (*T. gondii*), a pathogen associated with schizophrenia. In a different animal model, control and mutant DISC1 mice were challenged with immune activation with Poly I:C at embryonic day 9. Gene expression profiles, brain pathology, neurochemical alterations and behavioral abnormalities were examined in adult mice in both models.

Results: Early but not late infection with *T. gondii* produced locomotor hyperactivity and stimulants-induced impaired pre-pulse inhibition of the acoustic startle in male but not female mice. Sex-dependent effects of the parasitic infection were also present in abnormal gene expression in the cortex and cysts distribution in the brain although no differences in antibody titres were seen between sexes. Prenatal interaction produced abnormal affective and social behaviors and associated smaller amygdala and periaqueductal gray matter, and decreased density of spines on dendrites of hippocampal granule cells. Mutant DISC1 modulated Poly I:C-induced secretion of cytokines in fetal brains, and levels of endogenous mouse DISC1 and GSK-3β.

Conclusions: The present data suggest the timing of infection and sex of the host could play major roles in modulating schizophrenia-like neurobehavioral changes in mice. In addition, genetic predisposition to schizophrenia may modulate behavioral consequences of immune activation produced by microbes *in utero*. The present mouse models may facilitate a better understanding of the contribution of microbes to schizophrenia and related conditions.

S-25-003 Identifying interactions between genes and early environment in the mouse

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Objective: Much of the impact of genes on mood disorders is likely to depend on interactions between genes and the environment. Such interactions would lead to the expression of environmental effects only in the presence of a permissive genetic background. Human studies have demonstrated interactions between genes and life stressful events in the modulation of mood disorders. Research in this field can take advantages of animal models where the manipulation of the genetic and environmental components is easy to perform. During the past years in our laboratory we have been establishing mouse models of the interaction between genes and early environment in the modulation of anxiety and depression-like behavior.

Methods: In parallel experiments, we exposed mice carrying targeted mutations in selected genes (5HTT; BDNF; and 5HT1A receptor) to different maternal environment (''high'' vs. ''low'' levels of maternal care) during early development. The effect of the gene-by-early environment interaction (G × E) was evaluated using behavioral tests in adult mice. To identify the molecular substrates of the G × E, brains of these mice were all processed by HPLC, In Situ Hybridization, and autoradiography techniques.

Results: For 5HTT mutation, we clearly observed G × E effect with heterozygous 5-HTT knockout mice exposed to ''low'' maternal

care showing the highest level of anxiety and depression-like behavior among the experimental groups. A more complex G × E was observed for BDNF mutation, with a greater effect of the maternal care observed in heterozygous BDNF knockout mice than in wild type mice. For 5HT1A mutation, G × E effect was observed on social anxiety, with 5HT1A knockout mice being more responsive to augmented levels of maternal care than controls. Finally we identified several neural substrates of the environmental, gene, and G × E effect.

Conclusion: Mouse models of gene-environment interactions are a useful tool to expand the knowledge on the behavioral features and molecular mechanisms implicated in mood disorders.

S-25-004 Advanced paternal age: Modelling non-genetic risk factors in psychiatry

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Objective: Advanced paternal age (APA) is associated with an increased risk of neurodevelopmental disorders, such as schizophrenia and autism. We have developed a mouse model to explore the neurobiological correlates of APA. In this presentation the effects of APA on brain morphology and behaviour with relevance to neuropsychiatric disorders will be discussed.

Methods: We investigated structure-function relationships in the adult offspring of young (3 month-old, Control) and old (12–24 month-old, APA) C57Bl/6J sires. Mice underwent a behavioural test battery comprising tests for locomotion, anxiety, exploration, learned helplessness, social behaviour, avoidance learning, prepulse inhibition (PPI) of the acoustic startle response and amphetamine (AMPH)-induced locomotion. Brains of these mice were examined ex vivo using a 16.4T animal MRI scanner.

Results: We find no evidence of behavioural phenotypes that are commonly associated with models of schizophrenia, such as increased amphetamine-mediated hyperlocomotion or PPI deficits. Social behaviour was also unaltered, suggesting that the APA mouse model does not recapitulate classical features of ASD. However, APA appears to produce a robust anxiogenic phenotype that is increased with the age of the APA sire (APA ''dose''). Regarding the brain structural phenotype, we have shown that the trajectory of cortical development is altered in male APA mice, such that the cortex is smaller at birth ($F1,17 = 5.48$, $p = .03$) and larger in adulthood ($F1,17 = 7.61$, $p = 0.01$). In addition, the corpus callosum was significantly smaller in adult APA mice ($F1,79 = 5.14$, $p = 0.03$).

Conclusion: The APA mouse produces a robust anxiety-like phenotype that is directly related to increasing sire age. Although this behavioural phenotype would not appear to obediently map on to the neuropsychiatric conditions in which APA is implicated, structural and functional changes in corpus callosum have been consistently reported in both autism and schizophrenia. These studies have clarified APA ''dose'' as a possible explanation for the variable phenotype reported in other APA animal models and suggest the effects of APA in offspring may require sire age to reach a critical threshold rather than exist as a continuous variable. Studies are ongoing regarding the molecular features of this model.

S-26. Emerging opportunities to treat psychiatric disorders with muscarinic receptor agonists

S-26-001 Muscarinic receptors in schizophrenia: Are they a marker for a distinct pathophysiology?

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Objective: Decreased levels of muscarinic receptors have been widely reported to occur in the brains of people with schizophrenia. Studies have identified that cortical muscarinic M1 receptors are altered, whilst in the hippocampus the M4 receptors are decreased. We recently discovered that the decreases in M1 receptors did not occur in everyone with schizophrenia but are restricted to a small portion of subjects, who have large deficits. This raised the question of whether this subgroup has unique neurochemical deficits compared to people with schizophrenia who do not have the deficit in M1 receptors.

Methods: RNA was extracted from Brodmann's area 9 from 15 non-psychiatric controls and 30 subjects with schizophrenia, half of who had low muscarinic M1 receptor levels. cDNA was generated from all samples and run on Affymetrix Human Exon 1.0 ST microarrays. Using JMP Genomics, the quality control probes were checked and principle component analyses carried out prior to the data being analysed using an ANOVA. Genes with significantly different expression profiles were inputted into Ingenuity Pathway Analysis.

Results: 487 genes were differentially expressed. 157 were uniquely different between controls and schizophrenia with normal levels of M1 receptors and a further 330 between controls and schizophrenia with low levels of M1 receptors. Pathway analyses revealed that like other microarray studies, many of our transcripts were involved in metabolic processes. A number of pathways have been identified which differentiate between the three groups in the study including control of cell cycle and tyrosine metabolism.

Conclusion: This microarray study reveals a number of pathways that are changed in both groups with schizophrenia compared to controls. However, it also identifies pathways that are changed in only one group of subjects with schizophrenia, supporting the concept that people with schizophrenia who have low levels of M1 receptors may have a distinct pathophysiology.

Policy of full disclosure: Elizabeth Scarr is an Australian Research Council Future Fellow. Brian Dean is a National Health and Medical Research Council Senior Research Fellow. This project was funded by the NHMRC project grant (566967).

S-26-002 The role of muscarinic receptors in the pathophysiology of major depressive disorder, bipolar disorder and suicide

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Objective: Dysfunction of muscarinic receptors (CHRM) has been implicated in the pathology of bipolar disorder (BPD), major depressive disorder (MDD) and suicide. However, there is conflicting evidence regarding which CHRM is affected by the pathophysiology of these disorders. This lead us to undertake a systematic radioligand binding analysis of several CHRM antagonists in postmortem cortical tissue from subjects with BPD, MDD and age/sex matched controls, as well as individuals who did or did not commit suicide, to gain some insight into which CHRMs may be altered in the cortex of subjects with different mood disorders.

Methods: We used the muscarinic receptor selective radioligands [3H]pirenzepine, [3H]AFDX-384 and [3H]4-DAMP to CHRM1/CHRM4, CHRM2/CHRM4 and CHRM3, respectively. Radioligand binding was measured in postmortem tissue obtained from Brodmann's area (BA) 10, 46 and 40 in mood disorders and BA 9 from subjects analysed for effects of suicide.

Results: [3H]AFDX-384 binding was decreased in BA 46 in both BPD ($p < 0.01$) and MDD ($p < 0.05$). [3H]4-DAMP binding was decreased in BA 10 in BPD ($p < 0.05$) but not MDD ($p < 0.05$). [3H]AFDX-384 and [3H]4-DAMP binding were unaltered in any other cortical region examined for either disorder ($p < 0.05$). [3H]pirenzepine binding was not significantly altered in either disorder in any region ($p < 0.05$). Unlike some studies, our data showed no difference in any radioligand binding in subjects who had died by suicide.

Conclusion: Our data is consistent with previously published data implicating a role for CHRM2 receptors in the pathology of bipolar and major depressive disorder but provides no evidence to suggest muscarinic receptor density varies with suicide. The demonstration of a novel association between decreased CHRM3 receptor expression and bipolar disorder suggests bipolar and major depressive disorder differ in the underlying nature of their cholinergic dysfunction.

S-26-003 Genetic variation in Cholinergic-Muscarinic-2 Receptor gene modulates Muscarinic2-Receptor binding in vivo and accounts for reduced binding in bipolar disorder

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Objective: Genetic variation in the cholinergic muscarinic-2 (M2) receptor gene (CHRM2) has been associated with the risk for developing depression. We previously reported that M2-receptor distribution volume (VT) was reduced in depressed subjects with bipolar disorder (BD) relative to depressed subjects with major depressive disorder (MDD) and healthy controls (HCs). In this study, we investigated the effects of six single-nucleotide polymorphisms (SNPs) for CHRM2 on M2-receptor binding to test the hypotheses that genetic variation in CHRM2 influences M2-receptor binding and that a CHRM2 polymorphism underlies the deficits in M2-receptor VT observed in BD.

Methods: The M2-receptor VT was measured using positron emission tomography and [18F]FP-TZTP in unmedicated, depressed subjects with BD (n = 16) or MDD (n = 24) and HCs (n = 25), and the effect of genotype on VT was assessed.

Results: In the controls, one SNP (with identifier rs324650, in which the ancestral allele adenine (A) is replaced with one or two copies of thymine (T), showed a significant allelic effect on VT in the pregenual and subgenual anterior cingulate cortices in the direction AA < AT < TT. In contrast, in BD subjects with the TT genotype, VT was significantly lower than in BD subjects with the AT genotype in these regions. The BD subjects homozygous for the T –allele also showed markedly lower VT (by 27 to 37% across regions) than HCs of the same genotype. Post hoc analyses suggested that T homozygosity was associated with a more severe illness course, as manifested by lower socioeconomic function, poorer spatial recognition memory and a greater likelihood of having attempted suicide.

Conclusion: These data represent novel preliminary evidence that reduced M2-receptor VT in BD is associated with genetic variation within CHRM2. The differential impact of the M2-receptor polymorphism at rs324650 in the BD and HC samples suggests interactive effects with an unidentified vulnerability factor for BD.

S-26-004 Potential roles for allosteric Muscarinic receptor modulators for the treatment of psychiatric and neurologic disorders

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Objective: Preclinical and early proof-of-concept clinical studies have revealed that activators of specific muscarinic acetylcholine receptor (mAChR) subtypes are efficacious in animal models predictive of antipsychotic-like activity and cognitive enhancement, as well as in the treatment of the symptoms associated with schizophrenia and Alzheimer's disease. More recently, our group and others have used an innovative strategy to identify highly subtype selective ligands that act at allosteric sites on mAChRs, which are less highly conserved than the orthosteric site, including allosteric agonists and positive allosteric modulators (PAMs).

Methods: A combination of medicinal chemistry, HTS and cheminformatic approaches were used to identify subtype selective mAChR allosteric agonists and/or PAMs. In vitro studies using calcium mobilization assays were used in parallel to generate functional efficacy and potency data for all allosteric modulators and the pharmacokinetic properties of each ligand were determined in a rat plasma-brain-level study using LC/MS detection of drug levels after systemic dosing. In vivo efficacy was evaluated in several rodent models predictive of antipsychotic-like activity and enhancement of affective and/or cognitive functions.

Results: Here we report the pharmacologic characterization of several subtype selective mAChR activators, including the M1 allosteric agonist VU0184670 and M1 PAM BQCA. These M1 allosteric ligands modulate numerous behavioral and physiologic parameters consistent with enhancement of cognition, including stimulation of NMDA receptors and/or spontaneous excitatory postsynaptic currents in medial prefrontal cortex pyramidal cells and reversal of disruptions in learning and memory paradigms in rodents. We have also identified highly selective M4 PAMs, as represented by VU0152100, which are also efficacious in preclinical models of antipsychotic-like activity and in reversal of disruptions in hippocampal memory tasks.

Conclusion: Collectively, these allosteric mAChR activators are serving as key tools for further understanding the relative roles of the different mAChR subtypes in the observed efficacy of nonselective mAChR agonists in vivo.

S-27. Advances in translational research in serotonin neurobiology: Implications for mood disorders

S-27-001 Molecular target of seratonin neurotransmission – implication in therapeutics of mood disorders

X. Li. *Birmingham, USA*

Serotonin is a neurotransmitter with broad functions in brain development, neuronal activity, and behaviors; and serotonin is the prominent drug target in mood disorders. The multiple actions of serotonin are mediated by diverse serotonin receptor subtypes and associated signaling pathways. However, the key signaling components that mediate specific function of serotonin neurotransmission have not been fully identified. This presentation will provide evidence from biochemical, pharmacological, and animal behavioral studies showing that brain glycogen synthase kinase-3 (GSK3) is an important component in serotonin signal transduction. GSK3 is a protein kinase which abnormal activity is association with mood disorders. Several classes of mood-modulating drugs, such as lithium, antidepressants, and atypical antipsychotics, regulate GSK3 by inhibiting its activity in brain, which reinforces the importance of GSK3 as a potential therapeutic target in mood disorders. In animal studies, brain serotonin regulates the activation states of GSK3, mainly through serotonin 1A and 2A receptors. In return, GSK3 directly interacts with serotonin receptors in a highly selective manner, with a prominent effect on modulating serotonin 1B receptor activity. Therefore, GSK3 acts as an intermediate modulator in the serotonin neurotransmission system, and balanced GSK3 activity is essential for serotonin-regulated brain activity and behaviors. With this prominent relationship between serotonin neurotransmission and GSK3, drugs targeting GSK3 may elicit mood stabilizing effects by normalizing brain serotonin activity.

S-27-002 Role of the serotonin receptor adaptor protein p11 in depression

P. Svenningsson. *Stockholm, Sweden*

Objective: The molecular mechanisms underlying depression and therapeutic efficacy of antidepressants remain largely unknown. This presentation will introduce the possible role of p11 in depression and its treatment.

Methods: Using yeast two hybrid and co-immunoprecipitation experiments, p11 (S100A10, annexin II light chain) was found as an adaptor to 5-HT1B and 5-HT4 receptors. To study the functional role of p11, subsequent studies have used histological, molecular biological, biochemical, electrophysiological and behavioral approaches.

Results: A pronounced reduction of p11 has been found both in post-mortem human tissue from depressed individuals or suicide victims and in a rodent model of depression. Conversely, p11 is increased in rodent brains by antidepressants or electroconvulsive therapy. The expression of p11 is also controlled by L-DOPA and BDNF. p11 knockout mice exhibit a depression-like phenotype, abnormal emotional processing and have reduced or paradoxical behavioral, neurogenic and neurochemical responses to antidepressants as well as 5-HT1B and 5-HT4 receptor agonists. Viral or transgenic overexpression of p11 recapitulates certain behaviors on mood and anxiety seen after antidepressant treatment in mice. While p11 is wide-spread in the brain, there is some enrichment in populations of interneurons. In addition to serving as an adaptor protein to 5-HT receptors, p11 interacts with ion channels (incl. ASIC-1, TASK-1,

TRPV5/6), intracellular enzymes (incl phospholipase A2, PCTAIRE-1, tPA and cathepsin B) as well as its principal partner annexin 2.

Conclusion: The inducible protein p11 may contribute to certain aspects of depression symptomatology and mediate antidepressant actions.

Policy of full disclosure: Swedish Research Council Servier Dainippon Sumitumo.

S-27-003 Contribution of animal models to the understanding of epigenetic mechanisms in affective disorders and resilience

K.P. Lesch. *Wuerzburg, Germany*

Objective: Adverse childhood experiences are associated with increased risk for psychiatric diseases later in life, especially anxiety disorders and depression. Several studies indicate that whether a individual develops disorders of emotion regulation following early-life stress is influenced by variation of the serotonin transporter gene (5-HTT).

Methods: Multimodal fMRI in humans suggested that life stress interacts with the 5-HTT genotype to influence amygdala and hippocampal resting activation. There are also compelling data from non-human primates. In rhesus monkeys (Macaca mulatta), maternal separation during the first months of life results in deficient social adaptation and peer interaction.

Results: These deficiencies are related to brain serotonin system function, based on testing for interactions between early life stress and 5-HTT. In addition to main effects of 5-HTT genotype and early stress to variation in serotonergic function in later life, 5-HTT also interacts with deleterious early rearing experience to influence attentional and emotional resources, stress reactivity, and alcohol preference and dependence. However, the molecular mechanisms by which stress increases disease risk in adulthood are not known, but may include epigenetic programming of gene expression. Various gene-by-environment interaction (G × E) paradigms in the mouse allow investigations of the molecular mechanisms underlying epigenetic programming by early adverse environment in an animal model amenable to genetic manipulation. Using these G × E paradigms it was shown that prenatal stress or dominant/subordinate social interaction on anxiety-related behavior is modulated by inactivation of 5-HTT.

Conclusion: These findings suggest that the molecular mechanisms involved in these G × E models are relevant to the etiology of disease in humans.

S-27-004 Molecular imaging of serotonin vulnerability in mood disorders

G. Smith. *Baltimore, USA*

Objective: Findings from studies of animal models (including amyloid transgenic mice) can be translated into testable hypotheses in humans using molecular imaging methods. Studies of the functional neuroanatomy of geriatric depression have shown elevated glucose metabolism in cortico-cortico networks that include regions of the 'default network'. Citalopram treatment decreased metabolism in a subcortical-limbic-frontal network that was associated with improvement in affect (depression and anxiety), while decreases in a medial temporal-parietal-frontal network was associated with improvement in cognition (verbal memory and verbal fluency). Having identified the functional neuroanatomy, the next step is to examine the underlying pathophysiology.

Methods: Molecular imaging studies using high resolution PET (HRRT) and well-established radiotracers have focused on the role of the serotonin transporter (5-HTT) and beta-amyloid deposition (Aβ) as mechanisms underlying affective and cognitive network dysfunction, respectively, in geriatric depression.

Results: Lower 5-HTT concentrations in patients than controls were observed in cortical (including precuneus and posterior cingulate), limbic (parahippocampal gyrus) and subcortical (striatum, thalamus, midbrain [raphe] regions. Significant correlations between 5-HTT occupancy by citalopram and improvement of depressive symptoms were observed in these regions, as well the anterior cingulate (BA 24). Aβ overlaps with the regions in the cognitive network and is associated with less improvement in cognition by citalopram. The spatial covariance pattern of 5-HTT degeneration and Aβ was uncovered in the anterior cingulate, medial frontal, orbitofrontal cortices, posterior cingulate, precuneus, hippocampus/parahippocampal gyrus.

Conclusion: Serotonin degeneration associated with Aβ is observed in amyloid transgenic mice, as well as in human neuroimaging studies. This may represent a neurobiological basis for the association between late life depression and vulnerability to cognitive decline, as well as the increased risk of cognitive decline associated with neuropsychiatric symptoms (depression, agitation, anxiety) in mild cognitive impairment. These data may have implications for identifying subjects at risk and for identifying therapeutic targets for early intervention.

S-28. Novel targets for antipsychotic medication development

S-28-001 Efficacy of selective GABA A alpha 5 positive and negative allosteric modulators in the MAM model of schizophrenia.

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Objective: Using the MAM developmental disruption rat model of schizophrenia, we examined the efficacy of novel GABA A allosteric modulators in reversing the hyperdopaminergic state thought to underly psychotic symptoms in schizophrenia in humans. Our studies showed that this model demonstrated parvalbumin GABAergic interneuron loss in the hippocampus leading to hippocampal hyperactivity and increased dopamine neuron population activity and hyper-responsivity to amphetamine. Therefore, we used drugs that targeted the GABA A alpha 5 receptor, which is selectively concentrated in the hippocampus.

Methods: Methylazoxymethanol acetate (MAM) was administered at 20 mg/kg i.p. to pregnant rats at gestational day 17, and the offspring studied as adults. Recordings of dopamine neuron population activity (active neurons per electrode track) and locomotor response to amphetamine (0.5 mg/kg i.p.) was evaluated.

Results: MAM treated rats exhibited significant elevations in the number of DA neurons firing in the ventral tegmental area and hyper-responsivity to amphetamine. The alpha 5 positive allosteric modulator SH-053–20F-R-CH3 and the negative modulator selectively attenuated ventral hippocampal excitability in controls, and reversed the increased DA neuron population activity and response to amphetamine to control levels without significantly affecting controls. Interestingly, the negative allosteric modulator Ro4938581 increased DA neuron population activity in controls, but decreased it in MAM to control levels.

Conclusion: Unlike D2 antagonist antipsychotic drugs, manipulation of the GABA A apha 5 receptor appeared to restore the hyperreactive DA system in the MAM rat to control levels. The fact that this worked with both the positive and negative modulator suggests that the important point is not increasing inhibition, but restoring balance within a disrupted interneuron network. By attacking schizophrenia at the site of disruption is likely to be a more effective treatment for schizophrenia than is dopamine blockade, which works at least 5 synapses downstream from the site of pathology.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Galaxo Smith Klein, Otsuka, Takeda.

S-28-002 Translational pharmacodynamics of phosphodiesterase 10A (PDE10A) inhibitors for treatment of schizophrenia

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Objective: Phosphodiesterase 10A (PDE10A) is a dominant phosphodiesterase in striatal Medium Spiny Neurons. Inhibition of PDE10A leads to an increase of cAMP in these neurons and negatively modulates dopamine D2 receptor signalling in the striatum. Preclinical evidence suggests that PDE10A inhibitors are anti-psychotic, pro-cognitive and hold potential for treatment of negative symptoms. PDE10A inhibitors are currently being evaluated in clinical settings for the treatment of schizophrenia.

Methods: A novel PDE10A in vivo binding ligand was developed and validated. Rodents were dosed with selective PDE10A inhibitors and were tested in schizophrenia relevant assays. The occupancy of the PDE10A enzyme was monitored by in vivo binding.

Results: PDE10A inhibitors were efficacious in a number of in vivo assays relevant for schizophrenia including assays for positive and cognitive symptoms as well as motor side effect assays. The dynamic occupancy range overlaps between different efficacy assays although some differences are reported in this study. For most in vivo assays, relatively low PDE10A occupancy is needed, and in cognition assays as little as 15% occupancy has significant effect. Different selective PDE10A inhibitors had similar occupancies at efficacious doses in these assays.

Conclusion: The data supports the potential of PDE10A inhibitors as a drug target for treatment of schizophrenia across symptoms domains and provide a basis for selecting doses in clinical trials through evaluation of PDE10A occupancy with PET.

Policy of full disclosure: All authors are employees of H. Lundbeck A/S.

S-28-003 The glycine reuptake inhibitor (GRI) bitopertin: Going beyond antipsychotics towards a non-dopaminergic treatment for schizophrenia

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Objective: Deficient NMDA receptor signaling is considered a leading hypothesis in the pathophysiology of schizophrenia, including negative symptoms. Targeting the co-agonist glycine site of the NMDA receptor offers a safe approach to enhance NMDA receptor function. The effects of the glycine reuptake inhibitor (GRI) bitopertin (RG1678) on negative symptoms of schizophrenia were investigated in a phase II proof-of-concept study.

Methods: 323 clinically stable patients with predominant negative symptoms were randomized to 8 weeks of treatment with three doses of bitopertin (10 mg, 30 mg, 60 mg) or placebo once daily in combination with a stable antipsychotic treatment. Efficacy parameters included the PANSS negative symptom factor score (NSFS); proportion of responders ($\geq$20% improvement in NSFS); Clinical Global Impression – Improvement in Negative Symptoms (CGI-I-N), and Personal and Social Performance (PSP) scale.

Results: In the per protocol population (231 patients) the NSFS showed a significantly greater decrease from baseline (delta = 25%) in the 10 mg and 30 mg groups versus placebo (delta = 19%) (10 mg, $p = 0.049$; 30 mg, $p = 0.034$). The response rate was significantly higher for 10 mg group versus placebo (65% vs. 43%, $p = 0.013$). Differences in CGI-I-N were significant for the 10 mg dose group ($p = 0.025$). There was a trend towards functional improvement (PSP score) in the 10 mg dose group ($p = 0.072$). The largest effect sizes for the 10 and 30 mg were observed for NSFS items N1 (−0.32, −0.27), N2 (−0.37, −0.65 N4 (−0.39, −0.41) and G16 (−0.37, −0.36).

Conclusion: Bitopertin 10mg demonstrated a consistent reduction in negative symptoms, accompanied by the emergence of a positive trend on personal and social functioning. Bitopertin may exert its greatest effect on key negative symptoms that include emotional withdrawal and apathetic/social withdrawal. These results support glycine reuptake inhibition and enhancement of NMDA signaling as a therapeutic approach for negative symptoms in patients with schizophrenia.

Policy of full disclosure: All authors are employees of F. Hoffmann – La Roche, Ltd.

S-28-004 Modulation of glutamate function via mGlu5 receptor: Potential novel antipsychotic target?

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Objective: An emerging hypothesis regarding the neurobiological cause of schizophrenia suggests that the disease is due to altered glutamate neurotransmission in general and reduced NMDA receptor function in particular. For this reason, pharmacological approaches are being pursued to normalize glutamate or enhance NMDA receptor function. Direct approaches to increase NMDA receptor function are limited by the risk of seizures and neurotoxicity. As a result, indirect NMDA modulation has received recent attention. Administration of high doses of the NMDA receptor co-agonists glycine, D-alanine, and D-serine improve positive and negative symptoms, as well as cognitive deficits in schizophrenic patients (Heresco-Levy et al., 2002; Tsai et al., 2006). A promising, alternative strategy to indirect NMDA facilitation is to activate metabotropic glutamate 5 receptors (mGlu5). We have focused on developing positive allosteric modulators (PAM), rather than agonists, in the hope that we might achieve subtype selectivity and have a reduced risk of toxicity through excessive mGlu5 activation.

Methods: Selective mGlu5 PAMs are active in various rodent models predictive of efficacy on positive, negative, and cognitive symptoms. Although these findings with mGlu5 receptor PAMs are exciting, little is known regarding the side-effect liability of these compounds.

Results: We described structurally novel mGlu5 PAMs which are selective for mGlu5 receptors and exhibit anti-psychotic like activity. We demonstrated the potential for neurotoxicity in rats and wild-type mice but not in mice lacking the expression of mGlu5.

Conclusion: This study reveals for the first time that activation of mGlu5 with selective allosteric modulators can result in mechanism-based neurotoxicity. It is not yet clear that these effects will be seen with all PAMs and a detailed analysis of the pharmacological control of mGluR5 activation by a variety of mGlu5 receptor PAM may be an important step towards the finding of new generation antipsychotics.

Policy of full disclosure: Employee of Merck & Co., Inc.

S-29. Molecular and genetic substrates underpinning diagnosis of major depression

S-29-001 Molecular evidence for BDNF- and GABA-related dysfunctions in the Major Depression

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Objective: (1) To investigate primary evidence in support of low brain-derived neurotrophic factor (BDNF) and reduced GABA function in the postmortem brain of subjects with depression and matched controls. (2) To test causal links between BDNF levels and expression of markers of GABA interneuron subtypes, using mice with genetically altered and reduced BDNF function (BDNF-HZ and BDNF-IV-KO). (3) To focus on corticolimbic regions (amygdala and anterior cingulated cortex).

Methods: Large-scale quantification of gene expression profiles in depressed and control human subjects ($n = \sim 50$/group; amygdala LBNC nuclei and subgenual anterior cingulated cortex), followed by quantitative PCR (qPCR) and selected Western blot validations. qPCR in BDNF-HZ and BDNF-IV-KO rodent samples (amygdala BLA nuclei and pre-cingulate cortex) assessed the degree of BDNF-dependency on target genes.

Results: BDNF, or its receptor TRKB, were downregulated in depressed subjects. Robust downregulations were also observed for gene transcripts coding for GABA interneuron-related peptides that are known to be BDNF-dependent, including somatostatin (SST), tachykinin (TAC1), neuropeptide Y (NPY) and cortistatin (CORT). Changes extended to GABA markers (GAD1) that display low or no BDNF dependency. Notable regional (amygdala/cingulate cortex) and gender difference were observed. Out of all clinical and demographic factors investigated, only age further affected transcript levels of our genes of interest.

Conclusion: We provide both direct (low RNA/protein) and indirect (low BDNF-dependent gene pattern) evidence for reduced BDNF function in the amygdala and cingulate cortex of MDD subjects. Supporting studies in mutant mouse models suggest a complex mechanism of upstream BDNF-dependent and independent causal factors, thus partly linking the neurotrophic and GABA hypotheses of depression. Notably, the most consistently findings identified reduced markers of GABA interneuron subtypes that target the

dendritic compartment of excitatory pyramidal cells SST, NPY and CORT). Together the results suggest a common BDNF/GABA-related pathology in MDD with gender- and brain region-specific features.

S-29-002 Identifying differentially methylated regions in depression and suicide by next generation sequencing

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Objective: Suicide is a complex and heterogeneous phenomenon. We have recently described a molecular subphenotype characterized by extreme low expression of astrocytic genes. In this study, we investigated the potential role of genomic DNA methylation in this subphenotype.

Methods: Prefrontal brain samples from 184 subjects were screened using a combination of techniques to identify extreme low expressors (ELE). Of these, 21 (11.4%) suicides were ELE and were matched to 21 psychiatrically-unaffected controls according to gender, age, PMI and pH. Genomic DNA was sheared and methylated regions were isolated using methylated binding domain-2 (MBD) protein. Libraries were made using the Illumina ChIP-Seq library preparation protocol and each library used one lane of Illumina GAIIx, 36 base pair single read sequencing. Using the DESeq software, a negative binomial test was implemented to obtain DMRs between suicides and controls. The most significant results were validated by EpiTyper.

Results: A total of ~250 million reads were produced per group and were used to assess differentially methylated regions (DMRs). Reads were trimmed, duplicates removed and the resulting data was mapped to the human genome (hg19) using BWA. The genome was tiled using overlapping 500 bp windows at every 250 bp and reads were counted for each 500 bp interval. 989 DMRs passed multiple corrections using FDR.

Conclusion: These results point to a large number of genomic DMRs that may play a role in the neurobiology of suicides. Several of these DMRs may help explain the ELE phenotype. Studies using functional models will be useful to characterize these findings.

S-29-003 Role of MicroRNAs in depression: Evidence from animal and human postmortem brain studies

Y. Dwivedi. *University of Illinois, Chicago, USA*

Objective: microRNAs (miRNAs) are newly discovered gene expression regulators that have recently been implicated in a variety of human diseases, including neuropsychiatric diseases. The present study was undertaken to examine whether the miRNA regulatory network is altered in depression.

Methods: Expression of miRNAs was measured in prefrontal cortex of depressed and well-matched non-psychiatric control subjects using multiplex RT-PCR plates. Levels of dicer, drosha, DGCR8 mRNA, and several pri-miRs were determined by qPCR. In addition, miRNAs were measured in frontal cortex of learned helpless (LH), non-learned helpless (NLH) and tested control (TC) rats.

Results: miRNA expression was globally down-regulated in depressed suicide subjects and was accompanied by a significant decrease in inter-individual variability. Using individual tests of statistical significance, 21 miRNAs were significantly decreased. In addition, a set of 29 miRNAs, whose expression was not pairwise correlated in the normal controls, showed a high degree of co-regulation across individuals in the depressed group. Changes in some of the miRNAs were inversely correlated with target gene expression. Levels of dicer, drosha, DGCR8 mRNA and several pri-miRs were not significantly altered. NLH rats showed a robust adaptive miRNA response to inescapable shock whereas LH rats showed a markedly blunted response. One set of 12 miRNAs showed particularly large, significant down-regulation in NLH rats relative to tested controls. These were encoded at a few shared polycistronic loci, suggesting that the down-regulation was coordinately controlled at the level of transcription. We also identified a core miRNA co-expression module consisting of 36 miRNAs that were highly correlated with each other across individuals of the LH group but not in the NLH or TC groups.

Conclusion: These findings show that miRNAs contribute substantially to a reorganization of gene expression networks that occur in depression. miRNA profiling may assist in identifying factors that correlate with diagnosis, prognosis or response to treatment.

S-29-004 Genome-wide and candidate gene studies for neuroticism

D. Rujescu. *University of Munich, Dept. of Psychiatry, Germany*

Objective: The risk of suicide-related behavior is supposed to be determined by a complex interplay of sociocultural factors, psychiatric history, personality traits, and genetic vulnerability. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution that is independent of the heritability of Axis I and II psychopathology. There is strong evidence for a heritability of suicidal behaviour as shown by family, twin- and adoption studies. Several studies suggest heritability between 45 and 55%. There is no doubt that suicidal behavior is not caused by any single gene but it is a disease with complex genetic features.

Methods: Personality traits could be an intermediate phenotype of suicidal behavior, which is a trait that reflects a tendency toward negative mood states, and has been linked to internalizing depressive conditions.

Results: Neuroticism is one example of such an intermediate phenotype of suicidal behavior and has been linked to internalizing depressive conditions.

Conclusion: Dan Rujescu will present genome-wide and candidate gene studies on neuroticism, demonstrating a genetic approach for discovering potentially important pathogenic pathways for which clinically powerful (bio)markers may eventually be developed.

S-30. Dosing of antidepressants and antipsychotics: Are we doing right?

S-30-001 Central D2-occupancy and optimal dosing – does it apply for atypical antipsychotics?

L. Farde. *Karolinska Institute, Stockholm, Sweden*

Objective: 'Receptor occupancy' is defined as the fraction (%) of a receptor population that is occupied by an unlabelled drug. Positron Emission Tomography (PET) measurements of receptor occupancy have since the 1980's been extensively been applied for the study of antipsychotic drug binding. Of particular interest is that patients with acute extrapyramidal syndromes (EPS) had high D2-occupancy when compared with patients having no side effects. Based on these observations we suggested a PET-defined occupancy interval of 70–80% as optimal for clinical treatment with classical antipsychotics. Careful clinical titration to a dose which is lower than that which induces EPS is the proposed strategy to optimize individual treatment. PET-studies of receptor occupancy have more recently been implemented in the development of the new generation of antipsychotic drugs. The aim of the present presentation is to review the literature over the last 25 years.g.

Methods: [11C]raclopride is the most widely used radioligand for estiamation of antipsychotic drug induced D2-dopamine receptor occupancy. For comparative purposes, the present survey is limited to [11C]raclopride data.

Results: The prototype atypical antipsychotic clozapine is the major lead to identify new mechanisms, Several studies have shown that patients responding to a wide dose range of clozapine had low (20–67%) D2 receptor occupancy. More recent data indicate that optimal dosing with second generation antipsychotics such as risperidone or olanzapine correspond to an occupancy level within the 60–80% interval for typical antipsychotics.

Conclusion: The concept 'atypical antpsychotic' was coined for clozapine in the 1970's and has since then been widened to more recently developed antipsychotics. However, PET-studies of antipsychotic drug induced occupancy do not confirm that all second generation antipsychotics show efficacy at the same low occupancy as clozapine. These observations indicate that clozapine may act at targets other than the D2 dopamine receptor.

Policy of full disclosure: Employee and share-holder of AstraZeneca, Sweden.

S-30-003 Plasma concentration based dosing of antipsychotics and antidepressants

C. Hiemke. *University of Mainz, Germany*

Objective: Psychotropic drug concentrations in blood resulting are highly variable between individual patients due to variability in drug metabolism or adherence to the medication. In 1971, it was reported for nortriptyline that drug concentrations in blood correlate well with clinical amelioration. Animal studies have shown that antidepressant and antipsychotic drug concentrations in the brain correlate much better with drug concentrations in plasma than with the dose. Plasma concentration based dosing, i.e. therapeutic drug monitoring (TDM), is therefore superior to symptom based dosing to attain maximal clinical effectiveness.

Methods: To promote an appropriate use of TDM the TDM expert group of the Association of Neuropsychopharmacology and Pharmacopsychiatry (AGNP) updated their guidelines for TDM in psychiatry.

Results: Evidence-based ''therapeutic reference ranges'' and ''dose related reference ranges'' were elaborated after intensive literature research and intensive discussions for 30 antipsychotic and 26 antidepressant drugs. A ''laboratory alert level'' was newly introduced above which the laboratory should immediately inform the treating physician. Recommendations are also given when TDM should be supported with pharmacogenetic tests. Supportive information such as substrate, inhibitor or inducer properties of medications is provided for the interpretative service.

Conclusion: This presentation will show how to use the updated guidelines to improve outcomes of psychopharmacotherapy of many patients, especially in case of pharmacokinetic problems.

Policy of full disclosure: Dr. Hiemke has served served on the speakers' bureau of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Pfizer, Servier, and Wyeth. He is managing director of the psiac company.

S-30-004 Dosing of antipsychotics and antidepressants: Guidance from PET imaging

G. Gründer[1], C. Hiemke[2], M. Paulzen[1], T. Veselinovic[1], I. Vernaleken[1].
[1]RWTH Aachen University, Germany; [2]Mainz, Germany

Objective: Rational pharmacotherapy is based on the assumption that the wanted and unwanted clinical effects of a specific psychotropic drug are directly related to its occupancy of the molecular target. Here we show that positron emission tomography (PET) of drug targets in the brain (neuroreceptors and transporters) allows for establishment of these relationships, thereby providing guidance for clinical dosing regimens.

Methods: Associations between brain target occupancy, plasma concentrations, and clinical effects and side effects will be discussed for the most commonly used antidepressant and antipsychotic drugs. It will also be demonstrated that PET studies unmasked some traditional dosing strategies as wrong and potentially harmful.

Results: Research over the past two decades has clearly established relationships between target engagement of the most commonly prescribed antidepressants (especially selective serotonin reuptake inhibitors) and antipsychotics and clinically useful doses of these drugs. This is especially true for the class of antipsychotics. However, it will be demonstrated that the recommended doses of haloperidol (and some other first-generation antipsychotics) are still too high based on PET studies. In addition, some newer antidepressants (e.g., bupropion) exemplify that questions related to rational dosing directly allude to problems of mechanism of action.

Conclusion: Nuclear imaging with PET is one of the most powerful tools to determine and validate rational drug doses and the respective plasma concentrations. In the future, PET studies on the relationship between brain target engagement and plasma levels should complement the development of every psychotropic drug. This will allow for the establishment of TDM services and, consequently, for rational dosing right from the introduction of a new drug to the market.

Policy of full disclosure: Dr. Gründer has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Cheplapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka, and Servier. He has served on the speakers' bureau of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, and Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH, Düsseldorf, Germany. Dr. Hiemke has served as a consultant for Servier. He has received grant support from Pfizer and Sanofi-Aventis and served on the speakers' bureau of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Pfizer, Servier, and Wyeth. Dr. Paulzen declares no conflicts of interest. Dr. Veselinovic has received grant support from Bristol-Myers Squibb. Dr. Vernaleken has served on the speakers' bureau of Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline.

S-31. Lithium and novel targets in bipolar disorders

S-31-001 Interfering with the activating effect of calbindin D28k on inositol mono-phosphatase activity to mimic lithium's inhibitory effect on the enzyme at a different site of action

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Objective: Clinical efficacy of lithium (Li) is characterized by a lag in onset of 1–3 weeks suggesting that the therapeutic effect requires reprogramming of gene expression. Previous studies have shown alteration in gene expression following mood stabilizing drug treatment in a variety of genes, including genes involved in inositol metabolism. Inositol-monophosphatase (IMPase)-1 is inhibited by therapeutically-relevant Li concentrations in an uncompetitive manner, possibly resulting in decreased inositol, subsequent down regulation of the phosphatidylinositol (PI) cycle and dampening of assumed hyperactive neurotransmission through this pathway (the ''inositol depletion'' hypothesis). Li was also shown to down-regulate the expression of sodium myo-inositol co-transporter (SMIT)1, responsible for the uptake of myo-inositol from extracellular fluid. Both IMPA1 and SMIT1 homozygote knockout (KO) mice exhibit Li-like behavior in the forced-swim test (FST) and the pilocarpine-induced seizures paradigm. We aimed to identify gene networks and pathways affected in homozygote IMPA1 and SMIT1 knockout mice and in Li-treated mice compared with wild-type (WT) untreated mice.

Methods: Male, 2 month old, IMPA1 KO, SMIT1 KO and their littermate WT mice were used. Mice received powdered food. Li-treated WT mice received powdered food supplemented with 0.2% Li for five days, followed by 0.4% Li for another 10 days. DNA microarray analysis was performed using the Affimetrix platform. Results were analyzed using the software Ingenuity Pathway Analysis (IPA), GSEA and DAVID.

Results: We show that Oxidative Phosphorylation and Mitochondrial Function are the only significant pathways affected in the frontal cortex of SMIT1 and IMPA1 knockout mice and Li-treated mice. To verify this result the interrelationship between Li treatment and a pharmacological intervention in mitochondrial function by chronic mild treatment with rotenone, an inhibitor of the oxidative phosphorylation complex I, was studied behaviorally in bipolar disorder-related animal models. As hypothesized based on the microarray results, Li and rotenone counteracted each other's effects both in the FST model of depression-like despair behavior and in the amphetamine-induced hyperlocomotion model of manic-like behavior.

Conclusion: Our results corroborate previous finding in bipolar patients suggesting that improvement of mitochondrial dysfunction might underlie the therapeutic effect of Li, support the inositol depletion hypothesis of the molecular mechanism of mood stabilization and suggest that a consequent end point is amelioration of aberrant mitochondrial function in patients by its up-regulation.

Policy of full disclosure: Dieder Moechars, Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium.

S-31-002 Lithium is a gold standard in bipolar illness. Is it indicated for other conditions?

M. Alda. *Dalhousie University, Halifax, Canada*

Objective: Lithium is established as a first-line long term treatment of bipolar disorder, but it may be beneficial in other conditions as well. In this presentation I will review the effects of lithium based on published evidence and present data from two large datasets.

Methods: First we studied risk factors for completed and attempted suicide in 737 families of probands with bipolar disorder in Nova Scotia and Sardinia. In the second study we examined lithium use and prevalence of neurodegenerative conditions in the Province of Nova Scotia. Specifically, we linked population databases containing data on persons diagnosed with Alzheimer's disease, multi-infarct dementia, Parkinson's disease and stroke with prescription database of individuals older than 65 years.

Results: Published evidence suggests that lithium can be beneficial in major depression, aggressive behaviour, prevention of suicide, and cluster headaches among others; it is also being investigated for neuroprotective effects in neurodegenerative conditions such as amyotrophic lateral sclerosis or Alzheimer's disease. In the family study, the risk of suicide was significantly reduced in those subjects who showed partial or full stabilization on lithium. In the population study, rates of all studied conditions were significantly elevated in those with bipolar disorder not on lithium (n = 1173) compared with control subjects. History of at least one prescription of lithium (n = 797) was associated with moderate reduction of the risk of Alzheimer's disease and chronic stroke, but not the other diagnoses.

Conclusion: In addition to prevention of manic and depressive episodes in bipolar disorder, lithium appears beneficial in a range of conditions. The most intriguing are its antisuicidal and neuroprotective effects. Interestingly, the prevention of suicide may be independent of the mood-stabilizing properties. However, it remains to be determined if the neuroprotective effects of lithium are at the core of its prophylactic action in bipolar disorder.

S-31-003 Neurocognition as a lithium target in bipolar disorder

J. Rybakowski. *Poznan Univ Med Sciences, Department of Adult Psychiatry, Poland*

Objective: The aim of this study is to assess the performance on neuropsychological tests in patients with bipolar illness receiving long-term lithium prophylaxis compared to matched healthy control subjects, and to relate the cognitive performance to the functional Val66Met brain derived neurotrophic factor (BDNF) gene polymorphism, BDNF serum level and the quality of lithium prophylaxis.

Methods: Patients with bipolar mood disorder on long-term (5–25 years) lithium treatment were genotyped for Val66Met BDNF gene polymorphism. The Wisconsin Card Sorting Test (WCST) was compared in 30 lithium treated-patients, among which 7 were lithium non-responders (NR), with 30 age-and gender matched healthy control subjects. Also, four tests from the CANTAB battery (Spatial Working Memory, Spatial Span, Stockings of Cambridge and Rapid Visual Information Processing) and BDNF serum lithium levels were compared between 60 lithium-treated patients, 13 of which were excellent lithium responders (ER) and 84 healthy control subjects.

Results: The patients with Met allele of BDNF polymorphism showed significantly better response to lithium prophylaxis suggesting that lithium could be more effective in subjects with lower activity of BDNF system. NR performed worse on WCST compared to matched healthy subjects, significantly so on perseverative errors (WCST-P) and conceptual responses (WCST-%conc). The performance on CANTAB tests was significantly worse in lithium-treated patients as a group, compared with matched healthy control subjects. However, the results of ER as well as serum BDNF lithium level were not different from those of the healthy persons.

Conclusion: Favorable response to lithium may be connected with preservation or even augmentation of cognitive functions. In ER after many years of successful lithium prophylaxis, the performance on neuropsychological tests and BDNF serum level was not different from that of matched healthy control subjects. ER may constitute a specific group of bipolar patients in which long-term lithium administration can produce complete normality.

S-31-004 The Consortium on Lithium Genetics (ConLiGen): Genome-wide association studies of lithium response phenotypes in bipolar disorder

T. Schulze[1], U. Boer[1]. [1]*University of Goettingen, Germany*

Objective: Lithium remains a mainstay in the long-term treatment of BD. Response to lithium is variable. About 30% of patients treated with lithium have fewer illness episodes over time, while about 20% have no response. Data from pharmacogenetic studies of lithium are comparatively sparse, and these studies have generally employed small sample sizes and varying definitions of response. Genetic markers of lithium response would be valuable for treatment planning and could provide insights into the biological mechanism of lithium action. To put that idea into practice, the international Consortium on Lithium Genetics (www.ConLiGen.org) was established.

Methods: ConLiGen has now collected over 1400 lithium-treated bipolar disorder (BD) patients. All patients have been characterized for lithium response with an 11-point treatment response scale (''Alda Scale'', Grof et al., 2002). The Alda Scale assesses clinical improvement attributable to lithium, taking into account the history and frequency of episodes, duration of treatment, medication adherence, and concurrent treatment. Phenotype definitions were developed by consensus within ConLiGen. The whole sample has been genotyped using Illumina arrays to perform a genome-wide association study (GWAS) of lithium response.

Results: Inter-rater reliability of lithium response assessment was good, with kappa values > 0.7. Given a responder rate of 35%, the ConLiGen sample has > 80% power to detect a common allele that confers a genotype relative risk of response of 1.5, at genome-wide significance. At the time of abstract submission (12/2011) genotyping has been completed, and preliminary quality control data indicates excellent call rates. (> 99% of samples have a call rate > 98%) GWAS completion is expected for 04/2012.

Conclusion: Genetic findings from ConLiGen could have important implications for treatment planning and for developing new drugs that mimic the action of lithium but are better tolerated and more effective.

S-32. Novel NMDA amino acids for the pathophysiology and treatment of mental disorders

S-32-001 Novel mechanism of regulation of N-methyl-D-aspartate neurotransmission for CNS disorders

G. Tsai. *Harbor-UCLA Med CTR, Torrance, USA*

Objective: D-amino acid oxidase activator (DAAOA, or named G72) is a primate specific regulator of DAAO. Both DAAO and DAAOA are strong susceptibility genes for schizophrenia. DAAO metabolizes D-serine, which is a potent coagonist at the ''glycine'' site of NMDA receptor (see figure). To date, trials of NMDA-enhancing agents, including glycine, D-serine, D-alanine, and sarcosine (a glycine transporter I inhibitor), reveal beneficial efficacy for the symptoms of schizophrenia. In addition, benzoate is a DAAO inhibitor which can elevate synaptic concentration of D-serine.

Methods: We explored the effect of benzoate on prepulse inhibition (PPI) and forced swimming test (FST) in rodent and examined the efficacy and safety of add-on treatment of benzoate for schizophrenia by a randomized, double-blind, placebo-controlled trial. We also determine whether G72 can serve as a biomarker for schizophrenia.

Results: Benzoate can reverse ketamine-induced deficit in PPI and reduce the duration of immobility in FST. Benzoate treatment produces substantial improvement in the scores of PANSS, SANS, QOL, CGI and HAMD as well as 3 cognitive domains of MATRICS battery (processing speed, verbal learning, and visual learning). The expression of plasma G72 protein in schizophrenia was significantly higher than in healthy controls. G72 protein expression is similar

between drug-free vs. medicated schizophrenia patients. PANSS-negative score showed a negative correlation with G72 levels. The logistic regression analysis suggests that plasma G72 protein can be a diagnostic biomarker for schizophrenia (OR = 6.90, 95% CI = 3.45 – 13.85). The ROC curve showed that a cut-off level of 1.48 pg/μl of plasma G72 protein can reach 85% sensitivity and a 91% specificity for separating schizophrenia from control (AUC = 0.89).

Conclusion: Taken together the animal and human findings, DAA-DAAO-DAAOA is an novel NMDA pathway that can be exploited for the diagnosis and treatment of schizophrenia.

Policy of full disclosure: Dr. Tsai is the inventor for US patents 6228875, 6667297, 6420351, 6974821, 2010/0189818 for the use of NMDA agents in CNS disorders.

S-32-002 GlyT-1 and DAAO inhibitors as potential therapeutic drugs for schizophrenia

K. Hashimoto. *Chiba University, Japan*

Objective: Accumulating evidence suggests that the glycine modulatory site on N-methyl-D-aspartate (NMDA) receptor is a potential therapeutic target for schizophrenia. Increasing synaptic levels of glycine by inhibition of glycine transporter-1 (GlyT-1) on glial cells will lead to enhanced NMDA receptor activation. In contrast, D-serine, an endogenous co-agonist for the glycine modulatory site on NMDA receptor, is metabolized by D-amino acid oxidase (DAAO) which may decrease oral bioavailability of D-serine. In this study, we examined the effects of GlyT-1 inhibitors and a combination of D-serine with a DAAO inhibitor on animal models of schizophrenia.

Methods: The effects of GlyT-1 inhibitor NFPS on cognitive deficits in mice after repeated administration of NMDA receptor antagonist phencyclidine (PCP) were examined. Furthermore, we measured the levels of GlyT-1 protein and amino acids in the frontal cortex and hippocampus of mice treated with PCP. The effects of D-serine with or without a potent DAAO inhibitor 5-chloro-benzo[d]isoxazol-3-ol (CBIO) on prepulse inhibition (PPI) deficits in mice after administration of NMDA receptor antagonist dizocilpine were examined. Moreover, the extracellular levels of D-serine in the brain were measured using in vivo microdialysis method.

Results: Cognitive deficits in mice after the repeated administration of PCP were significantly improved by subsequent subchronic administration of NFPS and D-serine. Repeated administration of PCP significantly increased the levels of GlyT-1 protein in the hippocampus, but not frontal cortex. Furthermore, we found that co-administration of CBIO increased the oral bioavailability of D-serine in mice, and that co-administration of CBIO significantly enhanced the efficacy of D-serine in attenuating dizocilpine-induced PPI deficits in mice.

Conclusion: These findings suggest that GlyT-1 inhibitors and a combination with D-serine plus a DAAO inhibitor would be new approaches for the treatment of schizophrenia.

S-32-003 Treatment of NMDA agonist, glycine transporter I Inhibitor and D-Amino acid oxidase inhibitor for mental disorders

H.-Y. Lane. *China Medical University, Taichung, Taiwan*

Objective: Enhancement of NMDA neurotransmission has been proposed as a potential treatment of schizophrenia and other mental disorders. Several studies targeted at the glycine site of the NMDA receptor using full agonists (glycine, D-serine, D-alanine) or the partial agonist D-cycloserine. Another strategy to improve NMDA neurotransmission is increasing the synaptic glycine level by blocking the glycine transporter-1 (GlyT-1). The third strategy is increasing synaptic concentrations of D-serine and D-alanine by inhibiting D-amino acid oxidase (DAAO).

Methods: N-methylglycine (sarcosine), exiting in human tissues (including blood, muscle, brain) and many foods, is the prototype GlyT-1 inhibitor. Sodium benzoate, a legal food additive, is an inhibitor of DAAO. We conducted several studies.

Results: A pilot clinical trial demonstrated that sarcosine adjuvant therapy improved positive and negative symptoms in patients with chronically stable schizophrenia. More recent studies further suggest that add-on sarcosine, superior to D-serine, can benefit the negative symptoms in both acutely ill and chronically stable patients, and that sarcosine can be used as monotherapy in acute psychosis. Sarcosine also improves life quality and functioning. Our study also showed that sarcosine was more efficacious than a commonly used antidepressant, citalopram (a selective serotonin reuptake inhibitor), in the treatment of major depressive disorder. The sarcosine-treated patients improved more in global functioning and were more likely to be remitters. Sarcosine monotherapy also benefited drug-naïve patients with obsessive compulsive disorder. In a double-blind, placebo-controlled trial, 6-week, 1-g/day sodium benzoate adjunctive therapy significantly and safely improved positive, negative, general, and cognitive symptoms in patients with chronic schizophrenia.

Conclusion: These findings indicate that enhancing NMDA function via inhibiting GlyT-1 or DAAO can improve symptoms of schizophrenia or other mental disorders and can be a novel mechanism for drug development.

S-32-004 D-Serine, glia-synapse interaction and schizophrenia

T. Nishikawa. *Tokyo Medical and Dental University, Japan*

Objective: An endogenous coagonist for the N-methyl-D-aspartate (NMDA) type glutamate receptor (NMDA receptor), D-serine, and its metabolic pathways in the brain could be dysregulated in and the suitable targets for the development of a novel pharmacotherapy for schizophrenia, because (1) NMDA receptor antagonists cause positive and negative symptoms indistinguishable from those of schizophrenia and (2) D-serine has been reported to ameliorate these symptoms in schizophrenic patients as well as their animal models. To obtain further insight into these possibilities, we have investigated the molecular and cellular mechanisms underlying the D-serine metabolism and signaling.

Methods: A molecular cloning, quantitative analysis of various amino acids by high-performance liquid chromatography, in vivo microdialysis, and single nucleotide polymorphism genotyping technique were applied to the present animal and human studies that have been approved by the ethics committees of the Tokyo Medical and Dental University and National Center of Neurology and Psychiatry.

Results: In the rodent brains, the selective destruction or activity manipulations of the neurons and glia resulted in the changes in the tissue and extracellular contents of D-serine in a different ways from those observed in classical neurotransmitters, and a local application of agents acting at the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate type glutamate receptor and the GABAA receptor. Moreover, we have isolated a gene, D-serine-modulator-1, which encodes the protein influencing the intra- and extracellular D-serine contents when expressed in the Xenopus oocytes and its association studies are in progress.

Conclusion: These findings suggest that brain D-serine might participate in glia-glutamate synapse communication linked with the glutamate-GABA interaction, which could malfunction in a group of schizophrenia. The molecules composing these systems might be the new candidate targets for the D-serine modulating anti-schizophrenic agents.

Thursday 7 June 2012

S-33. Do psychotropics affect brain structure? Linking animal models, imaging and clinical studies

S-33-001 Contrasting effects of antipsychotics and lithium on the brain: In-vivo MRI and ex-vivo confirmation

S. Kapur. *Institute of Psychiatry, London, United Kingdom*

It has long been a matter of controversy whether psychotropic drugs, particularly antipsychotics and lithium, have an effect on 'brain structure'. To address this issue, we implemented a model in rats combining serial in vivo MRI, ex vivo MRI and post-mortem analysis with clinically relevant drug doses. Haloperidol (HAL, 2 mg/kg/d), olanzapine (OLZ, 10 mg/kg/d) or vehicle (β-hydroxypropylcyclodextrin,

20% w/v, acidified by ascorbic acid, to pH 6) was continuously administered to rats for 8 weeks (wks). In a second group, HAL (0.5, 2 mg/kg/d) or lithium chloride (LiCl, 2 mMeq./kg/d) was administered for 8 wks followed by an equivalent wash out period (16 wks total). Drugs were given subcutaneously via osmotic mini-pumps. Serial MRI scans were obtained, and after the terminal scan the animals were perfused, ex vivo MRI scans acquired and brain tissue processed for post-mortem analysis. Region of interest (ROI) volume analyses were performed on MR images and post-mortem brain tissue by 2 independent raters blinded to treatment group. Chronic (8 wks) HAL and OLZ treatment resulted in decreased whole brain and cortical volume, the magnitude of this effect being smaller in OLZ-treated animals. Chronic HAL, but not OLZ, increased striatal volume in vivo. In contrast, chronic LiCl (8 wks) increased whole brain and cortical volume in vivo. The drug effects tended to reverse with the washout, with the exception that LiCl-treated animals retained greater whole brain volume. These data were confirmed by ex vivo MRI and all MRI data were confirmed post-mortem using unbiased stereology. Thus, chronic treatment with APD and LiCl has contrasting effects on rat brain structure, though some of these effects appear to be reversible. The cellular basis of these changes is currently under investigation. The findings provide the first systematic MRI-post-mortem study of these drugs and provide a basis for understanding some of the clinical studies with MRI.

Policy of full disclosure: ● There is no ex vivo MRI data for animals who were ON then OFF drug for 8 weeks. We only confirmed the data post-mortem ● We have no data on drug withdrawal for Olanzapine.

S-33-002 Antipsychotic medications and progressive brain tissue loss in schizophrenia

N. Andreasen. *University of Iowa, Department of Psychiatry, Iowa City, USA*

Objective: Studies comparing brain volume measurements in patients at the time of onset with healthy normal volunteers have indicated that the patients have smaller mean volumes in many regions, particularly frontal cortex. Furthermore, longitudinal studies have shown that the mean differences in brain volumes continue to progress over time and that these differences have functional significance, in that they are related to cognitive impairments. The focus of scientific attention is now on determining why the tissue loss occurs and why it continues to progress. The loss is very likely due to multiple factors: genes and their expression, environmental factors such as substance abuse, effects of treatment, and effects of the course of the disease. This presentation examines two of these factors: treatment effects and disease progression as measured by number and duration of relapse.

Methods: We studied 202 patients drawn from the Iowa Longitudinal Study of First Episode Schizophrenia (ILS) for whom we have adequate sMR data (N = 661 scans, an average of 3/subject) obtained at regular intervals over an average time period of seven years. Because we obtained clinical follow-up data at six-month intervals, we were able to obtain measures of treatment intensity using dose-years and of relapse number and duration and relate them to sMR measures.

Results: Both antipsychotic treatment intensity and relapse duration were independently and significantly related to progressive brain tissue loss. However, the tissue types and regions affected were somewhat different.

Conclusion: Thus, paradoxically, two factors appear to account for the brain changes that occur after the onset of schizophrenia: relapse duration and intensity of antipsychotic treatment. Determining how to balance the impact of these factors poses a major clinical and scientific challenge.

Policy of full disclosure: Funding sources: research grants from NIMH and Janssen Scientific Affairs.

S-33-003 Drugs, stress and inflammation: Explaining progressive brain changes in schizophrenia

C. Pantelis. *University of Melbourne, Australia*

Objective: In schizophrenia the view since the 1980's was that brain pathology begins during foetal development and is static. This suggested that identification of abnormalities in patients with established disorder would provide markers relevant to early identification of at-risk individuals. However, the available neuroimaging evidence in early illness stages does not support such a notion. Rather, the evidence indicates that there is neuroprogression in psychotic disorders (Pantelis et al., Schizophr Bull, 2005). Such progressive change is also consistent with the clinical picture of psychosis. Thus, clinical deterioration is often observed over the first few years of the illness. While progressive brain changes over the initial phase of illness are consistent with the clinical deterioration, there is a continuing debate about their validity, and the nature of the underlying neuropathology. Criticism has been levelled at the methods, the possibility of artefact, the impact of therapeutic as well as illicit drugs, diagnostic heterogeneity, and the influence of factors like stress and HPA-axis function. Recent evidence has investigated these factors.

Methods: Our group has undertaken a series of longitudinal imaging studies across the stages of illness from pre-psychosis onset and has examined some of these potential confounds.

Results: I will present the findings from our series of studies investigating progressive brain changes in psychosis from before illness onset and examine confounds that may explain these changes (esp. cannabis, stress and the effects of medication).

Conclusion: Progressive brain changes begin from before illness onset and are most apparent over the first few years of illness. Factors such as drug use, the impact of stress and medication need to be taken into account in understanding these changes. I will also discuss the possible role of neuroinflammation and how this may be examined.

Policy of full disclosure: The studies were funded by National Health and Medical Research Council (NHMRC) of Australia and Australian Research Council (ARC). Additional support was provided by University of Melbourne, Melbourne Health, Jack Brockhoff Foundation, Ian Potter Foundation, AE Rowden White Foundation, Ramaciotti Foundation, Pratt Foundation, Woods Family Trust, Rebecca L Cooper Medical Research Foundation, Australian Computing & Communications Institute, Wellcome Trust, NARSAD, Stanley Foundation. The PET study was funded by Janssen-Cilag.

S-33-004 Lithium effects on brain gray matter volumes

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Objective: The monovalent cation lithium remains one of the first-line mood stabilizing agents for the treatment of bipolar disorder (BD) in both the acute and maintenance phases. A substantial amount of preclinical and clinical evidence suggests that lithium may exert neuroprotective and/or neurotrophic effects in response to a range of insults. This presentation will provide an overview of the evidence in support of neuroprotective and/or neurotrophic effects of lithium on the brain and suggest clinically related research directions for future studies.

Methods: The authors review animal and cellular studies that explore the effects of lithium on neurons and structural neuroimaging studies that investigate the relationship between lithium use and brain gray matter (GM) volume in BD patients.

Results: A number of preclinical studies have demonstrated that lithium increases the neuroprotective proteins, bcl-2 and brain-derived neurotrophic factor; inhibits glycogen synthase kinase 3β activity to regulate phosphorylated tau and β-catenin; and protects brain cells from glutamate-induced, N-methyl-D-aspartate receptor-mediated apoptosis. Several structural neuroimaging studies have supported the neuroprotective and potentially neuroregenerative effects of lithium in BD patients. Recent meta-analyses have also suggested that lithium use in BD patients may be associated with volume increments not only in total GM but also in hippocampus and amygdala. Longitudinal neuroimaging studies have corroborated the lithium-induced increase in GM volume of BD, especially in the prefrontal cortex. Interestingly, these neurotrophic effects have also been associated with positive clinical response to treatment in BD.

Conclusion: Preclinical and clinical studies suggest that lithium may have neuroprotective and/or neurotrophic effects and its use in BD patients may be related to volumetric increase of GM. Future studies will be needed to investigate possible lithium effects on the GM volume of specific brain regions related to cognitive and emotional symptoms in BD patients.

Policy of full disclosure: Professor Renshaw is a consultant to Kyowa Hakko and Ridge Diagnostics. Dr. Kim has no financial conflict of interest.

S-34. Molecular imaging biomarkers in major CNS diseases and drug development

S-34-001 Translational prediction and validation of imaging biomarkers

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Alzheimer's disease is featured at a molecular level by depositions of self-aggregating molecules, as represented by amyloid β peptides (Aβ) and tau proteins. Mutagenesis and multiplication of the genes encoding Aβ, tau and other pathogenic initiators may accelerate the incipient process Aβ and tau protein. Requirements for a side-by-side comparison of PET-detectable Aβ lesions in AD patients and amyloid precursor protein (APP) transgenic mice has revealed that these amyloid ligands preferentially bind to an N-terminally truncated, modified Aβ subspecies dubbed AβN3pE. A genetic deficiency of an Aβ-degrading enzyme, neprilysin, has given rise to selective overproduction of AβN3pE, enhanced amyloid PET signals and augmented cognitive deterioration in APP transgenics, supporting the notion that AβN3pE is a major constituent of binding sites for radioligands and disrupts neuronal integrities. Multi-tracer, multi-scan PET study is also of pivotal importance using PET ligand for translocator protein (TSPO) for capturing glial activation. Neuroimaging biomarkers would also promote bidirectional translational research between clinical and preclinical levels, since they serve as common indices shared by humans and animal models and thus ease extrapolation of pathobiological information in a reciprocal manner.

S-34-002 Amyloid imaging: A boost for drug development

K. van Laere. *Leuven, Belgium*

Since the first human imaging trials with 11C-PIB less than a decade ago, large efforts by industry and academia have resulted in a boost of specific and clinically applicable 18F-labeled radiotracers for beta-amyloid. This was led both by clinical demand for early and differential diagnostic tools for in vivo assessment of amyloidosis in Alzheimer's disease and other forms of dementia, as well as the commercial drive for a biomarker for objective quantitative assessment of disease burden in anti-amyloid trials. Early 2012, at least five 18F-labeled amyloid ligands are in phase II or III clinical trials, and three are expected to obtain FDA approval in the course of 2012–2013: 18F-flutemetamol, 18F-florbetaben and 18F-florbetapir. 18F-AZD4694 and 18F-MK3328 are two more recent compounds, currently in phase II trials. Despite some differences in dynamic range, all these ligands allow excellent separation of amyloid positive scans versus controls. Neuropathology correlations have shown the robustness of in vivo amyloid imaging. Whereas aspecific uptake in white matter is seen for all the above ligands, this does not seem to hamper high diagnostic accuracy in binary scan classification under clinical conditions either by visual read or simplified semiquantification. Ongoing multicenter efforts are showing that amyloid imaging in MCI has especially a very high negative predictive value for AD conversion. Regarding normal aging, a small proportion of elderly healthy individuals have positive amyloid scans and the significance of this finding is currently investigated in longitudinal studies. Amyloid PET is highly discriminative in frontotemporal dementia, while elevated tracer binding is observed in many Lewy body dementia patients. Although the first results of clinical trials using imaging show only modest efficacy of anti-amyloid therapies, the large scale availability of 18F-labeled imaging compounds will certainly contribute to further drug development and especially allow widespread clinical application in the very near future.

S-34-003 Imaging biomarkers in substance abuse

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Objective: Functional imaging has been increasingly used in the past decade for the characterization of patients with substance abuse disorders in order to gain insight in the neurobiology of these diseases and to enhance the development of drugs to treat them. Here we will review the current knowledge.

Methods: The available PET studies especially on the function dopamine systems in substance abuse will be reviewed, with a focus on alcohol and nicotine dependence and special emphasis on own studies in those patient groups. FMRI studies will be discussed where relevant for the interpretation and understanding of the PET studies.

Results: Irrespective of the abused drug, dopamine D2 receptors seem to be down-regulated and presynaptic dopamine function is apparently reduced in substance abuse disorders. Furthermore, the interaction between dopamine and other neurotransmitter systems, such as the opioidergic, seems to be dysregulated in a specific manner. FMRI studies demonstrate that the response of the reward system to drug-related cues is increased, while processing of cues not related to drug-use is diminished.

Conclusion: Substance abuse disorders irrespective of the abused drug share in common similar molecular imaging biomarkers, which can be used both for characterization of these disorders and for evaluation of anticraving drugs. Furthermore, functional magnetic resonance imaging can complement PET imaging, thereby providing information a single modality is unable to deliver.

Policy of full disclosure: Dr. Gründer has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Cheplapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka, and Servier. He has served on the speakers' bureau of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, and Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH, Düsseldorf, Germany. Dr. Vernaleken has served on the speakers' bureau of Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline. The other authors declare no conflicts of interest.

S-34-004 Novel PET biomarkers for dementia and psychosis and target engagement: Cannabinoids, metabotropic glutamate, glycine and beyond

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Objective: There are challenges associated with the development of new drugs, especially in neuropsychiatry, particularly in industry sponsored research. This is despite the continuing morbidity and challenges in treatment of schizophrenia and the exponential increase expected in dementia related disorders. There clearly is a need to meet these increasing public health needs. It has been suggested by some leaders in the drug development field that much of the effort should be placed on early human development (such as Phase I equivalent) and late preclinical discovery to try to select the most viable candidates early. Thus, the increasingly limited resources for CNS drug development should be focused with the greatest efficiency. Fortunately, several areas continue to appear to be great opportunities for therapeutic target methods.

Methods: In this presentation, we will present a number of novel potential biomarkers, both in imaging and related CSF and plasma levels, to aid in such drug development. Specific topics will include successful non-human primate and human target engagement dosing and mechanism of action studies for CB1 and CB2 cannabinoids, and metabotropic glutamate (mGluR5, mGluR2,3, GlyT1, PDE4, PDE10 and others). In the last few years, through successful collaborations between academia and industry, several new PET radioligands have been developed from novel structures and rapidly accelerated for dose ranging occupancy and correlation with early efficacy studies.

Results: Studies from our preclinical human research in glutamate mGluR, glycine, two [18F] amyloid radioligands and CB1 and CB2 cannabinoids will be presented.

Conclusion: The focus of this presentation will concentrate on this novel information.

Policy of full disclosure: Amgen – consulting Funded Research Avid Biotie GE Intracellular Johnson and Johnson Lilly Lundbeck Merck Orexigen Otsuka Roche Sanofi-Aventis.

S-35. Advances in understanding the causes and treatment of major depressive disorders

S-35-001 The role of tumour necrosis factor in the pathophysiology of major depressive disorder, bipolar disorder and schizophrenia

A. Gibbons. *Mental Health Research Inst, Parkville, Australia*

Objective: Altered plasma levels of pro-inflammatory cytokines have been reported in individuals with mood disorders and schizophrenia. Elevated protein levels of the transmembrane form of the pro-inflammatory cytokine tumour necrosis factor (tmTNF) were recently reported in the dorsolateral prefrontal cortex (DLPFC) but not the anterior cingulate (ACC) from subjects with major depressive disorder (MDD). By contrast, levels of the soluble form of TNF (sTNF) were not changed in either region. These findings have been extended by measuring cortical tmTNF and sTNF levels in bipolar disorder (BPD) and schizophrenia.

Methods: Experiments were performed on DLPFC and ACC obtained post-mortem from 10 subjects with BPD, 10 subjects with MDD and 10 matched controls and from 19 subjects with schizophrenia and 20 matched controls. Western blotting was used to measure the protein levels of tmTNF and sTNF in BPD and schizophrenia. TNF mRNA levels were measured using qPCR. Surrogate protein markers of glial (GFAP), microglial (CD11b) and pre- and post-synaptic neuronal (synaptophysin and PSD-95) cell type and IL-1B protein were measured using western blotting.

Results: tmTNF protein levels were increased in the ACC but not the DLPFC in BPD ($p < 0.05$). sTNF levels were unchanged in both regions compared to controls and TNF mRNA levels were also unaltered. There was no evidence of gliosis or apoptosis or of a broader cytokine response, indicated by unaltered cell-type marker and IL1B protein levels respectively, to suggest the increase in tmTNF is reflective of a pro-inflammatory response. Levels of tmTNF and sTNF protein or TNF mRNA were not significantly altered in schizophrenia.

Conclusion: Regionally specific increases in cortical tmTNF levels contribute to the pathophysiology of BPD and MDD but not schizophrenia. These elevated tmTNF levels are not consistent with a pro-inflammatory response, suggesting TNF's non-inflammatory signaling pathways are likely to be affected in the CNS of individuals with mood disorders.

S-35-002 The neuroanatomy of melancholy: An update circa 2012

J. Soares. *University of Texas-Houston, Department of Psychiatry, USA*

Mood disorders such as unipolar depression and bipolar disorder present brain abnormalities in key fronto-limbic brain circuits involved in emotional modulation. Over the past two decades a substantial number of neuroimaging studies have been completed and despite sometimes conflicting results, there is considerable evidence to support the fronto-limbic dysregulation hypothesis. Our presentation will review the anatomical and functional studies that focused on patients with major depression to summarize the status of knowledge in this maturing field. We will discuss a model where key abnormalities in the anterior cingulate, amygdala and hippocampus, as well as circuits that interconnect these regions, may be key steps involved in pathophysiology of these serious mental illnesses.

Policy of full disclosure: None.

S-35-003 Animal models of depression: Relevance to drug discovery

T. Norman. *University of Melbourne, Department of Psychiatry, Heidelberg, Australia*

Objective: This paper reviews some traditional as well as innovative approaches to the use of pre-clinical models for drug discovery.

Conclusion: Major depressive disorder is a complex, genetically inherited set of conditions, the underlying causes of which are far from completely delineated. Consequently development of pre-clinical models is doomed to fall far short of the goal of a complete analogy. Clearly some symptoms of depression cannot be modelled in animals. Nevertheless, despite these limitations, numerous ''so-called'' animal models of depression have been developed in the past. Traditional models have proven useful for the discovery of newer agents, but there have been some notable (and costly) failures. More recent approaches to the development of animal models have taken discoveries from the clinic and using various genetic strategies have attempted to develop models based on incorporating these findings. The utility of this approach for the discovery of truly novel agents awaits particular studies.

S-35-004 How to improve treatment strategies in depression

P. Blier[1], P. McGrath[2], R. Bergeron[3], J. Stewart[4]. *[1]Ottawa, Canada; [2]NewYork State Psychiatric Inst, New York, USA; [3]University of Ottawa, Canada; [4]New York State Psychiatric Inst., USA*

Objective: Two prior double-blind studies using mirtazapine combinations from treatment initiaion produced greater responses than antidepressants used in monotherapy, but not in a single-blind trial using low and/or conventional doses. High doses of escitalopram and bupropion were investigated based on their synergy between the serotonin and norepinephrine systems.

Methods: Patients with MDD (n = 241; minimum MADRS: 22) in 3 centers were randomized to escalating doses at weekly intervals of escitalopram (10–40 mg/day), bupropion (150–450 mg/day), or their combination, according to tolerability and/or achievement of remission status. Patients were assessed using the HAMD, the MADRS, and the CGI-severity and -improvement scales. Assessments were done weekly for the first 4 weeks and at weeks 6, 8, 10, and 12.

Results: The sample did not differ at baseline on the demographics between the 3 groups, although there were differences between sites. The overall dropout rates at week 12 were not statistically different: escitalopram-25%, bupropion-35%, and combination-30%. There were significantly more remitters at week 2 in the combination group vs. both monotherapies based on the HAM-D, MADRS, and CGI-I. At week 12, there were more remitters on escitalopram (54%) than on bupropion (33%), but not on the combination (42%): $X^2 = 7.67$, $df = 2$, $P = 0.02$.

Conclusion: Early remission was hastened by the combination. High doses of escitalopram outperformed optimal doses of bupropion. The combination was not the most effective treatment at study end in the overall analysis, although further analyses remain to be carried out to determine the influence of demographics and dropout rates.

Policy of full disclosure: Astra Zeneca, Bristol Myers Squibb, Euthymics, Janssen, Lundbeck, Merck, Pfizer, Servier, Takeda, Valiant.

S-36. Drug targets and novel treatment strategies in alcohol and drug addiction

S-36-001 Development of new medications for the treatment of alcoholism

C. O'Brien. *University of Pennsylvania, Department of Psychiatry, USA*

Objective: Translate findings from animal models of alcohol use disorder to the improved clinical treatment of alcoholism. Develop personalized treatment by studying genotypes relevant to the endogenous opioid system after animal models pointed the way.

Methods: An animal model of alcohol drinking in monkeys showed that blocking opioid receptors blocked alcohol self-administration. Translate to human alcoholics in double blind clinical trial. Study successful patients using human lab studies of drinking behavior, check family histories of successful patients, analyze DNA, search for genetic variants in the endogenous opioid system of successful v. unsuccessful patients.

Results: Patients randomized to naltrexone reported less craving for alcohol and less pleasure if they did drink. Successful patients had strongly positive family history of alcoholism & more pre-treatment craving. Those with an allelic variant of the gene for the μ opioid receptor had a high probability of success if randomized to naltrexone. Another opioid receptor antagonist, nalmephene, was

also found to reduce heavy drinking in clinical trials in the U.S. and Europe.

Conclusion: Alcohol produces reward via several mechanisms and one important mechanism involves activation of endogenous opioids. Blocking this effect with an opioid antagonist reduces the reward from alcohol and makes the patient more responsive to counseling. Unfortunately, in the U.S., anti-medicine philosophy dominates and few patients receive the benefits of this treatment. A recent advance is the introduction of a slow release depot product that improves compliance and thus improves the success rate of naltrexone treatment.

Policy of full disclosure: Consultant to Alkermes, producer of Vivitrol, slow release naltrexone.

S-36-002 The role of the GABAB receptor system in alcoholism and stress: The role of the GABAB receptor agonist baclofen

G. Addolorato. *Catholic University of Rome, Depart. of Internal Medicine, Italy*

Alcoholism and stress share some common neurobiological circuits, including the GABAergic system. In particular, the GABAB receptor seems to play an important role. The GABAB receptor agonist baclofen has been studied as a treatment for alcohol-dependent subjects. Baclofen administration in alcohol-dependent patients was able to promote abstinence, inducing the remission of withdrawal symptoms, reducing alcohol craving, and reducing alcohol intake. Baclofen also reduced anxiety in alcohol-dependent subjects, probably acting on brain stress circuitry and/or on other neuroendocrine systems. Baclofen also showed excellent safety and tolerability, even in alcohol-dependent patients with advanced liver disease (i.e., cirrhosis). Future studies should investigate which alcoholic subtype may better benefit of the administration of baclofen in the treatment of alcohol dependence.

S-36-003 Impact of the stress hormone system as a pharmacotherapeutic target in the treatment of alcohol and drug addiction

F. Kiefer. *CIMH, Univ. of Heidelberg, Mannheim, Germany*

The ability of most drugs to enhance dopamine neurotransmission particularly within the mesocorticolimbic dopamine (''reward'') system was demonstrated repeatedly. However, the past decade has placed the dopamine system within a broader context of neuronal circuitry involved in drug seeking, drug taking, and recovery. Specific effects on other receptors symptoms provide particular challenges given the almost ubiquitous expression of these receptors throughout the CNS. Additionally, new emphasis on various neuropeptide systems has re-emerged, including opioid peptides and the stress-related peptides of the hypothalamus-pituitary-adrenal axis. The stress hormone system serves as a pharmacotherapeutic target in the treatment of alcohol and drug addiction; new data based on a GWAS on alcohol dependence and a pharmacogenomic follow-up study point towards an involvement of neuroendocrine pathways in relapse-related behavior. Continued research is warranted on the various neurobiological based components that underlie the transition from drug intake to addiction to define drug targets for innovative pharmacological treatment options.

S-36-004 ADHD in drug addiction: A RCT on the feasibility of methylphenidate treatment in criminal amphetamine users

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Objective: The present clinical trial was designed to evaluate the feasibility and efficacy of methylphenidate (MPH) for the treatment of ADHD in patients with amphetamine dependence and comorbid ADHD, using relapse to drug use as the primary outcome variable.

Methods: The study was a double-blind, placebo-controlled trial with parallel groups design. Participants were recruited and assessed while serving a short (<1.5 yrs) prison sentence in a medium security prison. The efficacy of OROS MPH(max dose 180 mg/day) was compared with identical placebo (PL) in currently abstinent adult males. Fifty-four treatment-seeking patients fulfilling DSM-IV criteria for amphetamine dependence and ADHD were randomized to MPH/PL. The medication started 14 days before release from prison and continued at an outpatient facility with twice weekly visits and supervised urine drug screening. ADHD-symptoms, other psychiatric symptoms and relapse to criminality were also monitored. All patients participated in a relapse prevention training programme on a weekly basis.

Results: The mean age was 42.3 years (SD 10.5). All had i.v. amphetamine use and the mean debut age was 18 years, mean length of use 19.6 years (SD 11). The participants had been incarcerated on 11.3 occasions (SD 8.2). The most frequent axis-II diagnoses were antisocial (50%), obsessive-compulsive (23%) and borderline personality disorder (18%). Forty-four percent had prior alcohol dependence, 19% other substance use disorders and 13% anxiety syndromes. The average retention in treatment was 11.3 weeks (CI 8.7–13.8). Twenty-four percent (n=12) of the participants completed all 24 weeks of treatment. Retention in treatment was significantly higher in the MPH group. No unexpected adverse events were detected using the maximum dose of MPH.

Conclusion: This clinical trial demonstrates the feasibility and safety of studying long-acting MPH in convicted patients with ADHD and comorbid amphetamine dependence.

Policy of full disclosure: The study was supported by grants from the Stockholm County Council and the Swedish Research Council.

S-37. Stress and vulnerability – antecedents to psychopathology and implications for effective treatment

S-37-001 Early life adverse experience, 5-HT2 receptors and long term epigenetic modifications: Implications for affective vulnerability

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Objective: Prefrontal serotonin 5-HT2 receptors have been linked to the pathogenesis and treatment of affective disorders, yet their function in psychiatric vulnerability is not known. We examined the effects of 5-HT2 receptors in a rat model of early life stress, and addressed whether postnatal 5-HT2 receptor blockade would prevent the consequences of early stress on anxiety, hippocampal neurogenesis and dysregulated gene expression.

Methods: Control and maternally separated animals received treatment with the 5-HT2 receptor agonist DOI and effects on gene expression and behavior were assessed. Control and maternally separated litters received treatment with the 5-HT2 receptor antagonist, ketanserin, and were examined for effects on adult anxiety, stress-induced gene expression responses, transcriptional changes and hippocampal neurogenesis.

Results: Stimulation of 5-HT2 receptors potentiated head shake behavior and heightened transcriptional changes in maternally separated animals, indicating enhanced 5-HT2 receptor responses. Treatment with ketanserin during postnatal life blocked the effects of maternal separation on anxiety, perturbed gene expression and hippocampal neurogenesis. Ketanserin treatment also normalized the changes in serotonin type 2A receptor messenger RNA expression during postnatal life and in genes associated with G-protein signaling in adulthood.

Conclusion: Animals with an early stress history of maternal separation exhibited exaggerated 5-HT2 receptor mediated responses. Postnatal treatment with the 5-HT2 receptors receptor antagonist, ketanserin, blocked specific consequences of maternal separation, including anxiety behavior, changes in hippocampal neurogeensis and dysregulated gene expression in the prefrontal cortex and hippocampus. Our results suggest that enhanced 5-HT2 receptor function may contribute to the emergence of anxiety behavior and perturbed stress responses following early life stress.

S-37-002 Social isolation stress in a genetic rat model of depression: Effects of physical activity as an intervention

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Objective: There is evidence from both pre-clinical and clinical studies that physical activity can have an antidepressant effect. Moreover from rodent studies it is well known that social isolation by itself is a stress factor, which is likely to impact the affective state. In this study our aim was to test how Flinders Sensitive Line rats (FSL), which is a rodent genetic model of depression, respond to single-housing in cages with or without access to running wheels.

Methods: The single housed male FSL rats, runners, were allowed free access to a running wheel during 5 weeks whereas controls, non-runners, had no access. We analyzed effects of running on hippocampal size using volumetric 3-D in vivo Magnetic Resonance Imaging, 9.4 Tesla, long-term potentiation (LTP) induction in CA1 in hippocampal slices, and spine density in dentate gyrus. Levels of glutamate receptor and transporters were analyzed in hippocampus from rats with or without access to running wheels.

Results: Wheel running increased the size of hippocampus and number of spines in dentate gyrus compared to the non-running controls. Moreover, levels of the AMPA receptor subunit GluR2 and the glutamate transporter GLAST were increased in hippocampus after running. LTP, could not be induced in non-running FSL rats but was induced in the group of runners.

Conclusion: Physical activity can induce both structural and functional plasticity. In the FSL model of depression with social isolation we find an enlarged total hippocampal volume, increased dendritic spine numbers, increased sensitivity to LTP induction, and increased levels of glutamate receptors and transporters after physical activity. Thus, we present findings that are likely to be important for the protective effects of physical activity on depression.

S-37-003 Rodent models of vulnerability to emotional trauma: Neural correlates and novel treatment options

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Objective: There are individual differences in coping with emotional trauma, including the ability to extinguish learned fear responses, which is suggested as a biomarker predicting the vulnerability to develop specific anxiety disorders. Animal models of deficient extinction could be particularly useful to study underlying mechanisms and identify novel targets to inhibit pathological fear persistently.

Methods: Different pharmacological and non-pharmacological treatments were investigated for their fear extinction-promoting effects using classical conditioning/extinction paradigms in rodent models of impaired extinction, the Wister rat line selectively bred for high anxiety-related behaviour (HAB) and inbred 129/SvImJ (129S1) mice. Associated brain neuronal activity changes were assessed by quantification of immediate-early-gene expression.

Results: show that rescue of impaired extinction in HAB rats and 129S1 mice was achieved by neuropeptide S or α-2 adrenoceptor antagonist treatments. Further testing in 129S1 revealed that SSRIs and in particular novel treatments targeting the zinc system, histone acetylation, mGluR7-mediated transmission or deep brain stimulation rescued the highly impaired fear extinction in this model. Considerable differences in the efficacy of these treatments to inhibit return of fear persistently were revealed. In particular we observed that targeting histone acetylation and zinc systems very efficiently protected against spontaneous recovery and fear renewal in a novel context. Rescue of impaired extinction was associated with normalisation of aberrant functional brain activity in 129S1. This normalisation was observed in key regions of fear/extinction circuitries including the prefrontal cortex, intercalated cell masses of the amygdala and culminated in attenuation of hyperactivity of the medial subunit of the central amygdala, the main amygdala output region controlling fear behaviour.

Conclusion: These studies in psychopathologically relevant animal models identified extinction-enhancing treatments that promoted sustained inhibition of fear and furthermore, revealed important neural target correlates of such interventions. These findings should provide a basis for the development of novel therapeutic adjuncts in extinction-driven therapy.

Policy of full disclosure: Supported by the Austrian Science Fund (FWF) SFB-F4410 (NS).

S-37-004 Chronic stress, dysregulation of prefrontal cognitive function and mechanisms underlying the response to effective antidepressant treatment

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Objective: Cognitive flexibility, the ability to modify established thoughts and behaviors based on changes in the environment, depends upon prefrontal cortical function, and is compromised in many stress-related psychiatric disorders, e.g., depression. Using rat models, we address mechanisms by which chronic stress impairs cognitive flexibility, and by which therapeutic approaches exert beneficial effects.

Methods: The rat attentional set-shifting test was used as a measure of prefrontal cognitive flexibility. Prefrontal function was assessed by fos activation in response to MDT stimulation. Chronic stress included psychogenic chronic unpredictable stress (CUS) and metabolic chronic intermittent cold stress (CIC). Novel and traditional therapeutic strategies included monoamine reuptake blockers, anti-inflammatories, and a rat model of cognitive behavioral therapy (CBT).

Results: CUS impaired cognitive set-shifting and reversal learning, and attenuated activation of PFC. CIC selectively impaired reversal learning, related to serotonergic dysfunction in OFC. These deficits were reversed or prevented by chronic treatment with selective NE or 5-HT reuptake blockers, respectively. Alpha1 adrenergic receptors in mPFC facilitate set-shifting, and 5-HT2A receptors in OFC facilitate reversal learning. These mechanisms contribute to effective antidepressant response. However, noradrenergic facilitation in mPFC also contributes to the detrimental effects, as antagonist treatment during chronic stress protects against the cognitive deficit. Thus a paradox – how can elevating NE by chronic stress be bad, but elevating NE by chronic reuptake blockade is good? We hypothesize that noradrenergic facilitation interacts with other convergent stress-evoked signaling pathways in PFC, including cytokines, contributing to the detrimental effect. Finally, preliminary results indicate that a rat model of CBT has antidepressant efficacy.

Conclusion: Monoaminergic modulation in PFC enhances cognitive flexibility, and contributes to effective antidepressant response. Approaches that target other convergent pathways may improve treatment response. Further, behavioral or other strategies that engage the prefrontal circuitry compromised in depression can induce direct improvement, or provide an active substrate for monoaminergic facilitation.

Policy of full disclosure: This work was supported by research grants from NIH and the Department of Defense (USA). The author has received funds in the past year from Forest Laboratories for research on a product unrelated to any of the material or data presented in this talk.

S-38. Neurostimulation therapies: Current advances and controversies

S-38-002 Taking deep brain stimulation for major depression one step deeper – current data and outlook

T. Schlaepfer. *University of Bonn, Germany*

Objective: Conceptualizations of the underlying neurobiology of major depression – and consequently the development of novel

hypothesis-guided treatment approaches – concentrated for a long time on alterations on monoaminergic or endocrine systems. A more comprehensive and appropriate treatment might arise from modeling depression as a dysfunction of specific brain networks mediating mood and reward signals. DBS is currently being researched actively for its putative application in treatment resistant major depression (TRD). While first studies on three different targets in TRD (Brodmans Area cg25, anterior limb of the capsula interna and Nucleus Accumbens) showed prom-ising effects in comparable patient populations, only 50–60 % of patients responded at a clinically significant level. Furthermore, stimulation intensities ranging from 4–10V and large electrodes geometries were used ; somewhat undermining target specificity.

Methods: Seven patients suffering from extremely treatment resistant depression (TRD, mean lengths of current episode 7.6 years) underwent bilateral DBS electrode implantation in the supero-lateral medial forebrain bundle slMFB) after Diffusion Tensor Imaging (DTI) based personalized target site definition.

Results: Montgomery Åsberg Rating Scale for Depression (MADRS) scores decreased from a mean of 29.9 (SD 8.0) at baseline to 12.4 (SD 10.2) after 11 weeks of stimulation, onset of efficacy was typically observed within two days of start of stimulation and 6 patients reached the response criterion within 7 days. Stimulation intensity ranged from 1.5 to 2.5V.

Conclusion: These pilot data support the notion that slMFB DBS might be associated with more rapidly developing and significantly stronger antidepressant effects in patients with TRD.

S-38-003 Deep Brain Stimulation to the subcallosal cingulate gyrus for treatment resistant depression: An update

S. Kennedy. *University Health Network, Toronto, Canada*

Objective: Antidepressant treatments, including pharmacotherapy and psychotherapy, do not result in remission for the majority of patients with Major Depressive Disorder. Consequently, the high prevalence of treatment resistant depression (TRD) results in a high social and economic burden.

Methods: The emergence of neurostimulation therapies, including Deep Brain Stimulation (DBS) for TRD is a promising development that involves the bilateral implantation of electrodes to a neuroanatomical site, which receives remote electrical stimulation via a subclavicularly implanted pacemaker. Through the use of neuroimaging, and other biomarker testing, there is an opportunity to elucidate both the underlying circuitry of TRD and the mechanism of action of DBS. Studies on the neurocircuitry of depression support hyperactivity in the subcallosal cingulate gyrus-Area 25 (SCg25), which is ameliorated by neuromodulation treatments.

Results: The Neurostimulation team at University Health Network, University of Toronto has a seven-year experience involving over 30 patients who have received SCg25 DBS, and have been followed up to 6 years. These data support the long-term effectiveness of DBS for TRD, while highlighting the mortality rate associated with treatment resistance. Beyond the initial DBS trial to the SCg25, additional neuroanatomical targets are being explored, including the nucleus accumbens and internal capsule/ventral striatum, lateral habenula, and inferior thalamic peduncle.

Conclusion: To date, there are open-label reports on over 100 subjects, demonstrating acute and sustained effectiveness and safety. However, until published randomized controlled trials establish efficacy for this invasive treatment, the medical community and the media need to exercise caution in their enthusiastic endorsement of this appealing advance in psychiatry.

Monday 4 June 2012 – Wednesday 6 June 2012

RA-01. Rafaelsen Award Posters

RA-01-001 Regulation of inflammation and T cells by glycogen synthase kinase-3 (GSK3) and association with depression

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Objective: Accumulating evidence shows that inflammation strongly influences the development and treatment of depression. Inflammatory molecules are elevated in many patients with depression, administration of inflammatory cytokines induces depression in susceptible people, and inflammation in rodents causes depressive-like behaviors and impairs antidepressant therapeutic effects. Glycogen synthase kinase-3 (GSK3) is a critical regulator of the immune system, which may contribute to its action in increasing susceptibility to mood dysregulation. Previously, GSK3 was shown to have important influences in mood disorders: (a) GSK3 is inhibited by mood stabilizers and antidepressants, (b) pharmacological or genetic reduction of GSK3 activity reduces depression-like behaviors in rodents, (c) GSK3 is activated when serotonergic signaling is deficient, (d) brain-derived neurotrophic factor, that may be deficient in depression, normally inhibits GSK3, and (e) studies of human blood cells, postmortem brain, and polymorphisms implicate GSK3 in mood disorders.

Methods: GSK3 activity was increased by using GSK3a/β/21A/21A/9A/9A knockin mice with serine-to-alanine mutations to block inhibitory serine-phosphorylation of GSK3 or decreased by administration of GSK3 inhibitors (lithium, CHIR99021 and TDZD-8). Cytokines were measured by ELISA. Activation of the transcription factor signal transducer and activator of transcription-3 (STAT3) was assessed by immunoblotting. The learned helplessness paradigm of depression-like behavior was evaluated in adult male mice.

Results: Inhibition of GSK3 or knockdown of GSK3 inhibited inflammatory cytokine production by astrocytes and microglia and blocked the inflammatory activation of the transcription factor STAT3. Blocking cytokine production and downregulation of STAT3 by GSK3 inhibition diminished T cell differentiation towards pathogenic Th17 cells, whereas active GSK3 promoted depressive-like behavior in mice and increased Th17 cells in mouse brain.

Conclusion: Altogether, these findings indicate that GSK3 promotes inflammatory immune system activation and depression-like behavior. Activation by dysregulated GSK3 of these immune system actions may contribute to susceptibility to mood disorders and be controlled by mood stabilizers.

RA-01-002 Association of nicotine dependence susceptibility gene, CHRNA5, with Parkinson's disease age at onset: Gene and smoking status interaction

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Objective: Smoking is a well documented environmental factor that reduces susceptibility to Parkinson's disease (PD). Several genetic variants within the nicotinic cholinergic receptor gene cluster, CHRNA5-CHRNA3-CHRNB4 have been reported to be associated with nicotine dependence (ND), and this association has been validated in multiple studies. Due to the inverse correlation between smoking and PD susceptibility, we investigated whether ND-related genetic variants are associated with age at onset (AAO) of PD among smokers.

Methods: We performed a genetic association study in a sample of 667 Italian PD patients, ages 34–76. 438 had never smoked (NS), and 239 were current or past smokers (ever smokers, ES). Three independent SNPs within the CHRNA5-CHRNA3-CHRNB4 gene cluster (rs588765, rs16969968, rs578776) were analyzed for association with AAO.

Results: We demonstrated an interaction between the rs588765 SNP and smoking status (NS vs. ES) that was nominally significant in its effect on PD AAO ($p = 0.04$). The rs588765 ND risk allele, C, was associated with delayed AAO among ES, but had no significant effect among NS. In the ES group, a dominant model of inheritance was observed: carriers of the CC genotype presented delayed AAO compared to carriers of the CT or TT genotypes.

Conclusion: Our preliminary results suggest that the ND risk variant, rs588765, has a protective effect in PD, and is associated with later AAO, but only when the individual was previously exposed to nicotine. This may be explained by modulation of dopamine transmission by nicotinic cholinergic receptors expressed on dopaminergic neurons in PD relevant brain regions.

RA-01-003 Opioid receptors and reward: An fMRI study with naltrexone

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Objective: Opiates are known to be involved in facilitating consummatory behaviour in animals and humans. Opioid receptors are highly expressed in neural 'reward' areas such as orbitofrontal cortex, ventral tegmental area and nucleus accumbens. Naltrexone, an opioid antagonist, can decrease the behaviour-reinforcing effects of primary rewards and increase the effect of negative experience, such as pain. The aim of the current experiment was to examine the effects of the opioid antagonist naltrexone on rewarding and aversive taste processing in the human brain.

Methods: We used functional magnetic resonance imaging (fMRI) to examine the effects of naltrexone on the neural responses to pleasant chocolate and aversive sights and tastes of mouldy strawberry in a within-subjects double-blind crossover design ($n = 20$).

Results: Relative to placebo, naltrexone decreased the neural activation to the rewarding chocolate stimulus in the vmPFC but increased activation to the aversive strawberry stimulus in the same region. Results are consistent with studies showing opiates reduce reward but also how opioid antagonists may enhance the unpleasantness of aversive stimuli.

Conclusion: These findings provide novel insight into the mechanism by which opioid antagonists may reduce food intake not only through effects on reward but also effects on unpleasant food stimuli. These results have implications for the use of opioids as possible treatments for disorders of compulsion such as obesity.

RA-01-004 BDNF-TrkB signaling is involved in the antidepressant-like effect induced by genetic deletion of iNOS

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Objective: We have recently shown that the pharmacological or genetic inhibition of the inducible nitric oxide (NO) synthase (iNOS) isoform evokes antidepressant-like effects. However, the molecular mechanism underling this effect is still unknown. Brain derived neurotrophic factor (BDNF) is a neurotrophin implicated in the antidepressant effect and it can be modulated by NO in hippocampus (HPC) and pre-frontal cortex (PFC). Therefore, the aim of this study was investigate the hypothesis that inhibition of iNOS induces

antidepressant-like effects associated to increased BDNF signaling in hippocampus and PFC.

Methods: Male iNOS deficient (KO) and C57BL/6 wild-type (WT) control mice were submitted to forced swimming test (FST) and their immobility time was videotaped and scored. Naïve and stressed (FST) animals were sacrificed immediately after FST and their HPC and PFC were dissected. BDNF and its receptor, TrkB, as well as NOx levels were measured. Independent groups of KO and WT mice were treated with k252a, a Trk antagonist, and submitted to FST or to the open field test (OFT).

Results: iNOS KO animals presented a decreased immobility time in the FST compared to WT controls ($t14 = 3.18$; $p < 0.01$). KO animals had increased levels of BDNF in HPC and PFC (genotype × stress: HPC: $F1,32 = 5.41$, $p < 0.05$; PFC: $F1,28 = 4.48$, $p < 0.05$), which was not influenced by FST. iNOS KO mice also had increased levels of TrkB ($t14 = 3.29$; $p < 0.05$) and NOx ($t6 = 2.526$; $p < 0.05$) in PFC. In the HPC, only TrkB levels were increased ($t13 = 2.182$; $p < 0.05$). Systemic injection of K252a reversed the behavioral phenotype of iNOS KO mice, without changing the behavior of WT mice (drug × phenotype: $F1,18 = 13.21$, $p < 0.01$). No effects were observed in the OFT.

Conclusion: Our results indicate that there is a differential interaction between NO and BDNF-TrkB signaling in HPC and PFC. This interaction may be involved in the antidepressant-like phenotype of iNOS KO mice.

RA-01-005 MDMA, oxytocin and empathy: Preliminary results from a placebo controlled study

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Objective: Background. The neurobiological mechanism underlying MDMA-induced prosocial behaviour (PSB) is yet not known. Two potential mediators of these effects are oxytocin and the serotonin (5-HT) 1a-receptor as they seem to play a role in facilitation of positive mood, empathy and social interaction. Moreover, MDMA is known to increase blood oxytocin levels and the 5-HT1a-receptor is a mediator of the effects of MDMA and oxytocin. The study aim is to investigate the roles of oxytocin and the 5-HT1a-receptor in the MDMA-induced PSB effects.

Methods: Twenty participants will participate in this 4 way-crossover study (currently N = 5). Treatments are MDMA (75 mg, oral) alone, and in combination with a 5-HT1a antagonist (pindolol, 20mg, oral), Oxytocin (48 IU, intranasal), and placebo. Empathy and mood are assessed by means of two computer tasks (Reading the Mind in the Eyes Test and the Multifaceted Empathy test) and a questionnaire (Profile of Mood States). It is hypothesized that oxytocin will mimic MDMA-induced prosocial effects and that the 5-HT1A-receptor is an important mediator of these effects.

Results: Preliminary analyses of both empathy tests did not reveal statistically significant main effects of treatment. Analyses of the POMS revealed a main effect of treatment on the 'vigor' scale ($p = 0.032$) and a trend on the 'arousal' and 'elation' scale. These 'stimulant' effects were caused by the combined treatment and oxytocin. Closer inspection of the data however leads to the suggestion that an increase in power will lead to significant effects (also of MDMA) on more scales.

Conclusion: The data of the POMS questionnaire suggest that the three active treatments have 'stimulant' effects on different mood states. Inclusion of more subjects will provide more clarity on the role of oxytocin and the 5-HT1a-receptor in MDMA-induced PSB.

RA-01-006 Impact of the genome wide supported NRGN gene on anterior cingulate morphology in schizophrenia

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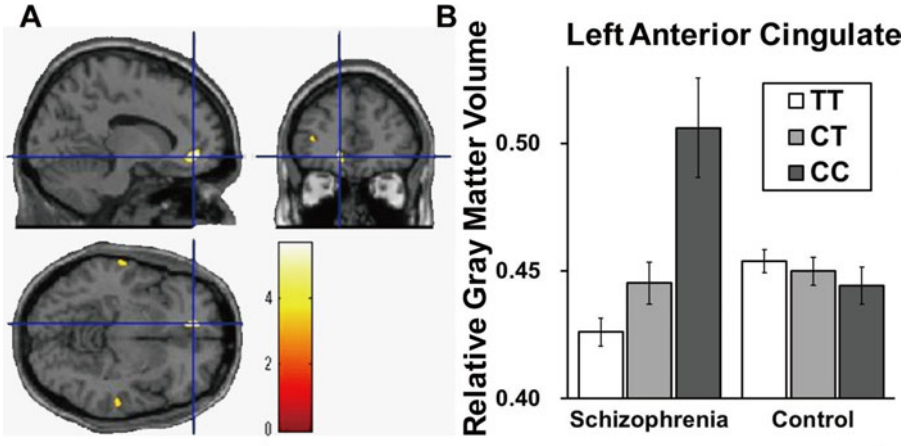
Objective: The rs12807809 single-nucleotide polymorphism in NRGN is a genetic risk variant with genome-wide significance for schizophrenia. The frequency of the T allele of rs12807809 is higher in individuals with schizophrenia than in those without the disorder. Reduced immunoreactivity of NRGN, which is expressed exclusively in the brain, has been observed in Brodmann areas (BA) 9 and 32 of the prefrontal cortex in postmortem brains from patients with schizophrenia compared with those in controls.

Methods: Genotype effects of rs12807809 were investigated on gray matter (GM) and white matter (WM) volumes using magnetic resonance imaging (MRI) with a voxel-based morphometry (VBM) technique in a sample of 99 Japanese patients with schizophrenia and 263 healthy controls.

Results: Although significant genotype-diagnosis interaction either on GM or WM volume was not observed, there was a trend of genotype-diagnosis interaction on GM volume in the left anterior cingulate cortex (ACC). Thus, the effects of NRGN genotype on GM volume of patients with schizophrenia and healthy controls were separately investigated. In patients with schizophrenia, carriers of the risk T allele had a smaller GM volume in the left ACC (BA32) than did carriers of the non-risk C allele. Significant genotype effect on other regions of the GM or WM was not observed for either the patients or controls.

Conclusion: Our findings suggest that the genome-wide associated genetic risk variant in the NRGN gene may be related to a small GM volume in the ACC in the left hemisphere in patients with schizophrenia.



RA-01-007 Circuit-wide effects of deep brain stimulation for neurological and psychiatric disorders: A comparison

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Objective: High-frequency electrical stimulation of specific brain structures, commonly known as deep-brain stimulation (DBS), has attracted substantial attention for treatment of neurological and psychiatric disorders that fail to respond to standard therapies. Here, we compare and contrast the circuit-level effects of DBS applied to either the nucleus accumbens (NAC), an effective target for treating OCD and depression, or the entopeduncular nucleus (EP), the rat homolog of the internal globus pallidus and a target for treatment of dystonia and Parkinson's disease.

Methods: We used simultaneous multi-site local field potential (LFP) recordings in urethane-anesthetized rats to assess the effects of high-frequency (HF, 130 Hz; clinically effective), low-frequency (LF, 10–15 Hz; clinically ineffective) and sham DBS delivered to either NAC or EP. For NAC DBS, LFP activity was recorded from the orbital and medial prefrontal cortices, mediodorsal thalamus, and the stimulation site. For EP DBS, we recorded from dorsal striatum, ventroanterior thalamus, primary motor cortex, and the stimulation site. Spontaneous and acute stimulus-induced LFP oscillation power and coherence were assessed at baseline, and after 30, 60, and 90 minutes of stimulation.

Results: Compared to LF and sham, HF NAC DBS was associated with widespread, time-dependent increases in fast (beta/gamma) oscillation power, whereas HF EP DBS produced no specific changes in spontaneous fast oscillation power. LF NAC DBS produced region specific increases in theta band power, and reduced induced gamma coherence between regions; LF EP DBS produced no significant changes. Notably, HF DBS of both EP and NAC DBS produced time-dependent increases in spontaneous and induced beta and gamma coherence between regions.

Conclusion: These data suggest that enhanced coherent activity in the beta and gamma bands along cortico-basal-ganglia-thalamic circuits may represent a common mechanism of action of DBS for different indications. Future studies will continue to dissect generalized and disease-specific therapeutic mechanisms to better optimize this technology.

RA-01-008 Psychopharmacological effect of naringin in unpredictable chronic mild stress model of depression: Behavioral, biochemical & neurochemical evidences

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Objective: A complex relationship exists among stressful situations, body's reaction to stress, and the onset of clinical depression. Chronic unpredictable stressors can produce a situation similar to clinical depression and such animal models can be used for the pre-clinical evaluation of antidepressants. Clinical studies reported neurotransmitter alterations, increased MAO activity, nitrodative stress and inflammation in patients with depression. The present study was designed to investigate the effect of naringin on unpredictable chronic stress-induced behavioral, biochemical and neurochemical alterations in mice.

Methods: Animals were subjected to different stress paradigms daily for a period of 21 days to induce depressive-like behavior. The sucrose preference, immobility period, locomotor activity, memory acquisition and retention were significantly altered in stressed mice. These behavioral deficits were integrated with decreased biogenic amine (dopamine, norepinephrine and serotonin) levels, increased nitrodative stress (increased lipid peroxidation & nitrite levels; decreased glutathione levels, superoxide dismutase & catalase activities), enhanced MAO and inflammatory cytokine (TNF-α & IL-1β) activities.

Results: Chronic treatment with naringin significantly and dose-dependently restored the unpredictable chronic stress-induced behavioral (increased immobility period, reduced sucrose preference), biochemical (decreased nitrodative stress, MAO and inflammatory cytokine activity), and neurochemical (dopamine, norepinephrine and serotonin levels) deficits in stressed mice.

Conclusion: The study revealed that naringin exerted antidepressant-like effects in behavioral despair paradigm in chronically stressed mice, specifically by modulating biogenic amines, MAO, nitrodative stress and inflammation. Thus, naringin may find clinical application in therapeutic armamentarium of stress induced depression.

RA-01-009 Estrogen affects neural processing in empathy task in women. An ultra-highfield 7 tesla functional MRI study

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Objective: Neural mechanisms of empathy, defined as a psychological construct of understanding and responding to other peoples' affective experiences, have gained focus in neuropsychological research. Studies revealed higher empathy scores in females and suggested that neural empathy networks are differentially modulated by gender. Furthermore, estrogen has been shown to influence brain activation in memory as well as emotional tasks in women. Following that, this study with functional magnetic resonance imaging (fMRI) aims to investigate the relation between estrogen plasma levels and brain activation during an empathy task.

Methods: 17 healthy female volunteers (26.4 ± 5.8 years) were analysed in this 7 Tesla ultra-highfield (Magnetom 7T, Siemens Medical) fMRI study undergoing an fMRI scan (245 whole brain volumes, matrix size $128 \times 128p \times 2 \times 32$, TR = 1.4 s, TE = 23 ms, FoV = 192×192 mm^2, 2 mm slice thickness). All subjects performed an empathy-related task, previously described by Lamm et al., Participants were watching video clips of actors who were instructed to emphasize a painful response to an auditory stimulation, whereas the participants where informed that they would see patients with a neurological disease experiencing auditory stimulations as a medical treatment intervention. Estrogen plasma levels were quantified by means of electrochemiluminescence, whereas blood samples were taken prior to the fMRI scan. Data pre-processing and analysis were performed in SPM8 based on a random effects model.

Results: Empathy task-related activations were found in the inferior frontal cortex (IFC), anterior medial cingulate cortex, supplementary motor area (SMA), anterior insula and amygdala-hippocampus-complex ($T > 5.5$; $p < 0.05$ FDR corrected). Empathy-related activation showed strong correlations with estrogen plasma levels in the right IFC, SMA and in the right amygdala-hippocampus-complex ($T > 4$; $p < 0.001$ uncorrected).

Conclusion: Our study revealed activations in the empathy task that are in line with previously reported findings. Furthermore, empathy related activations were associated with estrogen levels in healthy females, which might provide a neurobiological rationale of gender differences in empathy.

P-01. Antipsychotics

P-01-001 Treatment adherence pattern in patients affected by schizophrenia or bipolar disorder that switched from quetiapine IR to quetiapine XR

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Objective: In patients with schizophrenia and bipolar disorder (BD), non-adherence to medication can increase the risk of relapse. The Italian Burden of Illness on Schizophrenia and BD (IBIS) study aimed to describe pharmaco-utilisation of antipsychotic treatment in schizophrenia and BD patients. A secondary study objective was to assess differences in medication adherence for patients switching from quetiapine immediate release (QTP-IR) to quetiapine extended release (QTP-XR). Here we present interim adherence results collected from administrative databases in 6 of 20 Italian Local Health Units included in the study.

Methods: Multicentre, retrospective, observational cohort study (NCT01392482). Data were collected between 1 January 2008 and 31 December 2010. Patients were included for analysis when they switched from the antipsychotic medication QTP-IR to QTP-XR. Data were collected 6 months before and 6 months after the switch. A control group that received QTP-IR was matched to the switching group based on diagnosis, gender and age, for analysis. Adherence $\pm$SD was estimated using the Catalan method.

Results: Of 6,817 patients in the study population, 213 switched medication from QTP-IR to QTP-XR (86 with schizophrenia, 127 with BD). Overall, there was an increase in adherence to medication after switching (from 44.2$\pm$24.7% to 62.6$\pm$26.5% [p=0.009]). For patients with schizophrenia adherence increased from 48.3$\pm$23.5% to 56.5$\pm$27.0% [p=0.125], and for patients with BD adherence increased from 41.5$\pm$25.3% to 66.7$\pm$25.4% [p=0.036]. In the matched control group smaller increases in adherence were observed in the overall interim population, and stratified by disease: 51.8$\pm$22.5% to 53.4$\pm$26.4% [p=0.493] in total; 55.7$\pm$22.2% to 56.6$\pm$25.7% [p=0.816] in patients with schizophrenia; 49.2$\pm$22.4% to 51.3$\pm$26.8% [p=0.479] in patients with BD.

Conclusion: These interim results suggest that adherence improved in patients with schizophrenia and BD after switching from QTP-IR to QTP-XR.

Policy of full disclosure: The IBIS study was funded by AstraZeneca and the presenting author received a grant from AstraZeneca.

P-01-002 Variability of treatment patterns for patients affected by schizophrenia and bipolar disorder

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Objective: Schizophrenia and bipolar disorder (BD) are serious psychiatric disorders commonly treated with antipsychotic medications. Little is known about which combinations of antipsychotics are frequently used in clinical practice. The Italian Burden of Illness on Schizophrenia and BD (IBIS) study aims to describe the pharmaco-utilisation of antipsychotic and concomitant medications in patients with schizophrenia and BD.

Methods: Multicentre, retrospective, observational cohort study (NCT01392482). Interim data are shown from administrative databases of 6 of 20 Italian Local Health Units included in the study, collected between 1 January 2008 and 31 December 2010. Patients were retrospectively followed for one year from index date (first prescription of antipsychotics).

Results: In total, 6,817 patients were included in the study population (4,097 with schizophrenia, 2,720 with BD). In patients with schizophrenia, 65.5% were treated with a single antipsychotic, and 34.5% were prescribed more than one antipsychotic during the study period. A notable number of schizophrenic patients receiving either one or multiple antipsychotics, respectively, also received mood stabilisers (13.5%, 21.3%), antidepressants (15.9%, 17.5%) or both (5.5%, 15.2%). In patients with BD, 66.7% were prescribed a single antipsychotic and 33.3% multiple antipsychotics. Concomitant medications were more frequently prescribed in patients with BD than with schizophrenia; BD patients receiving single and multiple antipsychotics, respectively, also received mood stabilisers (31.0%, 27.0%), antidepressants (14.8%, 13.6%) or both (34.9%, 48.5%). Overall, in patients receiving multiple antipsychotics, up to 333 different combinations were used. Of the antipsychotic combinations reported in the study, 22.7% of schizophrenia patients received the 5 most frequently used combinations for schizophrenia, and 23.4% of BD patients received the 5 most common combinations for BD.

Conclusion: These interim results show a high level of treatment variability in schizophrenia and BD patients. Most were treated with a single antipsychotic, and concomitant treatment with mood stabilisers and antidepressants was common.

Policy of full disclosure: The IBIS study was funded by AstraZeneca and the presenting author received a grant from AstraZeneca.

P-01-003 Interactions between adenosine-A2A and alpha2 adrenergic receptors and their potential role in antipsychotic drug response

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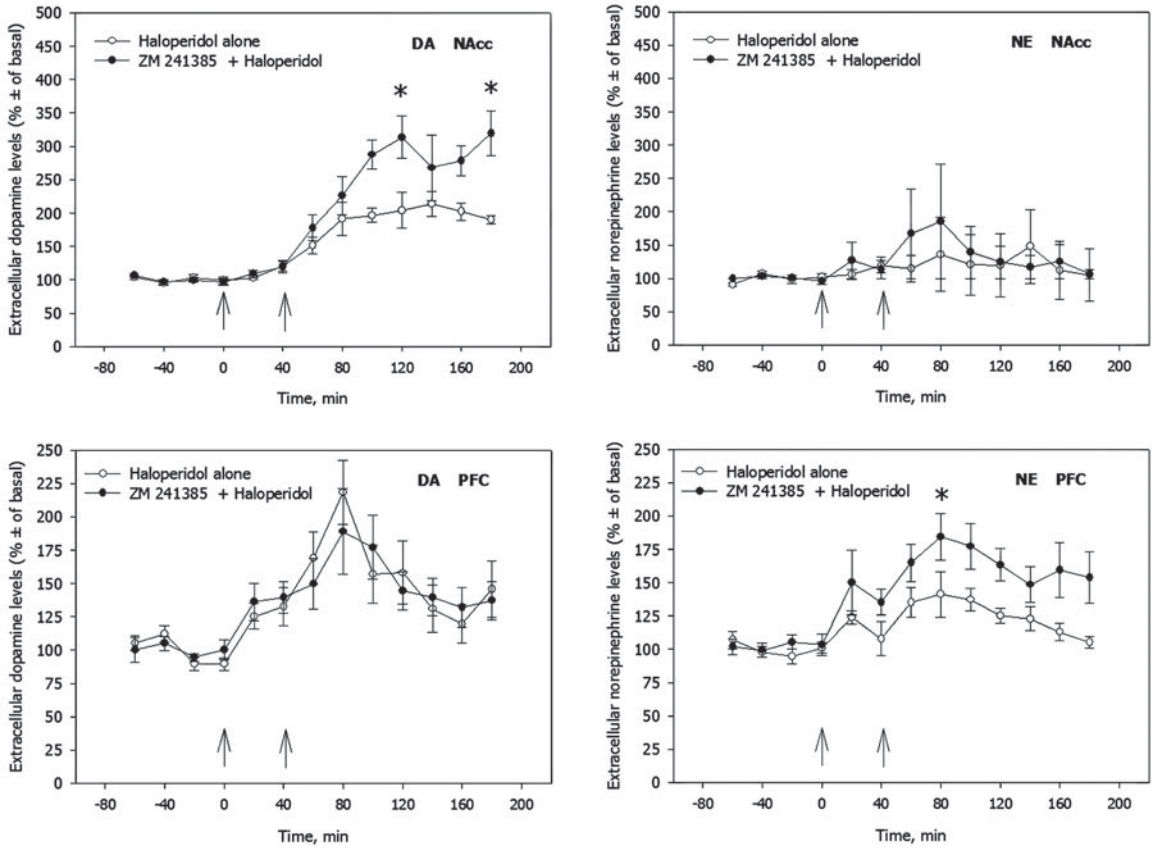
Objective: The aim of the current study was to investigate potential interactions between A2A and Alpha2A-adrenergic receptors and their putative role in antipsychotic drug response.

Methods: Male Wistar rats (300–350 g) were used in the experiments. In-vivo electrophysiology, under propofol (1.2 mg/kg/min, i.v.) anesthesia, was used to assess the firing activity of norepinephrine neurons in the locus coeruleus (LC). In-vivo microdialysis (in freely-moving rats) was used to assess dopamine and norepinephrine levels in the nucleus accumbens (NAcc) and prefrontal cortex (PFC). Microdialysis probes were implanted under isoflurane anesthesia, 24 hours prior to the experiment. The levels of catecholamines in dialysates were assessed using the high-performance liquid chromatography (HPLC) and electrochemical detection.

Results: The mean basal firing rate of norepinephrine neurons was 2.87$\pm$1.54 Hz. Selective agonist of A2A receptors, CGS 21680 (0.05–0.5 mg/kg, i.v.), significantly and dose-dependently decreased the firing rate of norepinephrine neurons (to 25% of baseline). Subsequent administration of the selective antagonist of A2A receptors, ZM 241385 (0.1–1 mg/kg), partially recovered the firing rate (to 50% of baseline). Finally, injection of clonidine (0.02 mg/kg) almost completely (>90%) inhibited norepinephrine neurons in the LC. Haloperidol (1 mg/kg, s.c) significantly increased dopamine levels in NAcc and PFC; norepinephrine levels were not altered. Pretreatment with ZM 241385 (0.5 mg/kg, i.p., 40 min prior to haloperidol administration) resulted in significant increase in norepinephrine levels in the PFC and in potentiation of haloperidol-induced elevation of dopamine levels in the NAcc (Figure 1).

Conclusion: CGS 21680 inhibits the firing rate of norepinephrine neurons; this inhibition is reserved by ZM 241385. ZM 241385 potentiates the effect of haloperidol on dopamine levels in the NAcc



and norepinephrine levels in the PFC. Antagonists of A2A receptors may be thus beneficial as adjuncts to antipsychotic drugs.

P-01-004 Metabolic syndrome in a sample of drug-naive egyptian patients with psychotic disorders

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Objective: The main objective of this study is to determine the rate of occurrence of metabolic syndrome (MetS) in a sample of drug-naive patients with psychotic disorders compared with a matched control group and to identify the significant criteria for this diagnosis.

Methods: This study is designed as a preliminary cross-sectional case–control study. Twenty patients were selected from inpatient psychiatric units at the Institute of Psychiatry, Ain Shams University, Cairo, Egypt, with an established diagnosis of acute psychosis or first episode schizophrenia according to ICD-10 classification during a period of 6 months and matched with 20 controls. The case group was assessed by a semistructured psychiatric interview sheet of the Institute of Psychiatry, Ain Shams University, and both the groups were subjected to measurements of (a) waist circumference (WC) and BMI and (b) laboratory investigations including an oral glucose tolerance test (OGTT), HDL and triglycerides, and (c) blood pressure measurements.

Results: MetS was detected in seven (63.6%) patients with schizophrenia, one (33.3%) patient had acute psychosis, four patients had unipolar depression, and only one had bipolar affective disorder compared with 7 (35%) participants in the control group. In addition, WC, BMI, and OGTT were found to be significantly correlated to development of MetS in the studied sample.

Conclusion: Drug-naive patients are more likely to develop metabolic changes; in addition impaired OGTT, increased WC, and obesity (BMI430 kg/m2) are significant predictors of developing MetS among patients with psychotic disorders even before starting their antipsychotic medications.

P-01-005 High doses of long acting atypical antipsychotics: Role in a severe mentally illness treatment retention

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Objective: To know the retention in treatment of severe mentally ill patients and the role of long acting atypical antipsychotics, taking into account high doses tolerability.

Methods: 3-year prospective, observational study of patients undergoing specific severe mental illness programme (September 2007 to September 2011). (N = 319; 44.2% of them with schizophrenia). Assessment included the Clinical Global Impression (CGI) severity scale, the WHO Disability Assessment Schedule (WHO/DAS), the Camberwell Assessment of Need (CAN), laboratory tests and weight, at the beginning and after three years of follow-up. Time in treatment, reasons of discharge, medications used and hospital admissions were registered.

Results: CGI at baseline was 5.72 + / − 0.8; After three years 35.7% of patients continued under treatment (CGI = 4.11 + / − 0.9; $p < 0.01$); 40.4% were medical discharged (CGI = 3.14 + / − 1.3; $p < 0.001$); DAS also decreased in the four areas (self-care and employment $p < 0.01$; family and social $p < 0.005$) and also CAN ($p < 0.01$) ; 8.5% had moved to other places; 14.1% were voluntary discharges. There were significant less hospital admissions than during the 18 months previous treatment ($p < 0.001$). Four patients dead. Time in the Programme was 23 + / − 7.1 months. 43% of patients received risperidone longacting inyectable (RLAI) (109.7 + / − 19 mg/14 day). Tolerability was good and there were almost no discharges (4.2%) due to side effects or to relevant biological parameters alterations or weight gain.

Conclusion: Retention of patients with severe mental illness in a specific programme was high. And the use of long acting atypical antipsychotics in patients who had needed high doses (over 75mg/14 day of RLAI) to get clinical stabilization and better functioning seemed to be useful in improving treatment adherence, due to their high tolerability.

P-01-006 The effect of clozapine on white matter in schizophrenia: A diffusion imaging and tractography study

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Objective: The pathophysiology of schizophrenia has been associated with structural brain changes and clozapine, an effective antipsychotic medication has been suggested to have neuroprotective effects in preclinical studies. However in vivo imaging studies report a decline in brain volume as a result of long-term clozapine use. Herein we explicitly test the effect of 6 months of treatment with clozapine on white matter organization quantified as fractional anisotropy (FA).

Methods: Twenty-one chronic treatment resistant individuals with schizophrenia(SZ, 16 male, mean-age = 35 ± 9) and twenty-one age- and gender-matched controls (HC, 12 male, mean-age = 39 ± 10) underwent psychiatric clinical assessment and diffusion-MR scanning before and after either six months of treatment with the atypical antipsychotic clozapine or no treatment, respectively. Analysis of FA included voxel-based (TBSS) and tractography (ExploreDTI).

Results: The SZ-group improved clinically by an average of 21-points(±13.53%) on the positive and negative syndrome scale (PANSS) from baseline (45 ± 14) to follow up (24 ± 16). Compared with baseline, patients treated with clozapine displayed reduced FA in the genu and body of the corpus callosum, the cingulum bundle, and anterior superior longitudinal fasciculus (SLF). There were no significant FA changes in the HC group. Tractography detected reduced mean tract FA in the genu following treatment with clozapine (DTI: 1.49%, $t(19) = 2.58$, $p = 0.018$; CSD:3.13%, $t(20) = 2.40$, $p = 0.026$) but not in the HC group (DTI: 0.20%, $t(19) = 0.51$, $p = 0.62$; CSD: 0.72%, $t(20) = 0.77$, $p = 0.45$).

Conclusion: Patients treated with clozapine for 6 months display reduced microstructural organization of the commissural fibers, cingulum bundle and SLF. It remains unclear whether this represents a side-effect or mechanistic element of clozapine treatment or a manifestation of illness progression, in which case clozapine does not reverse or halt microstructural disorganization in schizophrenia. CSD-based proved more sensitive than did tensor-based tractography in detecting these changes.

P-01-007 Involvement of 5-HT2A receptor and a2-adrenoceptor blockade in the asenapine-induced elevation of prefrontal cortical monoamine outflow

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Objective: The psychotropic drug asenapine is approved for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. Asenapine exhibits higher affinity for several 5-HT receptors and α2-adrenoceptors than for D2 receptors. Noteworthy, both blockage of 5-HT2A and α2-adrenergic receptors has been shown to enhance prefrontal dopamine release induced by D2 receptor antagonists. Previous results show that asenapine, both systemically and locally, increases dopamine, noradrenaline and serotonin release in the medial prefrontal cortex (mPFC), and that the increased dopamine release largely depends on an intracortical action.

Methods: Using reverse microdialysis in freely moving rats, we here assessed the potency of low concentrations of asenapine to cause a pharmacologically significant blockage in vivo of 5-HT2A/2C receptors and α2-adrenoceptors within the mPFC, and thus its ability to affect cortical monoamine release by these receptors.

Results: Intracortical administration of DOI, a 5-HT2A/2C receptor agonist, increased cortical monoamine release, effects that were antagonized both by asenapine and the selective 5-HT2A antagonist M100907. Application of clonidine, an α2-adrenoceptor agonist, significantly reduced monoamine release in the mPFC. The selective α2-adrenoceptor antagonist idazoxan blocked, whereas asenapine partially blocked clonidine-induced cortical dopamine and noradrenaline decrease. The effects of asenapine and idazoxan on clonidine-induced serotonin decrease were less pronounced.

Conclusion: Our results propose that low concentrations of asenapine in the mPFC exhibit a pharmacologically significant 5-HT2A and, to a weaker extent, α2 receptor antagonistic activity, which may contribute to enhance prefrontal monoamine release in vivo and, secondarily, its clinical effects in schizophrenia and bipolar disorder.

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P-01-008 Defined daily dose system as a tool for standardizing antipsychotic dosages. Reliability in high dose users

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Objective: There is a report that found the Defined Daily Doses (DDDs) system as a reliable tool for standardizing antipsychotic doses in drug utilization research (Nose et al., 2008). However, this study was based upon a population receiving a wide range of antipsychotic doses, with few of them being prescribed high doses defined as 1000 mg o more chlorpromazine equivalents (CPZEs) thus limiting the results. The aim of this study was to establish whether the DDDs system could be reliably applied to standardize antipsychotic dosages, focusing in high dose antipsychotic users.

Methods: The study was done in the Neuropsychiatric Hospital Dr. Alejandro Korn, Argentina. Data was esxtracted from clinical records on a census day 14th december 2009. The relationship between antipsychotic doses expressed as DDDs, CPZEs and percentages of the British National Formulary (BNF) maximum recommended daily dose were investigated by calculating Spearman's rank correlation coefficients. it was approved by an Independent Ethic Committee.

Results: The study sample were all of the167 inpatients with schizophrenia receiving > = 1000 mg CPZEs. Relationship between antipsychotic daily doses expressed as multiples of DDDs and CPZEs revealed a significant correlation (Spearman's rho = 0.983, $P < 0.001$). Similarly, the relationship between antipsychotic daily doses expressed as multiples of DDDs and percentages of the BNF maximum recommended daily dose revealed a significant correlation (Spearman's rho = 0.920, $P < 0.001$). We also analyzed both relationships in the 239 schizophrenic inpatients with low and medium antipsychotic doses showing similar significant positive correlations.

Conclusion: In conclusion, this study found that the DDD system is a reliable tool to standardize antipsychotic dosages even in the subpopulation on high dose regimens.

P-01-009 Prescription patterns in chronic psychiatric hospitalization: 1995–2009 comparison

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Objective: The aim was to identify changes in prescription patterns for patients with chronic hospitalization between two different periods in terms of availability of psychotropics, 1995 when clozapine was the only atypical antipsychotic and 2009 when there was access to a wider range of these drugs.

Methods: The study was performed at the Alejandro Korn Hospital, Argentina. All inpatients in the chronic rehabilitation wards were included on both census days 15–06–1995 and 14–12–2009. Data was extracted from clinical records. The study was approved by an Independent Ethics Committee.

Results: The total number of inpatients dropped from 1048 to 648 between 1995 and 2009. Mean age increased from de 52,9 to 58 years

and male population grew up from 44.2% to 57.2%. The most prevalent diagnoses were Schizophrenia and Mental Retardation with 45% and 28% respectively in 1995, and 40% and 31% in 2009. The length of hospital stay was above 20 years in almost 30% of the patients in both census. The mean antipsychotic dose was similar in both periods, 600 mg chlopromazine equivalents. The proportion in each census of schizophrenic (89% and 93%) and mental retardation patients (79% and 80%) receiving antipsychotic agents, was preserved. The rate of antipsychotic polypharmacy dropped. However, in both periods 53% of the patients with schizophrenia were prescribed 3 or 4 psychotropics agents simultaneously. Haloperidol was the most frequently antipsychotic used in both samples, and was prescribed to over 30% of the inpatients. The rate of patients with general clinical medications was higher in 2009 than 1995 (37.1% and 27.1% respectively).

Conclusion: In conclusion, there is an aging of the population of inpatients and a reversion in the gender distribution with a greater proportion of males in 2009. There are no significant changes in the overall prescription patterns despite the availability of different atypical antipsychotics in 2009 census.

P-01-010 Epidemiology of antipsychotic-induced hyperpolactinemia in psychiatric in-patients

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Objective: To evaluate prevalence of antipsychotic-induced hyperpolactinemia (AIH) in psychiatric in-patients.

Methods: Cross-sectional study in 143 psychiatric in-patients (F:M = 65:78) treated with antipsychotics, mostly for schizophrenia (93%). The patients were screened for serum prolactin and macroprolactin. Data is shown as median [1, 3 quartile]. Odds ratios (OR) for AIH with various antipsychotics were calculated, compared to AIH with haloperidol.

Results: Overall AIH prevalence was 57.0% (F, 72.0%; M, 43.6%). Macroprolactin was found in one patient only (2.0%). Prolactin levels inversely correlated with duration of mental disorder in women ($r = -0,3$, $p = 0.02$), but not in men. AIH prevalence in women with disease duration of <9 yrs was higher (85%) than in women with disease duration of $\geqslant 9$ yrs (60%, $p = 0.02$). AIH prevalence in men of 19–34 yrs was higher (57%) than in men of 35–45 yrs (28%, $p = 0.01$). In order of OR for AIH, antipsychotics ranged as follows: 1, risperidone (OR = 12.5); 2, amisulpride (OR = 6.3); 3, olanzapine (OR = 2.2); 4, thioridazine (OR = 1.4); 5, chlorpromazine (OR = 1.2); 6, clozapine (OR = 1.1); 7, trifluoperazine (OR = 1.0); 8, fluphenazine, zuclopenthixol, periciazine (OR = 0.9 each); 9, chlorprothixene (OR = 0.8); 10, perphenazine (OR = 0.6); 11, quetiapine and aripiprazole (OR = 0.5 each). With risperidone, AIH was most probable both in men and women (OR = 10.3 and 3, respectively). Besides, in men, AIH was predominantly associated with amisulpride and olanzapine (OR = 5.7 each), in women, with sertindole and sulpiride (OR = 1.4 each).

Conclusion: AIH found at screening is more than 1.5-fold prevalent than that diagnosed by referral (39%). In patients with AIH, measurement of macroprolactin is unnecessary. Men at risk for AIH belong to a younger age group, women at risk have shorter duration of mental disorder. The results cannot be fully explained by preferential use of atypical antipsychotics in the respective age and/or disease duration groups.

P-01-011 Thyrotoxicosis presenting with capgras delusion-a case report

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Objective: Psychiatric manifestations of hyperthyroidism are usually anxiety and depression. Psychosis is rare and affects around 1%.

Methods: Single case report.

Results: We present a 54 year old lady with hyperthyroidism who presented with psychosis as well as Capgras delusions. The symptoms resolved with correction of her hyperthyroid status and low doses of risperidone which was stopped after discharge.

Conclusion: Psychosis can be a rare presentation for patients with hyperthyroidism and it is important for clinicians to be aware of this.

P-01-012 Cost minimization analysis comparing paliperidone palmitate with risperidone long-acting injectable in Spain

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Objective: Estimate the savings produced by the use of Paliperidone Palmitate (PP) instead of Risperidone Long-Acting Injectable (RLAI) when treating schizophrenia patients, from the perspective of the Spanish National Health System.

Methods: The cost-minimization analysis used in the SMC (Scottish Medicine Consortium) evaluation was adapted for the treatment of patients with schizophrenia in Spain. Only direct costs were included: (1) medication costs (including oral antipsychotic drug supplementation cost) and (2) cost of administration in the community. Two different time horizons were used: 1 year (to compare initiation treatment) and 2 years (to compare maintenance treatment). The following assumptions were used for the base-case: (1) 50% of the patients initiate treatment in hospital and 50% in community; (2) 50% of patients initiate treatment from a long-acting injectable and 50% from an oral antipsychotic; (3) no reduction in the length of stay.

Results: PP use could save €648 per patient during the first year of treatment compared to RLAI. From the second year the saving could be €906 per patient/year also in favour of PP. These savings are mainly due to (1) lower drug cost of PP vs. RLAI in the community setting, (2) fewer visits to Community nurses for drug administration. Sensitivity analyses were done for the main parameters of the model and confirmed the robustness of the results, even in the most unfavourable scenarios: if 100% of the patients (1) initiate treatment in hospital the savings could be €628 per patient/year, (2) initiate treatment from an oral antipsychotic the savings could be €418 per patient/year. If PP could reduce the length of stay by approximately one third, as some studies indicate (SMC, Crivera), the savings could be €1,707 per patient/year.

Conclusion: To treat patients with PP instead of RLAI could be a cost-saving strategy for the Spanish National Health System.

Policy of full disclosure: This study was supported by Janssen.

P-01-013 Incidence and time course of extrapyramidal symptoms: A comparison of oral and long-acting injectable paliperidone randomized controlled studies

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Objective: To compare incidence and time course of extrapyramidal symptoms-related (EPS) adverse events (AEs) between oral and long-acting injectable (LAI) paliperidone.

Methods: Analysis included pooled data (safety analysis set; n = 2256 for non-placebo treated patients) from randomized, double-blind and controlled paliperidone studies (3 oral [6-wks each]; 4 LAI [13-wks each]), and assessed comparable doses (oral: 3–15 mg; LAI: 25–150 mg eq [US doses 39–234 mg] intramuscularly). We summarized incidence rates and time of onset for EPS-related AEs, categorized by MedDRA EPS group terms as tremor, dystonia, hyperkinesia, parkinsonism, and dyskinesia. Mean values over time for AIMS (Abnormal Involuntary Movement Scale; dyskinesia), BARS (Barnes Akathisia Rating Scale; akathisia) and SAS (Simpson Angus Rating Scale; parkinsonism) were graphed.

Results: Mean reductions (SD) from baseline to endpoint in EPS scores were larger for LAI (AIMS: −0.10[1.27]; BARS: −0.09[1.06]; SAS: −0.04[0.20]) vs. oral studies (AIMS: −0.08[1.32]; BARS: −0.03[1.24]; SAS: 0.0[0.23]). These differences favored LAI for BARS ($P = 0.023$) and SAS ($P < 0.0001$) but not AIMS ($P = 0.49$). Anticholinergic use (to treat EPS) was lower in LAI (12%) vs. oral studies (17%). Incidence for all categories of spontaneously reported EPS-related AEs was highest in the first 8 treatment days though generally lower for LAI than oral. Mean values for EPS scale scores were comparable (LAI and oral) without evidence of a dose response; scores increased between days 8–15 in LAI, but not oral studies.

Conclusion: Incidence of spontaneously reported EPS-related AEs was similar following approximately 90 days exposure with LAI and 40 days of oral paliperidone, at comparable doses.

Policy of full disclosure: All authors are full-time employees of Johnson & Johnson.

P-01-014 Clinical and sociodemographic characteristics of 140 male patients treated with long-acting risperidone during period of 4 years

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Objective: Risperidone long-acting injection is momentarily only long-acting second generation antipsychotic reimbursed in Croatia and it is registered for treatment of positive and negative symptoms of schizophrenia. Risperidone long-acting injection (RLAI) has been shown to improve clinical parameters, to decrease relapse rate and increase adherence in patients suffering from psychotic disorders. Objective of this poster is to describe demographic and clinical features of acute psychiatric ward male patients, who were in everyday practice clinically estimated as suitable for risperidone long-acting injection treatment.

Methods: Research included all patients treated with risperidone long-acting injection, in inpatient and outpatient setting of acute male ward of Psychiatric Hospital ''Sveti Ivan'' in Zagreb, Croatia, over time period of 4 years. Patients have been diagnosed by criteria of International Classification of Diseases (ICD), 10th revision. Data were collected by computerized search of digitalized medical records of Psychiatric Hospital ''Sveti Ivan''.

Results: Research sample included 140 male patients, in age range from 21 to 70 years. Results will be available next month and they will describe and show patients family status, education, place and conditions of living. They also show diagnoses, earlier antipsychotic medication and concomitant medication.

Conclusion: Poster data represent overview of our clinical experience with risperidone long-acting injection in naturalistic setting of an acute male ward in psychiatric hospital, over period of 4 years. Presented data describe demographic and clinical features of patients who were considered to be suitable for risperidone long-acting injection treatment and who were expected to gain benefit from it.

P-01-015 Effective pharmaceutical care by pharmacists in psychiatric medication therapy

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Objective: Evaluation in the pharmaceutical care by pharmacists on physician's prescriptions for mental illness.

Methods: -Design- Seventeen inpatients with schizophrenia who are given polypharmacy and/or excessive dose of antipsychotics are described. Interventions to correct medication-related problems in these patients are described. -Setting- Inpatients psychiatry service in Sawa hospital in Japan -Patients- Subjects are inpatients with chronic antipsychotics therapy. Average age is 49.2 years (SD = 15.0, n = 17) and duration of schizophrenia is 26.3 years (SD = 13.5, n = 17). Pharmacists monitored the prescriptions and the patient's outcomes. If the results end up failing, pharmacists intervene in them actively. -Interventions- We performed to optimize and/or simplify a formula in subjects who take polypharmacy and/or excessive dose of antipsychotics and to monitor side effects.

Results: Of the 14 patients, the number of antipsychotics (from 3.1 (SD = 1.2) to 1.2 (SD = 0.4) medications) and dose (from 1775.8 mg (SD = 744.8) to 594.8 mg (SD = 320.4) as chlorpromazine equivalent), were reduced and leaded to monotherapy in 12 patients. Reducing the dose of antipsychotics is attributed to decreasing the side effects as well as improving psychotic symptoms.

Conclusion: In the pharmaceutical care, medication-related problems are prevalent in psychiatric patient, contributing to polypharmacy and/or excessive dose. In this clinical practice, interventions by pharmacists on physician's prescriptions are performed. Thereby reducing polypharmacy can lead to decreasing the side effects as well as improving psychotic symptoms.

P-01-016 Psychopharmacology and psycopathology of dopeminergic system

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Objective: It is well known that psychotropic agents, which block the dopaminergic system, show remarkable effects in schizophrenia especially in those cases with positive symptom. Moreover, the equivalent amount of psychotropic agents actually works extremely well in dissociative identity disorder (multiple personality disorder) as well. There is also a certain amount of medical literature stating that anti-dopaminergic psychotropic agents are effective in the treatment of pathological gambling (compulsive gambling).

Methods: I experienced two cases of dissociative (conversion) disorders treated with haloperidol effectively. I introduce it in detail and consider their pharmacological/biologic bases and psychopathological bases as well as schizophrenia.

Results: They can be said that the development of schizophrenia, dissociative identity disorder (multiple personality disorder), and pathological gambling (compulsive gambling) somehow involves the dopaminergic system.

Conclusion: If so, what is the psychopathological feature common to these pathologies which involve the dopaminergic system in their development? The objective of this article is to start discussion of the psychopharmacology (psychobiology) of the dopaminergic system from this point. Schizophrenia.

P-01-017 Dose of atypical antipsychotic drugs and cognitive impairments in schizophrenia patients: Aripiprazole has different cognitive profile from other atypical antipsychotics?

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Objective: We investigated the effects of the atypical antipsychotics risperidone, olanzapine, and aripiprazole on cognitive functions in Japanese patients with schizophrenia from the view point of dosing schedule.

Methods: We performed a cross-sectional survey. Neurocognitive functions were evaluated using the Brief Assessment of Cognition in Schizophrenia, Japanese-language version (BACS-J) in 101 schizophrenia patients who were maintained with the same dose of one of the three above-named antipsychotics for at least 3 months.

Results: The BACS-J composite score was significantly correlated with the dosage of risperidone and olanzapine. On the other hand, no correlation was found between the BACS-J composite score and the dosage of aripiprazole. Moreover, the primary scores of verbal learning, motor function and attention and processing speed were significantly negative correlated with the dose of risperidone. The scores of verbal learning and motor function were also significantly negative correlated with the dose of olanzapine. No correlation was found between any scores of the BACS-J and the dose of aripiprazole.

Conclusion: Aripiprazole had a different pattern of relationship between doses and cognitive impairments, which might be due to its unique pharmacological profile.

P-01-018 Dopamine D2 receptor occupancy with risperidone long-acting injectable during maintenance treatment in schizophrenia: A cross-sectional study

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Objective: While 65–80% occupancy of dopamine D2 receptors with antipsychotics has been proposed to achieve optimal therapeutic response during acute treatment of schizophrenia, it remains unclear as to whether it is also necessary to maintain D2 receptor occupancy within this ''safe'' window for ongoing maintenance treatment. The data are especially scarce for long-acting antipsychotic formulations.

Methods: Clinically stable patients with schizophrenia (DSM-IV) receiving a stable dose of Risperidone Long-acting Injectable (RLAI)

as antipsychotic monotherapy for at least three months and free of any psychiatric hospitalization over the past six months were included. Dopamine D2 receptor occupancy levels at trough were estimated from plasma concentrations of risperidone plus 9-hydroxyrisperidone immediately before the intramuscular injection of RLAI, using a one-site binding model derived from our previous positron emission tomography data.

Results: 36 patients were included in this study (mean ± SD age, 49.3 ± 14.0 years; mean ± SD dose and interval of injections, 38.2 ± 11.6 mg and 16.5 ± 14.0 days, respectively). Mean ± SD D2 receptor occupancy was 62.1 ± 15.4 %; 52.8 % of the subjects (N = 19) did not demonstrate an occupancy of ⩾65 %. On the other hand, 13.9 % (N = 5) showed a D2 occupancy as high as over 80 % at the estimated trough.

Conclusion: More than half of patients on RLAI maintained clinical stability without achieving continuous blockade of dopamine D2 receptors > 65 % in real-world clinical settings. Results suggest that sustained dopamine D2 receptor occupancy levels of ⩾65 % may not be necessary for maintenance treatment with RLAI in schizophrenia.

P-01-019 Paliperidone in the treatment of hebephrenic type of schizophrenia

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Objective: Hebephrenic Schizophrenia is the type of the schizophrenic disorders range with the worst prognosis, given that it is related to disorganized behavior and residual symptoms, despite the relative absence of delirious ideas and delusions. Paliperidone (9-OH Risperidone), a metabolite of risperidone, blocks D2 Dopamine-receptors and 5HT-2A Serotonin receptors. The aim of the study is to elevate the effectiveness of Paliperidone for the treatment of Hebephrenia.

Methods: 20 patients (n = 20), 12 male and 8 female were studied in the inpatient facility and the outpatient setting of the Psychiatric Department of ''Konstatopouleio'' General Hospital, Nea Ionia, during the years 2009 and 2011. All patients received Paliperidone, in monotherapy, at a dose of 9–12 mg. The above patients were given the PANSS (Positive and Negative Symptoms in Schizophrenia), CGI-S (Clinical Global Impression of Severity), and QOL (Quality of Life) Scales before commencing treatment with Paliperidone, and again after 30 and 45 days of Paliperidone reception commencement. The age range of the patient sample was 18–31 years.

Results: 16 patients (85 %) out of 20 patients (n = 20), PANSS scoring reduced. 10 out of 16 patients (n = 16) were male and 6 female. On the remaining 4 patients (15 %), PANSS scores remained unchanged after 30 and 45 days of treatment. This effect urged the change of medication, or the addition of different antipsychotic medication. On the 16 patients above, CGI-S was reduced from 5 to 3.1, while QoL Scale scores also improved. Of those patients that interrupted treatment and showed adverse effects, 2 women showed galactorrhoea with an increase of prolactin, and 2 men showed severe insomnia and EPS. None of the 20 patients given Paliperidone treatment showed any cognitive deficits.

Conclusion: Paliperidone is known to be a safe and effective medication for the treatment of Hebephrenia. The release of long-action Paliperidone may also prove an effective treatment for this resistive form of schizophrenia.

P-01-020 Psycopharmacological treatment of cycloid psychosis

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Objective: INTRODUCTION: The concept of cycloid psychosis, pertains to particular types of acute, episodic, polymorphic psychotic disorders, which are, frequently, diagnosed by the formal diagnostic systems as either brief psychotic disorder, schizophreniform disorder or psychotic disorder not otherwise specified. Three overlapping cycloid subtypes (anxiety-happiness psychosis, confusion psychosis, and motility psychosis) have been described, representing a valid clinical construct that can be easily differentiated from the boundary disorders on clinical grounds. The favourable prognosis of this acute psychotic disorder in the long-term, makes it necessary to emphasize in the importance of the accurate diagnosis and the appropriate therapeutic approach. OBJECTIVES: To review in the bibliographic literature the psychopharmacological treatment of the cycloid psychosis and present a case report that exemplifies its clinical features.

Methods: A bibliographic search is made in PUBMED and CSIC database including the terms cycloid psychosis, looking for all the literature that contains scientific evidence about its pharmacological treatment. A case report is attached.

Results: – No controlled studies of cycloid psychosis treatment have been conducted to date; this being mainly due to the fact that the disorder remains largely unrecognized in the formal diagnostic systems.Data on treatment is based on clinical experience, uncontrolled studies, and anecdotal case reports. – Controversy in the use of pharmacological treatment in the acute episode and as a maintenance therapy. – Antipsychotics seem to be effective in aborting the episode, as we could see in the case report presented, but their potential to reduce relapse rates remains unclear. – Other treatments described: Electroconvulsive therapy, benzodiazepines, lithium and estradiol substitution.

Conclusion: The treatment with low-doses of atypical antipsychotics is a good alternative in the acute treatment of cycloid psychosis. – Future studies on the psychopharmacological treatment of this specific group of patients would be useful to ensure the appropriate therapeutic approach.

P-01-021 Simulation of dopamine D2 receptor occupancy by aripiprazole in steady state: Based on PK-PD modeling

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Objective: Receptor occupancy study has been performed to evaluate pharmacokinetic profiles in antipsychotic drug development. In particular, dopamine D2 receptor occupancy is a meaningful biomarker in that it reflects the antipsychotic action at the target site in the brain and predicts both the clinical response to antipsychotic drugs and the emergence of drug side effects. The importance of measuring dopamine D2 receptor occupancy by a novel antipsychotic drug is further emphasized by studies showing wide discrepancy between the time courses of drug concentration in plasma and receptor occupancy in the brain. While these findings highlight the value of measuring receptor occupancy in dose-finding study, a challenge is the impossibility of obtaining as many receptor occupancy data as would be necessary to design clinical trials with various dosing strategies. This raises the necessity of in-silico simulation of dopamine receptor occupancy by antipsychotic drugs.

Methods: We previously reported a novel methodology using pharmacokinetic-pharmacodynamic (PK-PD) modeling for the concentration-occupancy relationship analysis and estimated parameters for the PK-PD model after single administration of aripiprazole (J Cereb Blood Flow Metab. 2011 Dec 21. doi: 10.1038/jcbfm.2011.180.). Based on the parameter estimates from the PK-PD model, we simulated dopamine D2 receptor occupancy by aripiprazole in steady state.

Results: In the case of once-a-day dosing schedule, the simulation shows that dopamine D2 receptors would be almost fully occupied in steady state even with 10mg of aripiprazole. In addition, the fluctuation index (=(maximal level-tough level)/trough level) in steady state was lower than 5 % in occupancy while higher than 100 % in plasma concentration. These findings suggest that aripiprazole is likely to be given with higher dose and shorter interval than is required for the treatment of schizophrenia in terms of receptor occupancy.

Conclusion: This study shows in-silico simulation based on the PK-PD modeling can be useful for exploring appropriate doses for antipsychotic drugs.

P-01-022 Association of antipsychotic-induced akathisia with dopamine D2/3 receptor occupancy in ventral striatum: A high-resolution PET study with [11C]raclopride

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Objective: The neurobiological basis of akathisia is not well understood, although the strong affective component suggests that it is of a central origin. The authors examined the relationship between antipsychotic-induced akathisia and dopamine D2/3 receptor occupancy in striatal subdivisions using high-resolution positron emission tomography (HRRT) with [11C]raclopride to better understand its underlying neurochemical mechanism.

Methods: Twenty-one schizophrenic patients receiving stable doses of antipsychotics and 24 age- and gender-matched normal controls completed 3-Tesla magnetic resonance imaging and HRRT scans with [11C]raclopride in order to measure D2/3 receptor binding potential (BPND) in the striatum. The D2/3 receptor BPND was obtained using Logan graphical analysis with reference region input and receptor occupancy was calculated as the percentage reduction of receptor BPND with drug treatment relative to baseline. The data obtained from age- and gender-matched normal controls were used as an estimate of the patients' baseline, as previously proposed. Antipsychotic-induced akathisia was measured with the Liverpool University Neuroleptic Side-Effect Rating Scale. The striatum was divided into 5 anatomic regions of interests (ROIs), including the ventral striatum (VST), the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the post-commissural caudate (postCA), and the post-commissural putamen (postPU). Pearson's bivariate product-moment correlations were calculated between akathisia score and D2/3 receptor occupancy in subregions of the striatum. The strict level of significance for the analysis of 5 ROIs was adjusted as $p < 0.01$ using Bonferroni correction.

Results: The analysis revealed that akathisia score had significant positive associations with D2/3 occupancy only in the VST ($r = 0.56$, $p = 0.009$).

Conclusion: These results suggest that akathisia is significantly associated with D2/3 receptor blockade in the limbic subdivision of the striatum, i.e., VST, which plays a crucial role in the regulation of affect and motivation.

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P-01-023 Paliperidone ER versus risperidone for neurocognitive function in patients with schizophrenia: A randomized, open-label, controlled trial

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Objective: No direct clinical comparison between paliperidone extended-release (ER) and risperidone regarding cognitive function has been published. This study aims to determine the effectiveness of paliperidone ER on cognitive function in patients with schizophrenia in comparison to risperidone.

Methods: This was a 12-week, randomized, open-label study in schizophrenia patients who were receiving risperidone. The patients were randomized to a risperidone-continuation group or a paliperidone-switch group. The primary outcome measure was neurocognitive function, which was measured with a computerized battery. Secondary efficacy measures included the Positive and Negative Syndrome Scale, Social and Occupational Functioning Scale (SOFAS), and Calgary Depression Scale for Schizophrenia. Safety measures included extrapyramidal symptoms and laboratory measures.

Results: Fifty-eight subjects participated in this trial. The mean dose at endpoint was 4.9 mg/day for risperidone and 9.0 mg/day for paliperidone ER. The improvements in the recall following an interference phase on the verbal learning test were significantly greater in the paliperidone-switch than in the risperidone-continuation group. In the other six domains of neurocognitive measures, significant differences of changes were not observed. Improvements in the SOFAS were significantly greater in the paliperidone ER-switch group than in the risperidone-continuation group. In other efficacy outcome measures, no significant differences were observed between the two drugs. Paliperidone ER had a similar side effect profile to risperidone, including metabolic problems and prolactin-related adverse events.

Conclusion: Switching from risperidone to paliperidone ER may produce additional cognitive and social functional improvements.

Policy of full disclosure: This study was supported in part by an investigator-initiated grant from Janssen Korea Co. Ltd. Representatives of the company were allowed to comment on the report, but the final approval of content was retained by the investigators exclusively.

P-01-024 The effect of paliperidone ER on subjective well-being and attitudes toward medication among patients with schizophrenia

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Objective: This study aims to evaluate the subjective well-being and attitudes toward antipsychotic medication of patients with schizophrenia who had switched to paliperidone extended release (ER).

Methods: A total of 291 patients with schizophrenia treated with antipsychotics participated in this open-label, 24-week switching study. The primary outcome measures were the Subjective Well-Being under Neuroleptic Treatment Scale-short version (SWN-K) and the Drug Attitude Inventory (DAI).

Results: Data from a total of 243 subjects who received the study medication and had at least one follow-up assessment without a major protocol violation were analyzed. Scores on the DAI and SWN-K showed significant improvement between baseline and end-point measurements beginning during the second week. Scores on the Krawiecka scale, all five subscales of the Clinical Global Impression-Schizophrenia scale, and the Personal and Social Performance scale were also significantly improved at the end point compared with the baseline. Scores on the DAI and total SWN-K scores were significantly improved in subjects who were previously treated with risperidone but not in those who were previously treated with other antipsychotics.

Conclusion: Paliperidone ER was effective for improving the subjective well-being and attitudes toward antipsychotic medication of patients with schizophrenia, particularly those who had been previously treated with risperidone.

Policy of full disclosure: This study was supported in part by an investigator-initiated grant from Janssen Korea Co. Ltd. Representatives of the company were allowed to comment on the report, but the final approval of content was retained by the investigators exclusively.

P-01-025 Effectiveness of long-acting risperidone for patients with treatment refractory schizophrenia

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Objective: Up to 30–60% of patients with schizophrenia do not respond sufficiently to antipsychotics. Treatment-resistant Schizophrenia (TRS) can have several reasons, including early onset, nonadherence to oral medication regimens, and persistent negative symptoms known as deficit syndrome. Recently, dopamine supersensitivity psychosis (DSP) and tardive dyskinesia (TD), both of which

could be caused by inappropriate pharmacotherapy, as typified by excessive dosages of antipsychotics, have also been presumed relevant to TRS. Several lines of evidence suggest that both DSP and TD are closely linked to the supersensitivity of dopamine D2 receptors; this could be caused by a potent blockade of the receptors by antipsychotics. Several studies have reported that risperidone long-acting injection (RLAI) successfully reduced antipsychotic dosage and extrapyramidal symptoms, as well as relapse rate. Furthermore, some reports suggested greater improvement in the psychotic symptoms in RLAI compared to oral medication. We have therefore hypothesized that RLAI with narrower blood kinetics than oral medication could provide a continuous optimal blockade of dopamine D2 receptors, leading to the prevention and/or improvement of the supersensitivity state of the receptors.

Methods: Here we try to verify RLAI's effectiveness in a TRS group, including patients with a background of DSP. This study, which is in progress as of January 2012, is a naturalistic, one-arm design with a 12-month observation period of a moderate sample size (N = 150).

Results: Of the 43 TRS patients with 6 months observational period following RLAI initiation, 25 (58 %) were diagnosed as DSP.Following 6 months of RLAI treatment, 17 of these 25 DSP patients (68 %) had responded to RLAI, whereas the 18 patients without a history of DSP showed insufficient responses, indicating that RLAI is exceedingly effective in patients with DSP.

Conclusion: Although this is only a progress report, the present results strongly suggest that RLAI could become an effective treatment strategy for TRS with DSP.

P-01-026 These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics

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Objective: Paliperidone is a second generation antipsychotic medication approved for the treatment of schizophrenia. It is a useful option in the treatment of the acute symptoms of schizophrenia and may also be used in patients previously unsuccessfully treated with other antipsychotics. The aim of this work was to explore tolerability and treatment response of flexible doses of paliperidone ER (3, 6, 9, 12 mg/day) in adults suffering from resistant paranoid schizophrenia.

Methods: Four patients with resistant paranoid schizophrenia were included in this study. The patients were male, on the average 39.8 years old, diagnosed according to DSM-IV with schizophrenia from on the average 15.7 years, which had presented therapeutic resistance to some antipsychotics (haloperidol, clopixol, rispolepidone, olanzapine, clozapine). All subjects were treated with 3–12mg paliperidone ER, according to the severity of symptoms. Patient's Positive and Negative Syndrome Scale (PANSS), Clincal Global Impression-Severity (CGI-S), Adverse Events (AEs) were assessed at five time points: baseline, 1st, 2nd, 3rd, month of treatment. Personal and Social Performance (PSP) scale was assessed at every three month of treatment.

Results: Three patients completed the four month trial of paliperidone ER and one of them interrupted the medication (3mg/day) after one month because of the noncompliance. One patient started and finished the treatment with paliperidone XR 6mg/day, two patients started the treatment with 9mg/day, but during the last month they received 12mg/day for better improvement. The PANSS, CGI-S, AEs and PSP scales indicated that the treatment with paliperidone XR of three schizophrenic patients was effective and paliperidone did not produce adverse events. The treatment with this medication was noneffective only for one patient.

Conclusion: These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics.

P-01-027 Novel D2/5-HT6/5-HT7 receptor antagonist with a broad antipsychotic activity

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Objective: 5-HT6 and 5-HT7 receptor antagonism has been associated with potential procognitive as well as antidepressant and anxiolytic activity. Therefore, introduction of strong functional antagonism of those receptors is considered beneficial for the profile of a modern antipsychotic drug. We designed and synthesized a novel series of arylsulfonamide derivatives being strong D2/5-HT6/5-HT7 receptor antagonists, without significant anticholinergic and antihistaminergic effects or hERG channel blockade and tested them in a series of in vivo models.

Methods: The following animal models were used: ●amphetamine (2.5 mg/kg) and dizocilpine (0.2 mg/kg) induced hyperlocomotion in mice ●apomorphine (0.6 mg/kg) and dizocilpine (1.2 mg/kg) induced strereotypies in rats ●DOI (2.5 mg/kg) induced head twitches in rats ●Conditioned avoidance response and passive avoidance in rats ●Prepulse inhibition deficit induced by amphetamine (6.0 mg/kg) ●Tail suspension test in mice ●Porsolt's forced swimm test in rats●Four-plate test in mice ●Vogel's conflict drinking test and elevated plus maze test in rats.

Results: Minimal effective doses of the best compound (in mg/kg) are as follows: amphetamine and dizocilpine induced hyperlocomotion – 2.5 and 1.25, apomorphine and dizocilpine induced strereotypies – 10 and 3, DOI induced head twitches – 1, conditioned avoidance response – 3, prepulse inhibition deficit induced by amphetamine – 30, tail suspension test – 0.156, Porsolt's forced swimm test – 0.3, four-plate test – 0.312, Vogel's conflict drinking test and elevated plus maze test – 3 and 0.3. Not active in passive avoidance test up to 30 mg/g.

Conclusion: The most interesting compound displayed a wide antipsychotic activity in a broad range of mice and rat models. At the same time it proved to have no detrimental effect on cognition as well as to possess potentially beneficial influence on affective dimension of schizophrenia.

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P-01-028 Rabbit syndrome due to olanzapine

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Objective: There are very few case reports in the literature on rabbit syndrome due to olanzapine and other atypical antipsychotic agents.we describe a patient who developed this syndrome with olanzapine and it improved with reduction of dose and with introduction of antcholinergics(benzhexol).

Methods: 32 year old lady with learning disablity and bipolar depression (Severe Depressive disorder with psychotic symptoms). She developed rabbit syndrome after the dose of olanzapine was increased to 15 mg. Symptoms improved after the reduction of dosage to 5 mg and with the introduction of anticholinergic agents.

Results: Patient is currently receiving Olanzapine 5 mg/day and Mirtazepine 30 mg/day and the extrapyramidal symptoms have abated.

Conclusion: This case adds on to the existing literature of rabbit syndrome secondary to use of atypical antipsychotic drugs.

P-01-029 Antipsychotic preferences for psychiatrists and their family members

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Objective: We aimed to evaluate which antipsychotic drugs psychiatrists would prefer for themselves, their partners and children in case of a mental illness.

Methods: The study was conducted among psychiatrists in Serbia and we have assessed 90 participants: 68 (75.6%) psychiatrists and 22 (24.4%) psychiatric trainees who were asked to complete the questionnaire about their drug selection in hypothetical situations of becoming ill with schizophrenia or these conditions occurring in their partners and children.

Results: In case of schizophrenia, majority of participants reported that they would take atypical antipsychotic and risperidone was the first choice made by most psychiatrists for themselves (51.1%), their partners (55.8%) or children (43.3%), followed by clozapine (12.2%), haloperidol (10.0%) and olanzapine (10.0%). The preferred doses were slightly lower than the recommended ones (Risperidone 2.8 mg, Clozapine 181.8 mg, Haloperidol 5 mg, Olanzapine 11.7 mg). All the preferences were similar, regardless the respondent was specialists in psychiatry or psychiatric trainee.

Conclusion: Most psychiatrists would take or administer atypical antipsychotics as the first choice for themselves, their partners or children. These preferences are mostly in accordance with current treatment guidelines, but there is still room to narrow the gap between guideline recommendations and psychiatrists' medication choices in personally meaningful situations.

P-01-031 Dopamine D2 antagonist-induced striatal gene expression requires activation of mGlu5 receptors by cortical afferents

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Objective: Antipsychotic drugs are used to alleviate schizophrenia symptoms. Despite the fact that all antipsychotic drugs interact with dopamine D2 receptors, the exact mechanism that explains their activity still remains elusive. Here we explored the relationship between glutamate, adenosine and dopamine receptors in the modulation of the transcription factor Nur77 (NGFI-B, NR4A1) in the striatum, an important brain structure involved in antipsychotic drug effects.

Methods: We performed eticlopride (ETI; D2 antagonist) treatments in transgenic mice with a genetic deletion of the postsynaptic dopamine D2L receptor isoform, as well as in rats bearing an ibotenic acid-induced cortical lesion. Additionally, groups of mice receiving an acute injection of vehicle, MPEP (mGluR5 antagonist), SCH58261 (A2A antagonist), ETI or compound combinations have been investigated. Organotypic cultures of striatal slices exposed to these drugs were also performed.

Results: ETI was still able to strongly induced Nur77 mRNA levels in the striatum of D2L receptor knockout mice, while cortical lesions strongly attenuated ETI-induced Nur77 expression in the striatum. Systemic blockade of mGluR5 and A2A receptors strongly reduced ETI-induced Nur77 mRNA levels in the striatum, whereas MPEP or SCH58261 alone remained inactive. On the other hand, mGluR5 agonists can directly modulate Nur77 expression in striatal organotypic cultures. Furthermore, blockade of glutamate reuptake in organotypic striatal slices strongly activated Nur77 transcription that can be abolished by an mGluR5 antagonist. Interestingly, D2 agonist or antagonist cannot modulate Nur77 expression by themselves in the striatal slices.

Conclusion: These observations indicate that modulation of the transcription factor Nur77 in striatal cells following dopamine D2 antagonists (antipsychotic drugs) is mediated, at least in part, by an interaction of the drug with presynaptic dopamine D2S receptors located on corticostriatal afferents and subsequent activation of postsynaptic mGluR5/A2A receptors in striatal cells. JM holds a studentship from the Canadian Institute for Health Research (CIHR).

P-01-032 Role of the transcription factor NUR77 in haloperidol-induced hyperprolactinemia

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Objective: Antipsychotic drugs are used to treat schizophrenia symptoms. But, they are known to cause various motor and endocrine side effects and have a limited effectiveness. The main characteristic of antipsychotic drugs is to interact, and act as antagonists, with the dopamine D2 receptors. In lactotrope cells of the anterior pituitary, activation of D2 receptors inhibits prolactin (PRL) secretion and synthesis. Accordingly, antipsychotic drugs increase PRL transcription and induce hyperprolactinemia. However, the molecular mechanism leading to the hyperprolactinemia remains elusive. Previous works from our laboratory suggest that the transcription factor Nur77 (Nr4a1) is associated with motor side effects induced by antipsychotic drugs (Levesque and Rouillard, TiNS, 2007).

Methods: In the present study, we measured pituitary Nur77 and PRL mRNA levels using quantitative RT-PCR assays, and serum PRL levels were evaluated by ELISA, in wild type FHH and Nur77 knockout (-/-) rats (FHH-Nr4a1m1Mcwi, nonsense mutation Y130stop) treated with vehicle or haloperidol. Electrophoretic gel mobility shift assays (EMSA) were performed to identify transcription factor binding to the PRL promoter.

Results: We report that Nur77 is expressed in basal conditions in the anterior pituitary and that Nur77 mRNA levels are significantly up-regulated by haloperidol. Interestingly, in Nur77 knockout (-/-) rats, basal pituitary PRL mRNA levels are elevated, but haloperidol is unable to increase PRL transcription, as compared to their littermates. Consequently, haloperidol-induced serum PRL levels are strongly reduced in Nur77 (-/-) rats. In silico analysis reveals numerous putative Nur77 responsive elements (NBRE) in the PRL promoter and electrophoretic gel mobility shift assays (EMSA) indicate that Nur77 can bind to the PRL promoter.

Conclusion: Taken together, these results indicate that Nur77 regulates PRL transcription and secretion following the administration of a typical antipsychotic drug.

P-01-033 Regulating oligodendrocyte regeneration and development in vitro: A new feature of atypical antipsychotic drugs?

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Objective: Neuroimaging and microarray studies have indicated that oligodendrocyte and myelin abnormalities are important pathological changes of schizophrenia. Antipsychotic drugs (APDs) are effective in treatment of schizophrenia; but the underlying mechanism remains unknown. Our previous studies suggested that quetiapine, an atypical antipsychotic drug, promoted neural progenitor cells to differentiate into oligodendrocyte lineage cells and alleviated CPZ-induced demyelinating pathology. In this project, we further investigated the effect of different antipsychotic drugs on the oligodendrocyte in vitro.

Methods: A well established oligodendrocyte-lineage cell line, CG4 cells were used to exam the effect of three antipsychotic drugs: haloperidol, quetiapine and olanzapine. Antipsychotics showed no effects on proliferation of CG4 cells evaluated by CCK-8 proliferation assay. However, all of the drugs promoted differentiation of CG4 cells into mature oligodendrocytes when it was evaluated by the expression of CNPase, a maker of mature oligodendrocyte. Further to investigate the mechanism of antipsychotic drugs, we found the expression of oligodendrocyte transcription factor 1 (olig1) and 2 (olig2) were distinctly regulated by the drugs.

Results: The expression of olig2 was up-regulated by the all the drugs tested and olig1 was only increased by quetiapine and olanzapine, but not by haloperidol. These data suggested that olig1 and olig2 may play a key role in the regulation process of APDs on oligodendrocyte development and there may be some differences between the action of typical and atypical antipsychotics.

Conclusion: Our results indicate APDs have effects to promote the differentiation of CG4 oligodendrocyte cell line in vitro and oligodendrocyte/myelin may be a novel target for APDs.

Policy of full disclosure: Dr. Xin-Min Li accepted research grant from Astrazeneca Canada and Pfizer Canada.

P-01-034 Preventing and treating olanzapine-induced obesity with betahistine: A chronic animal model study

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Objective: Olanzapine, an atypical antipsychotic drug, is widely prescribed to treat schizophrenia, but induces serious weight gain/obesity side-effects. Antipsychotic drugs antagonistic affinity for histamine H1 receptors is the main indicator of weight gain side-effects. This study aimed to investigate whether chronic treatment with betahistine (H1 receptor agonist/H3 receptor antagonist) could prevent/treat olanzapine-induced weight gain at different stages of treatment.

Methods: Female Sprague-Dawley rats were administered under 5 conditions (n = 12): (1) Rats were treated with vehicle (control) during whole experimental period; (2) ''Obesity treatment group'': 5 weeks olanzapine treatment (1 mg/kg, t.i.d.), followed by 6 weeks co-administration of olanzapine with betahistine (9.6 mg/kg, t.i.d.); (3) ''Obesity prevention group'': 3.5 weeks olanzapine treatment, followed by 2.5 weeks withdrawed, then co-administration of olanzapine and betahistine (4.8 mg/kg, t.i.d.) was introduced; (4) Sole olanzapine treatment following the same time course as Group 3; (5) Rats were treated solely with betahistine (4.8 mg/kg, t.i.d.) during weeks 7–11.

Results: Compared to controls, olanzapine treatment increased body weight ($p < 0.001$), food intake ($p < 0.01$), inguinal fat mass ($p < 0.05$) and liver weight ($p < 0.01$). On the other hand, the ''obesity treatment group'' had lower weight gain ($p < 0.001$), food intake and inguinal fat ($p < 0.05$) than the sole olanzapine treatment group. The ''Obesity prevention group'' also showed significantly decreased weight gain ($p < 0.05$), compared to the olanzapine group.

Conclusion: This study revealed that chronic co-treatment of olanzapine and betahistine is effective at reducing olanzapine-induced obesity side-effects. These results provide support for further clinical trials to improve of olanzapine-induced obesity side-effects using betahistine co-treatment.

P-01-035 Insulin resistance, obesity and metabolic syndrome in psychiatric patients

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Objective: The treatment with certain antipsychotics, antidepressants, stabilizers of mood, in patients with schizophrenia, unipolar or bipolar disorder, can contribute to produce dismetabolism and to configure a metabolic syndrome with a coronary and brain vascular risk. Nutritional, carbohydrate metabolic disorders such as functional hypoglycemia, resistance to insuline, hiperinsulinism, diabetes, obesity can accompany, induce, aggravate the development of neuropsychiatric alterations. The objective is to prevent obesity, insulin resistance, that are determinant factors in metabolic syndrome, therefore the goal of recovery needs to combine the concept of general medical health with that of the healthy mind. When there is hiperinsulism it creates insulin resistance, obesity, there are more adipocites, liberation of free fatty acids, adipokinines, inflammatory cytokines, and these intervene in the metabolic disbalance producing a pro-atherogenic, prothrombotic state, endothelial disfunction, which are all present in the metabolic syndrome. Obesity is also associated with a state of inflammation and immune response characterized with elevation of reactive protein C, adipoquinines TNF alfa a mediator to insulin resistance.

Methods: We implemented a program with aerobic exercice, restriction of calories, refined sugars, flour, and a balanced diet with the addition of nutritional supplements, because food controls insulin, it can reduce oxidative stress, inflammation and prevent development of metabolic syndrome.

Results: We obtained a regulation in all parameters that were altered in the metabolic syndrome in the psychiatric patients and in ratio TGL/HDL, that is an indirect marker of the levels of inflammation and insulin.

Conclusion: We give importance to excercise and the nutritional factors that regulate insulin/glucagon axis, to prevent functional hypoglycemia, hyperinsulinism, insulin resistance obesity, diabetes, inflammation which conduce to metabolic syndrome. In patients with mental illness that are taking antipsychotics, antidepressants and stabilizers of mood it is necessary to elevate the metabolic monitoring in the care and in the management of cardiac and brain risk factors to prevent premature death.

P-01-036 Clozapine induces differentiation of human preadipocytes via the aryl hydrocarbone receptor

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Objective: Among the pleiotropic pharmacology of clozapine is the undesirable effect of preadipocyte differentiation, which can be antagonized by green tea extract (EGCG) in vitro. As this drug effect differs from fat cell hypertrophic changes seen under olanzapine, we hypothesize that an unshared molecular mechanism of clozapine should be responsible. The chemical structure of clozapine resembling a chlorinated polycyclic aromatic hydrocarbon led us to study the involvement of the aryl hydorcarbon receptor (AhR).

Methods: Human preadipocytes obtained as a by-product of abdominal plastic surgery were isolated and cultured in vitro. Cell differentiation was studied by histochemistry 14 days after the addition of hormones and clozapine vs. hormones and other neuroleptic compounds. EGCG and alpha-naphtoflavin (alpha-NF) were used as antagonists. AhR activity was studied by luciferase reporter gene assay and by RT-PCR of target gene CYP1A1.

Results: Unlike olanzapine and other atypical neuroleptics, clozapine addition significantly increased preadipocyte differentiation by up to 60%. This effect was fully antagonized by either EGCG or alpha-NF. Clozapine specifically increased both AhR promoter activity and transcription of target gene Cyp1A1.

Conclusion: Our study indicates that clozapine induced preadipocyte differentiation is mediated by AhR activation. This mechanism may be unique to clozapine, as it differs from fat cell hypertrophy effected by olanzapine and other neuroleptic compounds. AhR mediated effects by clozapine may have further relevance at the CNS and stem cell level, and could possibly account for some components of its complex pharmacology.

P-01-037 Use off label of antipsychotic medication – a 6 month descriptive study of the antipsychotic use in the first visits in our center for mental health

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Objective: To evaluate the characteristics of the first 100 new patients and to determine the use of antipsychotic in our Center for Mental Health between July and December 2011 and to determine the characteristics of the patients that were prescribed the use of antipsychotic.

Methods: Subjects: The population study were a hundred patients that were first time visited in the Center for Mental Health between July and December 2011. Procedure: This is a cross-sectional study – Independent variable were sex and age. Patients were diagnosed according to DSM's criteria-IV of Unipolar disorder, Bipolar affective disorder /Psychotic disorders /Substance use disorder / or comorbidity among axis II.

Results: From the selected sample of 100 patients 40 were male and 60 were female. The 24% were treated with antipsychotic in the first visit. The 86% of the selected sample were diagnosed Unipolar Depression or/and Anxiety disorders and only a 6% of Psychotic disorder and 7% of substances abuse disorder. The range of age in which more patients were treated with neuroleptics was between 17th and 35th years old (27.6% of patient between these ages were treated with antipsychotic). The 37.5% of the patients that were treated with

antipsychotic had diagnosis of personality disorders. To be men aged between 17th-35th years old were the main variables associated to be prescribed the use of antipsychotic [IC95% (24,8–55,2) p-value 0,002].

Conclusion: From our selected hundred patients visited from the first time in our Adults Center for Mental Health 24 were treated with antipsychotic in spite of the fact that only 6% of these patients were diagnosed of Psychotic disorder. The use of low-dose of typical antipsychotics in the treatment of personality disorders are useful not only to improve symptoms of psychotic type (cognitive dysfunction, perceptual, anxiety and paranoid ideation) but also the depressive spirit, the impulsiveness and the anger.

P-01-038 Mental health rehabilitation unit: The role of clozapine

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Objective: To analyse the prescription of clozapine in a sample of 37 patients admitted to the mental health rehabilitation unit.

Methods: This is a transversal study. All patients admitted for psychiatric rehabilitation treatment from the 01/01/2010 to the 31/12/2011 were included. Data about socio-demographical status, information about the admission and clinical situation were obtained. We then compared the patients who received treatment with clozapine with the ones who did not.

Results: The sample was composed by 37 patients (78.4% men; mean age: 36 + 10 years). The majority of them were single (89.2%). All of them were Spanish. Only the 5.4% of them were working and the most represented group (73%) were receiving a disabillity allowance. In the 70.27% of the cases schizophrenia was the diagnose motivating the admission. The 378% of all patients had a comorbid substance use disorder. Within the 26 patients with the diagnose of schizophrenia, 9 (34.61%) did receive clozapine during the admission. We compared the two groups (clozapine group vs. non-clozapine group) and obtained the following results: there were no significant differences between the groups in terms of sex, civil state or working state. Instead, it seemed that in the clozapine group the patients were older, had a major number of previous hospital admissions, had a larger trajectory of their disease and had more often committed suicide attempts.

Conclusion: Patients requiring treatment with clozapine had a major number of hospital admissions and had more often committed suicide attempts, suggesting a more severe course of the disorder. They were older as the non-clozapine group. This last may be related with the fact that clozapine is delayed in its use among treatment-resistant patients [2]. It's worth highlighting that only 3461% of the schizophrenic patients in the rehabilitation unit received clozapine. This could mean that clozapine is underprescribed.

P-01-039 How to conduct clinical bioequivalence trials with higher-dose quetiapine fumarate or pramipexole hydrochloride hydrate safely in healthy subjects

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Objective: The aims were (1) to determine the maximum tolerated doses (MTD) of quetiapine and pramipexole when given to healthy Japanese male subjects in gradually increasing single doses and (2) to evaluate the availability of this exploratory method for further bioequivalence trials.

Methods: This study was approved by Kyushu Clinical Pharmacology Research Clinic Institutional Review Board, and all subjects gave their written informed consent. In the quetiapine group, 18 participants received 25 mg in the first stage. In the second stage, they were divided into three groups of six subjects each and designated to receive either 50 mg, 75 mg or 100 mg depending on the severity of the symptoms in the first stage. In the pramipexole group, 18 participants received 0.125 mg and then received either 0.25 mg, 0.375 mg, or 0.5 mg in the same manner as the quetiapine group.

Results: In the group receiving 75 mg of quetiapine, three mild adverse events (AEs) and seven moderate AEs (e.g., nightmare and syncope) were reported from all six subjects. In the group receiving 0.5 mg of pramipexole, three mild and five moderate AEs were reported from five subjects. In both groups, although no severe or serious AEs were reported, we judged that doses equal to or greater than 75 mg and 0.5 mg of quetiapine and pramipexole, respectively, were not tolerated well in healthy subjects. The maximum concentration of the drug in each subject was not always correlated with severity of the AEs.

Conclusion: Doses of quetiapine 75 mg and higher and doses of pramipexole 0.5 mg and higher were not tolerated well in healthy subjects. Determining the MTD of psychotropic agents in bioequivalence trials was safely achieved by giving the agents gradually increasing doses based on severity of symptoms in the first stage and by carefully observing subjects in small groups (n = 6).

P-01-040 Antipsychotic-like properties of zolpidem in the rat

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Objective: Preclinical and clinical studies support the assumption that positive GABA-A receptor modulators may possess antipsychotic properties. Our preliminary research showed that selective alpha1 GABA-A receptor agonist, zolpidem, but not benzodiazepines, can produce neuroleptic-like cataleptogenic responses in the rat. The aim of the present study was to investigate a potential antipsychotic profile of zolpidem in a series of preclinical models of psychosis.

Methods: All experiments were conducted on drug-naive male Wistar rats. Zolpidem and comparator drugs (diazepam, midazolam, zaleplone, haloperidol, olanzapine) were tested in the following models: ●hyperlocomotion induced by amphetamine (1.0 mg/kg) and dizocilpine (0.3 mg/kg) ●apomorphine (0.6 mg/kg)-induced stereotypies ●dizocilpine (1.2 mg/kg)-induced stereotypies ●DOI (2.5 mg/kg)-induced head twitches ●pre-pulse inhibition (PPI) deficits induced by amphetamine (6.0 mg/kg) or dizocilpine (0.6 mg/kg) ●conditioned avoidance response (CAR).

Results: Low doses of zolpidem (0.3–3.0 mg/kg, i.p.) inhibited hyperlocomotion induced by amphetamine or dizocilpine. Higher doses of the drug (3.0–10.0 mg/kg) reversed apomorphine- and dizocilpine-induced stereotypies as well as DOI-induced head twitches. Zolpidem (3.0–10.0 mg/kg) also reversed PPI deficits produced by amphetamine and inhibited CAR.

Conclusion: Zolpidem produced dose-dependent antipsychotic effects in several preclinical models of psychosis. Its efficacy was comparable to haloperidol and olanzapine and was superior to less selective GABA-A positive modulators (diazepam, midazolam, zaleplone).

P-01-041 One-year open-label study of the cognitive efficacy of blonanserin in antipsychotic-naïve first-episode schizophrenia

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Objective: Cognitive impairment, a core feature of schizophrenia, has been established as an important symptom domain associated with long-term outcome. The purpose of this study was to evaluate the long-term effects of blonanserin, a novel second-generation antipsychotic drug developed in Japan in 2008, on cognitive function in first-episode schizophrenia.

Methods: Twenty-four antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Blonanserin (2–24 mg/day) was given in an open label design for one year. The Brief Assessment of Cognition in Schizophrenia (BACS-J) was administered as the primary outcome measure at baseline, 24, and 52 weeks. Clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Quality of Life Scale (SQLS-J), and the Clinical Global Impression-Severity of Illness Scale (CGI-S). This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Thirteen patients (6 males and 7 females; mean age, 28.2 ± 5.6 years) completed the study. The mean daily dose of blonanserin was 4.2 ± 3.0 mg/day at 52 weeks. One patient used anticholinergics (biperiden dose: 2 mg/day) at endpoint. At the 52-week endpoint, significant improvements were shown in letter fluency, executive function, and composite score, as measured by the BACS-J compared with baseline ($p < 0.05$). In addition, the psychosocial condition score ($p < 0.01$) and motivation/energy score ($p < 0.05$) on the SQLS-J, and all items on the PANSS ($p < 0.01$) and CGI-S ($p < 0.01$) significantly improved after 52 weeks treatment.

Conclusion: These results suggest that blonanserin has a beneficial effect on some types of cognitive function associated with prefrontal cortical function in patients with antipsychotic-naïve first-episode schizophrenia. However, the conclusions that can be drawn are limited by the small sample size and the lack of control groups to exclude the possibility of retest effects.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-01-042 Caregiver burden of patients with psychotic disorders

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Objective: To evaluate the presence of caregiver burden in psychotic outpatients who are treated in Mental Health Clinics and to know clinical features associated with the presence of burden.

Methods: Cross-sectional study conducted in naturalistic type of Mental Health Outpatient Clinics in Balearic Islands (Spain) belong to hospitals in Majorca (Hospital de Manacor and Hospital son Llatzer) and Menorca (Hospital Mateu Orfila). We used the Zarit Scale for assessing caregiver burden.

Results: We obtained a final sample of 77 caregivers. The mean score on the Zarit scale was 39 (+17.11) Patients with psychotic disorders assessed were male (62%) with a mean age of 43 years (+14.4) with a diagnosis of more than 5 years evolution (72.7%) schizophrenia was the most frequent diagnosis (55%) and risperidone long-acting injection (RLAI) the most widely used antipsychotic (55.8%).

Conclusion: 1. The patients on maintenance monotherapy with RLAI showed better adherence rates and more insight, evaluated by their psychiatrists. 2. 78% of patients receiving antipsychotic medication injections were satisfied with the treatment. 3. Patients with RLAI given in deltoid were satisfied in 65.7%.

P-01-043 Dopamine D2 receptor occupancy and remission in schizophrenia: Analysis of the catie data

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Objective: In treating schizophrenia, it has been established that 65–80% occupancy of dopamine D2 receptors optimizes therapeutic efficacy while minimizing risks of extrapyramidal symptoms and cognitive impairment. However, it is unclear as to whether it is necessary to keep D2 receptor occupancy within this therapeutic window to maintain clinical response.

Methods: The dataset from phase1 of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial was used. Patients receiving risperidone, olanzapine, or ziprasidone were included in the present analysis if they fulfilled the following definition of remission: a score of ⩽3 on 8 specific Positive and Negative Syndrome Scale (PANSS) items (i.e. P1, P2, P3, N1, N4, N6, G5, and G9) at baseline and months 1, 2, and 6. These criteria follow the definition proposed by Andreasen et al., (2005). Peak and trough D2 receptor occupancy levels at month 6 and endpoint were estimated from plasma antipsychotic concentrations using population pharmacokinetic analysis and our D2 prediction model.

Results: 30 subjects (15 men; mean ± SD age = 41.5 ± 11.8 years; risperidone, N = 12, olanzapine, N = 12, and ziprasidone N = 6; mean ± SD duration of follow-up 495.5 ± 78.1 days) fulfilled inclusion criteria. Peak and trough D2 receptor occupancy levels at month 6 were 70.3 ± 9.8% and 60.5 ± 20.2% (mean ± SD), respectively; among these individuals, 46.7% (N = 14) did not achieve continuous blockade of ⩾65% (i.e. trough D2 occupancy of <65%). 25 of these subjects completed phase 1 with improvement; of these, 52.0% (N = 14) did not achieve continuous blockade of ⩾65% at endpoint. No significant difference was found in peak or trough D2 occupancy between those who successfully completed phase 1 and those who did not.

Conclusion: Approximately half of patients who maintained remission did not achieve continuous blockade of D2 receptor occupancy ⩾65%. Results suggest that sustained D2 receptor occupancy over 65% is not always necessary for the maintenance treatment of schizophrenia.

Policy of full disclosure: Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported ''Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia'' (CATIE-Sz). This is a multisite, clinical trial of persons with schizophrenia comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract #N01MH90001 to the University of North Carolina at Chapel Hill. The ClinicalTrials.gov identifier is NCT00014001. The version of the dataset used was 1.0. This study was also supported by grant R01MH064173 from the National Institute of Mental Health and was ancillary to Clinical Antipsychotic Trials of Intervention Effectiveness, N01MH90001, from the National Institute of Mental Health.

P-01-044 A comparison of the pharmacotherapy of japanese mental disorders between inpatients and outpatients receiving home visit nursing service

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Objective: Japan's rapidly aging population has become a top medical issue. Similarly, Japanese mental disorders face the problem of aging. In contrast, the Ministry of Health, Labor and Welfare plan to reduce long hospitalization of Japanese mental disorders to improve their quality of life and restrain increases in medical expenses. One of the plans is home visit nursing service. The purpose of this study was to examine the pharmacotherapy of Japanese mental disorders between inpatients and outpatients receiving home visit nursing service.

Methods: We conduct a survey of prescription and demographics from inpatient's medical records dated 30th September 2009 and outpatient's dated 31st May 2011 at Showa University Karasuyama Hospital. This study was approved by the Medical Ethics Committee of Showa University School of Medicine.

Results: As a result, one hundred fifty-seven inpatients and sixty-eight outpatients (almost chronic schizophrenia) had similar outcomes and demographics. As they grew older, they had more physical diseases ($r = 0.43$, $p < 0.0001$) and took lower amount of antipsychotics ($r = -0.34$, $p < 0.0001$) (Pearson product-moment correlation coefficient). Outpatients had more physical diseases for their age than inpatients because outpatient's illnesses were more out of control. Both patients had diabetes mellitus, hyperlipidemia, bone fracture, difficulty swallowing and others, that could have influenced the pharmacotherapy for rapidly aging mental disorders.

Conclusion: In conclusion, these results indicate that aging outpatients were not healthier than inpatients. Various physical diseases they had will affect selection of drug by psychiatrists materially. Psychiatrists in an aging society, like Japan, should realize the necessity of managerial support for their illness and be more careful when prescribe for aging outpatients.

P-01-045 A case series on the use of atypical long acting injectables as first-line antipsychotic treatment: Who benefits and how?

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Objective: The use of long acting injectables (LAI) antipsychotics is mainly reserved as the second line treatment when all efforts to ensure patients' adherence to regular oral medication failed. We aim to describe the common clinical features of patients with schizophrenia who benefited from the use of LAI early in the course of illness.

Methods: We report four patients with first presentation of schizophrenia, all of whom were started with atypical antipsychotic LAI without prior history of oral antipsychotic. In all of the cases, the treating doctors independently did not use short acting major tranquilizers in the acute phase of psychosis because the patients were not agitated but remained adamant in refusing oral medications.

Results: We observed the four patients shared common clinical features of prominent delusion rather than hallucination amidst other psychotic symptoms, obstinate refusal of oral medication but without agitation, with good pre-morbid functioning and very poor insight. Interestingly, following the remission of the acute psychotic phase, all showed marked improvement in their insight and had better than expected therapeutic alliance.

Conclusion: We conclude that LAI may be used as the first line antipsychotic treatment in the acute psychotic phase in patients who are non-agitated but have prominent symptom of delusions with poor insight. LAI may improve the doctor-patient therapeutic alliance due to its minimal side effects and by ways of increasing the patients' sense of control and allowing psychoeducation to take place when the patient is ready.

P-01-046 Sexual dysfunction and changes in satisfaction with switch to aripiprazole

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Objective: This study looked into the usefulness of switching to aripiprazole in schizophrenic patients who experienced sexual dysfunction with antipsychotic treatment. In addition, changes in the levels of satisfaction with medication were also examined.

Methods: Patients with schizophrenia receiving treatment at our hospital and taking an antipsychotic drug were surveyed about their subjective perception of frequency and severity of side effects on a self-completed questionnaire, and the level of satisfaction with their medication, using the DAI-10 (Drug Attitude Inventory-10). Of them, for patients who checked one of the items concerning sexual dysfunction, attending physicians engaged in SDM (shared decision making), and those for whom it was judged reasonable to switch to aripiprazole and who agreed to switch became the subjects of this study. Prolactin levels were measured upon switching, and again after the completion of the switch, along with the self-completed questionnaire survey and evaluation using the DAI-10.

Results: Seven patients had their medication switched to aripiprazole. As a result of this switch, they showed resolution or improvement of sexual dysfunction, and improvements in prolactin levels (from 154.4 ± 94.0 to 65.5 ± 50.1). Improvements in DAI-10 were also seen. No deterioration of psychotic symptoms was observed after the switch.

Conclusion: One of the risks for the development of sexual dysfunction is increases in prolactin levels, and the improvement in prolactin levels associated with a switch to aripiprazole was considered to have resulted in the improvements in sexual dysfunction. This in turn was considered to improve the level of patient satisfaction with medication. These findings suggested that a switch to aripiprazole may be useful in patients who experience sexual dysfunction with antipsychotic treatment.

P-01-047 Mechanisms underlying the modulation of antipsychotic-induced extrapyramidal motor disorders by antidepressants

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Objective: Antipsychotic drugs are widely used not only for schizophrenia, but also for mood disorders such as bipolar disease and depression. To evaluate the interactions between antipsychotics and antidepressants in modulating the extrapyramidal motor functions, we examined the effects of various antidepressants on haloperidol (HAL)-induced bradykinesia and catalepsy in mice and rats.

Methods: Male ddY mice or SD rats were used. Animals were first given valious antidepressants and then treatred with HAL. The pole-test and catalepsy-test were performed 30 min after HAL injection to evaluate extrapyramidal disorders. Various 5-HT receptor antagonists were also examined in conbination with antidepressants.

Results: The selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the tricyclic antidepressant (TCA) clomipramine significantly potentiated HAL-induced bradykinesia and catalepsy in a dose-dependent manner. The 5-HT stimulant 5-hydroxytryptophan also enhanced HAL-induced extrapyramidal side effects (EPS). However, a noradrenergic and specific serotonergic antidepressant mirtazapine failed to augment, but rather attenuated EPS induction. Treatment of animals with ritanserin (5-HT2A/2C antagonist), ondansetron (5-HT3 antagonist), and SB-258585 (5-HT6 antagonist) significantly antagonized the EPS augmentation by fluoxetine. Intrastriatal injection of ritanserin or SB-258585, but not ondansetron, also attenuated the EPS induction. In addition, both BRL-44408 (alpha2A antagonist) and JP-1302 (alpha2C antagonist) significantly ameliorated HAL-induced EPS.

Conclusion: The present study suggests that SSRIs augment antipsychotic-induced EPS by activating 5-HT2A/2C, 5-HT3 and 5-HT6 receptors. In addition, mirtazapine seems to be superior to SSRIs or TCAs in combined therapy for mood disorders with antipsychotics in terms of EPS induction. This is probably due to its alpha2 antagonistic actions.

P-01-048 Pattern of clozapine use among patients in a nigerian neuropsychiatric hospital

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Objective: Previous studies on the prescription patterns of psychotropic medications have highlighted the use of Clozapine in the treatment of persons with Schizophrenia. Little is known about the prescription pattern of Clozapine in Nigeria. This study examined the prescription pattern of Clozapine in a Nigerian Neuropsychiatric Hospital.

Methods: A complete list of patients that had been on Clozapine in the past year was retrieved from the pharmacy register of a Nigerian Hospital. Information on pattern of Clozapine use was obtained from Casenotes using a standardized data collection form.

Results: A total of 39 patients had received Clozapine in the past year. Mean age was 43.3 years (SD = 13). Majority were males (51.3%), unmarried (66.7%) and unemployed (64.1%). About 8 (20.5%) had comorbid substance use disorder. Most (81.2%) reported side effects related to clozapine use. Hypersalivation (46.2%) was the commonest reported side effect followed by drowsiness (41%), urinary problems (17.8) and constipation (12.8%). Clozapine discontinuation occurred among 64.8% of the subjects. Reasons for discontinuing included financial constraints (36.4%) and low White Blood Cell count (22.7%).

Conclusion: This study highlighted the pattern of Clozapine prescription in an understudied population. Further research on factors influencing its prescription is required.

P-01-049 Neuroleptic malignant syndrome and catatonia spectrum disorders in a colombian psychiatric unit

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Objective: Our objective is to describe the clinical features associated in these patients related to treatment response and course of illness in

patients with NMS secondary to both typical and atypical antipsychotic agents as well as the description of 3 cases of catatonia with different patterns of outcome.

Methods: Case Series and Literature Review.

Results: We have recently diagnosed 5 cases of NMS in the psychiatric hospital and 3 cases of catatonia in the context of affective and psychotic disorders. A retrospective medical chart review of the cases was made along with the literature review. We found a positive response to a benzodiazepine trial in half of the cases.

Conclusion: The pathopsysiology of Neuroleptic Malignant Syndrome (NMS) and Catatonia remains enigmatic due to its unpredictable an often sudden emergence, and the absence of established vulnerability markers. In both conditions a variety of mechanisms have been proposed to account for the clinical characteristics including reduced central dopamine transmission, sympathetic nervous system dysregulation, disordered muscle metabolism, adrenal gland secondary dysfunction and altered central GABAergic function. Since its initial description by Kahlbaum over a century ago, catatonia has been associated with psychiatric, neurologic, and medical disorders. Contemporary authors view catatonia as a syndrome of motor signs in association with disorders of mood, behavior or thought.

P-01-050 Differential effects of aripiprazole and haloperidol on dopamine markers in the arcuate nucleus and prolactin levels in male rats

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Objective: Aripiprazole is a new antipsychotic drug with a high affinity for dopamine D2 receptors but reduced risks for inducing extrapyramidal (EPS) and hyperprolactinaemia (HPL) side-effects. Our previous study (Han et al., 2009, International Journal of Neuropsychopharmacology 12:941–952) showed that aripiprazole selectively reduced the expression of tyrosine hydroxylase (TH; a rate-limiting enzyme for the synthesis of dopamine) in the ventral tegmental area (VTA) but not the substantia nigra (SN), suggesting a selective reduction of dopamine synthesis in the VTA but not SN. However haloperidol affected on both nuclei. Since the tuberoinfundibular dopamine neurons in the arcuate nucleus (Arc) modulate prolactin secretion, this study investigated the effects of aripiprazole on the expression of dopamine markers in the Arc and plasma prolactin levels following short and long-term treatment. As a comparison, the effects of haloperidol on these measurements were also examined.

Methods: Male Sprague Dawley rats were treated with aripiprazole (0.75mg/kg, t.i.d.), haloperidol (0.1mg/kg, t.i.d) or control (vehicle) for 1-week or 10-weeks (n=6/group). Protein levels of TH, phospho-TH (pTH) and dopamine transporter (DAT) in the Arc, as well as plasma prolactin levels, were examined.

Results: Compared to controls, haloperidol significantly increased TH levels ($p<0.01$) after both short- and long-term treatment, and pTH and DAT after long-term treatment ($p<0.05$); however, aripiprazole had no significant effect on these dopamine markers in the Arc. Consistently, haloperidol ($p<0.01$), not aripiprazole, significantly increased plasma prolactin levels.

Conclusion: Aripiprazole and haloperidol have different effects on the expressions of dopamine markers in the Arc and prolactin levels. These results support the selective effects of aripiprazole on dopamine synthesis in different dopamine pathways as a possible mechanism for the long-term efficacy of aripiprazole with low EPS and HPL side-effects liability.

P-01-051 Metabolic syndrome in patients with schizophrenia treated with antipsychotics: Attitudes from psychiatrists

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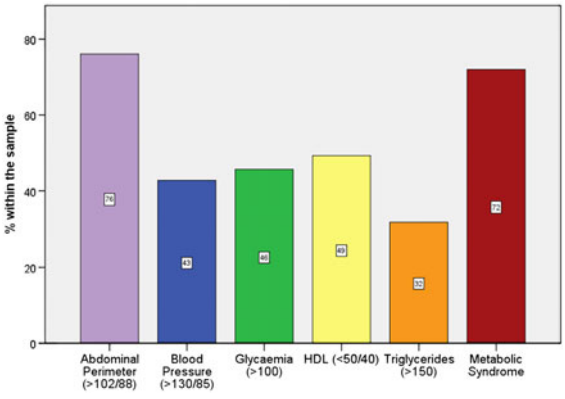
Objective: to evaluate the prevalence of metabolic syndrome in patients with schizophrenia and to investigate the consequent actions implemented in the Mental Health Services (MHS).

Methods: This was part of a longitudinal research focused in physical health of patients treated with antipsychotic medication, performed in two outpatient clinics. 147 patients (84 males) with a DSM-IV diagnosis of schizophrenia (n=111), schizoaffective disorder (n=18) or related psychoses (n=18) were included. Metabolic syndrome was defined according to NCEP-III criteria. Actions implemented after the evaluation of the patients were assessed with medical records and a structured questionnaire. Associated factors and actions were included in a logistic regression model.

Results: 52.7% of the patients fulfilled metabolic syndrome criteria. BMI was associated to all the metabolic factors ($p<0.001$), time of antipsychotic medication was associated with metabolic syndrome, abdominal perimeter and triglycerides. Tobacco use was associated to glycaemia and HDL and gender was related to glycaemia. The model for metabolic syndrome ($X^2=30.040$; R^2: 0.225; $p<0.001$) included gender, age, BMI and tobacco. Only 23 patients (15.4%) were receiving treatment for any metabolic factor. In patients with metabolic syndrome, 50% were intensified in the monitoring, 45.5% were referred to the GP and 3.9% received pharmacological treatment. Remission to GP ($X^2=29.584$; R^2: 0.189; $p<0.001$) only included glucose, triglycerides and HDL levels and polymedication as independent predictor factors. Interestingly, two fold differences between the Mental Health Services were observed in the rate of implemented actions.

Conclusion: Metabolic syndrome was highly prevalent and related to male gender, tobacco and BMI. Actions implemented appear to be conservative and unequal. Glucose, triglycerides and HDL levels were the factors implied in more actions. There is a need of implementation of standard procedures in MHS in order to reduce the impact on cardiovascular risk and the differences between services.



P-01-052 Early response to antipsychotic treatment as clinical marker of subsequent response in first episode schizophrenia patients

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Objective: The time-course of response to antipsychotic treatment has important implications for management of acute treatment of patients suffered from schizophrenia. In recent studies it has been shown that some patients with long-term schizophrenia have demonstrated a response to antipsychotic treatment within 2 weeks of initiating treatment. Early improvement of schizophrenic symptomatology has been associated with later response to antipsychotic treatment. However it is still unknown whether the predictive pattern of early response seen in patients with long-term schizophrenia exists for patients with first-episode psychosis as well. The aim of the study was to investigate whether early response in the second week can predict response in the fourth week of antipsychotic treatment in a population of the first episode schizophrenia patients.

Methods: First episode schizophrenia male patients were rated by PANSS in four consecutive weeks during monotherapy with risperidone. Response rates in particular weeks were calculated.

Responders were characterized by 20% decrease of total PANSS score at least.

Results: Fourteen patiens were included to the study, average age was 24 years and average duration of schizophrenia was 4,4 months. 71% of patients were assessed as responders (N=10) and 29% of them as nonresponders (N=4). In the second week of therapy later responders reached higher decrease of total PANSS score (about 43%) in relation to nonresponders (about 22%).

Conclusion: First episode schizophrenia patients are characterized by the high reactivity to antipsychotic therapy. The most prominent improvement of schizophrenic symptomatology occurs during first two weeks of treatment. Early response in the second week predicts consecutive response in the fourth week of the therapy. Acknowledgement: This work was supported by the project ''CEITEC – Central European Institute of Technology'' (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund.

P-01-053 Clozapine induced rash: Case report of successful desensitisation

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Objective: Clozapine is the drug of choice for patients with treatment-resistant schizophrenia. However a minority of them have been unable to continue with Clozapine due to side-effects, for example rash. This report looks at the use of graded desensitization in a patient who developed cutaneous reactions to Clozapine.

Methods: This report describes the management of a patient with treatment resistant-schizophrenia, mild learning disabilities and epilepsy, following a cutaneous reaction to Clozapine. Having been maintained on Clopixol depot until 4 years ago, he required a change in antipsychotics following a relapse of psychotic symptoms. He was then treated unsuccessfully with various anti-psychotics, before starting Clozapine, to which he showed a good response. Unfortunately he developed an eczematous rash on two separate occasions when the drug was introduced. Again he was tried on other antipsychotics, to which he also developed a rash. He was then put on a graded desensitization regimen of liquid Clozapine.

Results: Graded desensitization, using incremental increases in drug dose, allowed maintenance treatment with therapeutic doses of Clozapine to be achieved in the absence of cutaneous hypersensitivity reactions. The patient's previously treatment-resistant psychotic symptoms were improved by this method.

Conclusion: We should be aware of possibilities for the management of both the common and uncommon side-effects associated with Clozapine, as the result might vastly improve the patients' quality of life. Desensitisation regimens can be an effective means of overcoming drug hypersensitivity but should be used with great caution, especially when patients exhibit delayed-type hypersensitivity reactions (as here).

P-01-054 Psychotic episode in epilepsy-treatment modality

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Objective: The aim of this study was to compare parallel effects of risperidone and closapine in treatment of psychotic episode in verified Grand-mall epilepsy. Due to changes in organic substrate, psychosis is not rare comorbidity in epilepsy. There were no consensus about treatment options. It is known that antipsychotics lower seizure threshold, cause EEG abnormalities and put the patients in the risk for additional seizures.

Methods: The total of 85 adult patients of both gender (39 females) with clinically and EEG confirmed Grand-mall epilepsy developed psychotic episode. The psychotic state was evaluated using BPRS scale. Subject were treated either with risperidone (n=43) 5.7±.1.4 mg per day or with clozapine (n=42) 106.2±29.8 mg per day, orally. Results. The total BPRS scores in risperidone group at baseline, in 1st, 2nd and 3rd week were 134.1±41.3, 98.4±28.7, 88.9±21.9, and 78.3±14.8, respectively ($p<0.05$).

Results: The total BPRS scores in risperidone group at baseline, in 1st, 2nd and 3rd week were 134.1±41.3, 98.4±28.7, 88.9±21.9, and 78.3±14.8, respectively ($p<0.05$). The total BPRS scores in clozapine group at baseline, in 1st, 2nd and 3rd week were 138.3±33.7, 109.1±33.1, 97.3±22.8, and 90.7±21.4, respectively ($p<0.05$).

Conclusion: Our results showed that risperidone is more effective and comfortable drug than clozapine in the treatment of psychotic episodes in epilepsy.

P-01-055 Aripiprazole in the treatment of first episode of psychosis in a patient with hypogonadism due to hyperprolactinemia

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Objective: Aripiprazole is a new atypical antipsychotic with dopaminergic agonistic activity at a low dose. Dopamine is a prolactin-inhibiting factor and dopamine imbalance has been implicated in the pathophysiology of psychotic disorders. We investigated the probable relatioship between hyperpralactinemia and the development of psychotic symptoms and the role of aripiprazole medication, in a single case.

Methods: We present the case of a patient with hypogonadism secondary to chronic, untreated hyperprolactinemia who developed acute psychotic symptoms and the beneficial role of aripiprazole medication on both psychotic symptoms and on serum prolactin levels.

Results: Psychotic symptoms resolved soon after treatment with aripiprazole in conjunction with cabergoline, with a concomitant decrease in serum prolactin levels.

Conclusion: This is an interesting case indicating the beneficial role of aripiprazole treatment and also illustrating a complicated relationship among hypogonadism secondary to prolactinoma and dopamine and psychosis.

P-01-056 The effect of the atypical antipsychotics on cognitive deficit in schizophrenia

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Objective: While the typical antipsychotics do not improve cognition and may even alter memory due to their prevalent antimuscarinic and antidopaminergic features, recent studies show that atypical antipsychotics cause improvements in learning, processing speed, speech fluency and motor abilities. Objectives: The study aimed at defining the cognitive deficit in schizophrenia and the influence of the atypical antipsychotics on it. Another objective was to compare the neurocognitive effects of olanzapine, quetiapine, risperidone, ziprasidone, clozapine and sertindole.

Methods: The study was of the observational prospective type, lasting for 52 weeks was made on 7 groups of 20 patients each, according to the type of the antipsychotic used in therapy: olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, clozapine and sertindole. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and BACS (Brief Assessment of Cognition in Schizophrenia) test batteries have been applied.

Results: After 40 weeks, corresponding V10, every antipsychotic drug improved the compound score of the CATIE and BACS neurocognitive battery comparing to the moment of the inclusion in the study (Vi). There was a positive correlation: the patients who displayed a cognitive improvement at the V10 moment, also displayed benefits in the social and occupational fields, which suggests a functional relevance for the improvement of cognition.

Conclusion: There is an important cognitive deficit in the majority of the schizophrenic patients. Olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, clozapine and sertindole have displayed similar results in terms of their effects on various neurocognitive deficits.

P-01-057 Relapses in psychotic disorders treated with oral paliperidone: A 12-month follow-up

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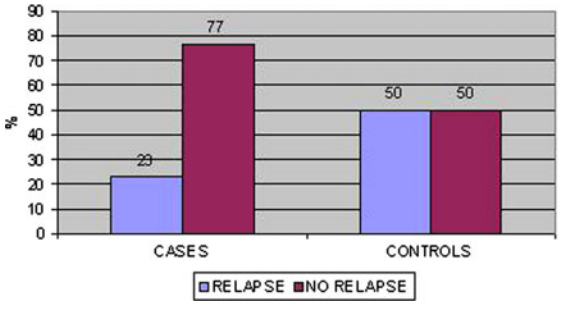
Objective: Describe and compare the relapse rate at 12 months in a sample of patients with psychotic disorders treated with oral Paliperidone versus other antipsychotics.

Methods: Descriptive observational study comparing two historical cohorts. Patients were recruited over a period of two years Sample of patients with psychotic disorder, mainly schizophrenia. We included patients aged ⩾18 years, diagnosis of psychotic disorder and relapse situation that requires hospitalization. Subjects that in the observation period did not present psychotic symptoms are excluded.

Results: 200 patients were included, all the patients were hospitalized at the time of inclusion in the study. Homogeneous groups in terms of size, demographic (except for sex) and clinical characteristics. 73% had a diagnosis of schizophrenia and 7.5% had other diagnoses with transitory psychotic symptoms. 23% of patients treated with oral paliperidone relapse and were readmitted at 12 months after discharge, compared to 50% in the group of patients taking other antipsychotics ($p < 0.05$). Both groups showed a non statistically significant difference ($p = 0.809$) in the number of total days of hospitalization since admission: case 35.46 days (SD 31.2), controls 34.27 days (SD 37.9). There was no differences regarding the use of adjunctive BZD (cases = 47%, controls = 45%, $p = 0.77$) and/or biperiden (cases = 17%, controls = 27%, $p = 0.088$). The mean dose of oral paliperidone at discharge was 10 mg/day (SD 4.41, range 3–24.

Conclusion: Due to the study design, no causal relationships can be established. However, data suggest that patients treated with oral paliperidone have fewer relapses and readmissions at 12 months follow-up than patients treated with other antipsychotic treatment. These results could be associated with favorable side-effect profile and a lower treatment discontinuation rate.



P-01-058 Switching from olanzapine to ziprasidone: A twelve-week, open-label, multicenter study evaluating the effectiveness and safety of ziprasidone in patients with schizophrenia

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Objective: To evaluate the effects and safety of switching from olanzapine to ziprasidone, due to inadequate response or intolerance to olanzapine.

Methods: Totally, 120 subjects with schizophrenia who were either suboptimal efficacy or poor tolerability to olanzapine treatment (dose range 10–20 mg/day) for ⩾8 weeks were enrolled in a 12-week, open-label, flexible-dose ziprasidone trial. Olanzapine was tapered and discontinued over the course of 2 weeks, while ziprasidone was titrated up and dosed at 40–80 mg b.i.d. The primary endpoint was the improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline. The second endpoint were the change in lipid profile, fasting glucose, glycosylated hemoglobin (HbA1c) and serum prolactin level in 8 weeks of treatment from baseline.

Results: The intent-to-treat population was 100, and 86 patients completed 12 weeks trial. At week 12, there was a statistically significant decrease in PANSS total score, with a mean change from baseline was 65% ±26% using the LOCF analysis. The CDSS total score and each items, except item 3, Self-depreciation, decreased significantly from baseline. There were significant decreases in levels of total cholesterol. The finding replicate the results of some earlier studies (Rsossi et al., 2008; Grootens et al., 2011)[1, 2]. Adverse effect of ziprasidone is transitory and mild, including insomnia, somnolence, and nausea. There were no significant changes in the QTc interval.

Conclusion: Subjects switching from olanzapine to ziprasidone showed a significant improvement in clinical symptoms and quality of life, and decrease in total cholesterol levels, regardless of their metabolic status and disease severity at baseline. Ziprasidone with a comparatively neural metabolic profile and the comparable efficacy relative to other atypical antipsychics may be an important alternative for patients experiencing no-response or lack of tolerability with olanzapine treatment.

P-01-059 Research of olanzapine: Comparison research of a tablet and a sustained release drug

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Objective: Lack of insight of the patients with bipolar disorder and/or schizophrenia is common. Therefore, maintenance management of medicinal use is important. There are many patients who do not take drugs. Changing the form of medication may make those patients feel the medicinal using easier, We aimed to evaluate the adherence at maintenance pharmacological management by changing a tablet of olanzapine into a sustained release olanzapine.

Methods: This is a prospective study in Japan. Subjects were the patients with schizophrenia and/or bipolar disorder diagnosed by DSM-IV or ICD-10 who were taking olanzapine. Olanzapine were changed into an equivalent amount of sustained release drugs from the tablet. The patients who had changed to the sustained release drug were assessed 2 times by DAI-10; one month and two months later. The patients who started the sustained release drug newly were excluded.

Results: The patient who changed from the tablet to the sustained release drug showed good adherence assessed by DAI-10. We found better adherence at two months. Conclusions: Adherence of the patient having changed into the sustained release drug from the tablet of olanzapine was quite good.

Conclusion: Our findings showed the possibility that the change of the form of medication would improve the patients adherence even in the same drug. That is very important for continuation of a patient's medicine. We expect that changing into a sustained release drug would decrease the reduction of relapse.

P-01-060 Clinical interventions to counteract antipsychotic polypharmacy: A systematic review

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Objective: While pros and cons of antipsychotic polypharmacy have been frequently discussed, it still remains unclear as to how to counteract this common but controversial practice. The objective of this study was to synthesize the evidence on trials to reduce antipsychotic polypharmacy in schizophrenia.

Methods: A PubMED search was performed to identify two types of clinical trials: studies that systematically switched antipsychotic polypharmacy to monotherapy in research settings, and studies that intervened physicians' prescribing behaviours in clinical settings (last search: Dec 2011). The following search terms were

used: (''antipsychotic'' or ''antipsychotics'') AND (''polypharmacy'' or ''polytherapy''). Cross-referencing of the identified articles was also performed.

Results: The literature identified only two clinical trials (one randomized controlled trial and one open-label trial) that systematically converted polypharmacy to monotherapy; in both of them, approximately two thirds of the subjects successfully completed the switch (40/58, 69.0%; and 34/44, 77.3%, respectively). Those who experienced clinical worsening following the switch were mostly managed by going back to the previous antipsychotics. We also identified 13 relevant articles that examined impacts of interventions, including educational sessions, to have physicians, when possible, refrain from the use of antipsychotic polypharmacy for the treatment of schizophrenia. A modest intervention with educational approach alone was effective in 3 of 5 articles (60%). On the other hand, a more assertive intervention that directly cautioned physicians on the use of multiple antipsychotics was effective in 9 of 11 articles (82%).

Conclusion: Switching from polypharmacy to monotherapy seems feasible in a majority of patients with schizophrenia. Assertive interventions, rather than educational approach alone, appear more useful to practically reduce the use of antipsychotic polypharmacy in clinical settings. In light of the paucity of the data, further investigations are needed on this prevailing but controversial issue.

P-01-061 Late-onset angioedema probably induced by risperidone in an elderly woman with schizophrenia

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Objective: Angioneurotic oedema is a rare adverse reaction which mainly involves oedema of the deep dermal and subcutaneous tissues. Few case reports have established its association with the use of specific antipsychotics such as risperidone, clozapine, ziprasidone, droperidol and chlorpromazine. The aim of this study is to present a case of angiooedema in an elderly woman with psychosis possibly induced by risperidone.

Methods: We reviewed the patient's case notes and the relevant literature.

Results: The patient is a 69 years old Greek woman who was hospitalized due to a psychotic relapse. Her symptoms included ideas of reference, persecutory delusions, passivity phenomena, visual and auditory hallucinations. She was diagnosed with schizophrenia of paranoid type according to DSM-IV-TR criteria. During her hospitalization she was administered antipsychotic treatment with oral risperidone which was titrated up to 3mg daily. Psychotic symptoms improved and she was discharged from the ward. Eight months later she presented at the emergency department of the hospital suffering from oedema of face and lower extremities. These symptoms were not better accounted by any other medical condition (e.g. systemic infection, cardiovascular or respiratory disease). At that time she was not receiving any other drug treatment except risperidone and had no known history of allergy. Therefore, risperidone was considered responsible for her symptoms and was discontinued. She initially received treatment with cetirizine followed by low dose of hydroxyzine. The swelling subdued over a period of two weeks. Laboratory tests were within normal limits, but measurement of complement pathway activity was not performed.

Conclusion: We conclude that our patient developed late-onset risperidone-induced angioneurotic oedema. To our knowledge there is no previous report in the literature about angioneurotic oedema occurring within months of risperidone onset. Further studies are needed to delineate the mechanism of this kind of allergic reaction.

P-01-062 Aripiprazol (abilify) application by schizophrenia patients' therapy and affective disorders

E. Valzdorf. *Irkutsk, Russia*

Objective: 25 patients were examined stationary. According to episodes clinic patients were divided into 6 groups. The 1st- of schizophrenia patients with affective delusive episodes included 5 people. The 2nd- with affective hallucinate episodes included 3. The 3rd- with hallucinate delusive episodes included 3. The 4th- with primary maniacal episode included 3. The 5th- with bipolar affective disorder, current maniacal episode included 7. And the 6th- with bipolar affective disorder, mixed episode included 4.

Methods: Clinic-psychopathological method.

Results: the therapy of atypical neuroleptic- abilify was being made to schizophrenia patients with productive psychotic for the 1st, 2nd and 3rd groups. The dose started from 15 mg a day with gradual dose increasing in 1–2 days to 30 mg a day intake. At the same time these patients took the dose of haloperidol – decanoat. The dose was 5 mg intramuscularly once four weeks altogether with such preparation as tsicllodol. Also these patients depending on emotional condition in episode took amitriptillin 50 mg a day or vellacsin 50 mg a day and litiya carbonate 0,9 g a day. The improvement of these patients was noticed the 5th week therapy. ''Voice'' intensity and its frequency were decreased, hallucinate ideas became less actual. The expression of negative disorders of some patients was also decreased. The patients with bipolar affective disorder, current maniacal episode and with primary maniacal episode took abilify in dose 30 mg a day. The improvement of primary patients was the 3rd week, but the improvement of secondary patients was the 5th treatment. The mood became much better, statements and behaviour was regulated.

Conclusion: The improvement of patients with bipolar affective disorder, current maniacal episode was the 3rd week abilify treatment together. The improvement of schizophrenia patients with productive psychotic symtomatology was caused by abilify after 5 weeks treatment conducting with traditional neuroleptic. Abilify decreased the expression of negative symptoms of some schizophrenia patients.

P-01-063 Effect of chronic antipsychotic drug treatment on the rodent cerebral cortex: Linking ex vivo neuroimaging findings with post-mortem neuropathology

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Objective: To identify the locus of volume decreases in the rat neocortex due to chronic haloperidol treatment and provide preliminary evidence for the mechanisms underlying this effect. Background: Antipsychotic drugs (APD) may affect brain structure directly in Schizophrenia patients (Ho et al., 2011). Indeed, pre-clinical studies suggest chronic haloperidol treatment results in a decreased total volume of the neocortex, which is reversible upon drug withdrawal (Vernon et al., 2012). However, the location of volume changes within the neocortex and the mechanisms underlying this effect are not fully elucidated. We now report preliminary results of automated MR image analysis and post-mortem studies to address these issues.

Methods: Male Sprague-dawley rats were treated chronically (8 weeks) with placebo ($n=8$) or haloperidol (2 mg/kg/day s.c. $n=8$). MRI scans were acquired ex vivo after cessation of treatment. Brain volume differences between treatment groups were analysed using a hypothesis-free deformation-based morphometry (DBM) analysis (Vernon et al., 2011). Volumetric differences in the neocortex identified by DBM were investigated post-mortem from nissl stained tissue sections (40 μm thick, 1/12 series) using unbiased stereology (Cavalieri probe) to validate the DBM-led approach.

Results: DBM analysis identified local tissue volume decreases in the neocortex, most prominently in the medial prefrontal cortex (mPFC) of haloperidol-treated animals ($p<0.05$ uncorrected). Post-mortem analysis confirmed significant decreases in the thickness of the prelimbic (PrL) region of the mPFC and in the volume of the anterior cingulate cortex (ACC), but not in the thickness of the primary motor, sensorimotor or visual cortices. Preliminary analysis of neuronal number in the ACC revealed no significant differences between vehicle and haloperidol-treated groups.

Conclusion: Chronic haloperidol treatment induces volumetric decreases in the mPFC of the rat neocortex, which is potentially not explained by neuronal loss. Further detailed cell counting is now in progress.

P-01-064 Medication adherence in schizophrenia and potential risk factors associated with non adherence in South West Ethiopia

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Objective: Non-adherence behavior is a significant issue in the management of psychotic disorders, for it is major cause of psychotic relapse and is strongly influenced by many factors. Medication adherence to antipsychotic drugs is detrimental to the perceived outcome of treatment. The objective of this study is to evaluate adherence rate to antipsychotic medications and identify the potential risk factors associated with non adherence.

Methods: A cross-sectional study was conducted on 336 patients using patients self report and pharmacy refill record where by both qualitative and quantitative methods of data collection was used. The self report involved the structured patient interview after verbal informed consent was obtained. Data were analyzed using SPSS for windows version 16.0. Chi-square test was used to observe the association of variables with adherence.

Results: The adherence rate of patients (n = 336) is found to be 57.5% based on their refill records, compliant fill rate. On the basis of patients self-report for their pattern of drug use, 52.1% participants said that they had never missed their doses, while 32.1% participants missed daily doses sometimes, 4.7% missed only time of taking, and 5.9% missed both time of taking daily dose sometimes. The most common reasons for missing dose were forgetfulness (36.2%) and being busy (21.0%). Pill burden, side effects of medications, exposure for social drugs have statistically significant negative association but, increased duration of maintenance medication is found to enhance rate of adherence.

Conclusion: Large proportion of the study patients failed to refill their medications properly which indicates the severity of the problem and calls due consideration in planning appropriate strategies to improve the existing conditions.

P-01-065 Effects of an adjunct nicotinic a7 receptor agonist to the atypical antipsychotic risperidone in animal models of antipsychotic activity and extrapyramidal side effect liability

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Objective: Cognitive impairment is debilitating in schizophrenia (SCH). Effects of adjunct treatment with cholinergic nicotinic α7 receptor agonists to antipsychotics (APDs) for cognitive improvement in SCH are under investigation in clinical studies with some positive reports. However, changes in retained antipsychotic efficacy of the simultaneously given APD, as well as changes in extrapyramidal side effect (EPS) liability, following adjunct nicotinic σ7 agonist treatment are, to the best of our knowledge, not well known. Therefore, we here investigated, experimentally, the effects of adjunct treatment with the selective nicotinic α7 receptor agonist PHA 543, 613 (1 mg/kg) to the atypical APD risperidone (0.2 or 0.8 mg/kg) in animal models of antipsychotic activity and EPS liability, in rats.

Methods: The conditioned avoidance response (CAR) test was used for assessment of antipsychotic activity. Assessment of EPS liability was performed using the catalepsy test. Statistical evaluation was performed by means of non-parametric statistics.

Results: CAR: Risperidone produced a dose-dependent, significant antipsychotic-like suppression of CAR. Compared with risperidone 0.2 mg/kg alone, pretreatment with PHA 543, 613 (1 mg/kg) showed a strong tendency to reverse risperidone 0.2 mg/kg – induced suppression of CAR that was close to statistical significance. PHA 543, 613 alone had no effects on CAR. Catalepsy: Compared with vehicle treated controls, risperidone (0.2 mg/kg) significantly increased catalepsy scores. Pretreatment with PHA 543 613 further enhanced risperidone-induced increase in catalepsy scores. Also PHA 543 613 alone significantly increased catalepsy scores. The difference in catalepsy scores between risperidone alone and combined PHA 543 613/risperidone treatment groups was close to statistical significance.

Conclusion: The data suggest that adjunct nicotinic α7 agonist treatment for cognitive impairment in SCH may come with a risk of reduced antipsychotic efficacy and an increase in EPS liability, at least when given with a low dose of the atypical APD risperidone.

P-01-066 Changes in metabolic parameters and Framingham cardiovascular risk scores after in-hospital antipsychotic treatment – preliminary results

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Objective: The objective of this study was to assess changes in the prevalence of metabolic syndrome (MetS) and cardiovascular risk scores after in-hospital treatment with antipsychotics.

Methods: 31 subjects (F 18/M 13; mean age 36.5 years) with schizophrenia were assessed on admission and at discharge. Height, weight, waist circumference, blood pressure, plasma lipids and glucose were measured. Smoking, illness duration, hospital stay duration, number and doses of antipsychotics, concomitant use of antihypertensives, antidiabetics or hypolipidemics were registered. International Diabetes Federation definition of MetS was used. Cardiovascular risk scores were calculated using the Framingham Heart Study algorithms.

Results: Mean illness duration was 126.9 months, mean hospital stay was 51.9 days. 25 patients (80.6%) were taking more than 1 antipsychotic. The majority of subjects (90.3%) were taking second generation antipsychotics. Overweight, obesity, abdominal obesity, lipid abnormalities and hypertension was were found in 13 (41.9%), 14 (45.1%), 24 (77.4%), 24 (77.4%) and 16 (51.6%) patients, respectively. At discharge metabolic parameters did not improve, while triglyceride levels increased ($P = 0.003$). MetS prevalence increased from 41.94% to 61.29% ($P = 0.029$). Number of MetS criteria met increased ($P < 0.001$). The rate of abdominal obesity ($P < 0.001$), raised TGA ($P < 0.001$), raised FPG ($P = 0.005$) and reduced HDL ($P < 0.001$) increased. No differences in age, sex, tobacco smoking, duration of hospital stay and schizophrenia, number and type of antipsychotics between subjects with or without MetS were found. Cardiovascular risk scores did not increase at discharge.

Conclusion: Between admission and discharge the prevalence of MetS, number of MetS criteria met, the rate of abdominal obesity, raised TGA, raised FPG and reduced HDL increased. Metabolic parameters did not improve during hospital stay, while triglyceride levels increased. No increase of cardiovascular risk scores was found. The majority of patients had abnormal body weight, abdominal obesity and untreated hyperlipidemia.

P-01-067 Animal model of treatment-resistant schizophrenia

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Objective: Animal models are invaluable for the screening of novel compounds for mental disorders such as schizophrenia. In most of the animal models, first generation antipsychotic drugs such as haloperidol are effective in reducing spontaneous and drug-induced hyperactivity but have little effect on behavioral changes related to negative symptoms and cognitive dysfunctions. In contrast, second generation antipsychotic drugs such as clozapine are reported to be effective in ameliorating most of the behavioral abnormalities, although one-fifth to two-third of patients are considered treatment resistant and show persistent psychotic and other symptoms despite the optimal use of antipsychotic medications. To identify compounds that may be more effective than existing antipsychotic medications in ameliorating the negative symptoms and cognitive dysfunctions in schizophrenia, animal models for antipsychotic drug-resistant schizophrenia are needed.

Methods: Transgenic mice expressing a dominant-negative N-terminal human DISC1 under the expression control of CaMKII promoter (DN-DISC1 mice) were injected with polyI:C during the neonatal stage, and their behavioral phenotypes were examined in adulthood.

Results: PolyI:C-treated DN-DISC1 mice exhibited the deficits of short-term memory, object recognition memory, social interaction,

hippocampus-dependent fear memory, and augmentation of MK801-induced hyperactivity after puberty, although polyI:C treatment or DN-DISC1 expression by itself has negligible effect on wild-type mice. Cognitive impairment in this model was ameliorated by repeated administration of clozapine, but not haloperidol. Both antipsychotic drugs suppressed the enhancement of MK801-induced hyperactivity in the model but have no effects on deficits of short-term memory and hippocampus-dependent fear memory, or impairment of social interactions.

Conclusion: These results suggest that adult DN-DISC1 mice with neonatal polyI:C treatment may be useful for the screening of potential antipsychotic compounds that could be more effective in ameliorating social and cognitive impairments in treatment-resistant schizophrenia.

P-01-068 Impact of switching to second-generation antipsychotics on the treatment of long-term inpatients with schizophrenia

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Objective: The purpose of this study is to investigate the impact of switching from the first generation antipsychotics (FGAs) to the second generation antipsychotics (SGAs) on clinical efficacy and adverse effect in the treatment for long-term inpatients with schizophrenia.

Methods: Eighty five patients with schizophrenia diagnosed by DSM-IV were selected among inpatients hospitalized for at least 12 years. Efficacy on Brief Psychiatric Rating Scale (BPRS) and adverse effect on Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) have been evaluated and analyzed with these patients' characteristics and the profiles of prescribed drugs including antipsychotics, antiparkinsonian agents and mood stabilizer.

Results: After switching to SGAs, the scores of BPRS and DIEPSS were significantly decreased, and the number of prescribed antipsychotics and antiparkinsonian agents was significantly decreased although the total Chlorpromazine-equivalent dose of antipsychotics has been unaltered for 12 years of inpatient duration.

Conclusion: These results suggested that switching to SGAs from FGAs in the treatment for long-term inpatients with schizophrenia brought a better outcome in both clinical efficacy and safety, and possible prevention of polypharmacy.

P-01-069 No association between hormonal abnormality and sexual dysfunction in Japanese schizophrenia patients treated with antipsychotics

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Objective: Although sexual dysfunction is believed to be caused by hormonal abnormalities, few reports have studied sexual dysfunction and its association with hormonal abnormalities in Asian populations with schizophrenia.

Methods: We employed a cross-sectional, case-control survey design to collect data from 191 (108 men) Japanese schizophrenia outpatients treated with antipsychotics and 182 (49 men) healthy subjects. Sexual dysfunction was evaluated using the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale. We measured plasma concentrations of prolactin in both genders and testosterone in men and estradiol in women.

Results: Multiple regression analyses revealed the following findings: the number of antipsychotics correlated with diminished sexual desire (standardized beta = 0.241, $p < 0.05$); the dose of antipsychotics correlated with gynecomastia (standardized beta = 0.277, $p < 0.01$), increased sexual desire (standardized beta = 0.229, $p < 0.05$), and ejaculatory dysfunction (standardized beta = 0.248, $p < 0.05$); and the dose of antipsychotics correlated with menorrhagia in women (standardized beta = 0.284, $p < 0.05$). However, neither plasma concentrations of prolactin, testosterone nor estradiol correlated with sexual dysfunction.

Conclusion: The present study demonstrated that an association between sex hormone abnormalities and sexual dysfunction is unlikely but that the dose or number of antipsychotics is associated with some sexual dysfunction.

P-01-070 Effectiveness of prn medications in psychiatric patients: A systematic review

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Objective: The use of ''pro re nata (prn)'' medications to manage patients' perturbed behaviors such as agitation and aggression is widespread in psychiatric clinical practice. However, it is unclear which psychotropic drugs are more effective and tolerable than others. The aim of this study was to synthesize the evidence on prn medications in psychiatric patients.

Methods: A MEDLINE search was performed to identify studies published in English between 1966 and December 2011. The following search terms were used: (''prn'' or ''p.r.n'' or ''pro re nata'' or ''as needed'' or ''as required'' or ''stat* med*'' or ''as necessary'') and (psychiatr* or mental* or antipsychotic* or psychotropic*). Cross-referencing of the identified articles was also performed.

Results: The literature search identified 13 studies that assessed epidemiological usage of prn medications and 13 retrospective studies that evaluated the effectiveness/safety as well as reasons for prn administrations. Patients studied were all inpatients, and the reasons for prn administration were commonly acute behavioral dyscontrol. On the other hand, diagnoses and outcome measures to assess effectiveness/safety varied and inadequately described. Medications under study included antipsychotics, mood stabilizers and benzodiazepines. On the whole, most studies reported that prn medications were effective in psychiatric inpatients. However, only three prospective studies were identified to evaluate the effectiveness/safety of prn medications; furthermore, all of them included solely a child/adolescent population. One was a preliminary double-blind study of diphenhydramine in a child population ($N = 21$). Another was concerned about child/adolescent patients for subjective perceptions of prn medications ($N = 42$). The other was a post-hoc analysis of the data from clinical records of 338 child/adolescent patients.

Conclusion: Our findings indicate that there has been only equivocal evidence to guide a choice of prn medications for psychiatric patients. Further clinical trials needed to investigate the effectiveness and safety of prn medications in various psychiatric disorders.

P-01-071 Not only dopamine D2 receptors involved in peony-glycyrrhiza decoction, an herbal preparation against antipsychotic-associated hyperprolactinemia

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Objective: Hyperprolactinemia (hyperPRL) is a frequent complication of antipsychotic treatment. Clinical studies have demonstrated the effectiveness of an herbal preparation called Peony-Glycyrrhiza Decoction (PGD) in alleviating antipsychotic-induced hyperPRL.

Methods: In the present study, we further examined the pharmacological action of PGD on prolactin (PRL) secretion using in vitro and in vivo models, with specific attention to the role of dopaminergic mediators and other sexual hormones.

Results: Treatment with PGD at 1 mg/ml and 5 mg/ml for 24 and 36 hrs significantly suppressed PRL secretion in MMQ cells, a model of hyperPRL derived from pituitary adenoma cells. PGD also suppressed PRL synthesis by MMQ cells in a dose-dependent manner. These suppressive effects were completely abolished by pretreatment with 10 microM haloperidol, a dopamine D2 receptor antagonist. consistent with a D2-action, PGD did not affect PRL secretion and

synthesis in rat pituitary lactotropic tumor-derived GH3 cells that lack the D2 receptor expression but significantly increased the expression of the D2 receptors and dopamine transporters (DAT) in PC12 cells. In a rat model of hyperPRL, produced by repeated injection of dopamine blocker metoclopramide (MCP), chronic PGD (2.5–10 g/kg daily) for 14 days significantly reduced elevated serum PRL. The reduction in magnitude was similar to that elicited by 0.6 mg/kg bromocriptine (BMT), a dopamine D2 receptor agonist currently used for treatment of hyperPRL. Neither PGD nor BMT altered serum estradiol, but PGD reversed MCP-induced decrease in serum progesterone to control level, whereas BMT did not.

Conclusion: These results indicate that the anti-hyperPRL effects of PGD are associated not only with D2 receptor and DAT modulation, but also with a normalization of other sexual hormone dysfunction. This experimental evidence supports clinical use of PGD as an effective treatment of antipsychotic-induced hyperPRL.

P-01-072 Effects of chronic oral treatment with aripiprazole on the expression NMDA receptor subunits and binding sites in rat brain

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Objective: The glutamatergic theory of schizophrenia proposes a dysfunction of ionotropic N-Methyl-D-aspartate receptors (NMDA-R). Several therapeutic strategies address NMDA-R function and effects of antipsychotic agents on NMDA-R expression have been described. Within the second generation antipsychotics, the partial dopaminergic and serotonergic agonist aripiprazole (APZ) was able to counteract behavioural effects of NMDA-R antagonists. We intended to investigate the effects of APZ on NMDA-R subunit expression and binding.

Methods: Male, wildtype Sprague-Dawley rats were treated for 4 weeks or 4 months with APZ in daily oral doses of 10 and 40 mg per kg body weight. Gene expression of the NMDA-R subunits NR1, NR2A, NR2B, NR2C and NR2D was assessed by semiquantitative radioactive in situ-hybridization, and in parallel receptor binding using 3H-MK-801 receptor autoradiography.

Results: Increased expression levels of NR1 (4 weeks), NR2A (4 weeks), NR2C (4 weeks and 4 months) and NR2D (4 months) were observed in several hippocampal and cortical brain regions. The parallel reduced expression of NR2B mRNAs (4 months) resulted in a relative increase of the NR2A/NR2B ratio. Marked differences between specific brain regions, the doses of APZ and the time points of assessment became obvious. On the receptor level, increased MK-801-binding was found after 4 weeks in the 40 mg-group and after 4 months in the 10 mg-group.

Conclusion: The effects of APZ converge in enhanced NMDA-receptor expression and a shift of subunit-composition towards adult-type receptors. Our results confirm regulatory connections between dopaminergic, serotonergic and glutamatergic neurotransmission. In consequence, APZ treatment may counteract a glutamatergic deficit state with positive consequences on cognitive and negative symptoms of schizophrenia.

P-01-073 New onset metabolic syndrome among patients receiving clozapine

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Objective: To study the prevalence of metabolic syndrome in patients receiving clozapine and prospectively evaluate the incidence of new onset metabolic syndrome after 3 months of therapy with clozapine.

Methods: For this study, 53 patients who were considered for clozapine therapy were evaluated for the presence of metabolic syndrome as defined by modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criteria. These patients were prospectively followed after 3 months for change in metabolic syndrome status.

Results: Slightly more than one third of the patients had metabolic syndrome prior to starting clozapine. Another one sixth of the patients who did not have metabolic syndrome prior to starting clozapine developed metabolic syndrome after receiving clozapine for a duration of 3 months.

Conclusion: Clozapine contributes to the metabolic disturbances.

P-01-074 Course of negative symptoms in first-episode psychosis on aripiprazole vs. other antipsychotics during a two years follow-up

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Objective: Severeal lines of evidence indicate that early intervention with appropriate pharmacological treatment can contribute to improve the course and outcome of the illness (Linszen et al., Br J Psych Suppl 1998). Aripiprazole is an atypical antipsychotic that appears to be well tolerated and it has a low propensity for causing extrapyramidal symptoms which can cause secondary negative symptoms (5). The present prospective naturalistic study sets out to investigate changes in overall functionallity, total symptomatology and, more specifically, negative symptomatology with aripiprazol and other second generation antipsychotics (SGA) in first episode patients during two-years of follow-up period.

Methods: Subjects with a first episode of psychosis were assessed and followed according to the first episode program of the centre (INAD). From the total sample of 130 recruited subjects, 42 completed the two years follow-up*. During the follow up period, patients were clinically assessed using PANSS scale (amongst others). Antipsychotic treatment was prescribed by specialized psychiatrists according to clinical criteria. In this naturalistic study we studied the association of antipsychotic treatment (aripiprazole vs. other SGA) at 2nd year of the follow up period and change in negative symptoms during the follow-up period.

Results: Patients on aripiprazole at 2nd year in comparison to the beginning of the follow-up period had a significant higher decrease of negative symptoms: Ari: 3.09 (SD: 4.0); Others: −0.79 (SD: 5.3), $p = 0.044$. There were no other significant differences in changes in positive symptoms or general functioning between groups.

Conclusion: Aripiprazole seems to improve negative symptoms more than other second generation antipsychotics without significant risk of increasing positive symptoms or worsening functioning. Important limitations of this study include that patients were not randomly assigned and that aripiprazole seems to be chosen by psychiatrists for those patients showing more negative symptoms. * Four patients included in another study were excluded from this analysis.

Policy of full disclosure: Travel expenses and congress attendance were facilitated by Otsuka.

P-01-075 Quetiapine prevents oligodendrocyte and myelin losses and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice

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Objective: White matter impairment is the feature of vascular depression. Antipsychotic quetiapine has been shown enhancing the therapeutic effects of antidepressants on vascular depression, but the mechanism remains unknown. In this study, we will try to find the white matter protective effects of quetiapine in vascular depression mice model in order to clarify the mechanism of effects of quetiapine on vascular depression.

Methods: Mice were assigned to receive a sham or global cerebral ischemia surgery, which generated four treatment groups: Sham (sham + saline), QTP (sham + quetiapine), GCI (GCI + saline) and G + Q (GCI + quetiapine). GCI was induced by bilateral common carotid arteries occlusion (BCCAO). Immunohistochemistry staining was used for pathological study. Myeline damage was observed by MBP staining. Loss and proliferation of Oligodendrocyts were observed by GST-pi, O4, NG2 and BrdU staining.

Results: we found that two weeks of treatment with quetiapine prior to bilateral carotid artery occlusion and reperfusion, an animal

model of vascular depression resulted in reduced myelin breakdown down and oligodendrocyte loss compared to placebo treated mice on postoperative day (POD) 7. For late stage of recovery (POD40), quetiapine treatment resulted in enhanced oligodendrocyte maturation relative to placebo.

Conclusion: The results suggest that quetiapine is a potential intervention for oligodendrocyte damage and may contribute its antidepressant effects through white matter protection in vascular depression.

Policy of full disclosure: Xin-Min Li has received funding from AstraZeneca. Other authors have no conflict.

P-01-076 Paliperidone palmitate treatment in schizophrenia

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Objective: Treatment with Paliperidone Palmitate, see its effectiveness, tolerability and adherence in schizophrenia, an experience with 17 patients.

Methods: In 17 schizophrenic patients (DSM-IV-Tr) who were being treated with other antipsychotics, previous treatment was discontinued in case of intolerance or insufficient response, and changed to Paliperidone Palmitate (75–150 mg/month) the follow-up performed was for 2 months. We used as a measure of efficacy, the PANNS and the ICG. We evaluated potential side effects reported by patients, evaluating tolerance and effectiveness of treatment. Antiparkinsonian drugs were only used in 3 patients during the first week, mainly due to presence of extrapyramidal symptomatology due to previous antipsychotic treatments.

Results: The mean baseline measurement on day 0 in the PANSS was 76 and the mean CGI was 4.5. The study is still carrying on since Paliperidone Palmitate was marketed in Spain in early November 2011, therefore we can not present at this time definitive data, except baseline scores. So far the impression is good, both in efficiency and in tolerance. We will give definitive results at the end of the study.

Conclusion: If the preliminarily data obtained are confirmed at the end of the follow up period we believe that Paliperidone Palmitate should occupy a prominent place in the treatment of schizophrenia. We also believe that will facilitate treatment adherence so necessary in these patients prone to abandonment and non-compliance.

P-01-077 Dose translation of aripiprazole between human and animal studies

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Objective: Aripiprazole is a newly developed antipsychotic which has a unique pharmacological profile of D2 receptor partial agonistic effect. As it has been approved for the treatment of schizophrenia, a growing body of studies has applied this compound to animal study with its novelty. To determine a suitable dose for animal study we compared the plasma concentration of aripiprazole and its metabolite in schizophrenic patients and rats.

Methods: Plasma concentration of aripiprazole was measured in 25 schizophrenic patients who were stably treated with aripiprazol at least six months and 12 SD rats that treated with aripiprazole 21 days. Plasma concentration of aripiprazole and metabolite was measures by LC-MS-MS. The dose range for schizophrenic patients was 10–30 mg per day and corresponding dose for rats that was estimated by using the body surface area (BSA) normalization method.

Results: The average oral dose of aripiprazole was 0.20 ± 0.08 mg/kg in human and a low dose (1.92 ± 0.05 g) and high dose group (3.78 ± 0) in rats. The average plasma concentration of aripiprazole and metabolite, opc14857 was 334.62 ± 205.35 ng/mL and 90.55 ± 70.23 ng/mL in human and 3.00 ± 2.57 ng/mL and 0.92 ± 0.52 ng/mL in low dose group and 9.83 ± 6.62 ng/mL and i1. 84 ± 0.58 ng/mL in high dose group n rats. The ratio of aripirazole and oral dose was 1736.38 ± 839.82 in human and 1.58 ± 1.37 in low dose group and 2.6 ± 1.75 in high dose group in rats.

Conclusion: Our results demonstrated that by using the BAS normalization method the oral dose for animal studies was ten times high compared with human study. However, the plasma concentration is one hundred times lower in animal. We advocate that a dose translation between human and animal studies in aripiprazole should be cautious.

P-01-078 A flexible-dose study of paliperidone ER in non-acute patients with schizophrenia previously unsuccessfully treated with other oral antipsychotics in the Asia Pacific region

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Objective: To explore tolerability, safety, and treatment response of flexible doses of paliperidone ER in adult Asian patients with non-acute schizophrenia, previously unsuccessfully treated with other oral antipsychotics.

Methods: Non-acute schizophrenia patients, who were unsuccessfully treated due to lack of efficacy, tolerability or safety issues, lack of compliance and/or other reasons, are transitioned to Pali-ER. The subjects were prescribed flexible dose Pali-ER 3–12 mg/day for 6 months.

Results: Data from 984 patients from 5 Asian countries were analysed. Data evaluated in two groups: Group A (switched due to lack of efficacy) $n = 424$; Group B (switched due to tolerability or safety issues, lack of compliance or other reasons) $n = 560$. 53% of Group A patients achieved more than 50% PANSS improvement from baseline to endpoint. Dosage distribution: 46% of Group A patients required Pali-ER 9–12 mg/day at end point; 58% patients in Group B required 6 mg/day at end point. There was an increase in the proportion of patients in both Group A (16%)and Group B (31%) achieving CGI-S categories of mildly ill or less at endpoint when compared to baseline. 43% and 73% more patients from Group A and Group B respectively at endpoint reported good to very good in terms of treatment satisfaction compared to baseline. 37% more patients from Group A and 35% more patients from Group B reached the PSP-defined categories of mild to no difficulties when compared to baseline. Visual analog scale shows that quality of sleep and drowsiness improved significantly ($p < 0.0001$) from baseline in both groups.

Conclusion: Flexibly dosed paliperidone ER treatment for up to 6 months shows improvements in non-acute schizophrenic patients who had an unsatisfactory outcome with previous antipsychotics, including PANSS, CGI-S, PSP, drowsiness and sleep quality.

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P-01-079 Oral vs. long-acting antipsychotics in a crisis resolution/home treatment team

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Objective: To describe the differences between schizophenic patients with oral vs. long-acting antipsychotic in a Crisis Resolution/Home Treatment (CRHT) Team in Barcelona.

Methods: We evaluated consecutive visits in a CRHT during 2 years in patients with psychotic disorder. A descriptive, observational and cross-linked study conducted in 163 patients. We collected demographic and clinical variables including the Global Assessment of Functioning scale (GAF), the Clinical Global Impression scale (CGI), the Severity of Psychiatric Illness scale (SPI), the aggressive behaviour and violence scale (AVAT), the Scale Unawareness of Mental Disorder (SUMD), the World Health Organization Disability Assessment Schedule (WHODAS), and the Positive and Negative Syndrome Scale (PANSS). The sample was divided on two groups, use of oral or long-acting antipsychotic.

Results: There are no clinical differences on most of the clinical scales. The results only showed differences in GAF scale (mean 37.6 SD 13.9 in oral treatment vs. 46.3 (32.5) in long-acting treatment). There are also differences in 'known psychiatric background' (75.0% vs. 97.3%) (oral vs. long-acting), 'Legally incapacitated' (17.5% vs. 40.5%), 'Previous hospital admission' (60.3% vs. 83,8%), 'Previous non-compliance treatment' (73.6% vs. 97.3%), 'Hospitalisation decision' (46.8% vs. 21.6%).

Conclusion: The results show that the decision to give a long-acting antipsychotic treatment is poorly correlated to clinical variables of

patients, being more important previous history referring to poor outcome in adherence to treatment. We also observe that patients with long.term treatment are admitted less frequently than those receiving oral treatment.

P-02. Addictive Disorders

P-02-001 Regulation of CB1 receptor protein and mTOR signaling in the cerebral cortex of cocaine addicts and cocaine-treated mice

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Objective: Endocannabinoids, CB1 receptors and dopamine D2 receptors interact to induce the effects of the psychostimulant cocaine. This study assessed the status of CB1 receptor protein and its downstream partner the mammalian target of rapamycin (mTOR, a serine/threonine kinase) in brains of cocaine addicts and cocaine-treated mice.

Methods: Postmortem prefrontal cortex (PFC/BA 9) was collected from cocaine addicts (5M/4F; 35±47 yr; 28±7 PMD) and healthy matched controls (5M/4F; 40±4 yr; 27±7 PMD). Toxicology at autopsy (blood and hair) revealed long-term abuse of cocaine only. CD1 mice were treated (i.p.) with saline/vehicle (n=7/5), cocaine (acute: 20 mg/kg, 2 h, n=5; chronic: 20 mg/kg, 7 days, n=8) or WIN55, 212–2 (CB1 agonist, acute: 8 mg/kg, 1 h, n=5; chronic: 1–8 mg/kg, 5 days, n=5). CB1 protein (total homogenate and subcellular fractions) and p-mTOR/mTOR ratio (kinase activation in total homogenate) were quantified by Western blot analysis with specific antibodies.

Results: Cortical CB1 receptor protein was reduced in long-term cocaine addicts (44±9%, $p=0.03$) compared to matched controls. Chronic cocaine in mice also reduced cortical CB1 receptor protein (44±8%, $p=0.01$). CB1 protein (chronic cocaine; human and mouse cortex) was reduced in membranes (10–31%) and augmented in cytosol (11–23%), indicating receptor internalization. Acute WIN55, 212–2 and acute cocaine activated cortical mTOR kinase (140% and 70%, respectively). In contrast, chronic WIN55, 212–2 and chronic cocaine did not induce mTOR activation (induction of receptor tolerance). Similarly, mTOR was not significantly activated in PFC/BA9 of long-term cocaine addicts (22±10%, $p>0.05$).

Conclusion: Cortical CB1 receptor protein is downregulated after chronic exposure to cocaine in humans and mice, which indicates the participation of endocannabinoids in cocaine addiction. In line with this novel finding, the signaling of CB1 receptors involving the activation of mTOR was dampened after chronic cocaine in human and mouse brains.

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P-02-002 Substance use disorders, psychiatric comorbidity, social vulnerability and long term outcome; a five year follow-up

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Objective: Although substance use disorders (SUD) among adolescents are poorly understood, it is well known that SUD in teenagers are associated with comorbid mental disorders and other adverse conditions in adult life. The aim of the study was to identify risk factors in early adolescence associated with presence of SUD five years later.

Methods: A representative sample of 180 adolescents, who had consulted a clinic for substance misuse problems, and their parents, were assessed at first contact with the clinic. The 180 adolescents and their 251 parents completed questionnaires and diagnostic interviews measuring psychopathology, substance use, maltreatment, victimization, criminality and poverty. Follow-up measurements took place five years from baseline including 147 participants from the original sample.

Results: Increased odds for presenting with SUD at five follow-up were shown for females with baseline experience of victimization by peers, sexual abuse, mothers with alcohol use disorder, fathers with drug use disorder and treatment for SUD. Male reports of baseline violent criminality and treatment for SUD elevated the odds for drug use disorder at follow up. Adjusting for baseline SUD, the odds increased among both males and females to present the same disorder five years later.

Conclusion: SUD were shown to be persistent over time. Treatment displayed no effect. Female SUD are shown to be affected largely by social context rather than individual factors. This was not shown for males.

P-02-003 Diagnosis of psychotic disorders in tirana psychiaric emergency in the context of substance use

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Objective: For patients, who actively use substances and manifest psychotic symptoms, remains a challenge to define whether psychotic symptoms are due to a primary psychotic disorder or caused by substance use. Therefore it is most important the clarification of the nature of psychosis in such patients, especially during first psychotic episode. This clarification impacts the plan to their further treatment.

Methods: Patients (males and females) aged over 16 years old presenting to the Emergency of Psychiatry and hospitalized during the period January 2008–December 2011 are included, diagnosed with psychotic disorders according to DSM-IV.

Results: Data gained from this study indicate the percentage of cases diagnosed with primary psychotic disorders and how many emergency admissions are not psychotic or psychotic disorders caused by the use of substances. Diagnostic agreement was generally low ($\kappa=0.32$). Percentage of patients diagnosed with primary psychotic disorders is higher than those diagnosed with psychotic disorders caused by substances, and are treated with antipsychotics ($p<0.001$).

Conclusion: Clinicians in Psychiatric Urgency seem to have a tendency to attribute the psychotic symptoms rather to a primary psychotic disorder than to a concurrent substance abuse. This is a fact, which shows the importance of psychotic symptoms. The diagnosis implies with the management of psychosis significantly in the future, so it is important to improve diagnostic techniques in psychiatric emergencies.

P-02-004 Preliminary study about the vulnerability to drug consumption associated with human single nucleotide polymorphisms of CNR1, FAAH and COMT genes

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Objective: Genetic variants, such as single nucleotide polymorphisms (SNPs), influence the vulnerability to addictive behavior. SNPs present in the cannabinnoid receptor 1 gene (CNR1) and the fatty acid amide hydrolase enzyme (FAAH) have been repeatedly associated with marijuana and alcohol abuse, whereas other SNPs in the dopaminergic D2 receptor D2 (DRD2) and the catechol-o-methyltransferase enzyme (COMT) have been related to cocaine and nicotine addiction. In this work we have tried to examine the association between several SNPs of the cannabinoid and catecholaminergic systems with self-reported drug consumption.

Methods: For this, DNA samples from voluntary students from the Complutense University of Madrid (Spain) were sequenced and their drug consumption habits were assessed. Moreover, participants were asked to complete valence ratings of drug-related and non-drug-related pictures.

Results: The results showed a significant association between five analyzed SNPs and drug consumption. Valence of drug-related pictures was much more positive within drug consuming participants. For example, tobacco smokers rated tobacco images significant more pleasant than ex-smoker or non-smoker.

Conclusion: Here, we provide preliminary evidences for the association of SNPs present in the cannabionid and catecholaminergic

system with drug consumption. In addition, it is very robust the effect that drug consuming people show higher emotional preference for drug-related stimuli than non-drug consuming people.

P-02-005 Patological gambling in patients under treatment for Parkinson disease

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Objective: The prevalence of Pathological Gambling (PG) is higher among patients with Parkinson Disease (PD) than within general population. (1). This fact could be related to the pharmacological treatments used in PD. This work aims to be a review about epidemiological, clinical and neurobiological features implied in PG in PD.

Methods: we looked trough Medline for articles published after to 2007 regarding PG in PD. Furthermore, we will present two cases of PD in which PG is developed.

Results: Prevalence of Impulse Control Disorders (ICD) in PD is assessed in 4–14%, this includes compulsive shopping (5.7%), PG (5%), compulsive eating (4.3%) and hipersexuality (3.6%)(ref). The most important risk factors for the development of PG in PD are treatment with dopaminergic agonists and L-dopa used, followed by early onset of PD, long course PD and either familiar or personal history of Adictive Disorders (AD) (2). It seems that the neurobiological mechanism of PG in PD has to do with the cortico- striatal pathways, changes in the phasic secretion of dopamine and over stimulation of D2 receptor, D3 senzitancion and long- term plastic changes as a result of the former. Management of PG in PD is complex; an early diagnosis, psicoeducation and behavior measures are of great importance. As to the pharmacological strategies, lowering doses of dopa agonists with augmentation of L-Dopa, switching for another dopa agonist, treatment cessation and use of other drugs (such as antipsychotics, SSRI, mood stabilizers, amantadine, or zonisamide might be helpful (3).

Conclusion: 1. The relationship between PG and PD seems to be mediated by PDs pharmachological treatment rather than PD itself. 2. A subpopulation of patients with PD could have subclinical features that make them prone to the development of PG.

P-02-007 Maladaptive schemas and coping strategies of substance dependents

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Objective: Substance dependence is a prevalent and chronic behavioral health problem. The aim of this study was to evaluate the substance dependents in terms of their maladaptive schemas and coping strategies.

Methods: Thirty one male patients ($M = 24.12 \pm 4.44$) who were diagnosed with substance dependence according to DSM-IV criteria and hospitalized for detoxification, participated in the study. Subjects were screened for HIV, HBV and HCV markers. Schemas and coping strategies of substance dependents were evaluated using Young Schema Scale and COPE. Socio-demographic properties, kind of substance use, frequency and duration of substance use were obtained via socio-demographic information form. Moreover, each participant was evaluated through SCID-I and patients with any comorbid psychiatric disorder were excluded from the study. The control group composed of 31 male subjects (23.32 ± 2.85) without any psychiatric disorders and was evaluated through the same procedure.

Results: MONOVA results revealed that in terms of schemas, substance dependents scored significantly higher than control group in abandonment/instability, mistrust/abuse, defectiveness/shame, social isolation/alienation, dependence/incompetence, enmeshment/undeveloped self, failure, insufficient self-control/self-discipline, subjugation, self-sacrifice, approval-seeking/recognition-seeking, negativity/pessimism, emotional inhibition, unrelenting standards/hypercriticalness, punitiveness. In terms of coping strategies, substance dependents scored significantly lower than control group in positive reinterpretation and growth, seeking social support for instrumental reasons, active coping, turning to religion, seeking social support for emotional reasons, and scored significantly higher than control group in alcohol-drug disengagement.

Conclusion: These findings support the importance of early maladaptive schemas which might be underlying the dependency problem and prevent the person to deal with the problem with more active and problem focused coping strategies. Therefore, in cognitive-based psychotherapeutic approaches for patients with substance dependence, it would be effective to focus on maladaptive schemas and coping strategies as part of the treatment procedure.

P-02-008 Suppression of alcohol-dependence using high-dose baclofen: A two-year observational study of 100 patients

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Objective: Evaluate alcohol-dependence suppression by baclofen in a large cohort of patients.

Methods: Patients with treatment-resistant alcohol dependence seeking baclofen treatment were treated with escalating doses of baclofen and observed for 24 months. A hundred treatment-compliant patients were included in this observational and compassion-motivated study. Alcohol consumption and craving for alcohol were assessed before treatment and at 3, 6, 12 and 24 months. Assessments were based on patients' statements. The outcome measure was the WHO criteria (''at low risk'', ''at risk'', ''at high risk'').

Results: 92% of patients reported that they experienced an effortless craving-suppressing effect of baclofen. While all patients were rated ''at high risk'' at baseline, approximately half of them were rated ''at low risk'' at 3, 6, 12 and 24 months. The low rate of relapse after 6 months was remarkable. The average maximal dose of baclofen taken was 147 mg/day. Significant relationships were found between the amount of alcohol taken before treatment and the maximal dose of baclofen required, and between the existence of a mental disorder and a lesser effect of baclofen. Side-effects were common, but always benign.

Conclusion: Baclofen produces an effortless decrease or suppression of alcohol craving in almost all patients when it is prescribed with no superior limit of dose. Potential limitations in the effectiveness of baclofen include the coexistence of a mental disorder, the concomitant use of other psychotropic drugs, a lack of real motivation in patients to stop drinking, and an impossibility to reach the optimal dose of baclofen because of a limited capacity of certain patients to tolerate undesirable side-effects.

P-02-009 The alpha-2-adrenoceptor agonist guanfacine significantly decrease voluntary ethanol intake in wistar rats

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Objective: Alcohol use disorder (AUD) is a chronic relapse disease. However, only three medications, with limited clinical efficacy, are available. Thus, new effective medications are needed. High rates of cravings, even after long periods of abstinence, in combination with decreased cognitive functions including impaired decision making and impulse control often lead to relapse in drinking. It has been suggested that increased release of noradrenalin during abstinence contributes to the impaired impulse control. Thus, enhancement of cognitive function through inhibition of the noradrenalin system may serve as novel treatment strategy for AUD. Recent studies show that the FDA-approved ADHD-medication guanfacine (an alpha-2-adrenoceptor agonist) attenuate reinstatement of alcohol seeking in rats. Here we evaluated the effects of guanfacine, on voluntary ethanol intake in Wistar rats following long-term voluntary ethanol consumption.

Methods: Wistar rats were given intermittent-access to 20% ethanol (three 24-hour-ethanol-sessions per week; Mon, Wed and Fri) for at least three months before treatment. Acute guanfacine treatment (0, 0.3 and 0.6 mg/kg) was given to rats voluntarily consuming low (1.9 ± 0.2 mg/kg/24 hr; $n = 7$) or high (4.3 ± 0.2 mg/kg/24 hr; $n = 11$)

amounts of ethanol. Repeated guanfacine treatment (0 and 0.6 mg/kg/day over 5 consecutive drinking sessions) were given to a group of rats consuming high amounts of ethanol (4.3±0.2 mg/kg/24 hr; n=12). All injections were given 30 minutes before the ethanol-drinking-session started. Thus, the rats had undergone 23 hours of abstinence at the time of treatment.

Results: Acute and repeated guanfacine treatment selectively decreased ethanol intake in high, but not low, ethanol consuming rats. The repeated guanfacine treatment indicating that no tolerance to guanfacine's ability to decrease ethanol intake develops over time. Moreover, there was no post-treatment rebound increase in ethanol consumption.

Conclusion: The present study gives further support for the hypothesis that the cognitive enhancer guanfacine may serve as a novel treatment for AUD.

P-02-010 Anterior cingulate (AC) glutamate, cravings for alcohol and depressive symptoms

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Objective: Converging evidence indicates acute disruption in glutamatergic neurotransmission is associated with symptoms of alcohol intoxication and withdrawal. We wanted to evaluate the relationship between AC glutamate and cravings for alcohol and depressive symptoms.

Methods: 14 subjects (mean age=43.0±13.0; 8 females and 6 males) with alcohol dependance admitted to residential treatment have enrolled in the study. Single-voxel 2D J-resolved PRESS H-MRS of the AC was measured ~5 days from last drink and reported as Glx/creatine (Glx/Cr). Cravings for alcohol were measured by the Penn Alcohol Craving Scale (PACS) and self report symptoms of depression were rated with the Patient Health Questionnaire (PHQ 2).

Results: Inverse correlations were found between Glx/Cr and PHQ-2 ($r=-0.62$, $p=0.019$) and Glx/Cr and PACS ($r=-0.51$, $p=0.066$) indicating depressed mood, anhedonia, and alcohol craving were associated with decreased AC glutamate. When subjects were divided into both depressed (PHQ 2 $\geqslant$3) vs. non-depressed (PHQ 2<3) and high-craving (split at median) vs. low-craving groups, GLX/Cr was significantly reduced in depressed and high-craving groups.

Conclusion: Alcohol craving and depressive symptoms during early abstinence may be associated with a glutamate deficit in the AC. Our findings are in contrast to previous clinical studies which may be related to different methodology including the length of early abstinence period. As this sample is 5 days from last drink we conclude that the acute withdrawal period has passed and our data captures a period of relative glutamate deficit prior to normalization.

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P-02-011 Sulforaphane as a therapeutic drug for methamphetamine abuse

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Objective: Accumulating evidence suggests a role of oxidative stress in the pathophysiology of substance abuse. Sulforaphane (SFN), found in cruciferous vegetables, is a potent antioxidant. It is, therefore, of interest to determine whether SFN can attenuate behavioral and neuropathological changes in mice after administration of psychostimulant methamphetamine (METH).

Methods: The effects of SFN on acute hyperlocomotion and the development of behavioral sensitization induced by the administration of METH were examined in male Balb/c mice. Levels of dopamine (DA) and its major metabolite 3,4-dihydroxyphenyl acetic acid (DOPAC) in the striatum were measured. In addition, immunohistochemistry for DA transporter (DAT) and MAC1 (microglia activation) was also performed.

Results: Pretreatment with SFN (1, 3, and 10 mg/kg) elicited a dose dependent attenuation of acute hyperlocomotion in mice after a single administration of METH (3 mg/kg). The development of behavioral sensitization after repeated administrations of METH (3 mg/kg/day, once daily for 5 days) was significantly reduced by pretreatment with SFN (10 mg/kg). In addition, the lowering of DA levels and DOPAC as well as DAT immunoreactivity in the striatum after repeated administration of METH was significantly attenuated by both pretreatment and the subsequent administration of SFN (10 mg/kg). Furthermore, SFN (10 mg/kg) significantly reduced microglial activation in the striatum after repeated exposure to METH.

Conclusion: These results suggest that SFN could be a potential therapeutic drug for the treatment of METH abuse since it is a safe for human consumption.

P-02-012 A study on the effectiveness of electroacupuncture as adjunctive treatment among methadone maintenance therapy clients in University of Malaya Medical Center, Kuala Lumpur, Malaysia

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Objective: To investigate the role of acupuncture as an adjunct treatment for opiate dependant individuals.

Methods: Prospective, open-labelled, parallel, randomized-control trial will be conducted in the University of Malaya Medical Centre from Feb 2012 till December 2013. One hundred and twenty subjects who fulfilled Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for the opiate dependence receiving methadone maintenance therapy were randomly assigned into two groups. Subject will receive the methadone based on the National Guidelines of Malaysian Ministry of Health. Treatment group will receive electroacupuncture stimulation at 1.1+80 Hz while control group will receive Sham acupuncture for 30 minutes per session as followed: first week (five times per week), second week (two times per week) and third week to following weeks until one year (once a week). Outcome assessment will use structured questionnaires such as Opiate Treatment Index (OTI) to measure drug use, HIV risk-taking behaviours, social functioning, criminality, health status and psychological functioning. The World Health Organization Quality of Life – BREF (WHOQoL-BREF) will use to measure physical health, psychological health, social relationships, and environment. In addition, Clinical Opiate Withdrawal Scales (COWS) will use to measure the withdrawal syndrome in opiate dependence individuals.

Results: From this study, we expected to come out with acupuncture group has better results of outcomes measures as compare to control group.

Conclusion: The result of this study suggests that acupuncture add on treatment on top of methadone therapy potentially have additional advantage in reducing withdrawal intensity and better outcomes for overall.

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P-02-013 Changes in serotonergic modulation of neuronal activity in the nucleus accumbens following repeated methamphetamine administrations in rats

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Objective: Electrophysiological studies were performed to determine whether or not serotonergic modulation on neuronal activities (including synapses) in the nucleus accumbens (NAcc) was affected after repeated methamphetamine (MAP) administrations.

Methods: Rats (age range: 5–8 weeks) were administered with either MAP (5 mg/kg; i.p.) or an equal volume of saline once daily for 5 days. Brain slices containing NAcc (thickness: 400 micro-m) were

prepared 5days after the final injection of MAP or saline. Population spikes (PS) induced by local stimulation of NAcc were recorded with a glass microelectrode placed in the same nucleus. All agents with the same dose (10 microM) tested were applied via a bath perfusion system.

Results: Compared with the saline-treated group, PS inhibition by 5-HT was significantly attenuated in the MAP-treated group 5 days after treatment. Although administration with 8-OH-DPAT (a 5-HT1A receptor agonist) suppressed PS, the inhibition rate was not significantly affected by repeated MAP treatment. In addition, alpha-methyl-5-HT (a 5-HT2 receptor agonist)-induced inhibition was slightly reversed without significance in the MAP group. However, significant different effects on PS with m-chlorophenylbiganide (5-HT3 receptor agonist) and RS-67333 (a 5-HT4 receptor agonist) were observed in the MAP group (vs. saline group). EMD 386088 (a 5-HT6 receptor agonist) did not affect PS in both groups. Interestingly, although slight (about 10%) enhancement effect on PS was noted in the saline group, AS 19 (a 5-HT7 receptor agonist) significantly enhanced PS in the MAP group.

Conclusion: In fact, 5-HT-induced inhibition of PS in NAcc was attenuated 5 days after termination of repeated MAP treatment: an effect probably due to enhancement of the excitatory modulation via the 5-HT7 receptor.

P-02-014 Dextromethorphan induced bipolar disorder

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Objective: There are very few case reports in the literature linking dextromethorphan inducing bipolar disorder We describe a patient who developed recurrent episodes of mania following sustained dextromethorphan use and which resolved after cessation of its use.

Methods: The patient is a 42 year old male, who had a history of heroin, subutex and midazolam use in the past but completely stopped its use in 2008. He started consuming dextromethorphan tablets about 30 tablets a day (450 mg daily) since May 2011 2 to 3 times a week. He did not consume any other illicit drugs or alcohol. He started exhibiting symptoms of mania 2 to 3 weeks after starting dextromethorphan which required inpatient admission for a week. Symptoms resolved after a few days of admission. He had a second admission on 17th June 2011 after he restarted dextromethorphan use after discharge. He exhibited short lived manic symptoms which settled after 1 week of admission. This was followed again by a third episode of mania which occurred in September 2011 which lasted for 2 weeks and required inpatient admission. There was no past history of either manic or depressive episodes prior to onset of use of dextromethorphan or any significant family history.

Results: All these 3 episodes of mania occurred after heavy consumption of dextromethorphan use and resolved with cessation of use.

Conclusion: This report adds to the existing sparse literature about dextromethorphan inducing manic episodes.

P-02-015 Sequence variation in Gata4 gene is associated with alcohol dependence

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Objective: Recent studies suggested that an intronic SNP (rs13273672) in the GATA4 gene encoding GATA-binding protein 4 is associated with alcohol dependence (Treutlein et al., 2010) and relapse following treatment with acamprosate (Kiefer et al., 2011). To replicate this finding and further explore potential associations between alcohol dependence and sequence variation in GATA4 gene we investigated the association of alcohol dependence with this SNP as well as 10 haplotype tagging SNPs in the GATA4 gene.

Methods: GATA4 SNPs were genotyped in 816 alcohol dependent cases and compared with the same SNPs 1248 controls previously genotyped as part of a genome-wide association study. When multiple SNPs in a gene are associated with a trait, a gene-level test may be a powerful approach for detecting association with variation in the gene. We therefore performed a global test for association of alcohol dependence with variation in the GATA4 gene using principle components analysis involving the 11 genotyped GATA4 SNPs.

Results: Our analyses did not provide significant evidence for association of alcohol dependence with SNP rs13273672. However, nominal evidence of association ($p < 0.05$) was obtained for five of the other ten GATA4 SNPs, including rs10112596, rs809204, rs804283, rs6601604, and rs12550668. Significant evidence of association between GATA4 and alcohol dependence was observed at the gene-level ($p = 0.009$).

Conclusion: Our findings do support potential role of GATA4 variation but not rs13273672 SNP in alcohol dependence. Further studies are needed to identify the potentially causal variant(s) and the functional mechanism contributing to this association. As part of the ongoing work of our NIAAA-funded alcoholism research center (Mayo Clinic Center for Individualized Treatment of Alcohol Dependence) we will investigate the association of these SNPs with response to acamprosate treatment.

P-02-016 Influence of betaxolol(BTX) on the methamphetamine(MAP) dependence mice

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Objective: We investigated the effect of BTX in MAP.

Methods: Animal mice were used in conditioned place preference test.Statistical analysis: one-way ANOVA/Kruskal-Wallis test.

Results: The repeated administration of BTX (5 mg/kg,i.p) 30 min prior to the exposure to MAP significantly reduced the development of MAP-induced CPP. When BTX was administered 24 h prior to the CPP testing session,it also significantly attenuated CPP, but not changed locomotor activity.In the drug-priming reinstatement study, the extinguished CPP was reinstated by MAP (0.125 mg/kg,s.c.) injection & this was significantly attenuated by BTX.

Conclusion: BTX has a therapeutic and preventive effect on the development,expression & drug-priming reinstatement of MAP induced CPP.

P-02-017 Anxiety-like response to methamphetamine in adult mice is not altered by prenatal exposure to modafinil

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Objective: Methamphetamine (MET) is a commonly abused psychostimulant drug. Modafinil (MDF), a drug registered for treatment of narcolepsy, is often consumed by young fertile generation for its stimulatory properties, and thus it is important to assess its behavioural toxicity in offspring. This study investigated influence of prenatal exposure to MDF and MET on anxiety-like measures after acute and chronic administration of MET in adult mouse males using elevated plus maze.

Methods: Pregnant female mice were given nine daily doses of saline (SAL, 10 ml/kg/day), MET (2.5 mg/kg/day) or MDF (50 mg/kg/day). Effects of the same treatment doses were evaluated in adult male offspring in six experimental groups: SAL or MET treated offspring with prenatal exposure to SAL, MET and MDF. Anxiety was assessed as % of entries and time spent in open and closed arms in the elevated plus maze on: Day 1 – naïve mice (no drug dose, baseline conditions), Day 8 – acute dose of SAL or MET, Day 15 – challenge dose after one week of repeated SAL or MET administration.

Results: At baseline conditions on the Day 1, prenatal treatment with MDF increased % of entries and time spent in the closed arms compared to SAL prenatal administration (but did not significantly affect behaviour in the open arms). Prenatal administration of MET did not alter anxiety-like behaviour compared to prenatally naïve animals. Anxiety-like response to acute dose (Day 8) or chronic treatment (Day 15) of MET in the elevated plus maze was not altered by different prenatal exposures (SAL compared to MET and MDF).

Conclusion: We can conclude that prenatal treatment with MDF increases anxiety at baseline conditions. However, there were observed no differences in reactivity to postnatal administration of

either drug (MET or MDF). Modafinil provoked behavioural toxicity although not linked to methamphetamine abuse.

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P-02-018 Are delerium tremens and alcohol-related seizures in inpatients admitted for alcohol detoxification related to daily alcohol consumption and breath alcohol content on admission?

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Objective: The primary aim of this study was to investigate whether daily alcohol consumption and Breath Alcohol Content (BrAC) affect the incidence of Delirium Tremens and Alcohol-related seizures in patients admitted for alcohol detoxification.

Methods: The study comprised of a cross-sectional survey in which data was collected from 100 consecutive inpatients admitted for alcohol detoxification in the unit in 2010. Data was collected from the clinical records of the patients and we looked at demographics, daily alcohol consumption, Breath Alcohol Content at admission and current episodes and past history of delirium tremens and alcohol-related fits.

Results: We noticed that 14 patients experienced Delirium Tremens and 10 patients experienced alcohol-related fits during their current admission whilst 56 patients had a past history of Delirium Tremens and 40 had a past history of alcohol-related fits. 2 patients experienced both Delirium Tremens and fits. All these patients had a daily consumption of alcohol higher than 30 units of alcohol. 86% (12/14) of the patients who developed Delirium Tremens and 90% (9/10) of patients who had alcohol-related fits had a Breath Alcohol Content of more than 1.00 at admission.

Conclusion: Daily alcohol usage and Breath Alcohol Content at admission could be related to a risk of developing Delirium Tremens and Alcohol-related fits during the detoxification process. This can aid in identifying high risk patients and help reduce their morbidity.

P-02-019 Cortisol levels and MDMA-induced memory impairment

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Objective: Ecstasy use is commonly linked with memory deficits in abstinent ecstasy users. Similar impairments are being found during ecstasy intoxication after single doses of MDMA. The concordance of memory impairments during intoxication and abstinence suggests a similar neuropharmacological mechanism underlying acute and chronic memory impairments. The mechanism underlying this impairment is to date not known. We hypothesized that cortisol might play an important role in this mechanism as cortisol, implicated in the regulation of memory performance, can be brought out of balance by stressors like MDMA. In the present study we aimed to block the MDMA-induced acute memory defect by giving participants a cortisol synthesis inhibitor (Metyrapone®) together with a single dose of MDMA.

Methods: Seventeen polydrug MDMA users entered this placebo controlled within subject study with four treatment conditions. The treatments consisted of MDMA (75 mg) and Metyrapone® (750 mg), alone and in combination, and double placebo. Pretreatment with Metyrapone or Placebo occured 1 h prior to MDMA or Placebo administration. Memory performance was tested at peak drug concentrations by means of several memory tests. Cortisol levels were determined in blood; this served as a control measure to see whether manipulations were effective.

Results: Main findings indicated that whereas treatment with Metyrapone blocked the expected MDMA-induced increase in cortisol levels in blood, it did not prevent the MDMA-induced memory deficit from happening.

Conclusion: We therefore conclude that MDMA-induced increases in cortisol concentrations are not responsible for impairing memory performance while intoxicated with MDMA.

P-02-021 Cocaine reverses naltrexone-induced reduction in operant ethanol self-administration

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Objective: Naltrexone is a clinically approved medication for alcoholism. We aimed to investigate the efficacy of naltrexone when there is an interaction with cocaine and their associations with immediate-early gene expression in the prefrontal cortex.

Methods: Using rats, we designed the experiments to maximise their predictive validity in humans. We used chronic operant ethanol self-administration and treatments (p.o.) prescribed for alcoholism. We performed real-time PCR analysis to determine gene expression levels.

Results: Only the highest dose of naltrexone (10 mg/kg) reduced ethanol intake. Cocaine increased ethanol self-administration dose-dependently (2.5, 10, 20 mg/kg) and reverted the naltrexone-induced reduction. Naltrexone failed to prevent cocaine-induced increase in locomotor activity observed in these animals. Ethanol caused a reduction in C-fos gene expression and an overexpression of the COX-2 and Homer1a genes in the rat prefrontal cortex. Neither the suppressive effects of naltrexone nor the cocaine-induced increase of ethanol self-administration were related to the genetic changes observed.

Conclusion: Chronic ethanol self-administration is prevented by naltrexone, but cocaine fully reverses this effect. This suggests that cocaine may overcome the efficacy of naltrexone as a treatment for alcoholism. The ethanol-induced reduction in C-fos gene expression in the prefrontal cortex reveals an abnormal activity of these neurons, which may be relevant for compulsive drinking of ethanol, the regulation of behaviour and the control of reward-related areas.

P-02-022 Modification of prepulse inhibition of the startle reflex during detoxification treatment in alcohol dependent males

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Objective: Prepulse inhibition (PPI) of the startle reflex refers to the ability of innocuous sensory events to reduce startle reflex and it has been described as an operational measure of sensorimotor gating. It has been reported that alcoholic withdrawing patients show a significantly decreased PPI, which reaches its lowest point on the first and third day of abstinence and increases progressively after the first week. The aim of this study was to explore modifications in PPI levels during alcohol withdrawal syndrome and detoxification treatment in alcohol dependent males.

Methods: 15 male patients, aged 18 to 55 years, who met DSM-IV criteria for alcohol dependence, were recruited through the Outpatient Alcohol Unit at the Hospital 12 de Octubre, Madrid. Patients were detoxified for a period of 10–14 days using benzodiazepines and/or anticonvulsants. They underwent testing for PPI at baseline and after detoxification had concluded.

Results: At baseline, patients exhibited remarkably low levels of PPI. After 10–14 days of detoxification treatment, PPI percentage significantly increased, specifically at both 30-ms ($p < 0.001$) and 60-ms ($p < 0.05$) prepulse-to-pulse interval. At 120-ms prepulse-to-pulse interval, no significant differences between baseline and post-detoxification were found.

Conclusion: These data suggest that sensory information processing could be damaged in withdrawing alcohol dependent patients, probably due to neurotoxicity of alcohol over CNS.

P-02-023 Methadone maintenance treatment in patients with dual diagnosis: Differential characteristics in response to the dose of methadone

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Objective: To describe a sample of dual diagnosed patients who were included in a methadone maintenance program at the time of discharge of a brief dual diagnosis unit. More specifically we try to find distinguishing characteristics between patients treated with standard therapeutic doses (SD; from 60 mg/day) and those treated with low doses of methadone (LD; less than 60 mg/day).

Methods: Data on demographic, family, and clinical factors were gathered among subjects admitted to our dual diagnosis unit between September 2007 and September 2011, all of them meeting DSM-IV criteria of any non-substance related Axis I or II disorder and comorbid substance use disorder (SUD). Statistical analysis was performed by using SPSS program.

Results: ●From the whole sample (N = 134), age 38.7 ± 7.6, most of them (68.7%) were male. Mean length of stay were 20.8 ± 20.6. ●Distribution of non-SUD diagnosis were as follows: psychotic disorders (40.3%), personality disorders (39.5%), depressive disorders (8.2%), bipolar disorders (6%) and adjustment disorders (6%). In our sample, most common comorbid SUD (except opioid use disorder) were cocaine (64.2%) and alcohol (32.1%). ●Comparing to LD group (N = 86; 64.2%), we found that SD group (N = 48; 35.8%) had more prevalence of sedatives SUD, sedatives treatment both at admission and at discharge, and antipsychotic treatment at admission. ●In addition, we also observed an early onset of consumption of sedatives, heroine and nicotine and, in turn, an earlier onset of problematic use of alcohol, sedatives, heroine, cannabis and nicotine. It also aimed to lower consumption of cocaine and heroin in the last 30 days prior to current admission.

Conclusion: Patients treated with standard therapeutic doses of methadone showed higher prevalence of sedatives SUD and a more severe profile of substance use in respect with those patients treated with suboptimal methadone dosis.

P-02-024 Suicide in personality disorders with substance use disorders comorbid

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Objective: To analyze differences between patients admitted for suicidal ideation and those who join for other reasons, within the group of patients with Personality Disorders and Substance Use Disorders(SUD)comorbid admitted to a brief dual diagnosis unit.

Methods: Total of patients admitted to our dual pathology unit between September 2007 and December 2011 and who met DSM-IV criteria for diagnosis of Personality Disorder and comorbid SUD were included. Data on demographic, family, and clinical factors were collected.

Results: From the whole sample (N = 250), age 38.58 ± 8.8, most of them (64.4%) were male. The main drugs of abuse were alcohol (47%), cocaine (26.9%) and cannabis (10%). Comparing to non-suicidal ideation group (N = 163; 65.2%), we found that suicidal ideation group (N = 87; 34.8%) had more prevalence of females (47.1% vs. 29.4%; $p = 0.008$), higher rates of taking a drug treatment regularly during the 6 months previous to hospital admission (32.4% vs. 18.9%; $p = 0.038$), had more previous history of suicide attempts (91.2% vs. 64%; $p < 0.001$) and more prevalence of comorbid Opioids Use Disorder (37.9% vs. 19.6%; $p = 0.002$). This group received more antidepressive drugs (64.4% vs. 41.7%; $p = 0.001$). Non-suicidal ideation group had more patients admitted involuntarily (35.6% vs. 9.2%; $p < 0.001$), more previous history of physical aggression (75.3% vs. 58%; $p = 0.038$), higher prevalence of comorbid diagnosis of Psychosis (23.3% vs. 3.4%; $p < 0.001$), Antisocial Personality Disorder (22.1% vs. 6.9%; $p = 0.002$), Amphetamines Use Disorder (9.2% vs. 0%; $p = 0.002$) and Cannabis Use Disorder (36.2% vs. 21.8%; $p = 0.02$). This group showed a tendency to receive more antipsychotic drugs (70.6% vs. 58.6; $p = 0.068$).

Conclusion: Sex, type of SUD and comorbidity with other axis I disorders, could distinguish Personality Disorders if they are or not admitted for suicidal ideation.

P-02-025 Efficacy of antidepressant in concurrent primary or substance-induced depression and alcohol use disorders: A systematic review and meta-analysis

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Objective: Antidepressants (AD) are commonly used in alcohol dependence to treat comorbid depression and for the potential action of these drugs on the underlying mechanisms of alcohol addiction. Two previous systematic reviews (1,2) evaluating the efficacy of AD in the treatment of concurrent depression and alcohol use disorder (AUD), did not support the use of AD in this dual disorder, but most of the studies included did not differentiate between Primary (PD) and Substance-Induced Depression (SID) Objective: To evaluate the efficacy of antidepressants in the treatment of concurrent PD or SID and AUD.

Methods: Included studies have to be randomized placebo-controlled (RCT) evaluating efficacy of antidepressants in PD or SID and AUD, from 1960 to December 2011. Studies should include outcome measures of depressive symptoms (Hamilton Depression Rating Scale) and alcohol consumption (self-report). Eligible studies will be identified from available systematic reviews, from searches in electronic databases (Pub Med). Two independent researchers selected the trials that scored >3 on Jadad scale.

Results: Only 6 RCT differentiate between PD and SID. No study evaluates the efficacy of the AD on SID. Five RCT show outcome measures in depressive symptoms (3 using Selective Serotonin Reuptake Inhibitors (SSRI) and 2 other AD). Data analysis show that other antidepressants no SSRI are effective to improve depressive symptoms (OR:2.70, [95% CI: 1.07–6.84]). Four RCT provide data from alcohol use (2 with SSRI and 2 other AD). Data analysis show that antidepressive treatment are not effective to reduce alcohol consumption.

Conclusion: Although limitations in comparing different RCT (different DSM criteria, antidepressant drug, dose use and status consumption at baseline..) the analysis show efficacy in treat depressive symptoms in concurrent PD and AUD with non-SSRI antidepressants. As in previous studies antidepressants were not effective to treat alcohol use.

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P-02-026 Synthetic cannabinoids: Psychoactive effects and diffusion in the web

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Objective: A new generation of synthetic cannabinoids, readily available on the web and in smart shops under the brand names of ''Spice,'' ''Aroma,'' or ''Dream'', has recently come on the market. Compared to THC, ''spice'' products possesses approximately a four-fold higher affinity for the cannabinoid CB1 receptor and a 10-fold higher affinity for the CB2 receptor. Spice blends better satisfy users' expectations, in that their psychoactive effects are perceived to be even stronger than cannabis. They produce psychoactive reinforcement, are highly attractive, perceived as safe drugs and not easily detectable in urine and blood samples.

Methods: The study focused on quantifying the existence of websites related to synthetic cannabinoid products and aimed at dividing their positions towards drug use in tree main categories: Anti Drugs, Pro Drugs and Harm Reduction Approach.

Results: A web mapping developed through the most well-known search engines as Google™ and Yahoo™ has underlined the existence of 61 main websites that shared information about the ''Spice'': 43 (70.5%) were Pro Drugs, 13 (21.3%) were Anti Drugs and 5 (8.2%) were Harm Reduction Approach.

Conclusion: Although the internet provides a wide range of information about the side effect of the ''Spice'' and many Countries have

banned it, there is still an high number of Pro Drugs websites that actively promotes to consume it. Very limited information is available on the safety of Spice ingredients in humans and the occurrence of serious health damage in abusers is highly probable, as is the likelihood of prompting the development of psychotic symptoms and full psychotic episodes.

P-02-027 Association between risk-taking behavior and voluntary alcohol intake in male outbred wistar rats

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Objective: Risk assessment and risk taking versus inhibitory control are evolutionary conserved behaviors of survival value implicated in the multifaceted construct of impulsivity. When maladaptive, impulsivity is associated with drug-taking behavior. Previous studies have shown that locomotor activity in a novel environment is useful for identifying individuals at risk for excessive intake of drugs of abuse. In this study we focus on individual differences in risk-taking behavior in a novel environment. We hypothesize that high risk-taking (HRT) animals are prone to higher alcohol intake compared to low risk-taking (LRT) animals.

Methods: Thirty adult male outbred Wistar rats were tested in the open field test. Based on the percentage duration of time spent in the central part of the open field, animals were divided into HRT or LRT. For further behavioral profiling the multivariate concentric square field™ (MCSF) test was used, which includes a variety of zones including sheltered, open and elevated areas, exploratory incentives, areas with different illumination, and wall-enclosed corridors. The rats then had access to 20% alcohol using a two-bottle free-choice paradigm, with intermittent 24 h access three times per week for five weeks.

Results: The results revealed that HRT animals displayed a higher risk-taking behavior also in the MCSF compared to the LRT animals. Moreover, HRT rats showed faster acquisition of alcohol intake, accompanied by higher alcohol preference. Furthermore, risk-taking behavior as defined in the open field test correlated with alcohol preference during the acquisition period.

Conclusion: While previous studies have focused on the association between locomotor activity and intake or sensitivity to drugs of abuse, we here demonstrate an association between individual differences in risk-taking behavior, of relevance for impulsivity, and voluntary alcohol intake and preference. The results demonstrate that screening of individual differences is a useful strategy in identifying subgroups of individuals at risk for excessive alcohol intake.

P-02-028 Overexpression of Shati in the nucleus accumbens affects the abnormal behavior induced by methamphetamine in mice

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Objective: The abuse of methamphetamine (Meth) has significantly psychiatric and medical consequences, including dependence, psychosis and even death. A novel molecule shati has been identified from the nucleus accumbens (NAc) of mice treated with Meth using the polymerase chain reaction-select complementary DNA subtraction method. In vivo and vitro studies, shati regulates Meth-induced dopamine (DA) release. However, it is not clear which brain regions are involved with the function of shati. In this study, we overexpressed shati in the NAc or dorsal striatum (dS) of mice specifically using adenoassociated virus vectors.

Methods: we overexpressed shati in the NAc or dorsal striatum (dS) of mice specifically using adenoassociated virus vectors.

Results: Overexpression of shati only in the NAc suppressed Meth-induced hyperlocomotion, sensitization and place preference in mice. Moreover, in vivo microdialysis method revealed that overexpression of shati in the NAc inhibits Meth-induced increase of DA release.

Conclusion: These results indicate that shati in the NAc, but not in the dS, plays an important suppressive role in the establishment of Meth-induced dependence by mediating extracellular DA levels.

P-02-029 Association between the fyn kinase gene and patients with methamphetamine psychosis

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Objective: Dysfunction of the N-methyl-D-aspartate (NMDA) receptor has been considered to underlie the pathophysiology of psychiatric disorder including schizophrenia and substance-induced psychoses. We previously reported the significant associations between methamphetamine psychosis and several genes, e.g. the dysbindine gene, the G72 gene, the serine rasemase gene and the GRIN1 and 2B genes, those are involved in the glutamatergic signaling and NMDA receptor functions. Fyn kinase is a member of the Src family of tyrosine kinases and mediates phosphorylation of glutamatergic NMDA receptor subunits. Previous studies showed that Fyn is involved in the pathophysiologies of neuropsychiatric disorders, such as schizophrenia, alcoholism, epilepsy and Alzheimer's disease. The FYN gene is localized in the 6q21, which was found in the region linked to neuropsychiatric disorders. Therefore, we investigated the association between the FYN gene and methamphetamine psychosis.

Methods: Subjects were comprised of 220 patients and 293 age- and gender-matched healthy controls. We genotyped three polymorphisms, rs706895, rs3730353 and rs6916861, in the FYN gene.

Results: There were no significant differences in genotypic or allelic distribution of any polymorphism in the FYN gene between the two groups. Clinical phenotypes of methamphetamine dependence, e.g. age of first consumption, latency from the first consumption to onset of psychosis, complication of spontaneous relapse of psychosis, and poly-substance abuse status, did not significantly associate with any polymorphism. The three SNPs, rs706895, rs3730353 and rs6916861, showed linkage disequilibrium with each other. We then analyzed the 2- and 3-loci haplotype distribution, but no significant difference was found between patients with methamphetamine dependence and control subjects.

Conclusion: This study suggested that the FYN gene is unlikely to play a major role in methamphetamine dependence liability and/or the development of methamphetamine induced psychosis, at least in a Japanese population.

P-02-030 Affective disorders of adolescent opiate addicts

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Objective: Research and evaluation of affective disorders of adolescent opiate addicts is the main goal of this paper. Affective disorders are considered to be the causes of determination to abuse drugs in adolescence.

Methods: Our sample consisted of 60 subjects Assessment of depression of opiate drug users group and the control group was done by using the following Depression scale: Hamilton Depression Rating Scale (HAMD). Scale for the Assessment of neurotic/endogenous depression-Newcastle (NERS). Self-assessment scale for depression (Zunge) Montgomery-Asberg Depression Rating Scale (MMPI).

Results: If we analyze the scale for the assessment of depression in opiate addicts we come to the following results. According to Becks scale, 55% of respondents expressed marked depression, while 35% had moderate signs of acute depression. In relation to the distribution of findings in the control group, the difference is of high statistical significance ($X^2 = 199.274$, $p < 0.001$). According to Montgomery-Asbergj scale 58.3% were estimated as medium depression, and 15% as marked depression. Distribution findings to strong points on the Montgomery-Asberg scale between a group of opiate addicts and control groups were also statistically significant ($X^2 = 116.444$; $p < 0.001$). According to MMPI scale, higher levels of depression manifested itself in 56.6% of opiate addicts. Compared to values in the control group, the difference is confirmed as highly significant ($t = 11.42$; $p < 0.001$).

Conclusion: There is a statistically significant correlation between affective disorders and opiate dependence. Under all experimental scales used in the research, opiate addicts exhibited marked depression as compared to the control group, significantly higher scores of depression ($p < 0.01$) in 93.3% of respondents were found and according to the Newcastle scale, in 78.3% of cases, it was a nonendogenous depression. According to Zunge scale depression 63.3%

meets the criteria for hospitalization. Opiate dependence regarding the degree of depression best discriminate against Hamilton and Montgomery-Asberg scale.

P-02-031 How empathetic are cocaine users? A social neuroscience approach

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Objective: Although it was proposed that social cognition might play a crucial role in the development and treatment of drug dependence, studies investigating social cognition in drug users are scarce. Chronic cocaine users display neurochemical and functional alterations in brain areas involved in social cognition (e.g., the medial prefrontal cortex and the ventral striatum). Therefore, we investigated mentalizing and empathy abilities in dependent and occasional cocaine users by means of video-based and photorealistic stimuli of every-day situations.

Methods: Seventy occasional cocaine users, 37 dependent cocaine users and 70 drug-naïve control participants completed the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). The MET assesses cognitive and emotional empathy by the judgement of emotional pictures. The MASC requires watching a short film and answering 45 questions about the actors' mental states (Theory-of-Mind, TOM).

Results: Dependent cocaine users performed significantly worse on the cognitive empathy scale of the MET than occasional users and controls. In the MASC, dependent cocaine users made more mistakes than occasional users and controls primarily because of exaggerated perspective taking. Furthermore, lifetime cocaine use was significantly correlated with test performance in the MASC. No significant differences were found between control subjects and occasional cocaine users.

Conclusion: These results indicate that dependent cocaine users show impairments in specific mentalizing abilities. Cognitive empathy seems to be affected more strongly than emotional empathy. Furthermore, cocaine users made more errors with regard to excessive TOM, indicating that they tried to take the perspective of others but failed. These alterations appear to be associated with the extent of cocaine consumption. Occasional cocaine users do not show significant impairments, but the dose-response correlation reflects that the performance lies on a drug-induced continuum. Impairments in social functioning in cocaine users should be considered and targeted in therapy.

P-02-032 To assess prevalence of chronic pain among subjects with alcohol dependence syndrome. To study the relationship of alcohol use and its effect on pain

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Objective: To assess prevalence of chronic pain among subjects with alcohol dependence syndrome. To study the relationship of alcohol use and its effect on pain.

Methods: Patients attending outpatient services of Center for Addiction Medicine in National Institute of Mental Health and Neurosciences, Bangalore, India who fulfilled the diagnostic criteria for alcohol dependence syndrome were screened for chronic pain. Patients having chronic pain were interviewed after obtaining informed consents by following instruments – Semi structured proforma to collect details on demography, pain related details and questions on relationship of alcohol and pain, Brief pain inventory and Severity of Alcohol Dependence Questionnaire (SADQ-C). This study was approved by the institution ethics committee.

Results: Chronic pain was prevalent in 18.2% of subjects with alcohol dependence syndrome with 49% of them reporting pain to be of severe intensity. Use of other substances (nicotine, benzodiazepines, opioids and inhalants) were found in 96.3% with nicotine use being most common. Use of alcohol to manage pain in last month was reported by 75% of patients while 62% reported pain as a reason to continue to use alcohol. Only 34% of patients were currently receiving treatment for chronic pain and 62% expressed interest in receiving treatment.

Conclusion: Chronic severe pain was prevalent in subjects with alcohol dependence syndrome attending an outpatient service. Significant number of them were using alcohol for pain relief and reporting it to be reason to continue to use alcohol. Few patients were taking treatment for pain while larger number expressed interest for effective treatment. Efforts should be made to better address the pain problems in this patient population.

P-02-033 Blockade of ventral midbrain NMDA receptors prevents neurotensin-induced sensitization to amphetamine

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Objective: Previous studies have shown that neurotensin, an endogenous neuropeptide that modulates limbic neurotransmission, plays a key role in the development of sensitization to amphetamine-induced locomotor activity. In this study, we tested the hypothesis that neurotensin acts within the ventral midbrain to initiate amphetamine sensitization and that this effect is dependent upon activation of local NMDA receptors.

Methods: Experiments were performed on adult male Long-Evans rats implanted with bilateral cannulae above the ventral midbrain. During a first initiation period, locomotor activity (ambulatory, non-ambulatory and vertical movements) was measured in different groups of habituated rats on three occasions, every second day (day 1, 3 and 5), for two hours after bilateral ventral midbrain injections of vehicle (0.5 ul/side), D-Tyr[11]neurotensin (1.5 nmol/side), RS-CPP (40 or 120 pmol/side), Ro04–5595 (200 or 1200 pmol/side), RS-CPP (40 or 120 pmol/side) + neurotensin (1.5 nmol/side) or Ro04–5595 (200 or 1200 pmol/side) + neurotensin (1.5 nmol/side). Five days after the third injection, on day 10, locomotor responses to a single injection of amphetamine sulfate (0.75 mg/kg, ip) were measured in all the animals.

Results: Results show that amphetamine induced significantly stronger locomotor responses (ambulatory, non-ambulatory and vertical activity) in neurotensin pre-exposed animals than in controls (vehicle pre-exposed). This amphetamine sensitization effect was prevented by the preferred GluN2A,2B subunit antagonist, RS-CPP, but not the selective GluN2B antagonist, Ro04–5595; the latter rather slightly enhanced the effect of neurotensin.

Conclusion: These results demonstrate that i) ventral midbrain neurotensin induces glutamate release to initiate neural changes that subserve sensitization to the behavioral effects of amphetamine and ii) this sensitization effect most likely results from activation of ventral midbrain NMDA receptors that are composed of GluN2A subunits. Supported by Canadian Institutes for Health Research(CIHR, Canada).

P-02-034 Impulsivity in Internet addiction: A comparison with pathological gambling and healthy controls

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Objective: he present study investigated trait impulsivity in Internet addiction compared with pathological gambling from the perspective of considering Internet addiction as an impulse control disorder.

Methods: Twenty-seven patients with Internet addiction (age, 24.78 ± 4.37 years), 27 patients with pathological gambling (age, 25.67 ± 3.97 years), and 27 healthy controls (age, 25.33 ± 2.79 years) were enrolled in this study. All patients were treatment-seeking, and only male subjects were enrolled. Trait impulsivity was measured by Barratt Impulsiveness Scale-11 and severities of Internet addiction and pathological gambling were Young's Internet Addiction Test and South Oaks Gambling Screen, respectively. Beck Depression Inventory and Beck Anxiety Inventory were also administered to all subjects.

Results: We found that the Internet addiction group showed increased level of trait impulsivity, which was comparable to that in patients with pathological gambling. In addition, severity of Internet addiction was positively correlated with level of trait impulsivity in patients with Internet addiction.

Conclusion: These results provide the evidence that Internet addiction is conceptualized as an impulse control disorder and trait impulsivity could be a vulnerability marker for developing Internet addiction.

P-02-035 Event-related potentials P300 in patients with alcohol dependence and pathological gambling

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Objective: This study was designed to evaluate the auditory and visual event-related potential P300 in the patients with alcohol dependence & pathological gambling.

Methods: Subjects were composed of patients with alcohol dependence (N = 24), pathological gambling (N = 24) and normal control (N = 24). Topographic auditory & visual event-related potential P300 was measured by ''Oddball paradigm'', which was known as a standard method, and was determined by a conventional method, Global Field Power method.

Results: In patients with alcohol dependence and pathological gambling, the amplitude of auditory & visual event-related potential P300 was significantly smaller than normal control ($p < 0.01$). The Auditory P300 between alcohol dependence and pathological gambling had no significant differences in the amplitude and latency. In patients with pathological gambling, the latency of visual P300 was significantly later in Fz, Cz, Pz than patients with alcohol dependence ($p < 0.01$).

Conclusion: It suggests that patients with alcohol dependence and pathological gambling have brain dysfunction in some neurophysiological aspects. In patients with pathological gambling, the latency of visual P300 was significantly later in Fz, Cz, Pz than patients with alcohol dependence, and this result suggest that patients with pathological gambling may have more impairment in cognitive function than patients with alcohol dependence.

P-02-036 Overuse and abuse of diphenoxylate hydrochloride three case report

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Objective: diphenoxylate hydrochloride is an opiate derivative used for treatment of acute diarrhea to be relative safe and with low abuse potential.in last few years we have come across young adults taking heavy doses of diphenoxylate hydrochloride and physically dependent on it.

Methods: we report 3 cases where the subjects were taking >100 tablets of diphenoxylate hydrochloride per day.

Results: we report 3 cases where the subjects were taking >100 tablets of diphenoxylate hydrochloride per day.all of them started taking the drug when they were trying to stop opiates 2 of them were using multiple substance of abuse.surprisingly the withdrawal symptoms were mild in spite of heavy doses.yawning, watering eyes,legs pain,sleep disturbance,none of them presented with diarrhea.

Conclusion: implication of the study and review of literature will be discussed in detail.

P-02-037 (-)-OSU6162 potentiates amphetamine-mediated effects in habituated but not in novel environments

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Objective: (-)-OSU6162 is a substance belonging to a new class of drugs, termed ''dopamine stabilizing drugs''. (-)-OSU6162 binds with low affinity to the dopamine D2 receptor and causes different behavioral responses when administered in novel compared to habituated environments. Here we characterized the environmental impact on the interaction of (-)-OSU6162 and amphetamine.

Methods: The locomotor response to (-)-OSU6162 or amphetamine themselves and the combination of the two were measured in animals given the drugs in habituated or novel environments. Immunohistochemistry and in situ hybridization was used as to analyze levels of protein and mRNA, respectively, of the immediate early gene c-fos in rats and mice after administration of (-)-OSU6162 and amphetamine.

Results: The behavioral studies showed that (-)-OSU6162 increased locomotion in animals habituated to their home cages, but not in animals given the drugs in a novel environment. (-)-OSU6162 caused a dose dependent increase of c-fos mRNA in striatum and nucleus accumbens in habituated animals, with a more homogenous induction compared to amphetamine, which was strongest in medial parts. Protein levels of c-Fos were elevated in medium spiny dopamine D1-receptor neurons of the dorso-lateral striatum after (-)-OSU6162 itself and even more elevated in the group receiving (-)-OSU6162 thirty minutes prior to amphetamine in their home cages.

Conclusion: Locomotion tests in rats given (-)-OSU6162 in combination with amphetamine show that (-)-OSU6162 attenuates amphetamine-mediated locomotion in a novel environment, but has an opposite effect in habituated animals. The c-Fos expression indicated that (-)-OSU6162 has an impact on D1-receptor medium spiny neurons in habituated animals, even though the effect is most likely not directly mediated via D1 receptors as no binding affinity has been reported for (-)-OSU6162 on D1-receptors.

P-02-038 The dopamine stabilizer (-)-OSU6162 attenuates voluntary ethanol intake and ethanol-induced dopamine output in the nucleus accumbens

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Objective: New medications for alcohol use disorder (AUD) are needed. ''Dopamine stabilizers'' is a new class of compounds characterized by the ability to suppress, stimulate, or show no effect on dopamine activity depending on the prevailing dopaminergic tone. Thus, they may be hypothesized to normalize dysregulated dopamine activity induced by, for example, long-term alcohol consumption.

Methods: The effects of acute and repeated treatment of the dopamine stabilizer (-)-OSU6162 (OSU6162) was evaluated in rats given intermittent-access to 20% ethanol for at least three months before treatment. OSU6162's effect on ethanol seeking, using the operant self-administration paradigm, was also evaluated. Furthermore, we studied the interaction of OSU6162 with ethanol on dopamine output and metabolism in awake rats, using microdialysis.

Results: OSU6162-treatment selectively decreased voluntary ethanol consumption and preference without decreasing intake of water or a salty solution. The effect on ethanol intake was more pronounced in rats voluntarily consuming high compared to moderate amounts of ethanol. There was no tolerance development to OSU6162's ability to decrease ethanol intake during repeated OSU6162 treatment and no rebound increase in ethanol intake after the treatment was terminated. We found that pretreatment with OSU6162 blunted the ethanol-induced dopamine output in the nucleus accumbens.

Conclusion: These results highlight OSU6162's ability to stabilize dopamine activity depending on the prevailing dopaminergic tone and indicate that OSU6162 might decrease ethanol intake by attenuating the acute rewarding properties of ethanol. The present study is to our knowledge the first indicating that OSU6162 may serve as a novel medication for AUD.

P-02-039 Influence of GIRK channel inhibition on relapse risk in Japanese alcohol-dependent inpatients

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Objective: We examined the influence of G-protein-activated inwardly rectifying K+ (GIRK) channel inhibition on relapse risk in Japanese alcohol-dependent inpatients.

Methods: The participants included 11 patients who received GIRK inhibition treatment and 39 patients who did not receive GIRK inhibition treatment. The participants answered a questionnaire, including the Alcohol Relapse Risk Scale (ARRS) and a questionnaire about their experiences of stressful events 2 weeks after hospitalization (time 1) and completed follow-up questionnaires 45–60 days after the first rating (time 2).

Results: A significant interaction was found between group and time on positive expectancy for alcohol scores on the ARRS ($F = 5.93$, $p = 0.02$). The simple main effect test showed that the scores at time 1 in the GIRK inhibition treatment group were higher than in the non-GIRK inhibition treatment group ($p = 0.03$). The scores at time 1 were higher than that at time 2 only in the GIRK inhibition treatment group ($p = 0.004$). Significant main effects of time were found on total ARRS score ($F = 5.10$, $p = 0.03$) and stimulus-induced vulnerability score on the ARRS ($F = 7.28$, $p = 0.01$), and these scores at time 1 were higher than at time 2. No significant interaction was found between group and time, with no main effect of either factor on the experience of stressful events.

Conclusion: The results of the present study suggest that GIRK inhibition treatment may improve the positive expectancy for alcohol, a component of relapse risk. However, the lower positive expectancy scores in patients who did not receive GIRK inhibition treatment at time 1 may be responsible for the lack of changes in positive expectancy scores. Although this result should be interpreted with caution, the present study suggests that the effects of GIRK inhibition treatment should be investigated further in future studies.

P-02-041 Usage of xenon for relief of acute abstinent syndrome in the treatment of drugs addiction

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Objective: The purpose of this study was to evaluate the clinical efficiency and safety of xenon therapy in the treatment of patients with opium dependence during abstinent syndrome. In the treatment of 80 patients with opium dependence was included inhalation of xenon via anesthetic machine «Drager» «Fabius» (Germany) in a ratio of $Xe : O_2 = 4 : 4$ l/min.

Methods: Assessment of the severity of abstinent syndrome and the effectiveness of the therapy was conducted using clinical-psychopathological method based on a specially designed scales daily during 15 days. During each treatment session was monitored ECG, blood pressure, dynamics of consciousness change, time to reach the desired level of anesthesia, duration of rest after anesthesia. Therapy sessions were held 3–4 times in the 1st day, 2 times during the 2nd day and once in the next 3 days. The whole course required 9–10 sessions of 40 minutes. The average time to reach the desired level of anesthesia coincided with clinical improvement of the patient.

Results: The clinical study showed that Xenon has analgesic effect and reduces the affective, astenic and behavioral disorders of patients with opium dependence. Xenon inhalations does not affect hemodynamics and respiration, therefore, is safe. The therapy that included course of Xenon inhalations was more successful for patients with opium abstinence syndrome, than therapy without this course. When repeating inhalation the tolerance to Xenon does not increase, like for other analgesics and psychotropic drugs, but decreases.

Conclusion: This phenomena authentically matches the clinical improvement of patient's condition and may be used as a test for severity of opium abstinent syndrome. Usage of Xenon inhalations for patients with opium dependence allows to relief faster the manifestation of disease and reduce attraction for the drug.

P-02-042 Influence of the family on the inclination to use alcohol, toxic and narcotic substances in teenagers

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Objective: 50 reports of the Commission of forensic psychiatric experts over the period from January 2004 to December 2006 were analyzed. The forensic psychiatric examination was carried out on an outpatient basis. The analysis showed that the fifty examined teenagers included 46 male and 4 female teenagers aged between 15 and 18.

Methods: The research is based on the statistical method along with the analysis of data of forensic psychological – psychiatric and forensic psychiatric examinations.

Results: The research revealed the following factors leading to consumption of alcohol, toxic and narcotic substances: group 1(14 persons), – a one-parent family, where the child was raised by one parent who did not abuse alcohol, group 2 (14 persons) – a one- parent family in which the parent abused alcohol, group 3 (5 persons) – teenagers who do not have parents and close relatives, group 4 (4 persons) – families with both parents abusing alcohol. At the same time 12 of 50 individuals had secure families (they were brought up by both parents who did not abuse alcohol). In group 1, 4 teenagers used alcohol, 5 – inhaled vapors of toxic substances, 2 – used drugs. In group 2, 3 individuals used alcohol, 4 – inhaled vapors of toxic substances, 2 – used drugs. In group 3 all teenagers used alcohol. In group 4 one person used alcohol, 1 – used drugs. However, even among the individuals who were brought up in secure families still there were 3 inclined to alcohol abuse and 2 – to drug abuse.

Conclusion: the teenagers raised in the families with one parent no matter if he/she abused alcohol or not, are more inclined to consumption of alcohol, drugs and other toxic substances. It should also be noted that the family security is not an absolute indicator for the absence of inclination to commit criminally punishable acts and abuse alcohol and narcotic substances.

P-02-043 Naltrexone effectiveness in alcohol dependence with comorbid cluster B personality disorders

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Objective: To evaluate the efficacy and tolerability of naltrexone use in patients with dual diagnosis- alcohol dependence and cluster B personality disorder.

Methods: A group of 32 patients, 19 male and 13 female, mean age 35.7, admitted in our department for alcohol dependence, were also diagnosed with cluster B personality disorders (antisocial $n = 9$, borderline $n = 10$, histrionic $n = 10$, narcissistic $n = 3$) according to the DSM IV TR criteria. Patients presented a documented history of alcohol dependence of at least 2 years prior to the baseline evaluation, with no more than one hospitalization for specific treatment in the last 24 months. The diagnosis of personality disorder was based upon Structured Clinical Interview for DSM IV Disorder (SCID –II) and clinical psychiatric evaluation. Patients received naltrexone 50 mg/day, single dose daily, after the initial detoxification period (mean duration 8.5 days). Patients were monitored using every 4 weeks for 6 months Inventory of Drug Taking Situations- alcohol focused version (IDTS), Global Assessment of Functioning (GAF) and Clinical Global Impressions –Severity and Improvement (CGI-S/I).

Results: At week 24, patients had an overall improved IDTS score (-49.1 points to baseline, $p < 0.01$), with greater improvements observed in areas like ''physical discomfort'' ($p = .0422$) and ''testing personal control'' ($p = .0324$). GAF values increased in the treatment group with 28.5 points, compared to baseline. CGI-I decreased from a mean value of 4.8 to 1.2 at week 24. A number of 7 patients discontinued treatment due to adverse events (vomiting, nausea, abdominal pains, $n = 4$) or non-compliance ($n = 3$). Mild and moderate adverse events were reported in 12 patients, especially gastrointestinal discomfort and anxiety.

Conclusion: Naltrexone is a good therapeutic option in alcohol dependent patients with cluster B personality disorder, because of its efficacy and low rate of adverse events. Naltrexone decreased significantly alcohol consumption in situations of ''physical discomfort'' and testing of personal control.

P-02-044 Pathological gambling and maintenance of attention

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Objective: Pathological Gambling (PG) is a persistent and recurrent maladaptive pattern of gambling behavior characterized by increased preoccupation with gambling activities, loss of control and continued

gambling despite problems in social or occupational functioning. In the study of addiction, attentional bias (AB) refers to the observation that substance-related cues tend to capture the attention of experienced substance users. This concept is based on Robinson and Berridge's incentive-sensitization theory, which suggests that the substance and its associated cues increase their motivational incentive and salience with each new administration. In this study we sought to assess AB at the level of maintenance of attention in a sample of Pathological Gamblers (PGRs). We build on prior work by using the Visual Probe Task (VPT), previously used to assess individuals with substance use disorders.

Methods: PGRs (n = 23) were recruited from two 12-step programs for PGRs in Madrid (Spain). The comparison group of healthy volunteers (non-gamblers; NG) (n = 21) was recruited through advertisements. The procedure for the Visual Probe Task was based on that of Lubman (Lubman et al., 2000).

Results: The reaction time of individuals with PG when the dot was in the same location as the gambling-related cue was significantly lower than the reaction time when the dot and the gambling-related cue were in different locations, indicating the presence of AB ($t = -3.9$, $df = 22$, $p = 0.001$). By contrast, in the group of healthy volunteers, reaction times did not differ significantly ($t = -0.5$, $df = 20$, $p = 0.6$). The reaction times were significantly slower in individuals with PG than in healthy volunteers.

Conclusion: Our finding that PGRs have AB for gambling-related cues is consistent with prior studies that have shown AB at early attentional process, but extend them by assessing maintenance of attention.

P-02-045 Morphine excites dopamine neurons(da) in ventral tegmental area(vta): The gating role of prefrontal cortex(pfc)

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Objective: We studied the gating role of PFC in morphine-excited DA neurons in VTA.

Methods: use of in vivo single unit recording techniques and microdylysis to study how PFC regulates VTADA neurons in rats in response to morphine.

Results: We found that morphine markedly increased DA cell activity. The effect of morphine can be reversed and prevented by naloxone, suggesting that the effect is associated with the activation of mu opiate receptor. Lesion of PFC by tetradotoxin produced no significant influence on basal DA cell activity in naïve rats. However, PFC lesion abolished the morphine's effects on DA cells, accordingly, the morphine – stimulated DA content in NAc was also abolished. This indicates that the PFC is critical in mediating the morphine's excitation on DA neurons and that the PFC might play a gating role in morphine's effect on DA cells. Interestingly, in rats pretreated with morphine 24 hours before morphine challenge, the gating role of PFC disappeared. It thus appeared that morphine -enhanced DA neuronal firing is independent of the function of PFC in rats that previously exposed to morphine. Furthermore, we found that morphine inhibited PFC pyramidal neurons in all recorded cells in naïve rats. Whereas only 46% (7 in 15) recorded pyramidal neurons was inhibited by morphine challenge in rats that were previously exposed to morphine.

Conclusion: our data provided evidences that the PFC play a gating role in acute morphine's effect on DA neurons, The underling mechanism may attribute to morphine – inhibited PFC pyramidal neurons which leads to the reduced output. However, single morphine pretreatment resulted in loss of the gating effect of PFC, which may associated with the single morphine-induced dysinhibition on PFC neurons.

P-03. Bipolar Disorders

P-03-001 Association of metabolic syndrome and clinical outcome among patients with bipolar disorder

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Objective: Bipolar disorder is with high prevalence of metabolic syndrome, ranged from 32% to 50%. However, the influence of metabolic syndrome for clinical outcome is not clear. This study evaluated the association of metabolic syndrome for clinical outcome among symptomatically stable outpatients with bipolar disorder.

Methods: The patients aged between 18 to 65 years with DSM-IV diagnosis of bipolar disorder and with clinical global severity less than 3 were enrolled. Metabolic syndrome was surveyed and clinical symptoms, side effects, insight, function, life quality, and cognitive executive function were assessed.

Results: The study enrolled 84 patients with 71.4% of female, and average age of 43.9 ± 12.2 years old. The prevalence of metabolic syndrome was 34.5%. The patients with metabolic syndrome tended to have elder age (48.5 ± 11.5 vs. 41.5 ± 11.9, $p = 0.084$), education years less than 12 years (75.9% vs. 56.4%, $p = 0.098$), higher frequency of first episode with manic episode (55.6% vs. 33.3%, $p = 0.092$), more hospitalization times (4.2 ± 3.8 vs. 2.8 ± 3.5, $p = 0.067$),more extrapyramidal side effect by Simpson and Angus rating scale (4.03 ± 5.5 vs. 2.0 ± 3.9, $p = 0.076$), poorer insight by Schedule Assessment of Insight (15.7 ± 5.1 vs. 19.1 ± 3.7, $p = 0.006$), poorer quality of mental health (41.6 ± 11.1 vs. 35.2 ± 12.4, $p = 0.023$), and poorer executive function of Wisconsin card sorting test percent of conceptual level response (29.0 ± 11.3 vs. 38.2 ± 12.6, $p = 0.014$).

Conclusion: The prevalence of metabolic syndrome was high to one third, and associated with poorer clinical outcomes, including more hospitalizations, more side effects, poorer insight, poorer quality of mental health and poorer cognitive executive function. Monitoring metabolic syndrome is important for patients with bipolar disorder.

Policy of full disclosure: The study was sponsored by Taiwan National Science council (NSC 99–2628-B-075–004 -MY3), there is no finical conflict of interest.

P-03-002 Correlation among impulsivity, temperament, character and neurocognitive performance in euthymic bipolar patients

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Objective: To investigate the prevalence of clinical impulsivity and its correlation with personality traits, affective temperaments and neuropsychological performance in bipolar disorder outpatients compared with healthy controls.

Methods: A sample of 63 adult (aged ⩾18–65 years) outpatients who fulfilled DSM-IV-TR criteria by SCID-I interview for bipolar disorder were included. All bipolar patients fulfilled clinical criteria for euthymia [YMRS ratings <6 and HAM-D ratings <8] and also did not meet criteria for DSM-IV mood episodes for at least 8 weeks before entry to the sudy. Healthy controls (N 40) did not meet criteria for any axis I (SCID-I). Strict exclussion criteria were used. All subjects completed a standard neurocognitive battery and personality traits were determined by the Temperament and Character Inventory. Impulsivity was assessed using the BIS-11. Affective temperaments were evaluated using the TEMPS-A Buenos Aires.

Results: Euthymic bipolar disorders subjects demonstrate significant differences on the Barratt Impulsivity Scale (BIS-11) subitems and total scores compared with healthy controls. However, there were no statistical differences in impulsivity scores between both subgroups of patients (bipolar I vs. II). We found a positive correlation between impulsivity scores and sensation seeking and a negative correlation with self-directedness, measured by TCI. Euthymic bipolar disorder individuals displayed significant higher scores on cyclothymic temperament and demonstrated impaired neuropsychological functioning across almost all domains, mainly executive function, attention and memory tasks, compared with healthy controls.

Conclusion: Preliminary results show that trait-like impulsivity was substantially higher in subjects with bipolar disorder than in healthy comparison subjects, regardless of symptoms. Within subjects with bipolar disorder during euthymia, high impulsivity scores were associated with specific personality traits, cyclothymic and anxious temperament and generalized impairment on neuropsychological functioning.

P-03-003 The risk of insulin resistance and type 2 diabetes mellitus in bipolar disorder

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Objective: Patients with bipolar disorder (BD) have up to a three times increased risk of type 2 diabetes mellitus (T2D). The prevalence of insulin resistance (IR) in BD, however, has not been systematically studied. The possible links between aberrant glucose metabolism and BD include treatment, lifestyle, neuroendocrine and neurotransmitter dysfunctions, and genetic predisposition. This study aims to establish the rate of IR in patients with BD and examine the correlates of abnormal glucose metabolism with the course and outcome of BD, including response to treatment and medical outcomes. We hypothesize that subjects with co-morbid T2D/IR will have a more refractory form of BD than those without T2D/IR, as well as poorer response to treatment.

Methods: Patients for this study are being recruited from The Maritime Bipolar Registry and Mood Disorders Clinic, reflecting primary and tertiary samples of BD respectively. The diagnosis of T2D is determined according to two measures of fasting plasma glucose (FPG) and OGTT if still equivocal. Fasting serum insulin and FPG is used to determine HOMA-IR to quantify insulin resistance in those with normal FPG.

Results: To date, 64 subjects have been included in the study; with diagnoses of BD I, II and NOS and age range of 24–85 years. Only 50% of all patients had euglycemia, 29.7% have IR and 20.3% T2D. In a preliminary analysis, patients with T2D had significantly higher rates of psychosis during mood episodes than euglycemic patients ($p = 0.04$).

Conclusion: In agreement with previously reported increased rates of T2D in BD, our preliminary results showed an increased proportion of T2D in BD. In addition, only half of bipolar patients had euglycemia; the rest of the sample showed some abnormality in glucose metabolism. Our completed study will look at the correlates of abnormalities in glucose metabolism, various clinical characteristics, prognosis and outcome.

Policy of full disclosure: Capital District Research Fund.

P-03-004 Bipolar disorders in emergency departments in Latin-America: Prevalence and associated comorbidity

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Objective: To investigate prevalence rates of BPD and associated comorbidity in ED in Latin American countries.

Methods: To identify patients with BPD, we used a combination of DSM IV-criteria interview and the Mood Disorder Questionnaire (MDQ). We analyzed data from patients from hospitals in Argentina, Brazil, Chile, Colombia, and Mexico and described the demographic and comorbidity between BPD and non-BPD patients.

Results: The estimate was based on a total of 1,535 patients, mean age 37 years, with response rates of 83.0%. Prevalence of BPD ranges from 3.8–6.0%. Compared to non-BPD patients, BPD patients were more likely to be obese (39.7% vs. 26.9%) and to report a diagnosis of asthma (16.7% vs. 9%), thyroid problems (12.8% vs. 5.8%) and seizures (23.1% vs. 3.0%), all $p \leqslant 0.05$. BPD patients versus those without BPD were also differentiated in their psychiatric comorbidity as follows: higher rate of alcohol abuse (30.8% vs. 10.0%), ADHD (50.0% vs. 12%), depression (81.6% vs. 45.7%), OCD (20.1% vs. 3.0%), panic disorders (23.1% vs. 12.3%) and other anxiety disorders (82.1% vs. 41.8%). Compared to non-BPD, suicidal plans and attempts were also significant higher in the bipolar group (11.5% vs. 2.8% and 10.3% vs. 1.8% respectively). Multivariate analysis identified ADHD, anxiety, depression, alcohol abuse, and last month suicide plan and attempts to be independently associated with BPD.

Conclusion: Our data suggest that the prevalence of BPD is elevated among ED patients in Latin American countries. BPD patients in ED are likely to have complex psychiatric, and medical histories, which will be necessary to take into account when evaluate and design ED-initiated interventions.

Policy of full disclosure: Dr. Castilla-Puentes is currently working as Global Medical Safety Physician with Johnson & Johnson, Pharmaceutical Research and Development.

P-03-005 The HCL-32 is a usefull tool in differentiating bipolar disorder from borderline personality disorder

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Objective: The selection of an adequate treatment strategy depends on an accurate diagnosis. A complex challenge in clinical practice is the differential diagnosis between bipolar disorder (BD) and borderline personality disorder (BPD). Previous studies suggest that phenomenologically, hypomania in BD is dissimilar to affective instability in BPD. Hence, a tool that discriminates hypomania form affective instability could aid in this difficult differential diagnosis. The HCL-32 is a ten minutes self administrated scale for the screening of hypomania. The aim of this study is to determine the usefulness of the HCL-32 in differentiating BD from BPD patients.

Methods: Patients with a diagnosis of BPD ($n = 20$) and BD ($n = 33$) were assessed using the HCL-32. The diagnosis of BPD or BD was established by two clinicians with a vast experience in these disorders and blinded to the results of the HCL-32. Both groups were compared using one way ANCOVA, controlling for anxiety trait and depression. All statistical analyses were performed using the SPSS 17.0 software package.

Results: Non significant statistical differences were found in demographic variables between the two groups. The group of patients with BD scored higher on the HCL-32, even when controlling for anxiety and depression (ps < 0.001).

Conclusion: These results suggests that HCL-32 could be a very useful instrument helping to differentiate BPD patients from BD patients.

P-03-006 Utility of the INECO frontal screening (IFS) for the detection of executive dysfunction in patients with bipolar disorder

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Objective: Bipolar Disorder (BD) patients present not only changes of mood, but also cognitive deficits, even during euthymic periods. These cognitive deficits include important executive functioning failures. The detection of executive dysfunction usually requires the administration of an extensive neuropsycological battery, because there are few screening tests specifically designed to assess executive functions. The INECO Frontal Screening (IFS) is as solid and brief tool, which has proved useful for the assessment of the executive functions in patients with dementia. The aim of this study was to assess the utility of the IFS to detect executive dysfunction in BD patients.

Methods: A total of 46 subjects, 20 of which were diagnosed with BD, and 26 of which were healthy controls, were assessed with classical executive tests and the IFS. The cutoff score was established by the analysis of the ROC curve (Receiver Operating Characteristics).

Results: The IFS total score was significantly lower in patients ($M = 24.40$) compared with controls ($M = 26/30$). A cutoff of 26/30 points on the IFS was associated with a sensitivity of 73% and specificity of 68.4%. Also, the IFS total score correlated with performance on classical executive tests (Phonological fluency task $> r = 0.03 <$ TMT-B: $r = 0.69$, $p = 0.00$; digits backwards span $r = 0.63$, $p = 0.00$;

letters and number sequence: r = 0.48, p = 0.001; arithmetic: r = 0.49, p = 0.001).

Conclusion: The IFS is a solid and useful tool for the detection of executive dysfunction in BD patients.

P-03-007 Altered feedback-related negativity in bipolar patients performing probabilistic reward learning

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Objective: Bipolar patients have the manic symptoms of grandiosity, increased goal-directed activity and excessive involvement in pleasurable activity indicating reward learning and behaviors. Feedback-related negativity (FRN) is elicited by positive feedback and appears as relatively more positive ERP deflection. We investigated if bipolar patients show impairments in adjusting behavior during and to examine the feedback-related negativity during reward learning process using probabilistic reward task.

Methods: We recruited 20 manic and 15 euthymic patients, and 26 healthy controls. We recorded the FRN to reward feedback while performing a probabilistic reward task. This task was designed to facilitate to make the response bias with signal-detection theory, which was consisted with three blocks.

Results: In response bias analysis, repeated measures ANOVA revealed the main effect of block ($p = 0.04$) and interaction of response bias and group ($p = 0.05$). In FRN amplitude analysis, repeated measures ANOVA revealed the main effect of block ($p = 0.05$). While FRN amplitudes were not different between block 1 and 3 in healthy controls ($p = 0.90$), FRN amplitudes in block 3 were more negative than that in block 1 in bipolar patients ($p = 0.01$).

Conclusion: Bipolar patients appeared to have the impaired acquisition of response bias and reduced FRN amplitude toward the more frequently rewarded stimuli. These results suggest that bipolar patients might have the dysfunctional reward learning over time and are related to the reduced electrophysiological activity during reward learning process.

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P-03-008 Impaired cognition in bipolar I disorder: Searching for a biological substrate

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Objective: It has been proposed that cognitive deficit could be found in bipolar I disorder (BDI) patients across different mood state. The goal of this study was designed to replicate precious findings in cognitive deficit in euthymic BDI patients and further explore the possible underlying substrates.

Methods: Thirty-three age, education matched healthy controls (HC) and twenty-three euthymic BDI patients who met the criteria of DSM-IV-TR were recruited. The definition of euthymia was that Montgomery-Asberg Depression Rating Scale (MADRS) scores less than 10 and Young Mania Rating Scale (YMRS) scores less than 7 within an 8-week consecutive period. Single photon emission tomography (SPECT) with radiotracer 123I-ADAM was used for the image of brain serotonin transporter (SERT). Specific uptake ratio (SUR) was determined for the measured outcome. Ten ml venous blood was drawn when subject underwent SPECT for the measurement of brain derived neurotrophic factor (BDNF).

Results: we found that SERT binding in both the midbrain and striatal regions was decreased in patients than that in HC. However, BDNF was not different in both groups. There was no correlation of SERT binding and BDNF. Although there were statistic significantly different in several sub-items of facial memory and Wisconsin Card Sorting Test (WCST) between patients and HC, the overall deficit in cognition were not significantly correlated with SERT binding and/or BDNF.

Conclusion: we replicated previous findings which showed the deficit of cognition in BDI patients. However, the underlying substrates of cognitive deficit may be beyond SERT and BDNF.

P-03-009 The change of cholsterol level and impulsiveness after pharmacotherapy in patients with bipolar disorder

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Objective: Many Studies supported significant relationships between low cholesterol levels and impulsiveness, aggression and mood. In this study, we investigated the association between total cholesterol levels and impulsiveness, and evaluated correlation between differences of total cholesterol level after pharmacologic treatments and changes of impulsiveness in patients with bipolar disorder.

Methods: Forty patients with bipolar disorder and 40 healthy normal controls were selected. They were evaluated twice with Korean version of Young Mania Rating Scale (K-YMRS), Clinical Global Impression Scale-severity (CGI-S) and Barratt Impulsiveness Scale (BIS) at admission (pretreatment) and after 6 weeks of treatment (post-treatment). The pretreatment and post-treatment serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) levels in the BD were measured, and were compared to those of healthy normal controls.

Results: Posttreatment YMRS scores were significantly lower than pretreatment YMRS scores in the patients group. The TC levels were significantly higher in posttreatment patients group than pretreatment group. Posttreatment BIS scores were significantly lower than pretreatment group. But it is found to be no correlation between TC levels and BIS scores after pharmacotherapy.

Conclusion: Our results supported earlier reports of significant increase in the cholesterol levels when BD patients were treated with pharmacotherapy for 6 weeks. Although the results in our study are statistically significant, their clinical significance requires further examination in longer-term studies and with larger subjects. Key words: Total Cholesterol, Barratt Impulsiveness Scale, Bipolar disorder.

P-03-010 Bipolar disorder and clarithromycin: More than a single manic episode

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Objective: To describe the onset of a Bipolar Disorder after being on treatment with clarithromycin.

Methods: Systematic search of the literature of MEDLINE, EMBASE, and the Cochrane Library. No references about bipolar disorders which break out after starting treatment with clarithromycin, were found.

Results: A 47-year-old woman with no previous psychiatry or substance abuse history, was brought to emergency department because of behavioral disturbances and manic symptoms. One week before the onset of the illness, the patient had an upper digestive haemorrhage due to a perforated ulcer. Infection by H pylori was confirmed, so she started taking clarithromycin, amoxicillin, and omeprazole 4 days after starting this treatment, she suddenly developed insomnia, hiperactivity, grandious delusions, irritability, pressure speech, tangenciale thinking and increased energy level. She was admitted in inpatient psychiatry service Clarithromycin was discontinued and Olanzapine 20 mg/day was administered from the beginning. One week after the admission the manic symptoms still persisted, so Divalproex sodium 2000 mg/day was added. Troughout the next days an improvement was noted, and manic and psychotic symptoms gradually dissipated, though expansive mood still persisted. She was discharged after three weeks of hospital stay. One month later, in the follow-up consultation, the patient still had hypomanic symptoms. She was diagnosed as Bipolar I Disorder, Single Manic Episode, Severe With Psychotic Features.

Conclusion: This patient developed an acute manic psychosis within a 4-day period. There was no evidence of infection, substance abuse, or hypoglycemia to account for her symptoms. The psychosis began approximately 3 days after the initiation of triple therapy with clarithromycin, amoxicillin, and omeprazole for H pylori peptic ulcer disease. In the reported Clarithromycin-induced manic episodes, a complete resolution of symptoms in 24 to 36 hours after finishing treatment is described [3]. Because of the severity and duration of the

affective symptoms and the family psychiatry history, the patient was finally diagnosed as bipolar disorder.

P-03-011 Attitudes of investigators and staff toward placebo response in a global bipolar depression trial

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Objective: Attitudes of clinical trials investigators and site staff were explored with respect to their ability to influence placebo response.

Methods: 165 clinical trialists from the US, Central Europe, India and Japan attending regional industry sponsored investigators' meetings for a double blind, placebo controlled, bipolar depression trial were queried regarding their ability to influence placebo response. Associations among responses were evaluated using the chi-square test statistic.

Results: 69.3% (n=109) had previously received training to reduce placebo response. 66.2% (n=100) indicated they could influence the magnitude of placebo response in a clinical trial ''markedly or moderately'', whereas 33.8% (n=51) responded ''slightly'' or ''not at all''. 75.5% (n=117) disagreed with the notion that ''My role in a clinical trial includes ensuring that subjects improve clinically'', whereas 24.5% (n=38) agreed. 62.9% (n=95) disagreed that ''It is unethical to continue subjects in a clinical trial who are not improving'', whereas 37.1% (n=56) agreed. Increased exposure to placebo response training was associated with: 1) increased confidence that the individual respondent's ($p<0.01$) or the site staff's ($p<0.01$) behavior can influence the magnitude of placebo response in a clinical trial; and 2) disagreement with the notions that the respondent's role in a clinical trial includes ensuring that patients improve clinically ($p<0.001$) or that it is unethical to continue subjects in a clinical trial who are not improving ($p<0.05$).

Conclusion: A high level of agreement was reported on the importance of placebo response and the ability to influence it in clinical trials. While the majority disagreed with the notion that clinical trials patients should improve clinically, a significant minority agreed. Increased exposure to placebo response training was associated with increased confidence in the ability to modulate placebo response and diminished belief that patients should improve during clinical trial participation. Further research should investigate which approaches to placebo response minimization are most effective.

Policy of full disclosure: David Daniel and Jean Dries are employees of United BioSource Corporation (UBC). UBC provided rater training to the investigators and provided funding for the statistical analyses. Antony Loebel and Josephine Cucchiaro are employees of Sunovion. Sunovion conducted the clinical trials noted in the abstract.

P-03-012 Phenotype definition and clinical correlates of antidepressant-induced mania

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Objective: Although a random effects meta-analysis showed weak evidence of association of the S allele with antidepressant induced mania (AIM+) status, a test of heterogeneity indicated significant differences in estimated genetic effects. It is likely that phenotypic variability is a source of heterogeneity. The purpose of this study was to rigorously define the AIM+ phenotype and subsequently attempt replication of previous association of AIM+with variation in the serotonin transporter gene SLC6A4.

Methods: Subjects with bipolar I or II disorder, confirmed by structured diagnostic interview, enrolled in the Mayo Clinic Bipolar Disorder Biobank. The medical record was reviewed by a psychiatrist with at least 10 years clinical experience. AIM+ was defined as within 60 days of starting or changing dose of antidepressant treatment. Each AIM+ case was matched to two separate AIM- controls matching, in hierarchical order, on gender, SSRI antidepressant, I vs. II subtype, and age.

Results: 518 (95.7% Caucasian) subjects completed enrollment with 12.1% (n=63) meeting criteria for a history of AIM+. The majority were female (60.7%), Bipolar I (88.5%) with onset of AIM+ at start (85.3%) of SSRI (68%) treatment with rapid cycling present only 28% of the time. In comparison AIM− (n=122), AIM+ patients had a higher rate of past history of attention deficit disorder, both as children (20 vs. 10%, $p=0.056$) and adults (25.4 vs. 11.6%, $p=0.018$). Preliminary data on genetic variation of candidate genes will be presented.

Conclusion: This early analysis emphasizes the importance of phenotype assessment prior to genomic analysis. Identifying a genetic variation associated with SSRI induced mania or may have high clinical translational value in individualizing treatment for bipolar depression.

Policy of full disclosure: Disclosure Declaration Mark A. Frye, M.D. 2012 Grant Support Pfizer, National Alliance for Schizophrenia and Depression (NARSAD), National Institute of Mental Health (NIMH), National Institute of Alcohol Abuse and Alcoholism (NIAAA), Mayo Foundation Speakers' Bureau NONE Financial Interest/Stock ownership/Royalties NONE.

P-03-013 Neurological side effects due to GSK-3 inhibition by chronic lithium or transgenesis can be prevented by blocking NFAT/FAS pathway

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Objective: Despite lithium's efficacy for treatment of bipolar disorder, its clinical use is often curtailed by its side effects. Lithium inhibits, among other enzymes, glycogen synthase kinase-3 (GSK-3) and this has been postulated to contribute to its therapeutic efficacy but also to its neurological toxicity. GSK-3 inhibition has been shown to result in increased apoptosis through extrinsic pathway. We reasoned that this may relate to the well documented side effects of lithium therapy and that understanding the underlying molecular mechanisms might help to apply treatments based on GSK-3 inhibitors. Here we aim to genetically dissect whether GSK-3 inhibition induces toxicity in a NFAT/Fas-dependent manner.

Methods: We have combined pharmacological and genetic sustained GSK-3 inhibition with two different approaches to block NFAT/Fas signalling: 1) Cyclosporine A (CsA) or 2) lpr mice, Fas-deficient.

Results: GSK-3 activity was inhibited by chronic lithium (Gomez-Sintes and Lucas, 2010) or by a conditional transgenic mouse expressing a dominant negative form of GSK-3 (Tet/DN-GSK-3 mice; Gomez-Sintes et al., 2007). In good agreement with the common neurological side effects of lithium therapy, lithium treated mice and Tet/DN-GSK-3 transgenic mice showed subtle motor deficits and neuronal apoptosis. We now demonstrate that NFAT/Fas signaling mediates both neuronal apoptosis and motor deficits induced by decreased GSK-3 activity (induced by two different approaches) as these are absent when NFAT nuclear translocation is prevented by CsA administration or when the experiments were conducted on Fas-deficient lpr mice.

Conclusion: Motor side effects and neuronal apoptosis induced by decreased GSK-3 activity are attenuated by blocking NFAT/Fas signalling. These findings may enable development of combined therapies not only to counteract the drawbacks of lithium treatment for mood disorders but also to extend the potential of GSK-3 inhibitors.

P-03-014 Compatability of pharmacotherapy for Korean bipolar disorder patients to treatement guidelines

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Objective: The aim of the current study was to investigate the overall pattern of pharmacotherapy for patients with bipolar disorders in Korea and to compare the pattern to treatment guidelines proposed.

Methods: We retrospectively reviewed the medical records of 1,527 patients with bipolar disorders from ten hospitals. The daily

prescription of subjects who admitted to inpatient units or visited the outpatient clinic between January 1st, 2009 and December 31st, 2009 were analyzed.

Results: The study sample includes 480 manic inpatients, 328 depressive inpatients, and 719 outpatients on the maintenance therapy. In the management of acute manic episodes, 83.3% of patients were treated with a combination treatment of mood stabilizer (s) (MS) and antipsychotic (s), followed by atypical antipsychotics (AAPs) only strategy (12.3%), and MS monotherapy (3.1%). The initially chosen mood stabilizer was valproic acid followed by lithium and determined by institution characteristics. The concordance rate of naturalistic treatments for manic inpatient with the Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline was 55.2%, while the concordance rate with the Korean Society for Depression and Bipolar disorder (KSDB) guideline was 76.0%. In the management of acute depressive episodes, 26.4% of patients were treated with antidepressant. Also, 29.3% were treated with lamotrigine. Other 29.3% were treated with MS(s) (excluding lamotrigine) and AAP. In bipolar depression, treatments for only 28.3% of subjects were concordant with the CANMAT guideline, while 75.1% were concordant with the KSDB guideline. In the maintenance treatment, 50.3% of patients were treated with MS (including lamotrigine) and AAP. Antidepressant combination strategy was used in 22.8% of subjects, followed by MS only (18.4%) and AP only (6.3%) strategy.

Conclusion: Results suggest that treatment strategy for acute mania has been relatively well established, while that for acute bipolar depression has not been standardized yet. More consensus on treatment for bipolar depression is warranted.

P-03-015 The relation of 'bright side' and 'dark side' hypomania to psychological functioning, sleep and physical activity in young adults

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Objective: No research has yet focused on hypomanic states in early adulthood. The aim of the present study was therefore to assess hypomania in a large non-clinical sample of young adults, to differentiate between favorable (bright side) and unfavorable (dark side) hypomanic stages, and to relate hypomanic stages with sleep and physical activity.

Methods: A total of 862 participants (university students; 74.1% females; mean age: M = 24.67; SD = 5.91) took part in the study. They completed a series of validated self-report questionnaires assessing hypomania (HCL-32), psychological functioning, sleep and physical activity.

Results: Based on the HCL-32, 81% of the participants were categorized as currently not being in a hypomanic state; 19% of the participants were categorized as currently being in a hypomanic state. Of those, 57.6% were classified as ''active/elated'' ('bright side'), whereas 42.4% were classified as ''irritable/risk-taking'' ('dark side'). Compared to non-hypomanic participants and the 'bright side' group, 'dark side' hypomanic participants reported more depressive symptoms, sleep disturbances, somatic complaints, perceived stress, negative coping strategies, and lower self-efficacy. By contrast, 'bright side' hypomanic participants had lower stress scores, more positive self-instructions, and higher levels of exploration, self-efficacy, and physical activity. Compared to the dark side hypomania, the bright side hypomania was associated with more goal-oriented and structured physical activity.

Conclusion: Among a non-clinical sample of young adults hypomania was frequently reported (19%). The present results underscore the notion of a continuity between a moderate mood state and both favorable ('bright side') and unfavorable ('dark side') hypomanic states. Moreover, 'bright' and 'dark side' hypomania differ with respect to psychological functioning and sleep. Our results suggest that 'restlessness/overactivity', a core symptom of hypomania, might be observed only in the dark side hypomania, whereas in bright side hypomania, amount of activity was related to more goal-oriented physical activity.

P-03-016 Serotonin transporter gene expression in bipolar disorder: A preliminary study in malaysia

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Objective: To analyze the relative SERT expression in bipolar disorder patients prior to and after being treated with olanzapine and valproate for 8 weeks. Relative SERT expressions were determined at weeks 0, 4 and 8 among patients and compared with healthy age, sex and ethnicity matched controls.

Methods: We compared 17 bipolar patients with 16 age, sex and ethnicity matched healthy controls in a prospective study. Patients were treated with olanzapine with the dose ranged between 10–20 mg/day and valproate at 20 mg/kg body weight and Young Mania Rating Scale (YMRS) was used to assess symptomatology in patients at weeks 0, 4 and 8. Blood samples were taken at weeks 0, 4 and 8 for the bipolar group and once for the control group for analysis of relative SERT expression.

Results: After 1 blood sample could not be analyzed, 1 patient relapsed and 2 defaulted, all the remaining 12 patients who completed the study responded to the treatment of olanzapine and valproate as they had more than 50% decrease in YMRS score both at weeks 4 and 8 ($p < 0.05$). Relative SERT expression of bipolar group prior to starting treatment was 0.065 and significantly lower than relative SERT expression in the control group ($p < 0.05$). After 8 weeks of treatment, relative SERT expression of patients increased compared to week 0.

Conclusion: Relative SERT expression of bipolar group prior to starting treatment was statistically lower than relative SERT expression in the control group. After 8 weeks of treatment, all patients who completed the study responded to treatment with olanzapine and valproate as measured by more than 50% decrease in YMRS score and there was up-regulation of SERT expression compared to week 0.

P-03-017 Long-term safety and efficacy of olanzapine in the treatment of japanese patients with bipolar I disorder, depressed

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Objective: Long-term safety and efficacy of olanzapine (OLZ) up to 48 weeks was evaluated in Japanese patients with bipolar depression.

Methods: An integrated analysis was performed on results from 2 studies of OLZ-treated Japanese patients with bipolar I disorder, depressed (N = 165). Study 1 was a global study and it included a double-blind placebo (PBO)-controlled treatment period and an open-label extension treatment period. Randomized patients received blinded OLZ (5–20 mg/day) or PBO for 6 weeks, and then continued into the open-label extension period with OLZ for 18 weeks. Study 2 was an open-label long-term treatment study conducted only in Japan. Patients who had completed Study 1 (both Pre-OLZ/Pre-PBO groups) received OLZ for an additional 24 weeks, and newly recruited patients received OLZ for 48 weeks (New-OLZ). Safety was assessed by treatment-emergent adverse events (TEAEs) and changes in weight/glucose/lipids. Efficacy was evaluated by the rates of remission (Montgomery-Åsberg Depression Rating Scale (MADRS) score $\leqslant 12$) and emergence of mania (Young Mania Rating Scale score $\geqslant 15$).

Results: Completion rate was 43.0% and the mean daily dose of OLZ was 7.79 mg/day. Common TEAEs were weight increased (47.9%), somnolence (37.0%), nasopharyngitis (23.6%) and increased appetite (21.8%). Most TEAEs were mild or moderate in severity. Mean changes in safety parameters were +3.54 kg (weight), +3.4 mg/dL (fasting glucose), +8.2 mg/dL (fasting total cholesterol), and +35.1 mg/dL (fasting triglycerides). Weight gains $\geqslant 7\%$ body weight were observed in 53.9% of patients. Remission rates were 79.8% (Pre-OLZ), 90.2% (Pre-PBO), 85.0% (New-OLZ). Emergence of mania was not observed in any patient.

Conclusion: Long-term safety, consistent with OLZ's known profile including weight/glucose/lipid increases, and sustained efficacy were shown in OLZ-treated Japanese patients with bipolar depression.

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P-03-018 Cognitive impairments profile in euthymic bipolar 1 disorder and their relation to functional recovery

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Objective: To demonstrate the range of neuropsychological deficits in the various cognitive domains in euthymic patients with bipolar I depending on the previous clinical state, to compare that to control and to correlate these cognitive deficits with illness characteristics and profile.

Methods: A case control, study included 60 subjects they were organized into two major groups, one stratified random sample of 30 patients in the euthymic phase of bipolar I disorder and one control group. The patients group diagnosed using Structured Clinical Interview for DSM-IV (SCID-I) and the euthymic state determined using Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HRSD) and we used WIMS & WMSR for cognitive assessment.

Results: Euthymic patients with bipolar I performed poorer than controls on tests of intelligence, attention, memory and executive functions Performance on most domains of WAIS was associated with age of onset of illness and the number of depressive episodes. These differences were with statistical significance with residual symptoms not reaching clinical significance.

Conclusion: We conclude that cognitive deficits associated with euthymia in bipolar disorder are considered both a consequence of the disorder, determinant of outcome in recovery and could be trait markers for bipolar 1 disorder.

P-03-019 Effect of lithium and valproate on brain activation patterns in FMRI within a working memory paradigm of bipolar patients

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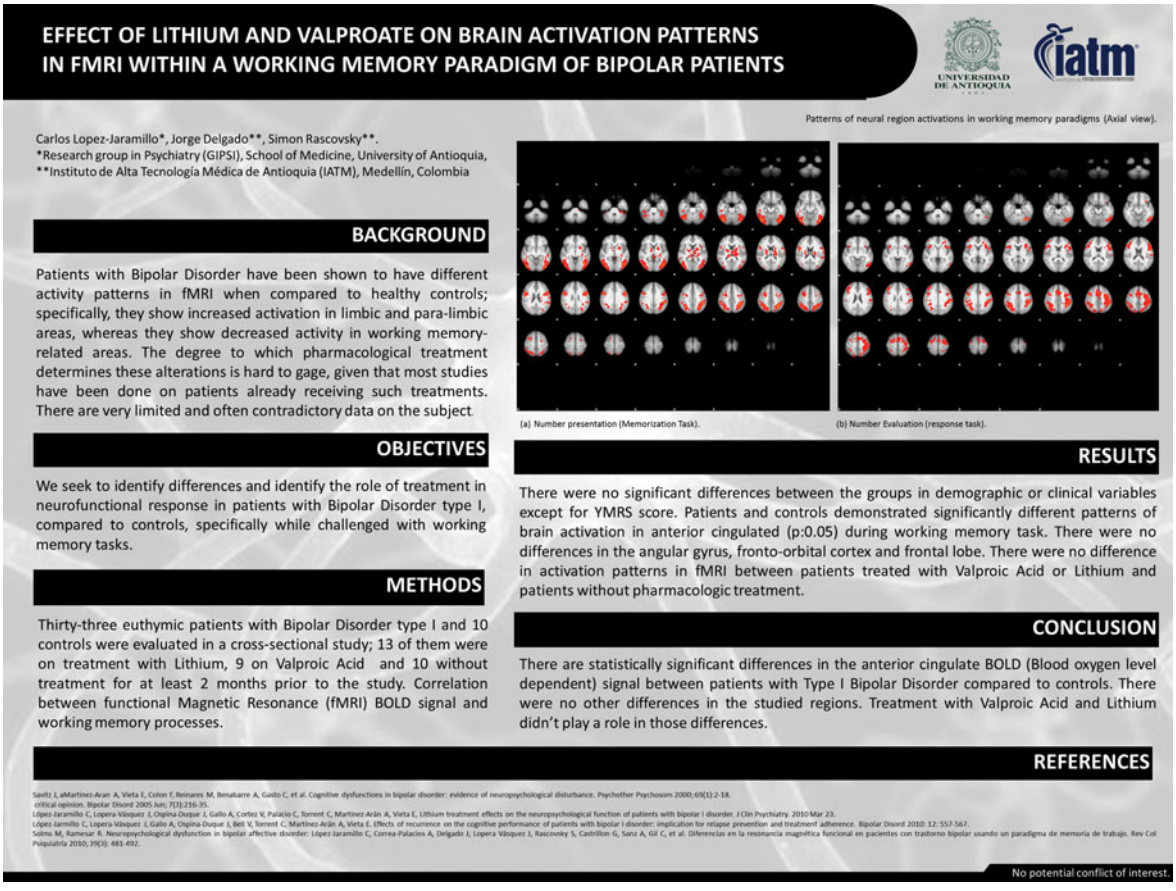
Objective: We seek to identify differences and identify the role of treatment in neurofunctional response in patients with Bipolar Disorder type I, compared to controls, specifically while challenged with working memory tasks.

Methods: Thirty-three euthymic patients with Bipolar Disorder type I and 10 controls were evaluated in a cross-sectional study; 13 of them were on treatment with Lithium, 9 on Valproic Acid and 10 without treatment for at least 2 months prior to the study. Correlation between functional Magnetic Resonance (fMRI) BOLD signal and working memory processes.

Results: There were no significant differences between the groups in demographic or clinical variables except for YMRS score. Patients and controls demonstrated significantly different patterns of brain activation in anterior cingulated (p: 0.05) during working memory



task. There were no differences in the angular gyrus, fronto-orbital cortex and frontal lobe. There were no difference in activation patterns in fMRI between patients treated with Valproic Acid or Lithium and patients without pharmacologic treatment.

Conclusion: There are statistically significant differences in the anterior cingulate BOLD (Blood oxygen level dependent) signal between patients with Type I Bipolar Disorder compared to controls. There were no other differences in the studied regions. Treatment with Valproic Acid and Lithium didn't play a role in those differences.

P-03-020 A multinational observational study of compliance associated with bipolar disorder: Results of the BALANCE study (bipolar longitudinal compliance)

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Objective: BALANCE study was conducted to explore factors associated with better compliance from diverse practice settings in patients receiving treatment for Bipolar Disorder up to 24 months.

Methods: Adult outpatients, receiving olanzapine (mono- or combination therapy) for at least 4 weeks and stable, Clinical Global Impression Severity $\leqslant 3$, were enrolled. Observations were recorded at baseline and 3, 6, 9, 12, 18, 24 months. Compliance to each medication regimen prescribed by treating psychiatrist was assessed by investigators using a single-item measure as noncompliant (<20%), low (20–59%), medium (60–79%), high (80–100%). Baseline and post-baseline factors including socio-demographics, disease severity, attitude toward medication, olanzapine mono vs. combination therapy, insight into illness, strength of the patient-physician relationship were used to predict the likelihood of high compliance utilizing generalized estimating equations repeated measures logistic regression model. Other data analyzed included quality of life, tolerability, functional status, and relapse.

Results: A total of 891 eligible patients were recruited into the study from Austria (239), Hungary (167), Korea (145), Mexico (61), Romania (180), Taiwan (99), of whom 73% completed the 24 months observation period and demonstrated high compliance ($\geqslant 80\%$ in 67%–80% of patients visit-wise). Results identified high baseline compliance as a strong predictor of later compliance (OR = 6.9, 95% CI: 5.0–9.5, $p < 0.001$), high compliance associated with higher life satisfaction ($p = 0.002$), better insights into illness ($p < 0.001$), lesser work impairment ($p = 0.007$) and shorter hospital stay ($p = 0.002$). Compliance also varied by country ($p < 0.001$) and length of post-baseline treatment regimen ($p = 0.014$).

Conclusion: Compliance to therapy in bipolar disorder was generally high and associated with baseline severity, insights into illness, work impairment and satisfaction with life.

Policy of full disclosure: Dr. David McDonnell is a full-time employee of Eli Lilly and Company.

P-03-021 Neurocysticercosis and bipolar disorder. A case report

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Objective: Cerebral cysticercosis is caused by neuronal infection by the pork tapeworm Taenia solium. In affected patients, psychiatric disorders, mainly depression and cognitive decline are highly prevalent.

Methods: We present the case of a 65 year-old woman with manifestations of bipolar disorder since 15 years with history of neurocysticercosis.

Results: She was initially diagnosed as suffering from depression-like symptoms 15 years ago and she was treated successfully for cysticercosis infection. Afterwards, she was retired due to her emotional and cognitive problems. During hospitalization she presented episodes characterized by elevated mood, hyperactivity and progressive development of psychomotor agitation and aggression (YMRS 18), followed after a short period of time by progressive development of psychomotor retardation, withdrawal, very poor speech and hypersomnia and dysphoric mood (HRSD 21). She was well oriented without memory dysfunction in clinical assessment (MMSE 26, 3-MS 89). The comprehensive neuropsychological evaluation by the use of Cambridge Neuropsychological Test Automated Battery has shown executive deficits. The MRI revealed brain atrophy and subcortical white matter lesions characteristic of cysticercosis infection, whereas, Tc99m -HMPAO (CERETEC) SPECT i.v adu. 20 mCu revealed normal diffusion in the cerebral cortex. The patient's symptoms were substantially ameliorated by olanzapine (20 mg/day) and valproic (500 mg/day) administration.

Conclusion: In our patient's case neurocysticercosis was linked with manifestations of bipolar disorder which was substantially ameliorated by valproic and olanzapine combination.

P-03-022 Reduced inferior frontal gyrus activation during emotion inhibition in young people at increased genetic risk for bipolar disorder

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Objective: There is growing interest in structural and functional brain imaging of young people at increased genetic risk for bipolar disorder as a means of identifying potential endophenotypes for this condition. Dysfunctional neural mechanisms for the cognitive control of emotion are postulated in the genetic predisposition to bipolar disorder, with aberrant activity in fronto-cortical, striatal, and limbic networks previously reported in subjects with established bipolar disorder during inhibitory and emotion processing tasks. We investigated functional brain activity during inhibition of emotional material in young people at increased genetic risk for bipolar disorder, using a facial-emotion go/no-go task during functional magnetic resonance imaging.

Methods: Data from 47 genetically high-risk individuals aged 18–30 years with at least one first-degree relative with bipolar disorder were compared with 49 controls (within the same age range but without a family history of bipolar disorder or other severe mental illness).

Results: Behavioural performance of all participants on the affective go/no-go task exceeded 75% accuracy. Whole brain corrected analyses revealed a highly specific and significant lack of recruitment of the inferior frontal gyrus when inhibiting fearful faces in the at-risk participants compared to controls ($p = 0.011$, FWE corrected).

Conclusion: This impaired inhibitory function of the inferior frontal cortex may represent a trait marker of vulnerability to bipolar disorder. These findings further implicate dysregulated cortical and sub-cortical brain networks as a neurocognitive endophenotype for bipolar disorder and add to the growing evidence for pre-existing functional and structural disturbances in those at high genetic risk for bipolar disorder.

P-03-023 Increase of serum brain-derived neurotrophic factor levels in two cases of treatment-resistant mood disorder remitted by lamotrigine augmentation

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Objective: Introduction We showed that lamotrigine (LTG) augmentation was effective for treatment-resistant mood disorder (TRMD). Animal studies reported that brain-derived neurotrophic factor

(BDNF) was an essential mediator for the antidepressant effects of LTG. We report two cases of TRMD remitted by the treatment of LTG augmentation, together with their BDNF levels increments.

Methods: Case reports Case A The patient was a 56-year-old female. She had first depressive episode at the age of 54. Her depressive symptoms showed no response to several antidepressants with enough doses and durations. Because she became hypomanic with mirtazapine treatment, the drug was withdrawn. Her hypomanic symptoms disappeared with valproate (VPA) treatment. However, she became gradually depressed again. The dose of VPA was increased up to 600 mg/day with some response. LTG was added to VPA at her MADRS score of 15. On the 8th week (LTG 75 mg/day), her MADRS score became 0. Her serum BDNF levels before and after 8-week LTG were 21.1 and 43.0 ng/mL. Case B The patient was a 67-year-old female. She had had first depressive episode at the age of 60. She had been remitted with fluvoxamine treatment. Because she became hypomanic at age of 67, the drug was withdrawn. Her hypomanic symptoms disappeared with VPA treatment. However, she became agitatedly depressed without any response to some antipsychotics. LTG was coadministered to VPA (800 smg/day) at her MADRS score of 20. On 8th week (LTG 75 mg/day), her MADRS score became 2. Her serum BDNF levels before and after 8-week LTG were 23.1 and 37.1 ng/mL.

Conclusion: These cases suggest that LTG shows antidepressant effects through BDNF increment in the treatment of TRMD.

P-03-024 Successful switching to olanzapine from polypharmacy in a bipolar II disorder patient with suicidal ideations: A seven-year follow-up study

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Objective: Pharmacological treatment of patients with bipolar II disorder in Japan is characterized by polypharmacy. We report on a seven-year follow-up of a patient with bipolar II disorder, whose medication was switched to olanzapine from polypharmacy. The objective of this case report is to focus attention on the significance of avoiding unnecessary and potentially harmful polypharmacy, and to demonstrate the effectiveness of olanzapine in bipolar II disorder.

Methods: A case report. This case study was conducted with the written informed consent of the patient. This study was approved by the ethical committee of Kwansei Gakuin University.

Results: The patient was a 30's woman with bipolar II disorder. Before her visit to our hospital, she had been treated with 2 anti-anxiety agents (alprazolam, diazepam), 10 hypnotic drugs (triazolam, estazolam, lormetazepam, flurazepam, zolpidem, brotizolam, nitrazepam, flunitrazepam, rilmazafone), one antidepressant (paroxetine) and 2 antipsychotics (risperidone, chlorpromazine) for about 6 months. Her condition had gotten worse as a result of the polypharmacy. She had quit her company job and attempted suicides. At the first visit to our hospital, she showed mixed episodes and amnesia. Her medication was switched to olanzapine and flunitrazepam. After 3 months of switching the medication, she became able to sleep, and her mood became stable. After 2 years, she found a new job. At the 7-year follow up, she was in good condition and was not suffering from any severe side effects.

Conclusion: This study suggested that polypharmacy caused mood instability, and that olanzapine was effective as a maintenance therapy for bipolar II disorder.

Policy of full disclosure: This study was partly supported by Grants-in-Aid for Scientific Research of Japan (22530776).

P-03-025 Nonlinear techniques as an approach for understanding mood regulation in bipolar disorder

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Objective: 1. To analyze if mood regulation in bipolar disorder (BD) subjects is essentially different from the one in healthy controls (HC). 2. To determine if entropy levels differ between HC and BD.

Methods: 30 HC and 30 euthymic BD patients (age- and sex-matched) rated their mood, anxiety, energy levels and sleep daily, twice a day, during 3 months, via a paper-based visual analog scale. We analyzed the data using methods suitable for the study of stochastic processes (time series analysis).

Results: HC showed low fluctuations (high variability) in their mood, anxiety, and energy levels. The differences between morning and evening ratings were not statistically different ($D = 1.0$, $p > 0.05$). The autocorrelation analysis showed a strong weekly periodicity in 70% of the HC sample. In contrast, BD patients showed less variability in their mood, anxiety and energy levels. All different entropy levels were significantly higher in the HC group compared to BD patients (all $p < 0.01$).

Conclusion: Mood fluctuates even in the absence of stimuli in healthy subjects, resulting in higher entropy levels. Our results suggest that the mechanisms of mood regulation in HC and BD patients may be essentially different. This understanding is a prerequisite for the development of protocols related to episode prediction.

P-03-026 Use of videotape recording of manic episodes to enhance adherence to pharmacological treatment in the maintenance phase of bipolar disorder

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Objective: Our aim in this presentation is to describe the impact of showing a group of patients in a remission phase of the acute episode the characteristics of their previous manic episode videotaped, in order to overcome denial and to improve pharmacological adherence and non pharmacological recommendations during de follow-up period.

Methods: Case Series.

Results: Videotaping of manic episodes had a positive impact on latter pharmacological treatment in a group of patients with bipolar disoders.

Conclusion: In the treatment of Bipolar Disorder (BD) high frequencies for poor adherence of patients in maintenance phase of pharmacological treatment regimens is well known. Denial of severity of illness is one of the predictors of non adherence.

P-03-027 Bipolar depression: Quetiapine XR short time effectiveness

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Objective: Quetiapine (QTP) has been shown to be effective as an acute treatment in patients with bipolar depression. Nonetheless, the time of onset of QTP antidepressive action as well as its minimum effective dose have not been clarified. We aimed to evaluate the short-term efficacy of QTP XR in bipolar depression. We also compared the different efficacy and side effect profile of 300 mg and 600 mg/day dosages.

Methods: 31 acutely depressed patients were recruited; 14 were treated with QTP XR 300 mg/day and 17 with 600 mg/day. Assessment was performed with Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Dosage Record and Treatment Emergent Symptom Scale (DOTES), HAMD clusters ''Core'', ''Psychic anxiety'', ''Somatic anxiety'', ''Activity'', ''Delusion''.

Results: QTP XR was effective since the first three days of treatment in reducing all the efficacy measures except for somatic anxiety. The comparison of 300 and 600 mg dosages did not show any significant difference in terms of efficacy, despite a clear trend was observed favoring the 600 mg group. The incidence of hypotension was significantly higher in patients taking QTP 600 mg ($p = 0.004$).

Conclusion: Our results suggest that QTP XR is effective against depressive symptomatology within the first days of treatment. Further, there is not a significant advantage for the 600 mg dose in comparison with the 300 mg one. The clinical effect seems to be not associated with sedation, suggesting that it may be due to the molecular drug effect. Nevertheless, further studies focusing on the first days of treatment are needed in order to confirm our findings.

P-03-028 A pooled analysis of the effects of asenapine on the persistent negative symptoms of schizophrenia

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Objective: Asenapine and olanzapine reduced persistent negative symptoms (PNS) of schizophrenia, in a study population that also met criteria for predominant negative symptoms, in 2 double-blind, randomized 26-week core and subsequent 26-week extension studies; superiority of asenapine over olanzapine was observed in one extension study. Post-hoc analyses of pooled data of the 2 core and 2 extension studies were conducted in order to further compare the long-term efficacy of asenapine and olanzapine in the treatment of negative symptoms in a population whose symptoms were both persistent and predominant.

Methods: Core study participants were randomized to asenapine (5 or 10 mg BID) or olanzapine (5–20 mg QD); extension participants continued existing treatment. Mixed model for repeated measures analyses, on the pooled intent-to-treat populations for patients entering the core or extension studies, assessed between-group differences on change from core study baseline in the 16-item Negative Symptoms Assessment (NSA-16) total score at weeks 26 and 52.

Results: Of 949 participants treated with asenapine or olanzapine (n = 485 and 464, respectively), 613 (n = 277 and 336) completed the core studies and 412 (n = 170 and 242) completed the extensions. Between-group differences in least squares mean ± SE NSA-16 total score change from core study baseline for asenapine versus olanzapine were not significant at week 26 (core participants, −11.1 ± 0.6 vs. −11.2 ± 0.6, P = 0.9457; extension participants, −13.1 ± 0.7 vs. −12.2 ± 0.6, P = 0.3710) but were significantly greater with asenapine versus olanzapine at week 52 (core participants, −14.6 ± 0.8 vs. −12.6 ± 0.7, P = 0.0497; extension participants, −16.5 ± 0.9 vs. −13.6 ± 0.7, P = 0.0083).

Conclusion: Asenapine and olanzapine reduced PNS in these post-hoc analyses, with statistical superiority of asenapine observed at week 52. These results should be interpreted in view of the fact that a large portion of participants did not enter the extension studies.

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P-03-029 The pharmacogenomics of bipolar disorder – acute and longitudinal treatment aspects: A systematic review

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Objective: Pharmacotherapy constitutes a mainstay in the treatment of both acute episodes and in maintenance therapy of bipolar disorder (BD). For more than two decades, there have been attempts to clarify the genetic basis of mechanisms of drug action, aiming at the possibility to offer a more personalized medicine. Here we compile the current state of pharmacogenomics of BD.

Methods: First, we decided to focus on the pharmacogenetics of first line treatments for BD on the basis of international guidelines. We focused on drugs recommended as monotherapies. PubMed was searched for articles published until using the search terms ''bipolar disorder'' or ''manic-depressive illness'' cross-referenced with drugs in question. We also manually reviewed reference lists of the identified publications. From these, we selected case-control-association studies, with the case-control-status being the drug response or the occurrence of adverse events.

Results: As regards response, we 28, with the following breakdown: lithium (25), lamotrigine (1), divalproex (1), olanzapine (1). As regards adverse events, our search algorithm yielded one study on divalproex. Most of the pharmacogenetic research in BD is about lithium, while there are only few case-control-association-studies concerning the other first line treatments. The candidate genes studied for lithium included 5-HT2A, 5-HT2C 5, HTTLPR, AP-2β, BCR, BDNF, COMT, DAT1, DGKH, DRD1, DRD2, DRD3, DRD4, FYN, Gβ3, GABRA1, GR, GRIA2, GRIN2B, GRK3, GSK3-β, HTR2A, IMPA1, IMPA2, INPP1, MAO-A, MARCKS, NR1D1, NTRK2, ODZ4, SDC2, SERTPE, SV2B, and XBP1.

Conclusion: There is a striking lack of replicated findings. For only two genes, the 5-HTTLPR and the BDNF gene, positive findings could be replicated in a second study. Also, most studies included very small samples, with the majority totaling less than 200 subjects. Future pharmacogenomic research should be based on larger samples, unified, exact criteria for response and adverse events, integrate knowledge from biochemical pathways, and also include pharmacokinetic aspects.

P-03-030 Neurotrophin levels and the efficacy of single ketamine infusion in bipolar depression resistant to antidepressants

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Objective: In our previous study performed on 10 patients, we observed an antidepressant effect of single intravenous dose of ketamine, as an addition to mood stabilizing drugs in patients with bipolar depression resistant to treatment with antidepressants. We also found an increase of serum brain derived neurotrophic factor (BDNF) in ketamine responders. The aim of this study was to investigate serum levels of three neurotrophins: BDNF, neurotrophin 4 (NTF4) and glial-derived neurotrophic factor (GDNF) in relation to ketamine efficacy, in larger group of patients.

Methods: The study comprised 25 patients (4 male, 21 female), aged 27–67 years, with bipolar depression, receiving mood-stabilizing medications. They were resistant to treatment with antidepressants which were discontinued for at least 7 days before single intravenous ketamine infusion (0.5 mg/kg body weight) between 8:00–8:45 h. Psychometric assessment was done using 17-item Hamilton Depression Rating Scale (HDRS). Response to ketamine was defined as 50% reduction of HDRS after one week, compared to baseline. Serum BDNF, NTF4 and GDNF levels were estimated by the ELISA method.

Results: The mean intensity of depression before ketamine infusion was 21 + 4 points on HDRS, reduced to 12 + 7 points after one week. There were 16 ketamine responders and 9 ketamine non-responders. In ketamine responders, the increase of BDNF after one week was not significant, however, in such patients a reduction of GDNF serum level (statistical trend p = 0.07) was found. In ketamine non-responders, a significant reduction of BDNF level was observed. No relationship between serum levels of NTF4 and response to ketamine was found.

Conclusion: The results of present study confirm an antidepressant effect of ketamine infusion as an add-on to mood-stabilizing drugs in bipolar depression resistant to antidepressant treatment. They may also indicate a possible involvement of such neurotrophins as BDNF and GDNF in this effect.

P-03-031 Elevated levels of circulating inflammatory cytokines in euthymic individuals with bipolar disorder

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Objective: To test the hypothesis that euthymic individuals with bipolar disorder (BD) exhibit abnormalities in pro- and anti-inflammatory cytokines.

Methods: Prospectively verified euthymic individuals (N = 45, mean age = 41.02 + 9.89) with DSM-IV-TR-defined BD-I/II as well as healthy volunteers (N = 29, mean age = 45.36 + 12.15) were enrolled. Inflammatory cytokines [granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL) 1β (IL-1β), IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, tumor necrosis factor β (TNF-α) and interferon γ (IFN-γ)] were measured in plasma with an ultrasensitive 10-plex bead-based immunoassay for Luminex. The Mann-Whitney U Tests and multiple logistic regression were used to compare levels of inflammatory cytokines between euthymic individuals with BD and healthy volunteers.

Results: Both pro-inflammatory (GM-CSF, IL-1β, IL-2, IL-5, IL-6, IL-8, TNFα, INFγ) and anti-inflammatory cytokines (IL-4 and IL-10) were elevated in euthymic individuals with BD as compared to healthy volunteers (all $p < 0.01$). A multiple logistic regression revealed that a model containing GM-CSF, IL-2, IL-6, TNFα, IL-4 and IL-10 significantly predicted BD (Model Nagelkerke $R2 = 0.806$; $p < 0.001$). Moreover, TNFα was the strongest independent predictor of BD in this model (odds ratio = 1.883 95% CI: 1.28–2.76; $p = 0.001$).

Conclusion: Bipolar disorder is marked by elevated levels of inflammatory cytokines that persist into euthymia. These results suggest that the inflammatory cytokine network is salient to the pathophysiology of BD and may constitute a viable target for novel treatment development.

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P-03-032 Hypermethylation of serotonin transporter gene in bipolar disorder detected by epigenome analysis of discordant monozygotic twins

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Objective: Bipolar disorder (BD) is a severe mental disorder characterized by recurrent episodes of mania and depression. Although high concordance rate of BD in monozygotic (MZ) twins supports the contribution of genetic factor in BD, importantly, it is not 100%. Because MZ twins have been regarded as having identical genomes, these facts suggest the importance of environmental or epigenetic factor for the onset of mental disorders.

Methods: We performed promoter-wide DNA methylation analysis of lymphoblastoid cell lines (LCLs) derived from two pairs of monozygotic twins discordant for BD. Promoter-wide DNA methylation profiles of the twins were examined by Affymetrix GeneChip Human Promoter 1.0R tilling arrays after methylated DNA was enriched using MBD2b and MBD3L1 conjugated beads. Fully unmethylated DNA obtained by whole genome amplification was used as a reference. To rule out the possible discordance of copy number variation (CNV) between twins, we performed CNV analysis.

Results: We found the copy number profiles were nearly identical between the twin pairs except for immunoglobulin-related regions. Three genes showing distinct difference of DNA methylation between one of the two pairs were obtained as candidate regions. Among them, hypermethylation of SLC6A4, encoding serotonin transporter (HTT), in the bipolar twin was confirmed by bisulfite sequencing. Promoter hypermethylation of SLC6A4 in LCLs of BD patients was confirmed in a case-control analysis. DNA methylation of SLC6A4 was significantly correlated with its mRNA expression level in individuals with the S/S genotype of serotonin transporter-linked promoter region (HTTLPR), and mRNA expression level was lower in BD patients carrying the S/S genotype. DNA methylation of the same site was also higher in the postmortem brains of BD patients.

Conclusion: This is the first study to report the role of epigenetic modification of SLC6A4 in BD using an unbiased approach, which provides a new insight to elucidate the pathophysiology of mood disorder.

P-03-033 "Paper-and-pencil" cognitive tests results in euthymic bipolar patients treated with lithium

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Objective: Cognitive deficits in bipolar patients may persist during remission. In our previous study using Cambridge Neuropsychological Testing Automated Battery (CANTAB) euthymic bipolar patients treated with lithium showed poorer performance on several neuropsychological tests than healthy controls and the quality of the response to prophylactic lithium treatment influenced the cognitive performance (Rybakowski and Suwalska, 2010). The aim of the study was to assess frontal lobe cognitive functions in euthymic bipolar patients treated with lithium.

Methods: Fifty-six patients with bipolar disorder in remission lasting for at least 4 months (21 male, 35 female; mean age 52.6 ± 10.0) and 77 healthy controls (22 male, 65 female; mean age 51.6 ± 13.6) entered the study. Duration of illness was at least 5 years and prophylactic treatment lasted for at least 2 years. Sixteen patients were excellent litium ELRs, defined as having had no affective episodes on lithium monotherapy. For the neuropsychological assessment, the following tests were used: the Trail Making Test (TMT), the Stroop test, the verbal fluency test, including semantic (categories: animals, fruit and vegetables) and phonemic fluency tasks (letters F, A, S).

Results: Bipolar patients performed significantly worse than healthy controls on semantic and phonemic verbal fluency, TMTA&B and Stroop test part B, whereas the results of excellent lithium responders did not differ from those of healthy people. Bipolar men performed significantly worse than bipolar women on semantic fluency test and Stroop test part B. Whilst bipolar women had worse results than healthy control women only in TMT A and TMTB, bipolar men performed poorer than healthy men on all tests.

Conclusion: Our results point to the presence of cognitive deficits in euthymic bipolar patients, protective effect of lithium in excellent lithium responders and gender-associated differences in the severity of neuropsychological dysfunctions. Rybakowski JK, Suwalska A (2010) Excellent lithium responders have normal cognitive functions and plasma BDNF levels. International Journal of Neuropsychopharmacology 13, 617–622.

P-03-034 Increased trans-membrane tumour necrosis factor in the anterior cingulate cortex of subjects with bipolar disorder

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Objective: Altered inflammatory signalling has been implicated in the pathophysiology of mood disorders and schizophrenia. We recently reported a 2.4-fold increase in the expression of a trans-membrane form of the pro-inflammatory cytokine, tumour necrosis factor (tmTNF) in Brodmann's area (BA) 46 but not BA24 of the frontal cortex from subjects with major depressive disorder (MDD). The expression of soluble TNF (sTNF) was not altered in these subjects. We have examined TNF expression in the frontal cortex of subjects with bipolar disorder (BPD) and schizophrenia.

Methods: Western blotting was used to measure tmTNF and sTNF levels in post-mortem tissue from BA24 and BA46 from 10 subjects with BPD and 10 matched controls and from 20 subjects with schizophrenia and 20 matched controls.

Results: tmTNF was increased in BA24 (CON) (mean ratio of internal control ± SEM) = 2.77 ± 1.03 vs. BPD = 7.15 ± 1.75; $p < 0.05$), but not BA46 (CON = 0.89 ± 0.10 vs. BPD = 1.84 ± 0.47; $p > 0.05$) from subjects with bipolar disorder. There was no change in the level of

tmTNF in BA24 (CON = 2.62 ± 0.55 vs. SCZ = 2.00 ± 0.38; p > 0.05) or BA46 (CON = 0.80 ± 0.07 vs. SCZ = 1.02 ± 0.171; p > 0.05) from subjects with schizophrenia compared to controls. Levels of sTNF were not changed in either BA24 or BA46 from subjects with BPD or schizophrenia compared to controls.

Conclusion: Our data further supports a role for tmTNF in the pathophysiology of mood disorders but not schizophrenia. Furthermore, abnormal tmTNF expression is localised to different cortical regions in BPD compared to MDD. Contrasting studies in the periphery, our data from the CNS does not support the involvement of sTNF-mediated, pro-inflammatory pathways in the pathophysiology of mood disorders.

P-03-035 Molecular conformational changes in microglia and differentiated monocitic cells induced by therapeutic concentrations of lithium

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Objective: Lithium (Li), a direct inhibitor of glycogen synthase kinase 3 (GSK-3), is a commonly prescribed mood stabilizer in the treatment of bipolar disorder. Li affects various types of immune cells, which play pivotal roles in the innate immune systems in both brain and peripheral tissues. Evidence suggests that GSK-3 regulates microglial migration and inflammation, and also mediates differentiation and activation of proinflammatory monocyte-derived dendritic cells (MoDCs).

Methods: Microarray gene expression profiles of resident differentiated monocytic cells (mouse microglia, mouse microglia and macrophage-like cell line, human MoDCs and monocyte-derived macrophages) along with undifferentiated mouse and human monocytes were evaluated using Illunima microarrays, and post prominently induced and suppressed molecules were validated using Q-RT-PCR and western blotting. Effects of GSK-3 inhibitors on the molecules were also evaluated.

Results: We found several molecules prominently induced by the therapeutic concentration of Li and GSK-3 inhibitors in the resident differentiated monocytic cells (mouse microglia, mouse microglia and macrophage-like cell line, human MoDCs and monocyte-derived macrophages), but not in undifferentiated mouse and human monocytes.

Conclusion: The findings indicate the mechanisms of lithium-induced functional changes in microglia and differentiated monocytic cells, and their possible involvements in the neuroprotective and mood stabilizing effects of Li treatment.

P-03-036 Bipolar disorder in patients with suicidal behavior

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Objective: to study prevalence of bipolar disorder (BD) in patients with suicidal behavior assisted at National Institute of Mental Health in a three-year period (2008–2010).

Methods: A prospective study using clinical assessment in ambulatory suicidal patients searching diagnostic criteria DSM IV-TR for BD.

Results: Over a sample of 1300 patients with suicidal behavior, 92 of them (7.1%) were diagnosed as Bipolar: 25 males (27.2%) and 67 females (72.8%), being 70% of them aged less than 33 years old. For Bipolar I: 71 patients (77.2%), Bipolar II: 21 patients (22.8%). There were 38 patients with bipolar depresive state (41.3%), 36 for mixed episodes (39.1%), 12 of them for pure manic episode (13%) and other 6 considered rapid cycling patients (6.5%). Psychotic features were found in 43 patients (47%). Most important co-morbidities were: excessive smoking in 25%, abuse of alcohol and other substances in 31% and BPD in 24%. Regarding suicidal behavior: it was found suicidal ideation in 35.8%, suicide attempt in 59.8%, and complete suicide in 4(4.4%). About suicide attempters, near half of them diagnosed as bipolar depressive episode, 47% as mixed episode and 3.6% as manic episode. Almost 75% of patients were in an inadequate treatment. Among 4 patients who completed suicide: 3 females/1 male, 2 of them diagnosed as mixed bipolar with psychotic features.

Conclusion: According the trial, prevalence of BD amongst suicidal patients is not too infrequent, being predominant in young female, mostly bipolar depression and mixed states, worsening in case of comorbidity with substances abuse and BPD, and also under inadequate approach; being authors advise an early and better identification of BD for its adequate treatment and effective suicide prevention.

P-03-037 Solar activity and mood episodes in bipolar disorder

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Objective: Some authors have been linked solar cycles with changes in human social evolution, proposing that exposure to solar activity can influence different aspects of human behavior. Currently there have been developed researches about the influence of the solar cyclic activity on various aspects of human health. Bipolar disorder is a psychiatric illness with cyclical developments. There are few and limited studies that have focused on the relationship between solar activity and epidemiology of bipolar disorder. The aim of this study is to evaluate the possible relationship between solar activity and the annual incidence of mood episodes, depressive or manic, in bipolar disorder.

Methods: Retrospective review of hospital admissions by psychiatric diagnoses in the country of Chile between 2001 and 2008, of which 3973 cases were due to depresive or manic episodes in patients with bipolar disorder.

Results: We found a significant inversely relation between the incidence of hospital admissions by depressive episodes and the intensity of solar activity ($p < 0.001$, F 128.54), and no relation between the incidence of manic episodes and intensity of solar activity during the same period, in bipolar disorders.

Conclusion: We conclude that the exposure to solar cyclic activity can influence the occurrence of depressive episodes in bipolar disorder.

P-03-038 Assessing the relationship between history of suicide attempts and cognitive dysfunction in bipolar affective disorder

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Objective: The objective of this study is assessing relationship between history of suicide attempts and cognitive impairment in bipolar disorder.

Methods: We examined 60 bipolar (depressive, manic/hipomanic, mixt, euthymic) patients (according to DSMIVTR). The comparison group consisted of 20 healthy subjects without history of neurological/psychiatric disorder. The cognitive battery included standardized test of IQ, attention, working memory, visual memory, verbal memory and executive functioning. Demographic data (gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, history of psychosis, duration of illness, age of onset and family history were collected. We analyzed statistically these data and assessed the relationships between history of suicide and cognitive deficits in bipolar patients from this study.

Results: Suicidality among bipolar patients seems to be associated with executive dysfunction, especially when highly lethal attempts are made. Depressed patients with a history of high lethality suicide attempts have lower performance on task of executive functioning compared to depressed patients without past history of attempts and patients with a history of low lethality suicide attempts. Neurocognitive function didn't differ between bipolar individuals with a history of nonviolent suicide attempts versus bipolars without history of suicide attempts. There are no significant differences of cognitive dysfunction between patients with violent versus nonviolent attempts. It seems that difficulties with response inhibition are associated with an increased rate of suicide attempts. Euthymic, manic, depressed and mixt-episode bipolar patients with past of suicide attempts also have more impulsive response when compared to bipolar individuals without a history of suicide attempts. Both bipolar disorder attempters and healthy controls exhibit impairments on

cognitive tasks assessing working memory, psychomotor speed and impulsivity.

Conclusion: Clearly, suicidality among bipolar disorder patients is a significant public health concern worthy of further extensive examination.

P-03-039 Assessment of cognitive function across the different phases of bipolar affective disorder

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Objective: The objective of this study is identifying specific domains of cognitive dysfunction for different phases of bipolar disorder.

Methods: We examined 60 bipolar (depressive: Hamilton Depression Rating Scale HAMD score > =17, manic/hippomanic: Young Mania Rating Scale YMRS score > =12, euthymic: 6 month of remission, HAMD score < =8, YMRS score < =6) patients (according to DSMIVTR). All the patients were free of psychotic symptoms at the moment of neurocognitive evaluation. The comparison group consisted of 20 healthy subjects without history of neurological/psychiatric disorder. The cognitive battery included standardized test of IQ, attention, working memory, visual memory, verbal memory and executive functioning. Demographic data (gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, history of psychosis, duration of illness, age of onset and family history were collected. We analyzed statistically these data and identified specific domains of cognitive dysfunction for different phases of bipolar disorder.

Results: Cognitive deficits involving executive functioning (working memory, executive control, verbal fluency, mental manipulation and cognitive flexibility), verbal learning and memory and attention are evident across all phases of illness and persist during euthymic phase too. Sustained attention (vigilance) is impaired in bipolar patients regardless of whether they are studied during periods of mania or depression (not remitted completely during euthymia). In addition, selective attention deficits during acute episodes don't normalize during euthymia. Depressed patients have the lowest verbal fluency and were particularly impaired in domains as affective processing. Performances on task that tapes domains of verbal learning and memory, and sustained attention were particularly impaired in manic patients.

Conclusion: Bipolar patients exhibit widespread neurocognitive dysfunctions during their lives. There are persistent cognitive deficits over the course of bipolar disorder and specific cognitive impairment of each phase of the illness.

P-03-040 Identifying and assessing the risk factors for cognitive impairment in bipolar affective disorder

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Objective: The objective of this study is identifying and assessing the risk factors for cognitive impairment in bipolar disorder.

Methods: We examined 60 bipolar (depressive, manic/hipomanic, euthymic) patients (according to DSMIVTR). The cognitive battery included standardized test of IQ, executive functioning, working memory, attention, visual and verbal memory. Demographic data (gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, psychosis history, illness duration, age of onset and family history were collected. We analyzed statistically these data and assessed the relationships between cognitive deficits and clinical and demographic variables in bipolar patients.

Results: Cognitive deficits are more frequent in bipolar patients with more severe course of illness, as indicated by: longer durations of mood disturbance (negatively correlated with executive function, psychomotor speed, attention, concentration and verbal memory-associated with a higher number of past manic episodes too), younger age at onset, history of multiple and frequent episodes (with manic episodes impacting neuropsychological impairment most extensively; attention and executive function deteriorated by the recurrence of episodes) and higher number of hospitalization (negatively correlated with visual and verbal memory, verbal fluency, spatial memory, psychomotor speed and executive function). Other risk factors are: pharmacological treatments, individual response, familial risk factors (positive family history for mood disorders negatively influences cognition), rapid cycling and seasonality, too. There's as well a specific relationship between executive functioning and admission for mania and between cognitive performance on several tasks and admission for depressive episodes. Females performed better on tests for verbal memory. Besides depressive and manic symptoms, anxiety and psychosis history negatively influence cognition too.

Conclusion: We evidentiated several risk factors that may influence cognitive function in bipolar disorder but there's a growing need for further clarification regarding the magnitude, clinical relevance and confounding variables of cognitive deficits in bipolar individuals.

P-03-041 Effects of asenapine in bipolar I patients experiencing manic episodes with depressive symptoms: Results from post-hoc analyses

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Objective: Asenapine demonstrated superiority over placebo in bipolar I disorder patients experiencing acute manic or mixed episodes in two 3-week, randomised, placebo-and olanzapine-controlled trials(1,2), and comparable efficacy to olanzapine in a 9-week non-inferiority double-blind extension trial(3). We assessed the effects of asenapine on manic and depressive symptoms in patients experiencing manic episodes with depressive symptoms.

Methods: 977 patients were randomised in the original trials to flexible-dose asenapine (10 or 5 mg twice daily), placebo, or olanzapine (5–20 mg once daily) for 3 weeks. In the intent-to-treat population, 295 patients had a mixed episode (placebo: 66, olanzpine: 122; asenapine: 107). Of these, 102 patients (olanzapine: 56; asenapine: 46) entered the 9-week extension study. Pooled data were analysed through analysis of covariance with treatment and centre as factors and baseline value as covariate on observed cases.

Results: Decreases in YMRS and MADRS total scores were significantly greater with asenapine (YMRS: −15.0; MADRS: −8.2) versus placebo (YMRS: −11.5; MADRS: −4.5) at week 3; differences between olanzapine (YMRS: −13.3; MADRS: −6.5) and placebo were not statistically different. The effect of asenapine on manic and depressive symptoms was maintained over the extension trial (week 12, YMRS: −22.4; MADRS: −11.9); non-statistically different from olanzapine (YMRS: −20.2; MADRS: −7.9). At week 3, asenapine was significantly superior to placebo in improving 'inability to feel', 'elevated mood, 'sexual interest', 'language/thought disorders', 'reduced appetite' and 'inner tension'; asenapine was significantly superior to olanzapine in improving 'inner tension'. At week 12, asenapine was significantly superior to olanzapine in improving 'disruptive/aggressive behaviour', 'appearance' and 'inability to feel'.

Conclusion: In these post-hoc analyses, asenapine had significantly better treatment effects on both manic and depressive symptoms than placebo, and more pronounced effects than olanzapine in some symptom domains.

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P-03-042 Increased expression of cortical selenium binding protein 1 in subjects with schizophrenia but not mood disorders

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Objective: We previously reported a significant upregulation of selenium binding protein 1 (SELENBP1) in three different cohorts of subjects with schizophrenia1,2,3. We also found a significant increase in SELENBP1 in the blood of a separate cohort1. In this study we aimed to (i) measure the expression of SELENBP1 in mood disorders (ii) measure the expression of SELENBP1 in subjects with schizophrenia in three different cortical regions to determine whether the increase in SELENBP1 is widespread and (iii) measure the effect of exogenous selenium on the expression of SELENBP1 in SH-SY5Y cells.

Methods: Using qPCR we measured SELENBP1 mRNA in Brodmann's area (BA) 9 from 10 subjects with major depressive disorder, 10 subjects with bipolar disorder and 10 matched non-psychiatric controls. We also measured SELENBP1 mRNA in BA 8, 9 and 44 from 30 subjects with schizophrenia and 30 non-psychiatric controls. SH-SY5Y cells were treated with vehicle or 175 μg/L selenium for one hour before RNA was extracted and SELENBP1 expression measured using qPCR.

Results: There was no significant difference in SELENBP1 expression in subjects with mood disorders compared to controls ($p = 0.655$). There were significant differences in SELENBP1 expression between subjects with schizophrenia and control subjects in BA8 ($p < 0.0001$), BA9 ($p = 0.036$) and BA44 ($p < 0.0001$). There was no significant effect of selenium treatment on the expression of SELENBP1 in SH-SY5Y cells ($p = 0.200$).

Conclusion: The increase in SELENBP1 expression in schizophrenia extends our previous findings, demonstrating that the change is widespread throughout the cortex. These results suggest that the increase in SELENBP1 is involved in the pathophysiology of schizophrenia, but not in mood disorders. Treatment with selenium had no significant effect on expression of SELENBP1, indicating that the increased expression of SELENBP1 in the brain may not be an acute response to increased selenium.

Policy of full disclosure: The authors declare no conflict of interest.

P-04. Anxiety Disorders

P-04-001 Prenatal exposure to modafinil alters anxiety-like responses in adult mice

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Objective: Modafinil (MDF), a psychostimulant drug currently indicated for treatment of narcolepsy, is often consumed by young generation in fertile age and thus there is an increasing importance to assess possible developmental behavioural toxicity. This study investigated influence of chronic prenatal exposure to MDF on anxiety-like measures in adult mouse males.

Methods: Pregnant female mice were given nine doses of saline (SAL, 10 ml/kg/day) or MDF (50 mg/kg/day). The same drug dosage regimen was used in their adult male offspring. Thus, there were four experimental groups: SAL and MDF offspring from SAL mothers and SAL and MDF offspring from MDF mothers. Anxiety was assessed as % of entries to open and closed arms in the elevated plus maze on: Day 1 – naïve mice, Day 8 – acute dose of SAL or MDF, Day 15 – one week repeated administration.

Results: Prenatal treatment with MDF increased % of entries to closed arms compared to SAL prenatal administration (but did not significantly alter % of entries to open arms). In prenatally naïve mice neither acute nor chronic MDF treatment induced changes in anxiety-like behaviour compared to SAL treatment. However, in offspring of MDF treated mothers acute MDF dose significantly decreased % of entries to open arms and chronic MDF treatment significantly increased % of entries to closed arms compared to the prenatally naïve controls.

Conclusion: We can conclude that MDF did not alter anxiety in prenatally naïve mice but there was observed partial increase in anxiety-like behaviour induced by combination of prenatal and postnatal MDF treatment.

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P-04-002 Ensemble classifiers operating on multimodal random subsample fMRI-data for robust between-subject classification in SAD

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Objective: Subject-level classification of functional imaging data in populations of controls and patients is typically complicated by the combined effects of high intra-class and low inter-class variation in imaging data with high dimensionality. To facilitate classification we propose combining task-specific derived modalities including (1) estimates of activation, (2) spatial autocorrelation of activation, (3) functional connectivity and (4) spectral density in a region of interest-based (ROI) approach adherent to the Automatic Anatomical Labelling (AAL) atlasing framework. Functional data from 72 subjects (47 controls, 25 patients) performing a facial emotion discrimination task in two different scanning environments regarding scanner-hardware, stimulus-design and acquisition parameters was available for validating our approach.

Methods: Prior to data-aggregation principal component analysis (PCA) was applied to check for components related to scanning-environment within each isolated modality. Components displaying clear separation of both datasets were selectively excluded from back-projection into original feature-space. Subsequent to data-aggregation, random forest feature ranking was performed on the resulting 7389 features. Ensemble classifiers were built from nine leave one out cross-validated (LOOCV) linear discriminant analysis (LDA) base-learners operating on random feature-partitions of size = 12, thus effectively including only the 108 most informative features.

Results: Averaged performances of 100 ensembles gave an overall accuracy of 86.03 ± 2.08 %, a sensitivity of 79.48 ± 4.61 % and a specificity of 89.51 ± 1.90 % (mean ± SD). Pooled votes from all ensembles gave 8 misclassifications with an overall accuracy of 88.89 %, a sensitivity of 84.00 % and a specificity of 91.49 %.

Conclusion: Our results indicate that even simple base-learners offer high potential for robust subject-level classification of multimodal fMRI data when ensembled so as to capture a maximum of informative features from the data at hand.

P-04-003 An investigation of attention process in chronic fatigue syndrome: Health-threat related attentional bias and the role of attentional control

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Objective: Attentional bias is an important psychological mechanism that has been extensively explored within literature for anxiety and more recently for chronic pain. Cognitive behavioural models of chronic fatigue syndrome (CFS) and chronic pain suggest an overlap in the mechanisms of these two conditions. The current study investigated attentional bias towards health-threat stimuli in individuals with CFS and in healthy controls, and also examined whether individuals with CFS have impaired executive attention, and whether this was related to attentional bias.

Methods: 27 participant with CFS and 35 healthy controls completed a Visual Probe Task measuring attentional bias towards health-threat stimuli, and an Attention Network Test measuring alerting, orienting and executive attention. Participants also completed a series of standard self-report measures.

Results: When compared to the control group, the CFS group showed a significantly slower reaction time, and a trend of greater attentional bias towards threat-words than pictures. The CFS group was significantly impaired on executive attention compared to controls. Post-hoc analyses indicated that CFS individuals with poor executive attention showed a threat-word bias when compared to controls and CFS individuals with good executive attention.

Conclusion: This was the first study to investigate attention processes using a combined experimental paradigm and report an interesting relationship between attentional bias and executive attention in CFS. The study demonstrated that attentional biases in individuals with CFS are dependent on their capacity to voluntarily control their attention, which suggests that adding attentional control strategies to current intervention models may be beneficial for CFS.

P-04-004 Human translocator protein (18 kDa) and its genetic variation in relation to stress sensitivity in patients with atopic dermatitis

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Objective: Expression of the translocator protein (18 kDa) (TSPO), formerly known as the peripheral-type benzodiazepine receptor, is correlated with trait anxiety in normal human subjects (Nakamura et al., 2002). Many dermatological diseases become more serious under stressful conditions, but their relations to individual's sensitivity to stress are not well understood.

Methods: To address this issue, we examined patients with atopic dermatitis (AD) for their expression and genomic variation of TSPO as well as their levels of anxiety using the STAI scores.

Results: The AD patients (30 males, 22 females) showed higher STAI scores, especially trait anxiety in males ($p < 0.001$), compared to healthy subjects. The expression of platelet TSPO was significantly higher in males ($p < 0.001$) and females ($p < 0.05$) compared to their normal controls (86 males, 70 females). A single-nucleotide polymorphism (SNP) of the human TSPO gene at exon 4 (485G > A) leading to an amino acid substitution of TSPO (Arg162His), which is associated with anxiety disorders (Nakamura et al., 2006), showed a significantly ($p < 0.05$) different frequency distribution in the AD patients compared to normal subjects: a lower frequency of G/G (44.2%) and a higher frequency of G/A (50%). The severity of AD (SCORAD) was significantly ($p < 0.05$) correlated with TSPO expression in male G/A patients.

Conclusion: The results suggest that the 485G > A SNP of the TSPO gene and the amino acid substitution of TSPO may be related to the sensitivity to stress and the pathogenesis of AD.

P-04-005 The long-term efficacy of escitalopram for the treatment of korean panic disorder patients: A prospective, open-labeled, multi-center trial

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Objective: Objective The purpose of this study was to examine the long-term efficacy of escitalopram for the treatment of Korean panic disorder (PD) patients.

Methods: The study subjects were 119 adult PD patients (18–70 years old) from 6 university hospitals in South Korea (Samsung Medical Center, Seoul Paik Hospital, Ilsan Paik Hospital, Wonkwang University Hospital, Ewha Womans University Mokdong Hospital, and Chonbuk National University Hospital). The structured clinical interview for the DSM-IV (SCID-IV) was administered to all subjects by experienced psychiatrists. The primary outcome measures were improvement on the Panic Disorder Severity Scale (PDSS) and the remission rate of panic disorder. Secondary outcome measures included improvement on the Sheehan Disability Scale (SDS). All Patients were assessed on the Hamilton Rating Scales for Depression (HAM-D), PDSS, and SDS at baseline and 4, 12 and 24 weeks after beginning treatment. We used the LOCF method. Repeated measure ANOVA was used to test for the improvement on the PDSS and SDS.

Results: Among 119 PD patients, 87 patients (73.1%) had attained a remission state during the 24 weeks of escitalopram treatment. The mean dose of escitalopram was 11.65 ± 3.83 mg/day. At the LOCF week 24 evaluation, a significant difference in PDSS total score was observed. (ITT: -11.16 ± 6.51, p-value < 0.0001) ($t = 18.71$). In the post-hoc analysis, we found a continuous significant improvement on the PDSS total score at baseline, week 4, week 12 and week 24. We found a continuous significant improvement on the 3 domains of SDS (work, social relationship, and responsibilities at home and with family) at baseline, week 4, week 12, and week 24. (p-value < 0.0001).

Conclusion: This study suggests that long term efficacy of escitalopram measured by the PDSS and SDS is high in the Korean PD patients.

P-04-006 Clinical characteristics of obsessive compulsive disorder with schizophrenia

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Objective: We investigated the prevalence of obsessive compulsive disorder (OCD) among patients with schizophrenia. We also investigated the differences in the psychotic symptoms and suicidality between patients with schizophrenia who did or did not have OC symptoms.

Methods: Seventy-one subjects with the DSM-IV diagnosis of schizophrenia were evaluated by the Structured Clinical Interview for DSM-IV Axis I disorders, the Yale-Brown Obsessive-compulsive Scale and the Positive and Negative Syndrome Scale.

Results: The OCD patients with schizophrenia were 20 (28.2%) among 71 subjects. The 20 subjects with OCD had significantly more severe negative and total psychotic symptoms evaluated with PANSS than subjects without OCD. The schizophrenia with OCD had significant higher recent suicidal attempt rate than the subjects without OCD.

Conclusion: The results of this study suggest the possibility that OCD symptoms in schizophrenia may be related to negative symptoms and the OC symptoms may be related to the impulsivity expressed as suicidal attempts.

P-04-007 Non-verbal memory dysfunction in checking type obsessive-compulsive disorder

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Objective: The purpose of this study is to examine the role of memory dysfunction in obsessive-compulsive disorder (OCD). Especially we tested the memory function of checking type of obsessive compulsive disorder compare to that of cleaning type and that of normal controls.

Methods: Subjects were 16 patients aged 18–45 years who met the diagnostic criteria of obsessive compulsive disorder and 8 normal controls. Informed consent was done. 16 OCD patients was divided into two groups, 8 'checking' type and 8 'cleaning' type patients by evaluation of Yale-Brown Obsessive compulsive scale and Maudsley Obsessive compulsive inventory. All patients were tested memory functions by Rey-Osterrich comlex figure test (RCFT) for non-verbal memory function, Hopkins verbal learning test (HVLT) for verbal memory function, Wisconsin card sorting test (WCST) and evaluated depression and anxiety by Beck Depression Inventory (BDI) and Taylor Anxiety scale.

Results: The Reyimmediate and Reydelayed memory test scores were significantly lower ($P < 0.05$) in checking types than in cleaning types and normal controls (student t-test). There were no significant differences of Reycopy test scores, and verbal memory test (HVLT) scores, BDI and Taylor Anxiety scale scores in checking, cleaning type groups and normal controls.

Conclusion: The non-verbal memory function of checking type OCD patients were significantly decreased than other OCD patients and normal controls. This non-verbal memory dysfunction is not related to depression and anxiety. This results suggest that checking symptoms development of OCD is related to non-verbal memory dysfunctions.

P-04-008 Caudate asymmetry in obesessive compulsive disorder: A voxel based morphometry study

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Objective: Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder, characterized by persistent intrusive thoughts (obsessions), repetitive actions (compulsions) and excessive anxiety. Numerous functional neuroimaging studies have suggested that OCD patients had a neurobiological abnormality in the orbitofrontal-cingulated-striatal-thalamic circuits. Voxel-based morphometry (VBM) is a fully automated and unbiased whole-brain method, which assesses regional differences between subjects in gray matter (GM). Several VBM studies have been conducted for OCD, showing volume alterations in these regions, although the findings were not entirely consistent. The application of high magnetic field MRI with increased signal-to-noise ratio would improve the ability to detect subtle abnormalities for VBM study, whereas there is only one study using 3-Tesla MRI on OCD study. The aim of this study is to contribute to the validation of morphometric findings using high magnetic field equipment.

Methods: Thirty-one patients diagnosed with OCD according to DSM-IV criteria and 31 age- and gender-mached healthy controls were participated in this study. T1-weighted three dimensional spoiled gradient echo (SPGR) images were acquired via 3-T MRI scanner (Signa, GE). MR images were spatially normalized and segmented using the VBM8 package. Statistical analysis was performed using statistical parametric mapping software. We compared the GM volume between two groups.

Results: Compared with healthy controls, OCD patients had a significantly lower GM volume in the left caudate, right thalamus, right medial prefrontal and anterior cingulated cortex ($P \leqslant 0.05$, FWE corrected), on the contrary, significantly higher right caudate GM volume ($P \leqslant 0.05$, FWE corrected).

Conclusion: This is the first study that revealed the asymmetry of caudate volume in OCD patients. Other findings are consistent with previous studies reporting abnormality in the orbitofrontal-cingulated-striatal-thalamic circuits.

P-04-009 Long-term treatment of panic disorder: Tapering out clonazepam and paroxetine

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Objective: We describe the successful tapering out of panic disorder (PD) patients treated for 3 years with clonazepam or paroxetine or their combination.

Methods: 94 asymptomatic PD patients after three years of drug treatment and wishful to leave the medication participated in this trial. The protocol envisaged a dose discontinuation phase protracted over 8 weeks and 12 months of follow-up. The dose of clonazepam was decreased in 2-week intervals by increments of 0.5 mg clonazepam until reaching 1 mg/day followed by weekly dose reduction of 0.25 mg; or 10 mg paroxetine until reaching 20 mg/day followed by weekly dose reduction of 5 mg.

Results: The mean dose at staring the tapering out was 1.9 ± 0.3 mg/day of clonazepam and 38.8 ± 3.9 of paroxetine. 57.8% of clonazepam and 18.2% of paroxetine patients were free of the medication after the 2 months of tapering as the protocol. 19 (26.0%) needed another 3 months to leave the medication. 9 (12.3%) of this last group used also mirtazapine or carbamazepine as adjunct therapy during this period. 3 (4.1%) patients gave up the tapering due to return of anxiety symptoms. The withdrawal symptoms were mild and observed in 55 (75.3%) patients. Insomnia, tremor, nausea, sweating, headache, and subjective anxiety were the main complains. Patients of the clonazepam group had during the withdrawal period fewer side effects/withdrawal symptoms than those of the paroxetine or combination group and significantly more patients of the clonazepam group were drug free, asymptomatic and without AE at the end of the first follow up year.

Conclusion: It is possible to take the clonazepam and paroxetine slowly out even after a long treatment without any major withdrawal symptom. The dose should be tapered slowly and some adjunct drug may be useful for some cases.

P-04-010 State of vegetative provision of women with anxiety-depressive disorders co-morbid with polycystic ovary syndrome

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Objective: We have conducted investigation of vegetative status of women with polycystic ovary syndrome having anxiety-depressive symptoms.

Methods: We have examined 50 women of reproductive age (18–45 years) with polycystic ovary syndrome (E 28.2 according ICD-10). Control group has been entered by 25 practically healthy women matched in age. Presence of vegetative dystonia syndrome was identified with ''Questionnaire for Revealing the Signs of Vegetative Changes'' (Veyn A.M., 2003). We rated spectral and time characteristics of variability of heart rhythm with apparatus-program complex ''VNS-Micro'' (Neurosoft). Results of the investigation were processed with program Statistica (version 8.0).

Results: According to results of testing with questionnaire of Veyn A.M. (2003) syndrome of vegetative dystonia has been diagnosed in 84% of the examined. Investigation of variability of heart rhythm has demonstrated reduction of current functional state ($TP = 1132.6 \pm 112.8$ mc^2/Hz; in norm 2393.0 ± 107.6 mc^2/Hz, $p < 0.01$), excessive activation of sympathetic-adrenal system (ratio $LF/HF = 1.93 \pm 0.18$; in norm 0.72 ± 0.06; $p < 0.01$) and reduction of activity (tonus) of parasympathetic system of regulation (HF-component = 426.2 ± 21.8 mc^2/Hz; in norm 984.4 ± 78.1 mc^2/Hz, $p < 0.01$). These changes are pathogenetic basis of development of reactions of disadaptation that manifest themselves clinically as vegetative dysfunction syndrome.

Conclusion: Vegetative dysfunction accompanies mental symptoms. Disorder of vegetative provision of the activity worsens quality of life of women with anxiety-depressive disorders co-morbid with polycystic ovary syndrome, conditions insufficient adaptation and is a predisposition to development of anxiety-depressive disorders. Complex investigation of status of vegetative neuroses system allows rating current functional state of the organism and its adaptive reserves, giving prognosis of the disease, developing recommendation in choice of optimal therapy taking into account background of neurohumoral regulation as well as accomplishing the subsequent control of conducted treatment.

P-04-011 Involvement of a polymorphism in the 5-HTT gene in impulsive response style in Japanese population

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Objective: The biochemical mechanism of the 5-HTTLPR gene is thought to result in enhanced neural processing of the amygdala, particularly during presentation of negative adverse environmental cues. Thus, the S-allele of the 5-HTTLPR gene could relatively increase neuroticism, anxiety (Kaufman et al., 2004), and emotional regulation disorders in the context of early and adult life adversity (Caspi et al., 2003). These observations led to the idea that 5-HTTLPR function does not directly affect the behavioral regulatory process itself, the single specific dimension of cognitive function, but possibly via evaluation of the potential risk accompanied by particular behavioral outputs.

Methods: The polymorphism of the 5-HTT gene promoter was analyzed by PCR using lymphocytes from 60 volunteers (34 men, age 29.1 ± 1.4) gave written informed consent and participated in the experiment. Impulsivity was defined as the number of commission errors (responding when one should not) made during a Go/No-go task. Stimuli and Procedure: Participants were required to respond to target stimuli (three-digit numbers) within 800 ms and inhibit their response to non-targets.

Results: We identified that while monetary punishment was given for impulsive behavior (responses for non-target stimuli), the S/S

homozygous made fewer commission errors than the L-allele carriers. Given that the S/S homozygous of the 5-HTTLPR gene could relatively increase neuroticism or anxiety, this result is consistent with our earlier study showing the positive correlation between a high tendency toward neuroticism and a more inhibited response style in a Go/No-Go task when it entailed the probability of receiving punishment (Masui, Kashino, Nomura, 2009).

Conclusion: These results suggest the impulsivity are modulated by sensitivity to punishment as a function of the 5-HTT genotypes; this was clarified in Japanese population that present results lead to the question that whether this effect could be also intermediated by various environmental factors including culture.

P-04-012 Disagreement between adolescent and parent reports of anxiety symptoms: Who is right?

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Objective: It is known that adolescent and parent ratings of adolescent mental health are poorly correlated. In a previous study of adolescent and parent estimations of anxiety using the Spence Children's Anxiety Scale (SCAS), a correlation of 0.41–0.66 was reported. This result, however, says little about whose ratings are most accurate. The aim of our study was to; 1) investigate the correlation between adolescent and parent ratings in a Swedish child- and adolescent psychiatric outpatient population, and 2) to compare these ratings with a semi-structured diagnostic interview (K-SADS), in this study regarded as gold standard.

Methods: 275 consecutive patients in a child and adolescent psychiatric outpatient clinic in the county of Vastmanland (adolescents 13–18 years and their parents) completed the SCAS. Cut-offs in each diagnosis was set to +1 Std. dev. above the mean. Thirty of these patients and their parents also completed a diagnostic interview (K-SADS) by a specially trained member of the staff, where the interviewers were blinded for the results from the self-assessments.

Results: Overall, parent ratings indicated lower levels of anxiety in their adolescents compared to the adolescents' own ratings. Kappa correspondences between parent and adolescent ratings ranged from 0.07–0.19. Preliminary results suggest, that adolescent derived-compared with interview derived diagnoses, have a high concordance with the diagnoses Generalized Anxiety Disorder and Social Phobia, (kappa value 1.0).

Conclusion: This study extends the literature in terms of evaluating adolescent self-reported anxiety symptoms. Unlike previous studies, our study demonstrates low concordance between adolescent and parent ratings with the SCAS, and a very high agreement between adolescent self-reported anxiety and diagnostic interview.

P-04-013 Relationship between child and adolescent anxiety disorders and alcohol use disorders: Synthesis of evidence and literature review between 1990–2012

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Objective: Background: While the research in adult population suggests an association between anxiety disorders and risk for alcohol use disorders, available studies in youth population have inconsistent and at times, conflicting results. Adolescents may show a relatively heightened sensitivity to some of positive alcohol effects e.g. social facilitation. The relationship of early onset anxiety disorders to alcohol use disorders appears to be complex and perhaps bidirectional. Objective: The present review was planned in order to examine and describe the nature of association between early-onset ($\leqslant$18 years) anxiety disorders and alcohol use disorders.

Methods: Relevant studies from English language literature were included from PUBMED/MEDLINE, PsychINFO and EMBASE search between 1990–2012 using key words such as [Anxiety or Panic or Phobia or Agoraphobia, Shyness], [Alcohol or Substance or Drugs] and [Youth or Early or Child or Adolescent OR Students]. Inclusion criteria were as follows (a) studies focusing on children and adolescents or, samples with mean age $\leqslant$18 years (b) reporting the original data (c) assessing the concurrent/prospective prevalence of (any or all) anxiety disorders and (any or all) alcohol use disorders as per DSM/ICD, or standard research instruments. Duplicate study data from same group of researchers were excluded, with the larger sample retained.

Results: The evidence and strength of relationship differs across the spectrum of anxiety disorders and whether the alcohol use is problematic, non-dependent or dependent, in addition to influence by a host of other factors e.g. co morbidity. Several lacunae emerged in the available literature, which are highlighted. Detailed analysis of the literature review and strength of evidence will be discussed along with the limitations and future directions.

Conclusion: The link between child and adolescent anxiety disorders and alcohol use disorders provides several interesting insights and need more research attention.

P-04-014 Acute administration of escitalopram exacerbates contextual fear in the startle paradigm in rat

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Objective: Selective reuptake inhibitors (SSRIs) generally display marked efficacy in treatment of anxiety disorders; however, during the first weeks of treatment patients frequently experience increased anxiety. The reason for this paradoxical affect is unknown, but revealing it would probably enhance our insight into the physiological role of serotonin for the regulation of fear and related emotions. Animal experiments performed in an attempt to investigate the effect of short-term SSRI administration on anxiety have shown diverse results: some have revealed increased anxiety-like behavior, whereas others have shown the opposite, with an immediate decrease in anxiety-like behavior after acute SSRI administration. In this study the effect of acute SSRI administration (escitalopram, 10 mg/kg, 60 min prior to the test) on the acoustic startle reflex in a putative animal model of anxiety, i.e. contextual conditioned fear, was investigated.

Methods: Startle reactivity was measured following fear conditioning. Furthermore, baseline startle, as well as startle in control animals that had not undergone fear conditioning, was investigated.

Results: Fear-conditioned animals treated with escitalopram 60 min prior to test exhibited significantly greater startle than controls. No significant effect of the drug was seen in non-conditioned animals.

Conclusion: These findings imply that conditions similar to those in humans are at hand also in rat, i.e. that short-term SSRI administration may exacerbate anxiety. This further supports startle reactivity as measurement of contextual conditioned fear as a useful animal model for investigating the mechanisms underlying the influence of serotonin on anxiety.

P-04-015 Assotiation of elevation endocannabinoid plasma levels with mild cognitive impairment and anxiety in people with obesity

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Objective: The endocannabinoid (EC) system has been proposed as regulator of anxiety, and modulator of cognitive, behavioral responses to stressful stimuli. (1, 2). Also obesity has an association with anxiety and depression (3).This study focuses on the effects of EC system modulation in people with obesity of cognition and emotion (anxiety).

Methods: Aim of this study was to evaluate a possible association between EC plasma levels, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and mental processes such as, cognitive functions and anxiety in obesity. Methods and results. Study participants (n = 67) were divided into three groups dye to there body mass index (BMI): control group BMI $\leqslant$24, 9, (n = 21); overweight group, BMI $\geqslant$25–30 (n = 27), obese group, BMI $\geqslant$30 (n = 19). All subjects were passed through tests: MMSE, HADS, and HARS.

Results: Elevation 2-AG plasma level, was significantly associated with BMI in all groups (0.62, $p < 0.5$; 0.62, $p < 0.5$; 0, 33, $p < 0.5$). Low MMSE data were significantly associated with elevation AEA plasma level in control group (-0.44, $p < 0.5$) and elevation 2-AG in obese group (-0.52, $p < 0.5$). In normal and obese group only elevation of AEA plasma level was associated with high anxiety (0.61, $p < 0.5$).

In overweight subjects high anxiety was associated with high 2-AG plasma level (0.47, $p < 0.5$).

Conclusion: Conclusions. Increased EC plasma levels of AEA or 2-AG are associated with increasing of anxiety and poor cognition up to the mild cognitive impairment.

P-04-016 Psychological problems in relatives of patients with severe mental disorder: Assessment and intervention

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Objective: This work has two objectives: 1) to identify the psychological problems in relatives of patients with severe mental disorder (SMD), and 2) to show the main components of psychological intervention with relatives.

Methods: Relatives of patients were examined in the Day Hospital of Mental Health of Granada (Spain). The Spanish versions of ''Beck's Anxiety Inventory'', ''Beck's Depression Inventory-II'' and ''Coping Strategies Inventory'' were used. The psychological intervention consisted of 20 weekly sessions of two hours each one. It included: 1) psycho education; 2) elaboration of mourning; 3) acceptance of life experiences and commitment to values-based living; and, 4) skills training. The sessions followed all of them a similar structure consisting of exercise review, functional analysis, use of metaphors, experiential exercises, and training techniques for emotional regulation and assertive communication.

Results: Regarding the first objective, 48 relatives were evaluated. 64.7% of them had depression and 52.2% anxiety. A high relationship between these two variables was found ($r = 0.734$, $p = 0.000$). With regard to the second objective, nine relatives participated in a psychological intervention program. Wilcoxon test showed that for people participating in the program the level of depression decreased and the use of strategies focused on problem solving increased ($p < 0.05$). Although anxiety also decreased as a result of treatment it not reached a significant level. 88% of relatives said that the intervention was useful, and that they applied what they have learned to their daily lives. 62.5% of relatives have recovered many valued activities of their lives.

Conclusion: The presence of psychological problems seems high prevalent among relatives of patients with SMD. The intervention program was successful, reducing some psychological problems and improving some coping strategies in relatives. They reported to have decreased their distress and have recovered valued activities previously abandoned because of their implication with the care of the patient.

P-04-017 Relationship between attachment styles and personality traits to wellbeing and stress related disorders

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Objective: The five most common worldwide diseases planned for 2020 will have stress as an underlying factor. People with this type of condition display a reversed role with primary caregivers. Insecure attachment styles and certain personality traits – neuroticism, have been associated with anxiety and stress related disorders. Because personality characteristics have emerged as some of the most robust predictors of anxiety, it was predicted that the link between attachment and stress response be through personality traits. The objective is to examine associations between attachment styles and personality traits to sensitization processes in anxiety development.

Methods: Thirty volunteer participants, 22 female (73.6%), 8 male (26.6%), aged over 21 years completed the personality assessment NEO-FFI, Adult Attachment Questionnaire and HARS.

Results: Overall, neuroticism, mediated relationship between insecure-resistant attachment and anxiety. Higher scores on neuroticism predicted higher expression of psychopathology and explained relationship between insecure-resistant attachment and anxiety disorders. Females score significantly higher than males in Neuroticism and symptoms of anxiety ($n:22$; $p < 0.001$) Anxious attachment style prevailed. Underlying factors related to attachment reveals low self-steem, need of approval, fear of rejection, as well as feelings expression and comfort with relationships, respectively, scored higher (46,17; 36,94).

Conclusion: Relationships between attachment style and anxiety appear as indirect, in that neuroticism fully mediates associations between insecure attachment and anxiety, predictive of maladjustment. Measurement of personality traits and attachment styles may lead the field toward a model that integrates these two issues as putative predictors of either anxiety or balanced affect.

P-04-018 Assessment of allostatic load and stress related disorders through translational evaluation of alprazolam on MHPG, cortisol and cognitive domains

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Objective: To assess impact of Alprazolam on salive MHPG and cortisol, cognitive functions and parameters of allostatic load in anxiety disorders and stress related disorders.

Methods: Fifty volunteer participants, 13 male (26%) and 37 female (74%) over 21 years, meeting following criteria: NEO-FFI scoring over 18 points, HARS over 7 points, over 3 parameters of Seeman – McEwen Allostatic Load Parameters and comorbid anxiety disorder plus at least a stress related disorder. Evaluations were conducted on days −7, 0, 7, 14, 28, 60 and 90, recieving Alprazolam on day 0 between 0,75 to 3 mg/day according to clinical status. Salivary concentrations of Alprazolam were monitored from day 7. Clinical progression was followed up with HARS, STAI, NEO-FFI, neuropsychological test battery (Continuous Performance Test, Digit Symbol, Digit Span, Verbal Fluency Test, Five Points Test, Revised Taylor Complex Figure Test, Stroop Test), and parameters of allostatic load measured through clinical and neurobiochemical trials (salivary MHPG and cortisol).

Results: Saliva MHPG significantly reduced 57.3% from visit 1 to visit 7 with Alprazolam correlating with descending levels of HARS and STAI (43.1% and 9.4%, respectively), along with steady decrease in cortisol (15.4%). Females score significantly higher than males in Neuroticism and symptoms of anxiety ($n:37$; $p < 0.001$) MHPG appeared influenced by life events. Improvement in executive functions through modulation of anxiety, stabilization in sustained attention, interference control and decrease in impulsivity rates.

Conclusion: MHPG appears as useful marker to assess stress response. Alprazolan impacts rapidly and steadily on ergotrophic activation to stress response, lowering anxiety scores and promoting clinical progression through modulation of response to allostatic load.

P-04-019 Efficacy and tolerability of agomelatine in generalized anxiety disorder (gad): A randomised double-blind, placebo-controlled trial with escitalopram as validator

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Objective: Agomelatine, a MT1/MT2 receptor agonist and 5-HT2C receptor antagonist, has demonstrated efficacy in GAD. This 12 weeks multi-centre, randomised, double-blind, parallel group study in GAD aimed to confirm the superiority of agomelatine (25–50 mg/day) vs. placebo, using escitalopram (10–20 mg/day) as a validator, on the Hamilton Anxiety Rating Scale (HAMA) total score.

Methods: 412 patients with a DSM-IV diagnosis of GAD were randomised to receive agomelatine (139), placebo (131) or escitalopram (142). The HAMA total scores at baseline in the Full Analysis Set (FAS) ($n = 409$) were respectively: 28.6; 28.2 and 28.6.

Results: At last value, the HAMA total score decreased significantly more with agomelatine −15.6 ($p < 0.0001$) and with escitalopram −15.6 ($p < 0.0001$) compared to placebo −10.6. In patients with more severe GAD symptoms (HAMA total score $>= 25$ and CGI-S $>= 5$ at baseline), the between group difference vs. placebo was 5.61

for agomelatine (SE = 1.49, $p < 0.001$) and 4.08 for escitalopram (SE = 1.50, $p = 0.007$). Significant improvement of patients' functioning was clearly shown on the Sheehan Disability Scale (SDS) for agomelatine and escitalopram compared to placebo at the last value with a SDS work score between group difference vs. placebo of 1.69 for agomelatine and 1.55 for escitalopram (SE = 0.35, $p < 0.0001$ for both comparisons). Similar results were observed on both the SDS social and family life scores (unplanned analyses). The proportion of patients reporting at least one Emergent Adverse Event (EAE) was 47.5% with agomelatine, 48.2% with escitalopram and 44.3% with placebo. Fewer patients discontinued the treatment for EAE with agomelatine (2.2%) and placebo (3.5%) than with escitalopram (8.5%). The most commonly reported EAEs were headache, nasopharyngitis, diarrhoea, and nausea.

Conclusion: This study confirms that agomelatine is efficacious and well tolerated in the treatment of GAD.

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P-04-020 Internet screening for anxiety disorders: Effects on treatment-seeking behaviour in a 3-month follow-up study

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Objective: The internet is an extensive resource for health information and is often used for self-diagnosis of mental health symptoms. This may be especially common for sensitive, stigma-prone mental health issues. Numerous barriers prevent people from seeking proper mental health treatment, however little is known about the relationship between internet self-diagnosis and treatment seeking behaviour.

Methods: A link to the MACSCREEN (a validated, self report screening tool for anxiety and depression) was posted on our homepage. Three months after completing the MACSREEN and a variety of symptom severity scales, respondents were emailed a follow up questionnaire asking about potential treatment-seeking behaviours.

Results: Of the 494 participants who completed the MACSCREEN, 48 completed the follow-up questionnaire. Prior to completing the survey, 89.6% had planned to seek further assessment. At 3-month follow-up, 62% reported seeking treatment. The most common barriers to treatment were fear/lack of desire to take medication (50%), cost of therapy (27.8%) and lack of impairment (27.8%). Compared to those who did not complete the follow-up questionnaire, follow-up participants were more likely to have received previous treatment ($p < 0.01$). All follow-up participants were assessed as having clinically significant diagnoses ($p < 0.001$). Higher scores were found on the Sheehan Disability Scale ($p < 0.01$), and higher rates of Obsessive Compulsive Disorder, Generalized Anxiety Disorder and Depression were assessed in the follow-up participants compared with those who did not complete the follow-up questionnaire ($p < 0.05$).

Conclusion: Some individuals with anxiety disorders use the internet for self diagnosis. Completion of a self report screening measure may have stimulated treatment seeking. Potential use of medication and cost of therapy appeared to be the largest factors preventing individuals from seeking help.

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P-04-021 Medication algorithm for generalized anxiety disorder in Korea: Treatment strategies for initial treatment, long-term treatment and comorbid conditions

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Objective: This study investigated the consensus about treatment strategies for initial treatment, long-term treatment and comorbid conditions in generalized anxiety disorder (GAD) in Korea.

Methods: The executive committee for Korean medication algorithm project for GAD developed questionnaires about treatment strategies for patients with GAD based on guidelines or algorithms and clinical trial studies previously published. Fifty-five (64%) of 86 experts on a committee reviewing GAD in Korea responded to the questionnaires.

Results: For initial treatment of GAD, antidepressants monotherapy and combination of antidepressants and benzodiazepines were recommended as the 1st line strategies. Escitalopram, paroxetine CR and venlafaxine XR were selected as 1st line treatments and alprazolam, clonazepam and lorazepam were preferred in benzodiazepines. For the long-term treatment strategy, venlafaxine XR, escitalopram, fluoxetine, paroxetine CR, sertraline and buspirone were selected as 1st line treatment. For the consensus of medication algorithm in the treatment of GAD, step 1 is the use of the one of a selective serotonin reuptake inhibitor (SSRI), a serotonin and noradrenaline reuptake inhibitor (SNRI) and buspirone for at least 4 to 6 weeks. Step 2, 'switch from a SSRI to a SNRI or a buspirone or vice versa', step 3, 'augment with atypical antipsychotic or add a benzodiazepine or antihistamine', step 4, 'switch to another combination that includes SSRI, SNRI, mirtazapine or tricyclic antidepressant', step 6, 're-evaluate the diagnosis', and 'benzodiazepines including clonazepam and alprazolam can be combined with another drug even from the initial period' were recommended as 1st line strategy. The consensus about treatment strategies in the case of GAD with comorbid depression recommended SSRIs and SNRIs as the 1st line drug treatment. SSRIs and SNRIs and benzodiazepines (e.g. alprazolam, clonazepam) were recommended in GAD patients with other comorbid anxiety disorders.

Conclusion: These results, which reflect the recent studies and clinical experiences, may provide the guideline about optimal medication treatment strategies for GAD.

P-04-022 Anxiolytic effects of Yokukansan, a traditional japanese medicine, via serotonin 5-HT1A receptors on anxiety-related behaviors in rats experienced with aversive stress

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Objective: Yokukansan, a traditional Japanese medicine (Kampo), has been reported in the treatment of behavioral and psychological symptoms of dementia (BPSD) such as aggression, anxiety and depression in patients with Alzheimer's disease and other forms of senile dementia. In the present study, we investigated the anxiolytic effects of yokukansan on anxiety-related behaviors in rats that have experienced aversive stress.

Methods: We used male Wistar/ST rats which received an electrical footshock as aversive stress. Yokukansan at a dose of 1.0 g/kg was administered orally once a day for 14 or 16 days before behavioral tests. To evaluate the anxiolytic effects, we used the contextual fear conditioning (CFC) test and elevated plus maze (EPM) test.

Results: In the CFC test, rats that had experienced footshock showed significant freezing behavior on re-exposure to the box 14 days after footshock stress. Yokukansan significantly suppressed freezing behavior in the CFC test. In the EPM test on the 16th day after the CFC test, yokukansan significantly increased the time spent in open arms after footshock stress compared to control rats.

These anxiolytic effects by yokukansan were antagonized by WAY-100635, a selective 5-HT1A receptor antagonist, in the CFC test, but not the EPM test. Furthermore, 5-HT1A receptor agonist buspirone significantly suppressed freezing behavior in the CFC test; however, buspirone induced no change in the time spent in open arms in the EPM test.

Conclusion: These findings suggested that yokukansan has anxiolytic effects on anxiety-like behaviors induced by both innate fear and memory-dependent fear. In particular, yokukansan produced anxiolytic effects via 5-HT1A receptors in memory-dependent fear induced by aversive stress. Furthermore, yokukansan could be useful as a therapeutic drug for the treatment of anxiety disorders and various mental disorders that have comorbid anxiety.

P-04-023 Study of benzodiazepine reception in C57Bl/6 and Balb/c mice

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Objective: The decrease of benzodiazepine binding in anxiety states is proved in a number of clinical and experimental investigations. In our previous experiments, stress in the ''open-field'' test (OF) caused reduction of benzodiazepine reception in Balb/c mice. In C57Bl/6 mice such effect was not observed. In the present research benzodiazepine reception in inbred mice C57Bl/6 & BALB/c with different OF behavior was studied: (1) anxiety factors affecting benzodiazepine reception, (2) duration of the anxiety-induced benzodiazepine reception reduction.

Methods: Open field, Elevated Plus Maze, Short Immobilization, Exposure to a predator, Radioligand binding assay.

Results: The level of specific [N-methyl-3H]-flunitrazepam binding with P1 + P2 membrane fraction of C57Bl/6 and Balb/c mice brain tissue was studied after tests OF, ''Elevated Plus Maze'' (EPM), 3 h immobilization, ''Exposure to a predator''. Stress-induced decrease of benzodiazepine reception was registered after test OF, EPM only in Balb/c mice. After test ''Exposure to a predator'' and 3 h immobilization significant decrease is obtained for both Balb/c and C57Bl/6. We found that stress in OF significantly changed the level of specific [N-methyl-3H]-flunitrazepam binding in Balb/c mice brain for 1.5 h. The restoration of reception to the control level occurred in Balb/c mice brain after 8 h and after 24 h in C57Bl/6 mice brain after the test ''Exposure to a predator''.

Conclusion: Thus, the duration of recovery of change in benzodiazepine binding depends on the phenotype of stress response, the strength of stress factors and can serve as an important marker of anxiety.

P-04-024 A novel open-field stress-induced activation of GAD67-containing 5-HT neurons in the dorsal raphe nucleus of rats

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Objective: The presence of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD) has been reported in 5-HT neurons in the dorsal raphe nucleus (DRN). However, neurochemical and functional properties of the GAD-positive 5-HT neurons remain unknown.

Methods: In the present study, we characterized GAD67-expressing 5-HT neurons in the rat DRN and also examined regional differences in neuronal responsiveness to emotional stress.

Results: Mild emotional stress induced by open-field exposure caused c-Fos expression in all three subdivisions of the DRN, particularly in the DRL. This response was selectively suppressed in the DRL by potentiation of GABA receptors with diazepam. In the DRL, the open-field stress-induced c-Fos expression was more prominent in 5-HT/GAD67 neurons than in 5-HT neurons.

Conclusion: These findings indicate that 5-HT/GAD67 neurons constitute a unique neuronal population in the DRN and high responsiveness to mild emotional stress.

P-04-025 Anxiety disorders among nursery students

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Objective: Evaluation of anxiety symptoms and panic disorder to Nursery students. We evaluated anxiety symptoms related to panic disorders where the signs of anxiety which occurred suddenly and the dynamic and spontaneous growth of fear seem to be very aggravated and easily understood.

Methods: The study was conducted on the period March–April 2011 (outside the exam season) that included nursery and master level students. To identify anxiety disorders, especially panic disorders, Beck Inventory for Anxiety was used. After completing the questionnaire, which consisted of 21 signs of anxiety all the screened persons who presented with more than four symptoms were evaluated by psychiatrists as candidates considered to have panic disorder. DSM IV criteria where used. The sample chosen in this study consisted of 795 students, 679 females and 116 males. The average age was 20.82 ± 1.29 years, $M = 20.82$ and $SD = 2.395$. Screening with BAI questionnaire, students were asked for symptoms they had last month and the day of completing the questionnaire. The differences were analyzed with Chi-square and student test.

Results: Variables with statistical significance found in this study are listed as follows: gender is correlated with the manifestation of anxiety with statistical significance $p = 0.012$, of which 34.27% of the interviewed females presented slight anxiety, 13.74% moderate anxiety and 6.65% (45 of sample students) had severe anxiety scale with interval rating scale 26–63. Through linear regression analysis a significant statistical relation between age and anxiety rate was found ($p = 0.001$), with smocking ($p = 0.04$) and consumption of alcohol ($p = 0.014$).

Conclusion: Anxiety is present to the Nursery students and is related to the age of the students and is related also to substance use.

P-05. Genetics

P-05-001 The ''DGPPN – cohort study'' – a national collaboration initiative by the German Association for Psychiatry and Psychotherapy (DGPPN) for establishing a large-scale cohort of psychiatric patients

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Results from genome-wide association studies (GWAS) have demonstrated the need for even larger samples than studied so far to comprehensively understand the complex genetic architecture of mental illness. Little is known about the course of various illnesses over time as information is usually collected retrospectively, and criteria and methodologies used in various studies are heterogeneous. Therefore, collaborations between different centres collecting the same information longitudinally are essential to understand the relationship between phenotypes and genotypes better. Ideally, any large-scale collaborative effort should bring together academic and non-academic centers. To foster such a research framework, the DGPPN has committed to establish a prospective national cohort of patients with major psychiatric disorders. The DGPPN Cohort Steering Committee (Deckert, J., Grabe, H.-J., Gruber, O., Juckel, G., Kircher, T., Reif, A., Rujescu, D., Walter, H., Maier, W., Falkai, P.G., Rietschel, M.) will supervise the collection of longitudinal data on a large national scale in centres spread across Germany, using existing information and re-recruiting patients to collect additional information, focusing on the course of illness over time. The use of uniform phenotyping, standardised measures, identical consent forms, shared databases and other resources, while simultaneously ensuring the highest standards of data protection and quality assurance, makes this a new and exciting attempt to advance our knowledge of psychiatric disorders. Another asset to this will be the use of a centralised biobank structure, achieved by networking already established ''biobanks''. This will make it possible to pool already existing data from various

centres, while meeting the highest data protection standards. By combining resources, the aim is to have a cohort of 100 000 patients by 2020. This cohort will not be restricted to genetic or other biological psychiatric research but constitute a valuable resource for research on epidemiological aspects, quality of care, and socio-demographic aspects of psychiatric morbidity.

P-05-002 Expression of Wnt/β-catenin signaling pathway genes in peripheral blood correlate with negative symptoms among Individuals with psychosis

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Objective: To correlate blood-based gene expression of the Wnt/β-catenin signaling pathway with negative and positive symptom severity indices of patients with a history of psychosis (i.e. schizophrenia or bipolar disorder).

Methods: A total of 19 subjects meeting DSM-IV criteria for at least one episode of psychosis were recruited and assessed using the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS). Twenty-five of the most well-characterized genes involved in the Wnt signaling pathway were selected, based on the Kyoto Encyclopedia of Genes and Genomes database. Spearman's correlations were conducted between expression intensities for each of the 25 selected Wnt pathway genes and SANS/SAPS global severity scores, adjusting for gender, ethnicity, age, education, current smoking (yes/no), and past six-month substance use (yes/no). A Bonferroni-adjusted alpha threshold of $0.05/50 = 0.001$ was used to reduce the risk of Type I errors.

Results: Two (DVL2 and GSK3B) of the 25 Wnt signaling pathway genes examined were correlated with scores on the SANS, however, only DVL2 remained significant after Bonferroni correction. DVL2 ($r = -0.70$, $p = 0.0008$) showed a negative correlation whereas, GSK3B ($r = 0.48$, $p = 0.039$) was positively correlated with the SANS ratings. Post-hoc exploration of the four subscales of the SANS revealed significant negative correlations between DVL2 expression and affective flattening ($r = -0.55$, $p = 0.015$) and alogia ($r = -0.65$, $p = 0.003$) severity. GSK3B expression was positively correlated with alogia ($r = 0.60$, $p = 0.007$) only. None of the 25 gene transcripts examined were significantly correlated with severity scores on the SAPS.

Conclusion: Our findings suggest that the Wnt signaling pathway may harbor biomarkers for severity of negative but not positive symptoms.

Policy of full disclosure: There is no financial conflict of interest.

P-05-003 Meta-analysis of COMT Val158/108Met association findings in major depression

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Objective: Many studies described the association of Val158/108Met polymorphism of the Catechol-O-Methyltransferase (COMT) Gene and psychiatric disorders including major depressive disorder (MDD). The COMT Val158/108Met polymorphism has been investigated regarding its role in aetiology, course of illness and therapy-response, although with conflicting results. In the present study we therefore perform a meta-analysis of the current literature.

Methods: To identify studies eligible for meta-analysis, we search the Pubmed and Medline with the Keywords: ''unipolar depression'', ''major depression'', ''depressive disorder'' and ''affective disorder'' combined with ''COMT'', ''polymorphism'', ''gene'' and ''allele''. Based on this literature research we aim to identify case-control-studies published in peer-reviewed journals which provide enough data to calculate an effect size. Studies are excluded from further examination if cases were selected by questionnaires assessing symptoms of depression, if the study didńt include a control group of subjects or included bipolar patients. The distribution of genotypes has to be in Hardy-Weinberg Equilibrium to be considered in this meta-analysis. In addition, references cited in these studies are reviewed to identify further publications not obtained by MEDLINE.

Results: The included case-control studies selected in this manner will be analysed by random effects meta-analysis.

Conclusion: The results of this meta-analysis on COMT Val158/108Met polymorphism in MDD will be presented.

P-05-004 Search of rare genetic variants of psychotic disorders in Algerian consanguineous families

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Objective: Several recent studies have reported associations of schizophrenia (SZP) with rare copy number variations (CNVs), such as 1q21.1 and 15q13.3 deletions. These CNV results suggest a broader neuropsychiatric spectrum of phenotypes, and support a ''Common Diseases – Many Rare Alleles'' hypothesis. The majority of these CNVs are de novo, and we lack information about the phenotypes associated with such variants when they are transmitted. These results also suggest that other types of rare mutations could be associated with psychotic disorders. We are studying four families from North-West Algeria identified through patients with psychotic disorders, in order to identify new rare variants responsible for these disorders.

Methods: We are studying four consanguineous families from Tlemcen in North-West Algeria with 30 patients with psychotic disorders, in order to identify new rare variants. Information was collected about direct interview (DIGS) and medical records. The Agilent Human Genome CGH Microarray Kit 44K is used for the genome-wide DNA copy number variation profiling, and the Illumina's Genome AnalyzerIIe for exome high-throughput sequencing.

Results: In three families all the affected members analyzed up to now are schizophrenics and in one bipolar I (BDI) with psychotic symptoms. Three new CNVs have been identified, one 1.6 Mb duplication on chromosome 4q26 and on small 28.8 deletion on chromosome 16q23.1 and deletion 21q21.1. Segregation of these new CNVs is currently analyzed. Sequencing data are not yet available.

Conclusion: This ongoing study of three Algerian families with SZP and one with BDI allow us to identify two new CNVs. Complete CNV analysis and exonic sequencing will be presented.

P-05-005 Quantitative smoking effects differences in male mu opioid A118G alleles

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Objective: The objective of the present study was to provide additional support for a role of mu opioid receptors in tobacco smokers. There are basic and clinical studies indicating that the endogenous mu opioid system is involved with several substances of abuse.

Methods: After overnight tobacco abstinence, 14 genotyped males smoked denicotinized (denic) and average nicotine (avnic) containing tobacco cigarettes in a PET brain imaging study using 11C-raclopride.

Results: Mean decreased dopamine (DA) binding was observed in the left dorsal caudate ($-14\ 6\ 11$; $t = 3.77$), left and right ventral putamen ($-26\ 3\ 8$; $t = 4.27$; $28\ 2\ 1$; $t = 4.25$, respectively), and right caudate ($17\ 18\ 1$; $t = 3.92$). The effects of the A118G genotype on the binding potentials for these four regions were analyzed after denic minus avnic tobacco smoking. Carriers of the G allele demonstrated larger magnitudes of DA release in response to avnic smoking than those homozygous for the more prevalent AA allele in the right caudate and right ventral pallidum ($t = 3.03$; $p = 0.008$ and $t = 3.91$; $p = 0.001$). A voxel by voxel whole brain SPM analysis using an independent samples t test did not reveal any other differences between genotype groups. In addition, the venous plasma cortisol levels of the volunteers from 8:30 a.m. to 12:00 p.m. were lower in the AG/GG alleles. Avnic smoking increased plasma cortisol in both groups, but they were higher in the AA group.

Conclusion: The present results indicate that the mu opioid receptor function has important tobacco smoking effects.

P-05-006 Investigating telomere length and psychological stress in South African rape victims

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Objective: Women are at an increased risk of depression and other mental health problems following rape. Various aetiological factors for depression, including predisposing genetic factors, have been identified. Telomeres are repetitive nucleoprotein structures located at chromosomal ends that protect them from premature degradation. Telomeres reduce in length with each cell division, resulting in cellular senescence and apoptosis. Additional factors, such as oxidative and psychological stress, can further induce telomere shortening.

Methods: This study performed relative quantification of telomeric repeats with the use of real-time PCR methods to investigate whether shorter relative leukocyte telomere length (LTL) in a cohort of rape victims was associated with resilience, the development of trauma-related major depressive disorder (MDD), as well as the development of PTSD after three months.

Results: No significant associations were observed between relative LTL and resilience or the development of MDD at either baseline or after three months in this cohort. However, a significant association was evident between relative LTL and PTSD status.

Conclusion: The significant association between relative LTL and PTSD suggests that shorter relative LTL might have acted as a predisposing factor to the development of PTSD after a severely traumatic event. Telomere shortening may be an important marker of PTSD risk, which has implications for early intervention and timely treatment.

P-05-007 Epigenome analysis in neurons of bipolar disorder and schizophrenia

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Objective: Epigenetic factors such as cytosine and histone modifications are involved in long-lasting gene expression change and are believed to play important roles for the pathophysiology of major psychiatric diseases. Here we performed comprehensive DNA methylation analysis using brains of patients with schizophrenia (N = 35), bipolar disorder (N = 35) as well as controls (N = 35).

Methods: Postmortem brains (prefrontal cortex, BA10) were obtained from the Stanley Medical Research Institute. We have previously established a method for the separation of neuronal and non-neuronal nuclei from the fresh-frozen postmortem brain using NeuN-based cell sorting. By using this separation method, neuronal (NeuN+) and non-neuronal (NeuN−) fractions were obtained from each brain sample. After the enrichment of methylated DNA with MBD2B protein, DNA methylation profiles were obtained with Affymetrix promoter tiling arrays. Methylated region was identified with MAT software.

Results: In both psychiatric diseases, we identified specific DNA methylation differences compared to control subjects. Representative methylation differences were extensively confirmed by qPCR analysis.

Conclusion: Some of DNA methylation differences were only found in neuronal or non-neuronal nuclei, suggesting the cell-type specific DNA methylation changes in patients' brain. Such DNA methylation change may contribute to the pathophysiology of psychiatric diseases.

P-05-008 Association between the CLOCK gene and autism symptoms in a Swedish twin sample

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Objective: Autism spectrum disorders (ASDs) are pervasive developmental disorders that include Autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Many patients with ASD have sleep impairments and timing problems, suggesting disturbances in the regulation of circadian rhythm as causative factors for these disorders. Indeed, low levels of melatonin are recurrent biological findings and we have previously found association between genes in the melatonin pathway and ASDs. Melatonin is closely related to the circadian rhythms, which is mainly regulated in the suprachiasmatic nucleus (SCN) by a set of clock genes. Genetic variation in the clock genes have previously been investigated in autism patients showing an association with the clock genes PER1 and NPAS2. In this study, we have investigated the possible association of five circadian clock genes on autism symptoms in a Swedish twin sample.

Methods: Single nucleotide polymorphisms in five circadian clock genes were genotyped in The Child and Adolescent Twin Study in Sweden (N = 1771, 9–12 years old). The measured autism symptoms were flexibility, language and social interaction. In addition, the CLOCK gene was screened for mutations in patients with autism (N = 90).

Results: Our results show a significant association in girls between rs1801260, in the 3-UTR, of the CLOCK gene, and the symptom flexibility ($p = 0.0003$), but not with the symptoms language and social interaction. The mutation screening revealed five rare, previously not reported, variants in six different patients.

Conclusion: In conclusion, our results support the hypothesis that clock genes may be involved in autism related disorders. Moreover, since all symptoms of autism did not show similar association with the investigated clock genes in this study, our findings also emphasizes that genetic research may benefit from taking a symptom-specific approach to finding genes associated with autism.

P-05-009 Involvement of the 5-HT2A receptor gene polymorphism in trait anxiety, in activity of VLPFC and in impulsivity: A NIRS study

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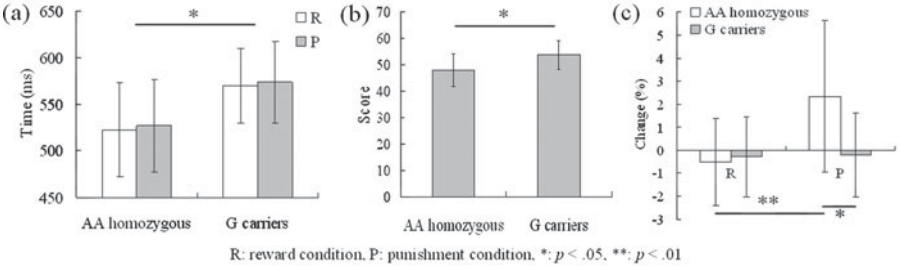
Objective: A polymorphism of the 5-HT2A receptor gene has been suggested to underlie the impulsive behavior. However, relations among this gene polymorphism, impulsivity and activity of brain (especially ventro-lateral prefrontal cortex, VLPFC) remain unclear. We examined whether and how this 5-HT2A receptor gene polymorphism modulates impulsivity in a reward-punishment Go/No-go task and related brain activity measured by near infrared spectroscopy (NIRS).



R: reward condition, P: punishment condition. *: $p < .05$, **: $p < .01$

Methods: Participants: Twenty-seven women (age 21.26 ± 2.91; AA carriers (AA, n = 7) and G carriers (AG and GG, n = 20)) gave written informed consent and participated in the experiment. Stimuli and Procedure: Participants were required to respond to target stimuli and to inhibit their response to non-target stimuli with either monetary reward or monetary punishment. The Go/No-go task was performed by each participant under two conditions (reward condition and punishment condition). Hemodynamic responses of the brain were acquired using NIRS. After the task, participants answered the STAI questionnaire.

Results: G carriers compared to AA carriers responded slower to Go stimuli ($p < 0.05$, Fig. 1 (a)) and made more omission errors ($p < 0.10$) in Go/No-go task. Correspondingly, STAI scores showed high trait anxiety of the G carriers compared with the AA carriers ($p < 0.05$, Fig. 1 (b)). Moreover, the AA carriers showed more activation in the right VLPFC under the risk of punishment (Fig. 1 (c)).

Conclusion: These results suggest that 1) G carriers are more cautious than AA carriers; which is consistent with previous study (e.g., Nomura et al., 2006), and 2) AA carriers have the possibility, under certain risky conditions, to show decreased function of the right VLPFC, which might trigger the impulsive behavior. Further behavioral studies with measurement of 5-HT2A receptor gene polymorphisms should be carried out to clarify the complex relationships between personality traits and vulnerability to impulsive behaviors.

P-05-010 Shared susceptibility of the peroxisome proliferator activated receptor-gamma gene in altered glucose levels and psychosis profiles in schizophrenia patients

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Objective: Glucose and lipid metabolisms are partly regulated by peroxisome proliferator activated receptor-γ(PPAR-γ). Schizophrenia like syndrome may be induced by retinoid toxicity or deficiency, through actions involving retinoid X receptor-α and PPAR-γ heterodimers. Interestingly, glucose and lipid abnormality is common in schizophrenia patients. We hypothesized a role of the PPAR-γ gene in metabolic and psychosis profile in schizophrenia patients.

Methods: Metabolic profile and single nucleotide polymorphisms (SNPs) of the PPAR-γ gene were examined in 394 schizophrenia patients, and 372 patients rated with Positive and Negative Syndrome Scale (PANSS).

Results: Associations of multiple SNPs were identified in HbA1c and FPG in linear regression models (GLMs). Two single SNPs were found associated with triglycerides and high density lipoprotein cholesterol (HDLC). No associations were found in other metabolic indexes. Haplotypes were formed from 6 SNPs associated with HbA1c, and further GLMs and permutation tests provided evidences supporting a role of the PPAR-γ gene in psychosis profile. Pro12Ala (SNP-11, rs1801282), a nonsynonymous variant at exon B, was associated HDLC but not HbA1c or FPG. This implicates that PPAR-γ isoform that contains amino acids coded in exon B, either protein or mRNA, may play a role in the regulation of HDLC. The consistency of G and A allele in the significant haplotypes suggested that 5′UTR and intron B may consist genetic variations essential to psychosis profile.

Conclusion: Our study suggests a shared susceptibility of the PPAR-γ gene in altered glucose levels and psychosis profile in schizophrenia patients, possibly by modifying the mechanisms involved.

P-05-011 Case report of a patient with schizophrenia and a mutation in the insulin receptor substrate-4 gene

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Objective: This report concerns a 50 year-old female patient, diagnosed with paranoid schizophrenia according to the DSM-IV criteria and on long-term treatment with perphenazine, who participated in a recent study regarding the insulin receptor substrate-4 (IRS-4) gene and schizophrenia (Melkersson et al., 2011).

Methods: The patient gave her written informed consent to participate in this case report. She was interviewed by a psychiatrist about her mental and physical health and a venous blood sample was taken in an EDTA-containing tube and stored at −20 °C until preparation of DNA. Then, DNA-sequencing of the whole IRS-4 gene on the X-chromosome was performed.

Results: The DNA sequence of the IRS-4 gene from the patient was compared to the reference sequence of the gene (http://www.ensembl.org/release 46) and it was found that the patient had what is referred to as a mutation: the G/A genotype instead of G/G, G/C or C/C at gene position 107863596, resulting in a change in amino acid coding from histidine to tyrosine at amino acid position 879.

Conclusion: Since the IRS-4 protein may be involved in neuronal growth and function in several areas of the brain, it is possible that this IRS-4 gene mutation underlies this patient's schizophrenia development. It also seems that this patient belongs to the group of schizophrenia patients who have multiple individually rare mutations, impacting genes in pathways of the brain important for neurodevelopment and/or neurotransmission, thereby contributing to schizophrenia (Walsh et al., 2008). Melkersson K, et al. (2011). The insulin receptor substrate-4 (IRS-4) gene and schizophrenia: no evidence for a main genetic factor, however one report of a single schizophrenia patient with a mutation. Neuroendocrinology Letters 32, 101–108. Walsh T, et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320, 539–543.

P-05-012 Convergent functional genomics of schizophrenia: From comprehensive understanding to genetic risk prediction

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Objective: We set out to comprehensively identify candidate genes, pathways and mechanisms for schizophrenia,expanding upon our earlier work on identifying genes for schizophrenia and biomarkers for psychosis, by integrating the available evidence in the field to date.

Methods: We have used a translational convergent functional genomics (CFG) approach to identify and prioritize genes involved in schizophrenia, by gene-level integration of genome-wide association study (GWAS) data with other genetic and gene expression studies in humans and animal models.

Results: Using this polyevidence scoring and pathway analyses, we identify top genes (DISC1,TCF4, MBP, NRCAM, NCAM1, NDUFV2, as well as ADCYAP1, BDNF, CNR1, COMT, DRD2, DTNBP1, GAD1, GRIA1, GRN2B, HTR2A, MOBP, NRG1, RELN, SNAP-25, TNIK), brain development, myelination, cell adhesion, synaptic long term potentiation, and glutamate receptor signalling as key to pathophysiology and as targets for therapeutic intervention. Overall, the data is consistent with a model of disrupted connectivity in schizophrenia, resulting from the effects of neurodevelopmental environmental stress on a background of genetic vulnerability. In addition, we show how the top candidate genes identified by CFG can be used to generate a polygenic risk prediction score to aid schizophrenia diagnostics. We also show, in three independent cohorts, two European-American (EA) and one African-American (AA), increasing overlap, reproducibility and consistency of findings from SNPs to genes, then genes prioritized by CFG, and ultimately at the level of biological pathways and mechanisms. Lastly, we compared our top candidate genes for schizophrenia from this analysis with top candidate genes for bipolar disorder and anxiety disorders from previous CFG analyses conducted by us, as well as findings from the fields of autism and Alzheimer.

Conclusion: Overall, our work maps the genomic and biological landscape for schizophrenia, providing leads towards a better understanding of illness, diagnostics, and therapeutics. It also reveals the significant genetic overlap with other major psychiatric disorder domains, sugesting the need for improved nosology.

P-05-013 Neuropsychological correlates of transcription factor AP-2β in healthy females

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Objective: Studies have shown that transcription factors indirectly influence the catecholamine metabolism. In particular, AP-2β is associated with the transcription of genes important for the function of the dopaminergic system. Studies postulated an association of the AP-2β-polymorphism to behavioural traits and CSF-HVA levels. As the dopaminergic system is associated with cognitive performance, this hypothesis-driven investigation focusses on the relationship between AP-2β, COMT, and cognitive performance.

Methods: 194 healthy, non-smoking females (mean-age 24.01y; SD = 3.35) are neuropsychologically tested. The Trail-Making-Test part-B (TMT-B), Stroop, and dsCPT (degraded stimulus Continuous Performance Task) were performed. Furthermore, blood samples (5–15 ml) for the genetic characterization (AP-2β & COMT) were withdrawn.

Results: Homocygotous carriers of the short (4/4) alleles (M = 40.33s, SD = 9.01) are significantly faster in the TMT-B compared with the long (5/5) allele carriers (M = 50.12s, SD = 11.54; $p < 0.0001$; Bonferroni corrected). Furthermore, the results show on trend-level that the 4/4 allele carrier made less mistakes during the dsCPT compared to 5/5 carrier. Additionally, participants with at least one short AP-2β allele show significant effects of COMT on TMT-B performance. In this group, allele carriers of val/val or val/met perform significantly better than met/met carriers ($T = 2.172$, $p = .034$).

Conclusion: The study followed a hypothesis-driven approach. The results show that AP-2β has a highly significant and clinically relevant impact on cognitive performance. TMT-B and dsCPT results point to the same direction (4/4 better than 5/5 carrier). Moreover, AP-2β seems to interact with COMT on cognitive performance. Further investigations have to replicate these results and need to prove whether these results are based on differences in the dopaminergic transmission/turn-over.

P-05-014 Transcription factor activating protein 2 beta (tfap2-β) genotype and co-occurring symptoms of attention deficit hyperactivity disorder and depression in two samples

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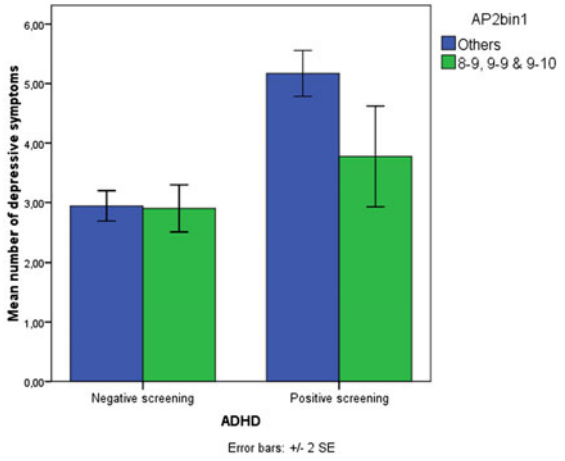
Objective: Familial studies of Attention Deficit Hyperactivity Disorder (ADHD) suggest that there may be a genetically determined subtype of ADHD, most common among girls, which is characterized by comorbid depression. Furthermore, variation in the first intron of the Transcription Factor Activating Protein 2 Beta (TFAP2-β) gene has been shown to influence monoaminergic neurotransmission in rodents and several genes of importance for monoaminergic function have binding sites for the TFAP-2β. The present study examines the possible role of a functional Variable Number of Tandem Repeats (VNTR) polymorphism located in intron 1 of the TFAP2-β gene in the context of co-occurring symptoms of ADHD and depression.



Methods: Symptoms of ADHD and depression were measured by self-reports in two population-based samples of adolescents (group A, n = 175 and group B N = 1506) from Sweden.

Results: There were 6.1 to 7.8% of adolescents who screened positively for ADHD and depression symptoms. In both samples symptoms of depression were more common among girls who screened positively for ADHD and who were not carriers of the 9 repeat version of the TFAP-2β intron 1 VNTR genotype.

Conclusion: The presence of the 9 repeat variant of the TFAP2-β intron I VNTR appears to protect girls with ADHD symptoms from developing symptoms of depression.

P-05-015 Influence of family and education factors on the inclination to commit crimes in Soviet times and today

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Objective: 35 reports of the Commission of forensic psychiatric experts over the period March 2010–1, 35 archive acts of outpatient forensic psychiatric examination that covered the period March 1991–2 were analyzed.

Methods: The statistic, comparative analysis and the method of random sampling.

Results: The study found out that 20-of 1 were held criminally responsible under article 131 of the RF Criminal Code-CC, 13–under article 132, and 2–135. Out of them 14-received incomplete secondary education, 7 did not receive any education at all, 6-received full secondary education, 4–incomplete secondary vocational education, 4–higher vocational education and 1-received education in the form of 8 years of special school. 10 patients were brought up in the family in which either 1 or both parents abused alcohol, 9-were raised and developed in a one-parent family, 8-did not have parents at all and only 8 were brought up in secure families.The 35-of 2 included 9-that were held criminally responsible under article 144 of the RSFSR CC, 5–under article 108; 4–103, 145; 2–under each of articles 117, 206, 246; 1 under each of articles 89, 102, 120, 148, 188, 212, 224. In 2 there were 15-with incomplete secondary education, 13-incomplete secondary vocational education, 5–full secondary education and 2–full secondary vocational education.The anamnestic data showed that 18 patients from 2 were brought up in the family where either one or both parents abused alcohol, 28 were raised in a two-parent secure family, 4-raised in a one-parent family and 3 did not have parents.

Conclusion: The study demonstrated clear relationship between the education level and some family factors affecting the inclination to commit criminal offences. In Soviet times there were mainly property crimes and they were committed by individuals whose education by the time of criminal responsibility was 9 years of secondary school and who were raised in two-parent families.

P-05-016 A novel mutation in exon 2 of the MAPT gene causing frontotemporal dementia

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Objective: Mutations in the microtubule-associated tau (MAPT) gene are associated clinically with frontotemporal dementia (FTD) with or without supranuclear palsy, corticobasal syndrome or parkinsonism. The pathogenic mutations are located mostly in exons 9–13, and in intron 10. Only two mutations are located in exon 1, coding for N-terminal part of the tau protein. The aim of the study was to identify the genetic basis of clinically diagnosed frontotemporal dementia in a female patient.

Methods: Clinical evaluation of the patient and genetic analysis of the MAPT.

Results: A novel mutation G55R located in exon 2 of MAPT was identified in a female patient with age of onset 51 y. and with a positive family history for dementia. The mutation is absent in a group of

45 FTD cases (familial, and some sporadic), as well as in a group of 100 neurologically healthy subjects (>65 y). Three years after the first symptoms developed the patient presented aphasic disturbances and spatio-visual disturbances with no psychotic symptoms, and no aggressive behaviors. In neurological examination deliberative symptoms were observed. Her MMSE score was 10. A brain MRI showed generalized brain tissue lesions, most pronounced in frontal lobes, parietal lobes and temporal lobes; ventricular enlargement. No parkinsonism, and no additional clinical symptoms were identified.

Conclusion: A novel FTD-causing mutation located in exon 2 of the MAPT gene was identified. In silico analysis predicted that the mutation is damaging on protein structure and function, and could influence the ability of tau protein to regulate the dynamic behavior of microtubules.

P-05-017 Association between polymorphisms in sex steroid related genes and autism symptoms in a Swedish population

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Objective: Sex differences in psychiatric disorders are common, which is particularly striking in autism that is five times more prevalent in boys. It has been hypothesized that high levels of testosterone during early development may be a risk factor for autism. This theory has been supported by several studies showing fetal testosterone levels, as well as indirect measures of prenatal androgenization, to be associated with autism and autism-related personality traits. Further, the importance of sex steroid related genes in autism is supported by studies reporting associations between polymorphisms in genes involved in sex steroid synthesis/metabolism and autism and/or autistic traits. The aim of the present study was to investigate possible associations between 29 polymorphisms in 8 genes related to sex steroids and autism symptoms in a general population.

Methods: Subjects used in the study are a subset from The Child and Adolescent Twin Study in Sweden (CATSS, N=1771). The parents of the subjects were asked to fill out the telephone interview Autism–Tics, ADHD, and Other Co morbidities inventory (A-TAC). Factor analyses in CATSS, using A-TAC, have revealed that the three dimensions of autism symptoms were social interaction, communication and flexibility. DNA was extracted from saliva samples using OraGene® DNA self-collection kit. The polymorphisms were genotyped with KASPar® PCR SNP genotyping system (KBiosciences, Herts, UK). The genotyping success rate was >95% and all SNPs were in Hardy-Weinberg equilibrium.

Results: About 14 associations between any of the investigated polymorphisms and autism dimensions were found at $p<0.05$. For two SNPs (in ESR1 and SRD5A2) the associations survivied Bonferroni correction for multiple testing.

Conclusion: In conclusion, polymorphisms in sex steroid related genes known to affect gene expression (the polymorphism in ESR1) and enzymatic activity (the polymorphism in SRD5A2) seem to increase the risk of autism symptoms in boys and girls respectively.

P-06. Pharmacogenetics/Pharmacokinetics

P-06-001 Influence of dopamine D3 receptor gene variation on electroconvulsive therapy response in depression

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Objective: The pathogenesis of major depression has been linked to dysfunction of the dopaminergic system, particularly in the mesocorticolimbic system. In turn, antidepressant medication and electroconvulsive therapy (ECT) have been shown to enhance dopamine D3 receptor binding in the striatum. Thus, in the present study the influence of dopamine D3 receptor gene (DRD3) variation on ECT outcome in treatment-resistant major depression was investigated applying a combined molecular and imaging genetic approach.

Methods: In a sample of 104 (f=71, m=33) Caucasian patients with treatment-resistant major depression, ten representative DRD3 gene variants were analyzed for association with response to electroconvulsive therapy. Additionally, in two independent samples of depressed patients (N=54) ventral striatum responsiveness to happy faces was assessed by means of functional magnetic resonance imaging at 3 Tesla.

Results: We observed significant association of DRD3 rs3732790, rs3773679 and rs9817063 SNPs with response ($p=0.02-0.03$) and remission ($p=0.01$) after electroconvulsive therapy. The rs3732790 T allele conferring a better treatment response was additionally found to be associated with stronger striatal responsiveness to happy facial expressions (sample 1: $p=0.002$; sample 2: $p=0.023$).

Conclusion: In conclusion, the present data suggests DRD3 gene variation to impact electroconvulsive therapy response in major depression. Alleles associated with a more favorable response to ECT were also associated with stronger striatal responsiveness to positive, emotionally rewarding social cues, suggesting a potential neurobiological underpinning for the beneficial effects of these alleles.

P-06-002 Clinical and pharmacogenetic study on psychotropic drug induced weight gain and other metabolic complications in a Swiss psychiatric population

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Objective: The weight gain-related side-effects of psychotropic drugs and their consequences on metabolic complications (hypercholesterolemia, obesity) in a large Swiss cohort of psychiatric patients (n=561) were studied. Pharmacogenetic factors influencing these side-effects were also analyzed.

Methods: A cross-sectional observational study (n=188) was performed in an out-patient psychiatric division with patients having received for more than one year the following drugs: clozapine, olanzapine, quetiapine, risperidone, lithium, amisulpride, aripiprazole and/or valproate. Another longitudinal study consisted of a follow up of patients being prescribed the same drugs for up to one year (n=373).

Results: For the cross-sectional study, the mean age was 41 years (range: 18–69). Weight gain (>=10% of initial weight) following drug treatment was reported in 43% of these patients. A high prevalence of overweight (BMI: 25–30) or obesity (BMI>30) was found in this cohort (63%). For the longitudinal study, the mean age was 48 years (range: 12–96). An increase in the overweight or obesity prevalence was found during treatment in adults (33%, 35%, 46% and 57%, before, after one, 3 and 12 months of treatment, respectively) and in children (21%, 29%, 31% and 50%, respectively).

Conclusion: In conclusion, high prevalence of overweight or obesity was found in an out-patient psychiatric population and confirms drug-induced weight gain complications during long-term treatment. Results on other clinical factors of the metabolic syndrome as well as on analyses of genetic factors linked to obesity and metabolic syndrome will also be shown. This study supports the recently published recommendations of monitoring of metabolic side effects during treatment with atypical antipsychotics and/or mood stabilizers. Moreover, the clinical and genetic weight gain predictors found in the present study could help to highlight patients with special health care management requirements.

P-06-003 Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of SSRI's, seroquel XR augmentation effect

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Objective: It has been recently reported that the short variant of the serotonin transporter (5-HTT) gene-linked functional polymorphic region (5-HTTLPR) influences the antidepressant response to certain selective serotonin reuptake inhibitors. We tested the hypothesis that allelic variation of the 5-HTT promoter could be related to the

antidepressant response to SSRI's and/or augmentation with Seroquel XR which has been suggested as an augmentation therapy for nonresponders.

Methods: 93 patients with major depression were treated with SSRI's or SSRI's augmented with Seroquel XR (300 mg) for 6 weeks. The severity of depressive symptoms was weekly assessed with the Hamilton Rating Scale for Depression. Allelic variation of 5-HTTLPR in each subject was determined using a polymerase chain reaction-based technique.

Results: Both homozygotes for the long variant (l/l) of the 5-HTTLPR and heterozygotes (l/s) showed a better response to SSRI's than homozygotes for the short variant (s/s). In the group treated with SSRI's plus Seroquel XR all the genotypes acted like l/l treated with SSRI alone.

Conclusion: Seroquel XR augmentation may ameliorate the rate of response in 5-HTTLPR short variant subjects, thus reducing the difference in the response rate among the genotype variants. If confirmed, these results may improve patient care by helping the clinician to individualize treatment according to the patient's genetic 5-HTTLPR pattern.

P-06-004 Effect of trialleic polymorphism in 5-ht transporter linked polymorphism on remission after selective serotonin reuptake inhibitor treatment

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Objective: Functional rs25531 polymorphism in 5-HTTLPR (5-HTT linked polymorphism region) effects on the transcriptional activity of 5-HTT (serotonin transporter) gene by changing the binding affinity of transcription factor, AP2 and produces trialleic polymorphism in 5-HTT, known as the primary target of selective serotonin reuptake inhibitors (SSRIs). We hypothesized whether the triallelic polymorphism in 5-HTT gene effects on the outcome after SSRI treatment during 6 weeks in late-life depressed patients.

Methods: Two hundred seventy seven patients with late-life depression enrolled and entered a 6 week clinical trial with an SSRI, with documentation of plasma drug concentrations. Patients were classified from genomic DNA for 5-HTTLPR polymorphism in the 5-HTT gene using primer flanking the promoter region. Then PCR products were determined by visualizing on agarose gel for 5-HTTLPR polymorphism, and also processed the sequencing analysis for rs25531. Remission was defined as the decrease of HAM-D score $>50\%$ and HAM-D <7 score at 6 week after antidepressant treatment. Genotypic comparison between two groups was analyzed using Fisher's exact test in SPSS ver.10.1.

Results: No differences were any characteristics of subjects such as age, gender, age of onset, duration of illness between remission and non-remission group. An association to treatment outcome was found in the triallelic polymorphisms between 106 remission group and 171 non-remission ($p=0.048$, by Fisher's exact test).

Conclusion: Functional trialleic polymorphism of 5-HTT gene affect on the outcome to SSRI treatment in late-onset depressed patients. This is the first reports of the association between rs25531 and remission after SSRI treatment in Asian population. These results underscore the importance of study in evaluation of candidate genetic marker as predictor of outcome to treatment of late-onset depression.

P-06-005 Estimation of unbound drug cerebral exposure using a merging approach of in vitro and in vivo assays

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Objective: It is openly accepted that the unbound cerebral drug concentration is the main pharmacokinetic determinant of CNS activity of neurotherapeutics. A clinically relevant picture of the extent of brain drug delivery can be achieved by evaluation of neuropharmacokinetic parameters: unbound volume of distribution in the brain (Vu, brain), unbound brain-to-plasma concentration ratio (Kp, uu, brain) and unbound extracellular-to-intracellular concentration ratio (Kp, uu, cell). The goal of this study was to estimate unbound CNS exposure of thirty compounds according to the Kp, uu, brain methodological approach established by Hammarlund-Udenaes et al.

Methods: Thirty compounds developed at Janssen R&D covering a wide range of physicochemical properties and various pharmacological CNS targets were selected. Vu, brain was measured using the rat brain slice method. Unbound brain (fu, brain) and plasma (fu, plasma) fractions were determined using equilibrium dialysis. Brain partition coefficient was measured in rats and/or mice.

Results: The compounds were distributed in the brain tissue with Vu,brain 2.9–624 ml·g brain-1, i.e. all compounds showed binding to brain parenchyma (Vu, brain >0.8 ml.g brain-1). Estimated Kp, uu, cell was 0.15–24 with 8 of the compounds indicating the ability to accumulate in the cell (Kp, uu, cell >1). Assessment of Kp, uu, brain showed that BBB equilibration was 0.02–2.65 showing active efflux of 20/30 compounds (Kp, uu, brain <1), dominating passive transport for 4/30 compounds (Kp, uu, brain ≈ 1), and active uptake into the brain of 6/30 compounds (Kp, uu, brain >1). Among the 8 effluxed compounds with Kp, uu, brain <0.1 only two were identified as P-glycoprotein substrates in vitro.

Conclusion: The brain slice method combined with in vivo brain partition coefficient measurement is a reliable tool for the assessment of unbound CNS exposure in early drug discovery stages, increasing the probabilities of success in early drug discovery stages.

P-06-006 Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder

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Objective: We examined the association between serotonin transporter (5HTTLPR) genotype (SS vs. SL vs. LL) and sertraline treatment outcome in posttraumatic stress disorder (PTSD).

Methods: Outpatients ($n=330$) with PTSD underwent 5HTTLPR genotyping. All patients received sertraline (100 mg/day) for 12 weeks. Patients were assessed using the Clinician-Administered PTSD Scale (CAPS) and other instruments. Patients and rater were blind to the genotyping results. The primary outcome was completer sample CAPS improvement at 12 weeks. Response was defined as $>30\%$ improvement in CAPS total score with a CGI-I score of 1 or 2.

Results: The discontinuation rate was 31.5%. Adverse events led to drop out in 18.1%, 15.3%, and 5.9% of SS, SL, and LL patients, respectively ($P=0.038$). Among completers, there were 95, 43, and 88 patients with the SS, SL, and LL genotypes, respectively. At endpoint, CAPS total scores improved by 26% vs. 46%, respectively, in SS and SL vs. LL patients ($P<0.001$); much of this improvement (15% vs. 31% in SS and SL vs. LL patients, respectively; $P<0.001$) was apparent by week 4. The findings were largely similar for the other outcome measures. The response rate was 0%, 0%, and 47.7% in the SS, SL, and LL groups, respectively ($P<0.001$). Limitations: We administered a fixed dose of sertraline. For geopolitical reasons, we planned a completer analysis only.

Conclusion: Relative to the SS and SL 5HTTLPR genotypes, the LL genotype is associated with greater responsiveness of PTSD to sertraline (100 mg/day) and with lower drop out due to adverse events.

P-06-007 Pharmacogenetic analysis in psychiatry: A descriptive study of a clinical experience with 21 patients

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Objective: To perform a pharmogenetic analysis to 21 psychiatric patients, with 39 different psychiatric drugs.

Methods: We have conducted a descriptive study of 21 patients of whom 16 were admitted to the inpatient unit of the Psychiatry Service at the Hospital Ramon y Cajal in Madrid, and 5 in the psychiatric day hospital in the same center, who underwent the test Neurofarmagen (AB-Biotics), that search for genetic biomarkers in the DNA. Molecules were analyzed individually, and in its therapeutic group, (antidepressants, antipsychotics, anticonvulsants, mood stabilizers, and miscellaneous.

Results: Grouping antidepressants, 9.5% did not associate any favorable marker to any antidepressant, 28% for one antidepressant, for two 23.8%, for three 14.3%, for four 19%, and one patient for seven. The clustering of antipsychotics with potentially favorable response markers: 33% for one antipsychotic, 28.6% for two antipsychotics, 14.3% for three antipsychotics, 1 patient for four antipsychotics, 14.3% for six antipsychotics, and one patient for 7 antipsychotics. The Mood Stabilizers group included lithium, and Valproic Acid, the presence of favorable response markers, for lithium occurs in 85.7%. The Anticonvulsant drugs: 76.2% had a marker associated with potentially adverse effects for 8 of the drugs analyzed. The Miscellaneous group includes: Clobazam, Clonazepam, Atomoxetine, Methadone, Naloxone, Naltrexone, Pramipexole, and Pregabalin. There were none positive indicators for any of the group molecules in 28.6%. For one drug in 57.1%, for two drugs in 9.5%, and a patient for four drugs.

Conclusion: We decided to change the treatment in 57.1%. We identified that 81% were receiving suboptimal treatment. We evaluated, how many of our patients had received previous treatment with unfavorable, or insufficient,response 61.9%. Without the test results of Neurofarmagen, this change presumably would not have occurred, and in many of these cases, would have been unlikely to obtain an adequate therapeutic response.

P-06-008 Cytochrome P450 2D6 genetic polymorphisms of ugandans

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Objective: Marked interindividual variation in the cytochrome P450 (CYP) 2D6 activity has been reported. This variation can be explained, at least in part, by genetic polymorphisms causing defective, decreased, or increased enzyme activity. Therefore, genotyping of CYP2D6 might be useful in expecting individual drug response to the substrate drugs (e.g. haloperidol, risperidone, paroxetine, mirtazapine). Therefore, this study investigates the CYP2D6 genetic polymorphisms of Ugandans, which have not been studied so far.

Methods: Healthy black Ugandans (n=99) were recruited from among students at Butabika School of Psychiatric Nursing, Uganda. CYP2D6*2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *17, *35 alleles and gene duplication were determined by LA-PCR or PCR-RFLP methods. The CYP2D6*1 allele was assumed when none of the abovementioned alleles was found. The protocol of this study was approved by the ethics committees of Hirosaki University Graduate School of Medicine and Makerere University Faculty of Medicine.

Results: The allele frequency of CYP2D6*1, *2, *4, *5, *10, *17, *2xN and *4xN was 20.5%, 40%, 2.5%, 9%, 1.5%, 22%, 4% and 0.5%, respectively. None of CYP2D6*3, *6, *7, *8, *11, *12 or *35 was found. The genotype frequency of *1/*1, *1/*2, *1/*5, *1/*17, *2/*2, *2/*4, *2/*5, *2/*10, *2/*17, *4/*17, *5/*5, *5/*10, *5/*17, *17/*17, *2xN/*2, *2xN/*17 and *4xN/*2 was 5%, 16%, 4%, 10%, 18%, 1%, 4%, 1%, 16%, 4%, 3%, 2%, 2%, 5%, 6%, 2% and 1%, respectively. The frequency of the subjects with three, two, one and zero functional alleles were 8%, 71%, 18% and 3%, respectively.

Conclusion: When treating Ugandan patients, and probably other black African and African American patients with CYP2D6 substrate drugs, genotyping of CYP2D6 might be useful in expecting individual drug responses. Among a number of variant alleles reported, determination of the *4, *5, *10, *17 and gene duplication (*2xN) might be important.

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P-06-009 Integrating clinical and biomarker data to predict antidepressant treatment outcomes

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Objective: To report the results of the integration of both clinical and genomic factors designed to predict antidepressant treatment outcomes.

Methods: A pharmacogenomic probe study of 398 treatment adherent subjects with major depression was conducted using citalopram or escitalopram over an eight week period of systematically administered treatment. Blood levels of these medications were monitored to document adherence to the protocol. Treatment outcomes were determined to be remission or response using conventional changes in depression rating scores. Clinically relevant variables included gender, age, age of onset, length of current depressive episode, employment status, educational status, marital status, family history of mood disorder, and history of suicide attempts. Genome-wide association analyses identified a number of candidate SNPs of interest although none of these associations reached the traditional level of genome-wide significance. The SNPs with the highest level of association were subsequently studied to determine their functional significance. Variants in the G protein coupled receptor kinase gene (GRK5) and the riboflavin kinase gene (RFK) were identified to have differential function. Multivariate strategies were used to investigate the contributions of individual genomic variants to achieving better estimates of the probability of treatment outcomes.

Results: The integration of clinical variables associated with a lower probability of achieving a positive antidepressant treatment outcome, such as unemployment and a history of a suicide attempt, and carrying at risk SNPs in GRK5 or RFK were explored. This strategy was anticipated to provide better predictions of the probability of a range of treatment outcomes when compared to either set of variables alone. A variety of methods of combining these predictive variables were employed and their relative strengths and weaknesses were evaluated.

Conclusion: The integration of clinical variables with the presence of biological variants associated with treatment outcomes provides a novel strategy for the future development of more individualized methods of antidepressant treatment.

P-06-010 Case-control association study for 10 genes in patients with schizophrenia: Influence of 5HTR1A variation rs10042486 on schizophrenia and response to antipsychotics

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Objective: The aim of this study is to investigate possible associations between a set of single-nucleotide polymorphisms (SNPs) within 10 genes with Schizophrenia (SCZ) and response to antipsychotics in Korean in-patients treated with antipsychotics.

Methods: Two hundred and twenty-one SCZ in-patients and 170 psychiatrically healthy controls were genotyped for 42 SNPs within ABCB1, ABCB4, TAP2, CLOCK, CPLX1, CPLX2, SYN2, NRG1, 5HTR1A and GPRIN2. Baseline and final clinical measures, including the Positive and Negative Symptoms Scale (PANSS), were recorded.

Results: Rs10042486 within 5HTR1A was associated with both SCZ and clinical improvement on PANSS total scores as well as on PANSS positive and PANSS negative scores. The haplotype analyses focusing on the four, three and two blocks' haplotypes within 5HTR1A confirmed such findings as well. We did not observe any significant association between the remaining genetic variants under investigation in this study and clinical outcomes.

Conclusion: Our preliminary findings suggest that rs10042486 within 5HTR1A promoter region could be associated with SCZ and with clinical improvement on PANSS total, positive and negative scores in Korean patients with SCZ. However, taking into account the several limitations of our study, further research is needed to draw more definitive conclusions.

P-06-011 Cytochrome P450 2D6 polymorphism and its impact on decision-making in psychopharmacotherapy: Finding the right way in an ultrarapid metabolizing patient

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Objective: The cytochrome P450 (CYP) superfamily represents the most important phase I drug metabolizing enzyme system. Genetic mutations play an important role in the activity especially of CYP2D6. Genetic polymorphisms within CYPs affect the metabolism of drugs as substrates for the particular enzymes, resulting in variations in plasma levels of the drugs, differences in drug response, or altered risk for adverse effects.

Methods: We report the case of a 55-year-old woman from Turkey. She neither reached therapeutic drug concentrations of different drugs (metabolized via CYP1A2, CYP2D6, and CYP3A4) ''natively'' nor reached therapeutic plasma levels by pharmacologic blocking of CYP1A2 or CYP2D6.

Results: Genotyping of the patient revealed an ultrarapid metabolizer status for CYP2D6 with identification of the CYP2D6*2XN allele with at least more than 1 copy of *2 variant in chromosome 22. For CYP2C19, the allele CYP2C19*1 was identified, reflecting normal enzyme activity.

Conclusion: Neither daily doses above the approval limit nor the well-directed use of pharmacokinetic blockade of the cytochrome system was able to improve clinical response. Only with a therapeutic regimen that bypasses liver function was partial remission finally achieved. Considering the normal activity of CYP2C19 in our patient, and that very high activity of CYP2D6 can result in increased metabolism of the substances via usually negligible metabolic byways, it is possible that drugs exclusively metabolized by CYP2C19 or other CYP isoenzymes (like agomelatine) or drugs that have no CYP-related metabolism such as milnacipran may exert sufficient antidepressant effects.

P-06-012 Plasma levels and cerebrospinal fluid penetration by venlafaxine in a patient with a non-fatal overdose during a suicide attempt

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Objective: Newer antidepressants seem to be less toxic thank trizylics even in suicidal attempts. Very few is known about the penetration of venlafaxine into the cerebrospinal fluid especially in the case of acute intoxications.

Methods: We report a case of an acute intoxikation with 15 gramms of venlafaxine. Due to unclear unconsciousness a lumbar puncture was done. Therapeutic Drug Monitoring for Venlafaxine in plasma and csf was done two hours after ingestion. Later on genotyping as well for the cytochrome P450 2D6 subsystem was done as well as for the ABCB1 gene expecting influence on CSF levels of venlafaxine due individual characteristics in p-gp activity.

Results: TDM revealed plasma levels for venlafaxine (VEN) and O-desmethylvenlafaxine (DES) of more than 24.000 ng//mL (active moiety). CSF-Levels for VEN and DES were more than 6.400 ng/mL. Genetic testing revealed an extensive metabolizer for 2D6 and showed the constellation of ABCB1 G2677T : GG and C3435T : CT.

Conclusion: This case shows the very high rate of CSF penetration of venlafaxine with the massive amount of 6.400 ng//mL in the CSF. This high rate of CSF penetration requires more understanding of active transporter mechanisms like p-gp clearing venlafaxine into CSF.

P-06-013 Biotransformation of alcohol is increased by systemic administration of methamphetamine

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Objective: Methamphetamine (METH) is a central nervous system stimulant that causes feeling of increased self-confidence, sociability and energy. Drugs of abuse are often used together with alcohol as it is the most frequent combination that leads to visit of Emergency Department in U.S. in 2008. However, the opposite point of view – the influence of METH on alcohol metabolism is still poorly understood. The recent study was focused on the influence of chronic systemic administration of METH on the biotransformation of alcohol in the preclinical study.

Methods: The experiment was carried out on male Wistar albino rats. Animals were randomly divided into two groups per 10 individuals. Animals from the control group were injected intraperitoneally with a single dose of saline. The other group was administered with METH at the dose of 10.0 mg/kg/day. After 10 days the in vivo animal pharmacokinetic experiment was performed. Both groups of animals were treated with alcohol (ethanol) at the dose of 2.0 g/kg in 5% glucose solution administered by intragastric probe. Blood was sampled in the 40th, 120th, 240th and 300th minute after the p.o. administration of alcohol. The alcohol levels were measured using GC method. Measured concentrations were statistically analyzed by ANOVA method with subsequent Fisher post-hoc test.

Results: Taken together our results suggest that repeated pretreatment with MET led to the acceleration of alcohol biotransformation in time points between minutes 0–120 after single acute alcohol administration.

Conclusion: The present preclinical experiment suggests that chronic administration of METH increased biotransformation rate of alcohol in animal model. It is found in humans that with simultaneous administration of alcohol and METH, slowdown of METH p-hydroxylation and N-demethylation occurs. To our best knowledge the effect of METH on the biotransformation of alcohol has not been described in the literature available, either in humans or in animals.

P-06-014 The clinical utility of ABCB1 genotyping in antidepressant treatment

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Objective: The gene product of the ABCB1 gene, the P-glycoprotein (P-gp), functions as a custodian molecule in the blood brain barrier and regulates the access of most antidepressants into the brain. Studies showed that ABCB1 polymorphisms predict the response to antidepressants that are substrates of the P-gp, whereas the response to non-substrates was not influenced by ABCB1 polymorphisms (Uhr et al., 2008). The aim of the present study was to evaluate the clinical utility of ABCB1 genotyping in clinical depression therapy.

Methods: Data came from 57 depressed inpatients from the MARS (Munich-Antidepressant-Response-Signature, www.mars-depression.de) study whose ABCB1 gene test results were implemented into the clinical decision making process. Hamilton scores, remission rates and duration of hospital stay were documented with dosage and kind of antidepressant treatment.

Results: The group where ABCB1 genotyping was conducted had higher remission rates (Chi-square(1) = 3.436, p = 0.032, one-sided test) and lower Hamilton sores (t(22.72) = −1.780, p = 0.044, one-sided test) at the time of discharge from hospital as compared to a group without ABCB1 testing. Among patients with the less favourable genotype, an increase in dosage was associated with a shorter duration of hospital stay (rho(24) = −0.364, p = 0.034, one-sided test) whereas other treatment strategies (e.g., switching to a non-substrate) showed no significant associations with treatment outcome.

Conclusion: Results suggest that the treatment of depression can be optimized by an application of an ABCB1 gene test. Especially patients carrying the unfavourable ABCB1 genotype that impedes brain penetrance seem to benefit from an increase in dosage. The efficacy of specific ABCB1 genotype-dependent treatment strategies is currently tested in a controlled prospective clinical study.

Policy of full disclosure: The presenting author is an employee of HolsboerMaschmeyerNeuroChemie GmbH.

P-06-015 Lymphoblastoid cell lines as models for pharmacogenomics

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Objective: Drug treatment of depression is characterized by a high rate of therapy failure, and so far it is not possible to predict the individual response to a particular antidepressant drug therapy in individual patients. There is therefore an urgent need for biomarkers for depression treatment that could be used to tailor the individual therapy. The aim of this project is to use individual genomic and transcriptomic information for assessing pharmacogenomic variability in cytotoxic effects of antidepressant as a surrogate of treatment response in lymphoblastoid cell lines from patients. Epstein-Barr virus (EBV) immortalized human lymphoblastoid cell lines (LCL) are generated from blood cells of patients who have been treated with antidepressant drugs and characterized for the clinical course of drug response in the context of the Munich Antidepressant Response Signature (MARS) study by the Max Planck Institute of Psychiatry.

Methods: We examined the effects of 3 different antidepressants on cell growth and viability at different concentrations. The experiments were repeated three-times in each cell line.

Results: In 21 cell lines screened so far, between-subject variability was 2fold higher than within-subject variability. The concentration ranges leading to 100% inhibition of cell growth were 110 μM, 30 μM, 600 μM for imipramine, paroxetine, mirtazapine, respectively. We determined the approximate drug concentration that inhibited the cell growth by 50% (IC50: imipramine 80 μM, paroxetine 15 μM, mirtazapine 300 μM) and tested the correlation between gene expression of CHL1, a gene that had been previously described to be associated with paroxetine growth inhibition in cell lines as well as with toxic effects of antidepressant drugs in patients from the Star*D study. Basal gene expression of CHL1 was associated with cell growth at IC50 of imipramine ($r=0.54$, $p=0.017$) and mirtazapine ($r=0.71$, $p=0.002$).

Conclusion: Polymorphisms in CHL1 and other gene regions will be tested as potential prognostic biomarkers in patient cohorts that are characterized for antidepressant therapy outcome.

P-06-016 Relationship of DRD2 TAQ1A polymorphism with perospirone and aripiprazole efficacy in japanese schizophrenia patients – a randomized controlled study

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Objective: To detect the therapeutic efficacy and tolerability effect by DRD2 Taq1A polymorphism on perospirone (PER) and aripiprazole (ARP) in patients with schizophrenia.

Methods: All patients were diagnosed as schizophrenia according to DSM-IV-TR. The patients who gave the informed consent to this 12-week and flexible-dose trial were randomly assigned to PER ($n=51$) or APZ ($n=49$). The clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) before and every 4 weeks after treatment. The efficacy was assessed by changes from baseline for PANSS score. Genotyping for DRD2 Taq1A polymorphism was analyzed. The study was approved by the Ethical Review Board of Kansai Medical University.

Results: The clinical efficacy of PER and ARP were almost the same. In the total sample (PER + ARP sample), the significant difference was not found in the improvement of PANSS total, PANSS positive, negative and general psychopathology subscales scores between Taq1A genotype. In subsequent subsymptom analysis, the patients with A1/A1 allele ($n=17$) group showed significant better reduction overtime for PANSS–Excited Component (EC) scores ($p<0.05$) compared to A2 carrier group ($n=83$). In stratified analysis by each drug, a similar significant difference was found in the ARP group only (A1/A1 allele: $n=9$, A1/A2 and A2/A2 allele: $n=40$, $p<0.05$). When separated by each genotype groups, no significant difference was observed for improvement of PANSS-EC between two drugs in both genotype.

Conclusion: Our findings show that PER and ARP exhibit similar efficacy in the treatment of Japanese schizophrenia patients in both genotype. Our data suggest that PANSS-EC significantly improves in A1 homozygote group as compared with A2 carrier group, especially in ARP treatment group.

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P-06-017 Association study of the neuropeptide Y gene polymorphism and sertraline antidepressant response in major depressive disorder

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Objective: The goal of this study was to elucidate whether the NPY polymorphisms are associated with the Sertraline antidepressant response in subjects with MDD.

Methods: In a sample of fifty-six Chinese Han patients with MDD, 6 single nucleotide polymorphisms (SNPs) in NPY gene with minor allele frequencies >20% were successfully genotyped by ligase detection reaction. MDD patients were evaluated during 12 weeks of sertraline treatment. The severity of depression was assessed with the 17-item Hamilton Depression Rating scale (HAMD-17). The response to 12 weeks' treatment with antidepressant was determined by changes in HAMD-17 score. Genotypes of single SNP associations with treatment response were analysed by Plink software.

Results: At 12 weeks, 71% of patients treatment with sertraline met response (decreased score rate of HAMD-17 > 50%). All SNPs NPY was not significantly associated with antidepressant response.

Conclusion: Response rate was 71% in MDD patients treatment with Sertraline. We did not find that SNPs of NPY gene were associated with sertraline treatment response in this sample.

P-06-018 The metabolism of levomepromazine by human cytochrome P450 isoenzymes

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Objective: Levomepromazine, a phenothiazine neuroleptic, is used in psychiatry as a sedative and in the management of schizophrenia. It is also used in terminal pain control and postoperative analgesia, and in the control of nausea. The contribution of cytochrome P450 isoforms (CYPs) to the metabolism of levomepromazine has not been studied in humans so far. Therefore, the aim of the present screening study was to identify CYPs involved in the 5-sulfoxidation and N-demethylation of levomepromazine in human liver.

Methods: Levomepromazine metabolism was examined in vitro using cDNA-expressed human CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) at a therapeutic concentration of the neuroleptic (10 microM). The amount of levomepromazine and its metabolites formed by CYPs was assayed using HPLC with UV detection.

Results: The preference of CYPs for catalyzing levomepromazine metabolism was as follows (pmol of product/pmol of CYP isoform/min): 3A4 > 1A2 > 2B6 > 2D6 > 2C8 > 2C19 > 2A6 = 2E1 > 2C9 for 5-sulfoxidation and 3A4 > 1A2 > 2C19 > 2B6 > 2C8 > 2D6 > 2C9 > 2A6 = 2E1 for N-demethylation. Considering the obtained results and the relative expression of various CYPs in human liver, it has been estimated that CYP3A4 is the main isoform responsible for levomepromazine 5-sulfoxidation and N-demethylation at a therapeutic concentration of the drug. Moreover, CYP1A2 contributes to a lesser degree to 5-sulfoxidation of the neuroleptic. The role of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 in the catalysis of the reactions studied seems negligible.

Conclusion: The obtained results may have significant implications for the prediction of potential drug-drug interactions involving levomepromazine and CYP3A4. Supported by grant no. 2011/01/B/NZ4/04859 from the National Science Centre, Kraków, Poland and and by statutory funds from the Institute of Pharmacology, PAS, Kraków, Poland.

P-07. Post Traumatic Stress Disorder/ Obsessive-Compulsive Disorders

P-07-001 One trauma three outcomes: Case report

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Objective: Same trauma may affect each exposed person differently. We want to report different representations of the same traumatic event based on several psychometric measures and cortisol levels.

Methods: Three survivors of same severe combat related trauma were assessed with CAPS, Mississippi, HAM-A, HAM-D, IES-R, DES and MMSE. Venous blood was collected to detect serum cortisol levels. The patients performed computerized version of Wisconsin Card Sorting Test (WCST) three hours after venous blood collection.

Results: Patient A had no complaints about the traumatic event. Patient B had sleep disturbance, avoidance and anger. Patient C had same complaints as Mr. B also reported memory impairment. Patient A was diagnosed as PTSD in remission and Patients B and C were diagnosed as PTSD. Patient C had also comorbid TBI. Patients A, B, and C's psychometric measurement scores were as follows; CAPS: 23-129-154; Mississippi: 68-117-118; HAM-A: 4-15-43; HAM-D: 1-19-20; IES-R: 25-85-51; DES: 13-51-41; MMSE: 30-28-28. Serum cortisol levels were detected in normal range (6.87 mcg/dL) for Patient A; and low (0.71 mcg/dL and 0.41 mcg/dL) for Patients B and C respectively. Total categories completed in WCST were; 1.1 and 4 respectively.

Conclusion: We reported three outcomes of the same traumatic event in several psychometric measures and cortisol levels. These findings support HPA axis disturbances levels may be responsible for the PTSD symptomology. However, WCST scores were found irrelevant with cortisol levels and symptom severity. This finding made WCST usefulness arguably in PTSD assessment, even one of the major sites of glucocorticoid receptors is in prefrontal cortex.

P-07-002 Use of donepezil in the treatment of cognitive impairments of severe traumatic brain injury

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Objective: Donepezil is a pro-cholinergic drug that slows down cognitive and functional impairment in patients with Alzheimer's disease. Little research has been carried out to study its effect in other types of neurobehavioral disorders. The purpose of this case was to report the response to donepezil therapy in patients with neurobehavioral disorders due to traumatic causes.

Methods: Two patients with PTSD and comorbid TBI were assessed with psychometric tools (CAPS, HAM-A, HAM-D and MMSE). Treatment progress was evaluated with the same tools.

Results: Donepezil was administered to two patients with mild cognitive impairment due to traumatic brain injury. Following an average time of six months, the effects exerted on the cognitive, functional and behavioral areas were evaluated. Patients showed greatest improvement on 10 mg donepezil. In general, memory, attention, depression, apathy and psychotic traits tended to improve. Aggressiveness and irritability tended to get worse. The functional repercussions of these changes were negligible or inexistent.

Conclusion: Although traumatic brain injury (TBI) frequently results in significant handicap, empirical investigations of pharmacological treatment of the neurobehavioral sequelae of TBI are rare. These cases presents evidence that supports hypotheses of a cholinergic mechanism underlying some neurobehavioral sequelae of TBI, as well as a cases of the preliminary evidence supporting the efficacy of cholinergic agents in TBI. Despite numerous methodological limitations, preliminary evidence exists for the efficacy of cholinergic agents in ameliorating attention and memory deficits following TBI. Treatment with donepezil improved cognition and conduct in patients with neurobehavioral disorders due to post-traumatic causes. These results will have to be confirmed and expanded by means of controlled studies, and research must continue into the characteristics of responding patients and the relevance of their responses.

P-07-003 Cytokine enviroment in PTSD patients of armenian nationality

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Objective: Post-traumatic stress disorder (PTSD) is a serious and debilitating condition triggered by terrifying events. It is proposed that the inflammatory mediators may have a significant input in PTSD-associated neuronal and behavioral changes that resemble some key features of this disease. Our aim was to evaluate the relationship between the levels of the proinflammatory and chemotactic cytokines IL-1β, IL-6, IL-8, TNF-a, MCP-1 in PTSD patients.

Methods: Patients with chronic PTSD (DSM-IV; mean age $M \pm E42 \pm 4,6$), and nontraumatized healthy controls (mean age 39 ± 3.1) were examined. Blood levels of cytokines were determined by ELISA.

Results: Compared to healthy controls, patients with chronic PTSD had significantly higher levels of IL-1β, IL-6, IL-8, TNF-a and MCP-1 ($p < 0.05$). In addition, a significant correlation has been observed between the blood levels of: IL-6 and IL-1β; IL-8 and IL-1β; IL-1β and MCP-1.

Conclusion: PTSD is associated with altered cytokine environment. Inflammatory processes are among pathological processes, which play a decisive role in PTSD progression.

P-07-004 Measuring symptom exaggeration in PTSD using the MMPI-2 and the PAI symptom validity scales

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Objective: We investigated whether PTSD patients have a higher tendency of exaggerating the extent of their psychological symptoms compared to other psychiatric patients.

Methods: Medical records of patients, who had received psychiatric treatment at 4 University hospitals in Korea between January 2009 and December 2010, were retrospectively reviewed. We compared a group of 37 patients diagnosed with PTSD, and another group of 41 patients diagnosed with Neurotic, stress-related and somatoform disorders according to the ICD-10. To compare the extent of malingering in the two groups, we compared the validity scales of MMPI-2 and PAI. We detected the number of participants feigning their responses from both groups using various cutoff scores of the validity indicators.

Results: The PTSD group showed significantly higher scores on F($p = 0.001$), F(B)($p = 0.000$), F(P)($p = 0.030$), F-K($p = 0.003$) scale of the MMPI-2 compared to the Other psychiatric patients group. The PTSD group had a significantly higher NIM score ($p = 0.001$) but a lower PIM score ($p = 0.020$) of the PAI compared to the Other psychiatric patients group. Using the cutoff scores, the PTSD group showed significantly more participants with feigned responding compared to the Other psychiatric patients group: Fb $\geqslant 75$ ($p = 0.010$), F-K $\geqslant 1$ ($p = 0.005$), F-K $\geqslant 10$ ($p = 0.011$) from the MMPI-2, and NIM $\geqslant 80$ ($p = 0.001$) from the PAI.

Conclusion: These results suggest that PTSD patients have a tendency of exaggerating symptoms by overreporting their condition on standardized personality assessments such as the MMPI-2 or PAI, compared to patients diagnosed with other psychiatric disorders. Additional research is required to determine the factors influencing symptom exaggeration in PTSD.

P-07-005 Effects of stress and corticosterone on glutamate release: Modification of the readily releasable pool of vesicles in prefrontal and frontal cortex

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Objective: Stress and its mediators cause structural changes and in turn lasting consequences in the brain, which may be associated with triggering of neuropsychatric disorders. Several studies suggest a critical role of glutamatergic neurotransmission in the stress response. In previous studies, we demonstrated that Footshock

(FS)-stress induces a marked increase of depolarization-evoked glutamate release from prefrontal and frontal cortex (P/FC) synaptosomes, via glucocorticoid receptor activation and SNARE complexes accumulation in synaptic membranes. The increase of glutamate release was prevented by chronic antidepressants.

Methods: In order to investigate the presynaptic mechanism whereby acute stress enhances glutamate release in P/FC we performed the following studies: 1. Measurement of release of endogenous glutamate evoked by depolarization or hypertonic sucrose (which mobilizes exclusively the pool of synaptic vesicles ready for release, RRP) from isolated superfused synaptosomes of P/FC from FS-stressed rats. Measurement of depolarization-evoked or hypertonic sucrose-evoked release of glutamate from control synaptosomes incubated in vitro with corticosterone. 2. Analysis of RRP in synaptosomes by Total Internal Reflection Fluorescence Microscopy, which allows visualization of the synaptic region within about 100 nm from the membrane. Synaptic vesicles were labeled with FM1–43, and synaptosomes were incubated in vitro with corticosterone, ± selective inhibitors of glucocorticoid or mineralocorticoid receptors. 3. Patch-clamp recordings in slices of prefrontal cortex from control PFC slices incubated with corticosterone (± selective inhibitors of glucocorticoid or mineralocorticoid receptors).

Results: The results obtained suggest that the increase of the RRP size induced by acute stress is promoted by a local action of corticosterone on (presumably membrane-located) synaptic glucocorticoid receptors. However, in vitro incubation with corticosterone blocks the depolarization-dependent glutamate release, suggesting that additional mediators released by postsynaptic neuron and/or glia, are necessary to trigger release.

Conclusion: The combined results of this study give more insight into the basic mechanisms whereby behavioural stress affects excitatory transmission in the forebrain.

P-07-006 Valproate use in post traumatic stress disorder: Report of 3 cases and literature review

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Objective: Our aim is to review the possible implied mechanisms and appraise the evidence for the use of the anticonvulsivant Valproate for the treatment of Posttraumatic Stress Disorder.

Methods: Case Series and Literature Review.

Results: Three cases of non-combat related posttraumatic stress disorder refractory to conventional treatment are treated with Valproate as an adjunt medication. These patients showed adecuate response by meassuring outcomes with the Post Traumatic Diagnostic Scale (Spanish Version) and the Beck Inventory Depression Scale (Spanish Version).

Conclusion: Anticonvulsivants have been used in clinical practice for the treatment of Posttraumatic Stress Disorder (PTSD). Several biologic models have been discussed as contributing significantly to PTSD symptoms with a focus on alterations in noradrenergic and serotonergic systems and in the endocrine hypothalamus-pituitary-adrenocortical axis. In addition, kindling has been proposed by several investigators to be involved in the pathophysiology of PTSD. This hypothesis suggests that anticonvulsants may be promising in the treatment of PTSD, since they are thought to exhibit their efficacy in part through an antikindling activity. Valproate is an anticonvulsant with antikindling activity and enhances the inhibitory effect of the neurotransmitter g-aminobutyric. A systematic investigation of their effects in the context of the treatment of PTSD is currently lacking from the literature.

P-07-007 DRD2 receptor polymorphism carries a higher risk for PTSD developpment

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Objective: Dopaminergic neurotransmission is implicated in stress responses. The dopamine D2 receptor gene (DRD2) has been studied by the authors to assess its possible role as a predictor of those who are at a higher risk to develop PTSD after major psychological trauma.

Methods: Over one year period 75 children and adolescents 6–18 yrs of age who had been exposed to moderate to severe burns were recruited from the burn unit at the Alexandria University Hospital for the study. Patients and their family were interviewed within the first 10 days of exposure. After signing a written consent form a 2 ml blood sample was obtained for genetic studies of the TaqA1/A2 polymorphism site of the DRD2 gene. Patients were re-evaluated three and six months later for assessment of PTSD.

Results: Among the 75 children recruited in the study, 26 died due to their burn injury, 19 dropped out as parents refused follow up and 30 continued the study follow up visits. Fourteen carried the A1A2 genotype. Of these 11 (78.6%) developed PTSD. Sixteen carried the A2A2 genotype. Of these only one child (6.3%) developed PTSD. The results were significant at $p < 0.001$ with a relative risk 12.5.

Conclusion: Following exposure to severe stress, the presence of the Taq A1 allele of the DRD2 gene results in a significant increase in the risk of developing PTSD.

P-07-008 Facing violence and burnout in health services: Intervenction and prevention program

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Objective: The aim of this work is to present the experience of a group psychological intervention program conducted with professionals from emergency health services.

Methods: Three intervention groups were made (N = 39) with doctors, nurses, guards/drivers, administrative assistants, social workers and physiotherapists from emergency health services in the province of Granada. The program had eight weekly sessions of three hours each one, structured into three modules: 1) prevention and management of violent situations, 2) coping of burnout, 3) assertiveness training. An active-participatory methodology was followed using modeling, role-playing and homework. After the program, a questionnaire for evaluating the program was given.

Results: 87.5% of professionals evaluated the program as very useful for their professional activity, 65.6% reported a high level of learning and 90,6% showed high levels of satisfaction.

Conclusion: The professionals valued the experience as very useful and satisfactory, and considered very important to have well structured coping skill training programs available to professionals working in health services, in order to help them to face violence in working environment and burnout.

P-07-010 Brain-derived neuroptrophic factor, posttraumatic stress disorder and memory

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Objective: Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin that helps to support the survival and encourage the growth and differentiation of neurons in both the central and peripheral nervous systems. BDNF has been associated with mood disorders and trauma exposure, but there is less information regarding its association with Posttraumatic Stress Disorder (PTSD). The first aim of this paper was thus, to compare BDNF levels in trauma-exposed adults with and without (i) Acute Stress Disorder (ASD), (ii) PTSD, or (iii) depression. As BDNF levels have also been associated with memory, the second aim of this paper was to correlate BDNF levels with memory.

Methods: We collected blood samples from 37 participants who had been involved in a motor vehicle accident in the previous 2 weeks (59.5% male; mean age: 33.35 ± 11.54 years). We used clinical and self report measures to assess for ASD, PTSD and depression, both at the time of blood collection and 3 months later. Neuropsychological measures were used to assess for disturbances in auditory, visual and working memory.

Results: We did not find any significant differences in BDNF levels between those with and without ASD, PTSD or depression at the baseline visit, as well as in those with PTSD or depression at the 3 month follow-up. Additionally, BDNF levels and memory did not correlate. We did, however, find that those with PTSD 3 months post-trauma had higher levels of depression than those without PTSD.

Conclusion: Our findings suggest that in our sample, alterations in BDNF level could be due to trauma exposure, rather than to a psychiatric diagnosis. These findings are, however, limited by the small sample size.

P-07-011 Effects of recent earthquake on the prescribing pattern of antidepressant and antipsychotic drugs in the southern Iitalian province of L'Aquila

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Objective: To assess the effects of earthquake that occurred on April 6, 2009 on the use of antidepressant and antipsychotic drugs in the province of L'Aquila.

Methods: We conducted a cross-sectional, drug utilization study. Data sources of this study were the dispensings database of the Southern Italian Local Health Unit (LHU) of L'Aquila and Caserta. All the antidepressant and antipsychotic drugs (except for prescriptions in dementia patients) are reimbursed by Italian National Health System and therefore are retrieved in such a database. We measured the monthly prevalence of use of these drugs one year prior and after the date of earthquake in L'Aquila LHU. We used as control the LHU of Caserta, as this area was not affected by the earthquake. All the analyses were stratified by age groups, gender and drug classes (Selective Serotonin Reuptake Inhibitors, Tryciclics, and other ADs; atypical and typical antipsychotics).

Results: Overall, the monthly prevalence of use of ADs and APs was higher in L'Aquila than Caserta. With respect to trend over time, we observed an increase in the use of antidepressants (mostly N06AA) and antipsychotics in the first two months after the earthquake in L'Aquila but not in Caserta. This increase was almost two-fold higher in women older than 75 years. The use of ADs and APs in general tended to decrease in the summer period in Caserta, while such a trend was not observed in L'Aquila after the earthquake. After the first two months from the earthquake, the use of ADs and APs is stabilized at the pre-earthquake levels in L'Aquila.

Conclusion: The earthquake determined a very short term increase in the use of antidepressants and antipsychotics mostly in older women of L'Aquila. Long term evaluations of the effects of the earthquake on mental health in L'Aquila are needed.

P-07-012 Development of somatoform disorders in individuals found mentally sane during the outpatient forensic psychiatric examination

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Objective: The objective of research is to study the types of somatoform disorders in individuals that were found mentally sane during outpatient forensic psychiatric examination. Material and methods of research. Thirty mentally sane persons (25 males and 5 females aged between 16 and 55) against whom the criminal cases were opened underwent outpatient forensic psychiatric examination.

Methods: The research employed comparative, clinical-psychopathological and statistical methods in combination with the analysis of data on somatoneurologic condition as well as instrument-psychological research (drawing tests, Rosenzveig tests, MMPI, incomplete sentence test, Pictogram, Ebbinghaus test, and Wechsler subtest).

Results: The research revealed 15 persons who during the examination showed emotional-volitional instability and found 15 patients to be mentally sane. At the same time 9 of 15 mentally sane patients exhibited somatoform disorder of vegetative nervous system, 4 patients exhibited other somatoform disorders and 2 patients – a stable somatoform pain disorder. The 12 of 15 patients with the features of emotional-volitional instability exhibited comorbid somatoform dysfunction of vegetative nervous system and 3 persons – other comorbid somatoform disorders.

Conclusion: Based on results of the research we can conclude that the individuals showing emotional-volitional instability exhibited comorbid somatoform dysfunction of vegetative nervous system more often, while mentally sane individuals according to clinical findings had a stable somatoform pain disorder along with somatoform dysfunction of vegetative nervous system.

P-07-013 Impact of mental disorders on commission of criminally punishable acts by teenagers

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Objective: The research aims to study the impact of the revealed mental disorders (or their absence) in teenagers on commission of homicide or infliction of grave harm to health, causing manslaughter by negligence. 32 reports of the Commission of the forensic psychiatric examination over the past half a year were analyzed. The forensic psychiatric examination was carried out on an outpatient basis. The analysis revealed that out of 32 examined teenagers, 30 were males and 2 – females at the age of 15–18.

Methods: The statistical method along with the analysis of data of forensic psychological-psychiatric and forensic psychiatric examinations was applied.

Results: The research revealed that 14 individuals were held criminally liable under article 105 of Criminal Code (CC) of the Russian Federation (RF) (homicide), of them 4 showed light mental retardation, 2 – organic personality disorder against the background of brain injuries and epilepsy, 1 – socialized conduct disorder, 7 individuals turned out to be mentally sane; 18 individuals were held criminally liable under article 111 part 4 of CC of RF (intentional infliction of grave harm to health, causing manslaughter by negligence) including 4 teenagers with light mental retardation, 3 – with organic personality disorder against the background of brain injuries and epilepsy, 2 individuals exhibited light cognitive impairment, 1 – emotionally unstable personality disorder, 1 person showed opioid addiction, and 7 teenagers appeared to be mentally sane.

Conclusion: Thus, the research revealed that according to the reports of the outpatient forensic psychiatric examination of teenagers aged between 15 and 18 such criminally punishable acts as homicide and infliction of grave harm to health, causing manslaughter by negligence, were most often committed by teenagers without psychopathology and by those exhibiting light mental retardation.

P-07-014 Obsessive comuplsive behaviour following traumatic brain injury

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Objective: To describe the psychopathology and treatment outcomes of a patient who exhibited obsessive–compulsive behavior following a frontotemporal traumatic brain injury.

Methods: Neuropsychological cognitive and personality assessments were conducted. Descriptive psychopathology and treatment outcome elucidated.

Results: The patient displayed marked obsessive–compulsive behavior along with cognitive impairment and personality changes. The psychopathology of the obsessive compulsive behavior differed from the classical DSM description and the treatment outcome using different treatment modalities was poor.

Conclusion: The patient presented in this report had both fronto temporal lobe dysfunction signs and obsessive compulsive behavior. The etiological significance of head injury and frontal lobe involvement in obsessive–compulsive disorder is discussed in the context of the clinical and therapeutic outcomes.

P-07-015 Cognitive-behavioral group therapy with and without pharmacotherapy for obsessive-compulsive disorder

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Objective: Although cognitive-behavioral group therapy (CBGT) and pharmacotherapy have proven effective in reducing symptoms of obsessive-compulsive disorder (OCD), there is no consensus about which of these forms of treatment is more effective. The aim of this study is to compare the effectiveness of combined therapy (CBGT + pharmacotherapy) with psycotherapy alone (CBGT).

Methods: Thirty-six patients with an OCD diagnosis, according to DSM-IV criteria were recruited into the study. 20 of them randomly assigned to antidepressant pharmacotherapy plus Cognitive behavioral group therapy and 16 of them were received only CBGT. The CBGT therapists were blind to patients' whether taking

pharmacotherapy or not. CBGT process consists of 14 sessions. Efficacy of treatments was rated according to the reduction in scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS), Beck-Anxiety Inventory (BAI), Beck-Depression Inventory (BDI) and the Clinical Global Impression Scale (CGI). The trial was performed in four successive periods from August 2011 to January 2012.

Results: According to end-point analysis both groups did well in therapy. Patients treated with only CBGT obtained a mean YBOCS reduction of symptoms of 45%, while those treated with antidepressant plus CBGT treatment have 53% reduction. The reduction rates were found statistically significant according to initial scores (Paired t-test; CBGT only group ($z = -2.81$, $p = 0.002$), combined therapy group ($z = -3.07$, $p = 0.001$)). There was no significant difference between these two groups at the end of CBGT (Mann-Whitney $U = 50.50$, $p = 0.54$). Also there was significantly reduction for BAI, BDI and CGI scores.

Conclusion: Cognitive-behavioral group therapy has shown to be effective in reducing OCD symptoms regardless of antidepressant treatment. We suppose that CBGT could be an effective treatment choice for OCD.

P-07-016 The use of aripiprazole in serotonin reuptake inhibitor resistant obsessive-compulsive disorder: A naturalistic, retrospective case series of 24 patients

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Objective: We conducted a naturalistic, retrospective chart review to evaluate the effectiveness and safety of aripiprazole augmentation- or mono-therapy for the treatment of resistant obsessive-compulsive disorder (OCD).

Methods: A total of 24 patients diagnosed with OCD according to DSM-IV-TR criteria and having a history of resistant to treatment with serotonin reuptake inhibitors (SRIs) were included in the study. Aripiprazole was started at 3 mg/day and increased to 24 mg/day at the clinician's discretion. The patients were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Clinical Global Impressions-Improvement (CGI-I) Scale, and the Global Assessment of Functioning (GAF) Scale at baseline and at the final visit of aripiprazole treatment. Safety assessments included evaluation of vital signs, weight, and treatment-emergent side effects. Follow-up period for a case was one year and a case who discontinued the drug for less than one year was also counted. Data were collected from January 2007 to December 2010.

Results: The mean daily dosage of aripiprazole at endpoint was 12.0 ± 7.2 mg/day. The mean total Y-BOCS score decreased from 27.2 at baseline to 18.0 at endpoint ($P < 0.0001$) and the mean GAF score increased from 47.1 at baseline to 60.6 at endpoint ($P < 0.0001$). The mean CGI-I score was 2.4 points (much ~ minimally improved). The observed side effects included weight gain (2 patients), akathisia (2 patients), mild sedation (2 patients) and insomnia (1 patient).

Conclusion: These results suggest that aripiprazole augmentation- or mono-therapy can modestly improve the outcome for the treatment of resistant OCD. Larger, randomized, double-blind studies are necessary to establish the efficacy and safety.

P-07-017 Clinical predictors of drug response in patients with obsessive-compulsive disorder

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Objective: The aim of this study was to evaluate which clinical variables might influence the antiobsessional response to proserotonergic drugs in a sample of patients with obsessive-compulsive disorder (OCD).

Methods: Two hundred forthy-nine patients with DSM-IV OCD underwent mean 13-month treatment with selective serotonin reuptake inhibitors. According to treatment response, defined as a reduction of the Yale-Brown Obsessive Compulsive Scale total score > 35% and CGI 1 or 2, patients were divided into two groups.

Results: One hundred fourteen patients responded to treatment and one hundred thirty five patients did not. Responders had a significant high long duration of treatment, short duration of pre-treatment medication and higher frequency of drug naïve cases and lower baseline Y-BOCS scores.

Conclusion: The pre-treatment factors including pre-treatment period, drug naïve or not and baseline OCD symptoms and the factor of duration of treatment may influence drug treatment response in OCD patients.

P-07-018 Relationships between plasma fluvoxamine levels and OCD symptoms in adult patients

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Objective: Different randomized, double-blind, controlled studies confirm the efficacy of fluvoxamine in obsessive-compulsive disorder (OCD). An experimentally determined relationship between plasma levels and the pharmacological effect of fluvoxamine may represent an useful method in monitoring clinical response and in the identification of predictors of response in order to maximize the therapeutic effectiveness, but the information on this topic is limited. Therefore, in this study we explored the possible relationship between plasma fluvoxamine levels and clinical features in OCD patients treated with this drug for at least 6 months.

Methods: Twenty OCD outpatients of both sexes taking fluvoxamine were included in the study. The symptoms severity was assessed by means of the Y-BOCS. The fluvoxamine plasma levels were measured by HPLC analysis. All evaluations were performed after 4 weeks (t1) and six months (2) of fluvoxamine intake.

Results: The plasma levels of fluvoxamine remained stable at the two assessment times, with no sex-related differences. Sixteen (80%) patients showed a significant improvement, but men's compulsions ameliorated more than those of women. Significant and positive correlations were detected between fluvoxamine plasma levels at t1 and t2 and the difference (delta) of the Y-BOCS total score at t1 and t2. Another significant, albeit negative, correlation was measured between the delta of drug concentrations and that of the compulsion subscale score.

Conclusion: These findings underline the potential importance of evaluating fluvoxamine plasma levels in OCD and their relationships with specific symptoms, as well as the influence of gender on drug response.

P-07-019 Neuroanatomical correlates of naturalistic long-term outcome of OCD treated with selective serotonin reuptake inhibitors

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Objective: The structural imaging studies have reported the involvement of areas in the fronto-subcortical regions as neurobiological substrates in OCD. We hypothesized that baseline volumes of orbitofrontal cortex, cingulate cortex, dorsolateral prefrontal cortex, caudate nucleus and globus pallidus would predict improvement in obsessional symptoms in long-term. With this hypothesis we aimed at elucidating the structural brain predictors of naturalistic outcome in drug naïve adult subjects with obsessive-compulsive disorder (OCD).

Methods: We examined the brain volumes using optimized Voxel Based Morphometry (VBM) paradigm and examined their relationship with 2 to 5 year naturalistic outcome in 29 drug naïve OCD patients. Statistical parametric maps were constructed to examine correlations between regional gray matter volume in the apriori hypothesized regions and percentage reduction in YBOCS scores at the endpoint.

Results: VBM analysis revealed significant positive correlation between the percentage of reduction on Y-BOCS total score and left anterior cingulate gyrus volume ($X = -3$, $Y = 15$, $Z = 22$, $T = 3.31$, uncorrected 'p' = 0.001; FWE-corrected 'p' [SVC] = 0.014).

Conclusion: ACC is a key region implicated in OCD and as we hypothesized, higher ACC volume at the baseline correlated with better clinical outcome. To the best of our knowledge, this is the first study to report of imaging predictors of long-term outcome of OCD.

Apriori delineation of such biomarkers can potentially help in ascertaining the prognosis and treatment outcome.

P-07-020 Antiserotonergic second generation antipsychotics are associated with obsessive-compulsive symptoms in schizophrenic patients

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Objective: Epidemiological investigations show that up to 30% of schizophrenic patients suffer from obsessive compulsive symptoms (OCS). The comorbidity is associated with negative impact on the general prognosis. It has been proposed that antiserotonergic second generation antipsychotics (SGA) might induce OCS, but investigations of large samples integrating psychopathology, neuropsychology and psychopharmacology are missing.

Methods: We stratified 70 patients with schizophrenia according to their mode of antipsychotic treatment: clozapine and olanzapine (group I) compared with aripiprazole and amisulpride (group II). The groups were matched according to age, sex, educational levels and severity of the psychotic disorder (PANSS: Positive and Negative Syndrome Scale). As primary endpoint, we evaluated the OCS-severity (YBOCS: Yale-Brown-Obsessive-Compulsive Scale) in a cross-sectional evaluation.

Results: OCS was significantly more prevalent and severe in group I, in which OCS severity correlated with dosage of clozapine and duration of treatment. Pronounced cognitive deficits in group I were found in visuo-spatial perception and visual memory (WAIS-R block design, Rey-Osterrieth Complex Figure Test), impulse inhibition (Go/Nogo-Test), higher perseveration scores (Wisconsin Card Sorting Test) and reduced set-shift abilities (Trail Making Test B, Set-shift Task). These cognitive domains also correlated with OCS severity.

Conclusion: OCS in schizophrenia is associated with antiserotonergic SGA treatment, but longitudinal studies have to provide further evidence for a causal interaction. Before starting treatment with antiserotonergic SGAs such as clozapine, specific neurocognitive domains should be evaluated, that might indicate an increased risk for second-onset OCS and further allow the early detection of OCS secondary to antipsychotic treatment in schizophrenia.

Tuesday, 5 June 2012

P-08. Schizophrenia

P-08-001 D-serine production is modulated by DISC1 and serine racemase interaction in astrocytes

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Objective: Disrupted-In-Schizophrenia-1 (DISC1) is a strong candidate gene for psychiatric disorders. The majority of studies have focused on neuronal functions of DISC1. Recent reports have identified expression of DISC1 in glial cells, including astrocytes. Our study sought to elucidate roles for DISC1 in astrocytes as abnormal astrocytic functions may contribute to psychiatric disease.

Methods: To study the DISC1 functions in astrocytes, we used a mouse model of GFAP promoter-driven selective and inducible expression of mutant DISC1 in astrocytes to impact endogenous DISC1 in a dominant-negative manner. We evaluated the effects of mutant DISC1 on glutamate uptake, d-serine production, and expression of the major astrocytic markers in primary astrocytes and the brain of transgenic mice at different time points during postnatal development. In addition, GFAP-DISC1 transgenic mice were assessed in a series of behavioral tests relevant to aspects of schizophrenia.

Results: Astrocytic expression of mutant DISC1 did not produce gross developmental abnormalities in mice but was associated with elevated anxiety, mild cognitive deficits and exacerbated responses to a NMDA antagonist, MK-801. Notably, the effects of MK-801 were ameliorated by D-serine treatments predominantly in mutant DISC1 mice. Mutant DISC1 had no significant effects on glutamate uptake, levels of GFAP, GLT-1 or connexins in primary astrocytes or the brain tissue. In contrast, we found significantly decreased expression of endogenous mouse DISC1 and serine racemase (SR), leading to diminished levels of D-serine in primary astrocytes derived from mutant DISC1 newborn mice. Our biochemical experiments suggest that DISC1 may partner with SR to modulate production of D-serine.

Conclusion: Our results suggest that DISC1 may play an important role in modulating production of D-serine and resultant NMDA neurotransmission relevant to the pathophysiology of schizophrenia.

P-08-002 Predictors of psychiatric hospitalization during 6 months of maintenance treatment with olanzapine long acting injection

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Objective: This study aimed to identify the predictors of psychiatric hospitalization in the maintenance treatment of schizophrenia patients with olanzapine long acting injection (olanzapine_LAI) and assess four hospitalization parameters: the prevalence of hospitalization, its incidence rate, duration, and the time to first hospitalization. This analysis also compared olanzapine_LAI with pseudo-placebo (a very low dose of olanzapine_LAI) and with oral olanzapine on the hospitalization parameters.

Methods: This was a post hoc exploratory analysis of a randomized double-blind study comparing the safety and efficacy of olanzapine_LAI (pooled active depot groups: 405 mg/4 weeks, 300 mg/2weeks, 150 mgs/2 weeks) with oral olanzapine and olanzapine_LAI 45 mg/4 weeks (pseudo-placebo) during 6 months maintenance treatment of clinically stable outpatients with schizophrenia (n = 1064). Within the olanzapine_LAI group, patients with and without a hospitalization were compared on baseline characteristics. A logistic regression model was used to identify the best predictors of hospitalization. Comparisons between olanzapine_LAI, pseudo-placebo, and oral olanzapine on hospitalization parameters employed Chi-square, Wilcoxon-Mann and Whitney tests, and the Kaplan Meier estimator.

Results: Hospitalization was best predicted by suicide threats at baseline and by prior hospitalization. Compared with pseudo-placebo, olanzapine_LAI was associated with a significantly lower hospitalization rate (5.2% vs. 11.1%, $p = 0.009$), lower mean number of hospitalizations (0.07 vs. 0.15, $p = 0.009$), shorter mean hospitalized duration (1.50 days vs. 2.85 days, $p = 0.008$) and similar median time to first hospitalization among hospitalized patients (35 vs. 60 days, $p = 0.476$). Olanzapine_LAI did not significantly differ from oral olanzapine on studied hospitalization parameters.

Conclusion: During the 6-month maintenance treatment of schizophrenia patients with olanzapine_LAI, psychiatric hospitalization was best predicted by patients' suicide threats at baseline and prior psychiatric hospitalization. Olanzapine_LAI was associated with a significantly lower prevalence and incidence of psychiatric hospitalization and shorter hospitalized duration compared to pseudo-placebo therapy. Olanzapine_LAI did not significantly differ on these hospitalization parameters from oral olanzapine.

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P-08-003 Long-term safety and tolerability of once-monthly aripiprazole intramuscular depot for maintenance treatment in schizophrenia

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Objective: To understand the safety and tolerability of aripiprazole intramuscular depot (ARI-IMD) in maintenance treatment of schizophrenia.

Methods: Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) over 4–6-weeks (oral conversion phase; P1followed by 4–12-week oral aripiprazole (oral aripiprazole stabilization phase; P2). Subjects meeting stability criteria (4 weeks) entered an ARI-IMD stabilization (400 mg/injection) with co-administration of oral aripiprazole the first 2 weeks (P3). Subjects meeting stability criteria (12 weeks) were randomized (2:1) to ARI-IMD or placebo (52-week, P4). Primary endpoint was time to impending relapse. Safety was assessed across phases by time of first-onset of AEs, changes in movement disorder rating scales and changes in weight/metabolic parameters.

Results: The study stopped early because efficacy was demonstrated by pre-planned interim analysis (after 64 relapses). ARI-IMD was well tolerated with similar rates of AEs across phases. Discontinuations due to TEAEs: 3.8% (P1); 3.0% (P2); 4.9% (P3); 7.1% (P4). Most AEs were mild/moderate. Severe AEs were $<5.0\%$, all phases. AEs $>5\%$ were: insomnia (all phases), headache (P1, P3 and P4), anxiety, akathisia, weight increase (P3, P4), injection site pain (P3) and tremor (P4). Headache, somnolence, nausea had a peak first-onset within 4 weeks of study initiation. EPS-related events were: P4: ARI-IMD14.9% vs. placebo 9.7%. Mean baseline weight ranged 80.4–84.8 kg (all phases). Mean baseline weight changes: -0.2 kg (P1); 0.1 kg (P2); -0.2 kg (P3); -0.2 kg (ARI-IM-depot, P4), -0.4 kg (placebo, P4). No unusual shifts in laboratory values or fasting metabolic parameters (all phases). Normal-to-high shifts in metabolic values were low in P4.

Conclusion: No unexpected AEs emerged with ARI-IM-depot. Similar rates of AEs in P1 and P2 suggest that the switch strategy was useful. ARI-IMD offers a new option with a different risk–benefit profile than currently available treatments.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Pamela Perry, Na Jin, Brian Johnson, Robert A Forbes, Robert D McQuade, William H Carson and Ross Baker are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

P-08-004 Effects of microinjections of MK-801 and NMDA into the inferior colliculus on prepulse inhibition of the acoustic startle reflex in rat

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Objective: Prepulse inhibition (PPI) is the reduction in the startle response caused by a low intensity non-startling stimulus (prepulse) which is presented shortly before the startle stimulus (pulse), and is an operational measure of sensorimotor gating. PPI may reflect the functioning of a pre attention filtering system protecting the brain from sensory overload. Deficits in PPI have been observed in several neuropsychiatric disorders, including schizophrenia and can be induced in rats by systemic administration of N-methyl-D-aspartate (NMDA) glutamatergic antagonist. The inferior colliculus (IC) is a critical part of the auditory pathway mediating acoustic PPI. The activation of the IC by the acoustic prepulse reduces startle magnitude. The aim of this study was to investigate the role of glutamatergic transmission of the IC on the development of acoustic PPI.

Methods: Male Wistar rats were unilaterally implanted with stainless steel guide cannula in the IC. Seven days after the surgery, the animals received unilateral intracollicular microinjections of the glutamate NMDA receptor antagonist MK-801 (30 mmol/0.5 μl); of the NMDA receptor agonist N-methyl-D-aspartate (NMDA, 30 nmol/0.5 μl) or of physiological saline (0.5 μl). Five minutes later, the animals were tested to PPI. They were exposed to 4 types of stimuli: a startle pulse [P-alone: a 120 dB 40-ms broad band burst] and 3 types of prepulses [68, 71 or 77 dB 20-ms broad band burst] presented 100 ms prior to the startle pulse. During test session, 50 trials (12 P-alone, 8 NOSTIM, and 10 of each prepulse trial types) were presented in pseudorandom order. A variable inter-trial interval averaged 15 s.

Results: The results showed that microinjections of MK-801 into the IC disrupted PPI while microinjections of NMDA into this structure did not alter PPI.

Conclusion: We concluded that glutamatergic neurotransmission of the IC can be involved in the mediation of PPI in rodents.

P-08-005 Normobaric hyperoxia treatment of schizophrenia

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Objective: Several studies of normobaric hyperoxia in neurological conditions have found positive results. The impaired energy metabolism due to mitochondrial dysfunction and frontal lobe hypofunction in schizophrenia might be improved by increasing O2 supply to the brain. Normobaric hyperoxia may be a potential treatment for schizophrenia.

Methods: Participants in this study, outpatients suffering from chronic schizophrenia and inhabitants of community-based psychiatric institutions (hostels), underwent baseline psychiatric/cognitive assessment and were randomly assigned to either a treatment intervention of oxygen enriched air inhalation (normobaric hyperoxia of 40% FiO2), or to regular air inhalation (21% FiO2), through a nasal tube, for four weeks. Patients were given the air/oxygen inhalations during the night (mainly while sleeping), for at least 7 hours a night. After completing four weeks of treatment, patients were switched (crossed-over) to the other treatment intervention.

Results: Fifteen patients completed the entire study. Five additional patients completed Phase A only. There was significant improvement in total PANSS score of patients that received oxygen compared with control group. There were positive effects of oxygen on memory and attention in neuropsychological performance tests. The effect size is small despite the statistical significance but the patient group was extremely chronic and severely impaired.

Conclusion: These results are a proof of concept and normobaric hyperoxia should be studied in patients with milder forms of the illness and earlier in the course of illness.

P-08-006 Cariprazine in the treatment of acute mania in bipolar disorder: A double-blind, placebo-controlled, phase III trial

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Objective: Cariprazine is a D3-preferring dopamine D3/D2 receptor partial agonist antipsychotic in development for the treatment of schizophrenia and bipolar mania. A Phase III clinical trial (NCT01058096) evaluated the efficacy, safety, and tolerability of cariprazine in patients with acute mania associated with bipolar I disorder.

Methods: In a 6-week, multicenter, placebo-controlled, parallel-group, flexible-dose study, patients (18–65 years) with acute mania and a Young Mania Rating Scale (YMRS) score $\geqslant 20$ were randomized

to cariprazine 3–12 mg/day or placebo for 3-week double-blind treatment. Patients were hospitalized for a 4–7 day wash-out screening period and at least 14 days of treatment; a 2-week safety period followed. Primary efficacy endpoint: YMRS total score change from baseline to the end of Week 3 analyzed using a mixed-effects model of repeated measures (MMRM) approach on the intent-to-treat (ITT) population; secondary efficacy: Clinical Global Impressions-Severity (CGI-S). Safety analyses included adverse events (AEs), laboratory values, ECGs, and extrapyramidal symptom (EPS) scales.

Results: 312 patients were randomized and received at least 1 dose of double-blind treatment (placebo, 154; cariprazine, 158); 69% of placebo and 68% of cariprazine patients completed the study. Baseline YMRS scores were similar between groups (placebo, 32.0; cariprazine, 32.8). Improvements were significantly greater for cariprazine 3–12 mg/day versus placebo on YMRS (LSMD, −4.3; $P<0.001$; MMRM) and CGI-S (LSMD, −0.4; $P<0.01$; MMRM). Overall premature discontinuation rates were similar (cariprazine, 32%; placebo, 31%); 10% of cariprazine and 7% of placebo patients discontinued due to AEs. Treatment-emergent AEs (TEAEs) occurred in 80% of cariprazine and 63% of placebo patients; AEs occurring at ⩾10% and twice the rate of placebo were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting; 46% of cariprazine and 12% placebo patients had EPS-related AEs.

Conclusion: Cariprazine was effective in the treatment of acute mania associated with bipolar I disorder. Cariprazine was safe and generally well tolerated.

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P-08-007 COMT Val158Met polymorphism and antipsychotic treatment interaction on cognitive remediation outcomes in schizophrenia

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Objective: Cognitive deficits negatively affect recovery in schizophrenia and poorly respond to pharmacotherapy. Cognitive remediation therapy (CRT) is effective in improving cognition in schizophrenia, but results are still variable and putative predictors of successful remediation need to be better analyzed in order to optimize individual outcomes. The COMT Val158Met polymorphism is known to have a functional effect on the rate of dopamine (DA) degradation and thus DA availability in the prefrontal cortex (PFC), which may affect CRT response. Two studies evaluated the effect of COMT genotype on cognitive improvement following CRT, with contradictory results [1,2]. Among factors affecting CRT outcomes, pharmacotherapy appears of major relevance. Antipsychotics could interact with COMT polymorphism on DA availability, influencing individual capacity to recover from deficit. The present study aims to analyze the possible effect of COMT Val158Met polymorphism and antipsychotic treatment (clozapine vs. drugs with greater dopaminergic D2 receptor blockade activity) on CRT outcomes. We hypothesized that antipsychotic- induced changes in PFC DA availability may interacts with COMT genotype.

Methods: 91 clinically stabilized patients with diagnosis of schizophrenia, receiving antipsychotic monotherapy since at least 3 months, were recruited. Patients attended a CRT program for three months. Cognitive performances were evaluated, at baseline and after 3 months, with ''Brief Assessment of Cognition in Schizophrenia'' (BACS).

Results: Analysis conducted by Repeated Measures ANOVA showed a significant interaction ($F=4.0212$, $p=0.0484$) between COMT genotype and pharmacological treatment, on symbol coding performances change.

Conclusion: The findings support the hypothesis of an interaction between Val158Met COMT polymorphism and pharmacotherapy on dynamic modulation of cognitive functions through CRT. Val/Val subjects, only when treated with clozapine, show an improvement in symbol coding, a task related to speed of processing and executive functioning and currently regarded as a possible endophenotype of schizophrenia. Clozapine, known to increase prefrontal DA levels, could recover the genetic disadvantage.

P-08-008 Increasing of LINE-1 copy number in postmortem brains of psychiatric disorder patients

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Objective: Some retrotransposons have the activity of moving through the genome, resulting in the generation of variations in the human genome. Recently, it has been shown that one of the well-characterized retrotranposons, the LINE-1 (long interspersed nuclear element 1), possess the retrotranspose activity in neural progenitor cells. Interestingly, copy number of the LINE-1 was higher in brains compared with other tissues, and that it was differed among brain sub-regions. These findings implicate that aberrant LINE-1 activity might be associated with the pathophysiology of psychiatric diseases such as schizophrenia. Here, we quantified the copy number of the LINE-1 in genomic DNA of two independent postmortem brain sample sets.

Methods: Samples consist of schizophrenia, bipolar disorder, major depression and controls. Both of sample sets were obtained from the Stanley Medical Research Institute. Copy number of the LINE-1 was determined by real time PCR method, according to the previous report (Coufal et al., Nature 2009). We calculated the relative LINE-1 content of brain/liver in one set. In another set, we separated brain tissue into neuronal and non-neuronal cell nuclei using NeuN-based sorting technique, and calculated relative LINE-1 content of neuron/non-neuron.

Results: There were significant increases in relative LINE-1 contents in schizophrenia in two sample sets. Confounding factors such as age, gender, postmortem interval, and sample pH did not affect the LINE-1 content in brains.

Conclusion: These results suggest that aberrant retrotranposon activity in the neural progenitor cells may be associated with the pathophysiology of schizophrenia.

P-08-009 Effects of ARI-IM-depot on secondary efficacy outcomes in maintenance treatment of schizophrenia

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Objective: To evaluate secondary efficacy outcomes of once-monthly aripiprazole intramuscular depot (ARI-IM-depot) as maintenance treatment for schizophrenia.

Methods: Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) during a 4–6-week oral conversion phase (Phase 1). Phase 2 was a 4–12-week oral aripiprazole stabilisation phase. Subjects meeting stability criteria (4 weeks) entered an IM-depot stabilisation phase (400 mg/injection) with co-administration of oral aripiprazole the first 2 weeks (Phase 3). Subjects meeting stability criteria (12 weeks) were randomised (2:1) to ARI-IM-depot or placebo (52-week: Phase 4). Secondary efficacy assessments included mean changes in Personal and Social Performance scale scores (PSP) scale scores to assess functional outcomes, and Investigator's Assessment Questionnaire (IAQ) scores to assess treatment effectiveness.

Results: 710 subjects entered Phase 2, 576 in Phase 3 and 403 in Phase 4. The study stopped early because efficacy was demonstrated by pre-planned interim analysis (after 64 relapses). Mean changes in PSP scale scores (LOCF) showed improvement during the oral (3.0) and ARI-IM-depot stabilisation (2.6) phases. Mean change in PSP scores in Phase 4 showed greater functional stability with ARI-IM-depot (−1.7) than placebo (−6.2; $p=0.0002$ vs. placebo). Mean IAQ total score remained stable (Phase 2, 31.3; Phase 3, 30.6) and mean change in Phase 4 was +1.3 for ARI-IM-depot vs. +3.8 for placebo ($p<0.0001$).

Conclusion: Improvements in symptoms, functioning and overall response to treatment were achieved during stabilisation and maintained in Phase 4. ARI-IM-depot offers a different risk–benefit profile than currently available treatments.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics,

Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Pamela Perry, Na Jin, Ross A Baker, Robert A Forbes, Robert D McQuade, William H Carson are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

P-08-010 Treatment of schizophrenia: Does gender matter?

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Objective: There is little information about gender differences concerning treatment of schizophrenia. We have used data from the e-STAR (electronic Schizophrenia Treatment Adherence Registry), an international, prospective, observational study assessing use of risperidone long acting injection (RLAI) in patients with schizophrenia or schizoaffective disorder. The aim was a comparison between male and female patients participating in e-STAR in both Czech and Slovak Republics.

Methods: The e-STAR was designed to evaluate clinical outcome in patients who have initiated RLAI as part of their continuing therapy in routine clinical practice. The decision to initiate pts on RLAI and their clinical management was determined solely by the treating physician. The demographic, clinical and treatment related data were collected at baseline and than prospectively for 2 years. We have focused on gender differences in demographic and clinical data (hospitalizations, concomitant medication and clinical improvement using CGI, GAF and PSP).

Results: Totally 868 patients, 488 male and 380 female were included. At baseline women were significantly older than men 42.1 (12.8) respective 34.8 (11.1) women were also significantly more frequently diagnosed as schizoaffective disorder. Concerning the proportion of pts hospitalized in the retrospective and prospective period there was no difference between men and women (including length of stay). Comparing the concomitant medication at 24 month the male group used less antidepressants and benzodiazepines than the female group (controlled for baseline values). The improvement in CGI-S and PSP scores was similar. However, the improvement in GAF score was significantly higher in men than in women.

Conclusion: The comparable severity of illness is achieved in women later. In spite of comparable severity women reacted better in some measures of social functioning. The gender differences should be more intensively studied and should be taken into consideration in guidelines. Supported by research grant from Janssen CR and the project CEITEC (CZ.1.05/1.1.00/02.0068).

P-08-011 The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia

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Objective: Alteration of oxidative stress markers has been reported in many studies, but with inconsistent results. Recently evidences show that oxidative stress could be involved in the pathophysiology of schizophrenia. Thus, accumulating evidence indicates that alterations in NO function may be involved in the pathophysiology of schizophrenia and these original findings motivate further investigations of the potential utility of NO modulation as a novel pharmacological treatment for schizophrenia. Objective: The objective of this study was to investigate the benefit of L-lysine, an aminoacid that occurs naturally in food and which interferes with nitric oxide production, as a treatment for schizophrenia.

Methods: The study was designed as a duble-blinded, cross-over study where patients were randomly assigned to initial treatment with either L-lysine or placebo and screened at baseline, after four weeks when treatment was crossed over, and after eight weeks, when treatment was terminated. L-lysine, 6 g/day, was administered to 20 patients with schizophrenia as an add-on treatment to conventional antipsychotic medication.

Results: The four-week L-lysine treatment caused a significant increased in blood concentration of the amino. The analysis of outcome measures from the remaining 16 patients showed a significant decrease in symptom severity (measured by PANSS). Furthermore, the patient's ability to solve the Wisconsin Card Sorting Task was significantly improved indicating increased problem solving capacity and cognitive flexibility.

Conclusion: These findings suggest potential beneficial effects of nitric oxide inhibitors on symptom severity and cognitive deficits in patients with schizophrenia.

P-08-012 Positively biased recognition of emotional valence in schizophrenia

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Objective: Schizophrenia is characterized by impairments in recognizing affect. To evaluate affect recognition of patients with schizophrenia, facial expressions or words have been used in most previous studies. Few studies have tackled the issue via reading written sentences, which is another important component of perceiving social contexts. The present study aimed to evaluate affect recognition of various emotionally valenced sentences in patients with schizophrenia.

Methods: A 28-item questionnaire was devised based on preliminary survey consisted of one hundred written sentences with various emotional valence selected from newspapers and Korean novels. The questionnaire was administered to both healthy control ($N=32$) and patients with schizophrenia ($N=9$). Participants were asked to rate the emotional valence of each sentence in a 7-point Likert scale, ranging from 1 (very negative) to 7 (very positive). The independent samples t-test was conducted to compare the difference in the means of two groups.

Results: Of the 28 items, seven showed either statistically significant (three items $p<0.05$) or a trend of group differences (four items $p<0.10$). On all cases showing group differences, the patients showed positively biased emotional recognition. For example, the patients responded more positively to a sentence 'Yuna Kim became Olympic gold medalist getting over difficult times' (6.89 ± 0.33 versus 6.25 ± 0.62, $p<0.01$ in patients and control subjects respectively).

Conclusion: The tendency to recognize emotion more positively than normal people may influence on patients with schizophrenia to overlook negative emotions or exaggerate positive emotions of others, and consequently, may interfere with successful social interaction.

P-08-013 Negative symptoms of schizophrenia, antipsychotics and clinical outcome

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Objective: Negative symptoms such as social withdrawal, emotional blunting, apathy and anhedonia are more subtle in nature, more insidious and more difficult to treat with antipsychotic drugs compared with positive symptoms in schizophrenia. Nearly one third patients with schizophrenia have predominant and persistant negative symptoms. In schizophrenia the presence of negative symptoms has been associated with poorer clinical outcome. In this study we correlated changes in negative symptoms, as measured by scores on the 16-item Negative symptoms Assessment scale (NSA-16), with changes on the Global Assessment of Functioning (GAF), and on the Social and Occupational Functioning Assessment Scale (SOFAS), and with antipsychotic used in therapy.

Methods: In the study authors assessed in total 60 patients with schizophrenia or schizoaffective disorder. The patients were treated

with antipsychotics: olanzapine, quetiapine and risperidone. They were assessed with 16-item Negative symptoms Assessment scale (NSA-16), with Global Assessment of Functioning (GAF), and Social and Occupational Functioning Assessment Scale (SOFAS), at the baseline, after one month of the treatment and after 3 months of the treatment. All of the patients were out-treated.

Results: Changes in negative symptoms rated with NSA −16 showed statistically significant correlation with changes recorded on all of the outcomes measured by GAF and SOFAS scales (HI2 = 4.27, $p < 0.05$: HI2 = 5.69, $p < 0.05$). There were no statistically significant changes between the groups of patient treated with different antipsychotic drugs (olanzapine, risperidone, quetiapine).

Conclusion: In this study, negative symptoms assessed by NSA-16 showed association with improvements on GAF and SOFAS. We can conclude from the results of this study that treatments that are effective in reducing negative symptoms, also reduce the functional disability associated with these symptoms in patients with schizophrenia.

P-08-014 Comparison of outcomes in patients with early versus later phase schizophrenia treated with olanzapine long-acting injection

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Objective: The present analyses were conducted to compare treatment outcomes for patients initiating olanzapine long-acting injection (LAI) within 5 years of onset of illness (''Early Phase'' group) versus those initiating olanzapine LAI greater than 5 years after illness onset (''Later Phase'' group).

Methods: Data were obtained from the 8 studies in the clinical trial database involving olanzapine LAI (dose range: >45 mg/4 weeks to 300 mg/2 weeks). Outcome measures included rates of and time to study discontinuation, relapse, remission, and sustained remission, as well as mean changes from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) total and subscale scores.

Results: Of the 1879 patients in the analysis, 24.2% were in the Early Phase group and 75.8% were in the Later Phase group. The Early Phase group showed a longer median time to discontinuation ($P = 0.003$), longer time to relapse ($P = 0.018$), and, among patients not in remission at study initiation (45.8%), a shorter median time to sustained remission ($P = 0.012$). Rates of remission and sustained remission were also higher for the Early Phase group relative to the Later Phase group ($P < 0.001$, both measures). The Early Phase group also showed greater symptom reduction in their mean PANSS total, negative, positive, and general psychopathology scores, and in their BPRS total, positive and anxiety/depression scores ($P < 0.01$, all measures).

Conclusion: Consideration must be given to the post-hoc nature of this analysis and the fact that these clinical trials were not specifically designed to address the issue of treatment timing and clinical outcomes. Nevertheless, these findings support the assertion that clinical outcomes with use of a depot antipsychotic such as olanzapine LAI are significantly improved in patients who begin the depot earlier in the course of their illness compared with patients who begin the depot later.

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P-08-015 Within-drug benefit/risk of olanzapine LAI at 1 and 2 years of treatment

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Objective: Evaluate 1- and 2-year within-drug benefit/risk of olanzapine long-acting injection (LAI).

Methods: Subjects were 1192 patients with the opportunity for ⩾2 years Olanzapine LAI treatment for schizophrenia. Frequencies of key benefits and risks were evaluated versus average duration of those events for all patients. Next, authors independently rated olanzapine LAI using the Transparent Uniform Risk/Benefit Overview method (TURBO), weighting the 2 most medically serious and/or frequent events versus primary benefit (effectiveness) and an ancillary benefit. Averaged ratings were placed on a t-score grid from 1–7 (worst balance to excellent).

Results: The most frequent event was remaining relapse-free (91% at 1 year; 88% at 2 years). Mean cumulative days without relapse was 306 at 1 year and 546 at 2 years. Next most frequent was meeting symptomatic remission criteria at anytime (82% at 1 year; 84% at 2 years). Incidence of ⩾7% weight gain was 33% at 1 year and 42% at 2 years; mean days duration = 54 ± 99 at 1 year and 124 ± 210 at 2 years. Per-patient post-injection delirium/sedation syndrome (PDSS) incidence was 0.8% at 1 year and 1.5% at 2 years; mean duration = 0 days at 1 and 2 years. For those with an event (9 patients at 1 year; 18 at 2 years), mean duration was 2 days at 1 and 2 years. For TURBO analysis, PDSS and weight gain were selected as key risks; choice of ancillary benefit varied. Mean benefit rating was 5; mean risk rating was 2.8 of 7, yielding a benefit/risk balance t-score of 5 (''acceptable'').

Conclusion: Olanzapine LAI's benefit/risk balance was in the ''acceptable'' range based on TURBO ratings. Quantitative evaluation showed benefits (such as remission, relapse-free days) outweighed lower-probability events (PDSS), but higher-probability risks (weight gain) remained a significant clinical concern.

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P-08-016 Influence of neuroleptic therapy on neurocognitive functions of schizophrenic patients in remission

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Objective: Recovery of neurocognitive functions is the key indicators of remission quality in schizophrenia, because this parameter determines the functional outcome for the patient. Over the last decade researches pointed out on advantages of atypical antipsychotics on classic antipsychotics in neurocognitive failure treatment in schizophrenia. However, the obtained results may be related not only to pharmacological charasterictics of drugs, but also to the methodology of research and interpretation of the results. We have surveyed 88 patients with symptomatic episode of paranoid schizophrenia, out of which 43 were under atypical antipsychotics and 45 under classic antipsychotics therapy. Assessment of neurocognitive disorders was carried out taking into account the clinical signs of remission. After the determination of remission, doses of drugs were reduced to a level where the stimulating effect is higher than sedation.

Methods: We have assessed verbal fluency, audio-verbal memory, visual memory, performing function and attention. The analysis of dynamics showed a significant improvement of neurocognitive function after the onset of clinical remission. Indicators of tests of visual and audio-verbal memory changed insignificantly throughout the study in both groups.

Results: For verbal fluency, performing function and attention tests the results have significantly improved in all indicators after the transfer of patients from therapeutic doses to support doses. While comparing two groups of drugs it was shown that atypical antipsychotics had better effect on verbal fluency, executive functions and attention before the onset of clinical remission (approximately six months of therapy). Subsequently, differences between groups were smoothed out. After 12 months of remission atypical antipsychotics have shown positive effects on verbal associative productivity (characteristic of verbal fluency).

Conclusion: However, the significance of this improvement remains controversial, since this parameter has no essential effect on quality of life of the patients.

P-08-017 Biological and psychotherapeutic models of of chronic acoustical hallucinations therapy at a paranoid schizophrenia

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Objective: To study the clinical and psychological factors causing synchronization and resistance of acoustical hallucinations at paranoid schizophrenia for the purpose of optimization of conducted therapy.

Methods: clinical, the standardized scales according to alarm level of, depression of Zung, a questionnaire of vital styles an original scale of understanding of the patient's frustration.

Results: results of research it has been revealed that patients suffering the paranoid schizophrenia over 5 years (57%), had persistent synchronization of acoustical hallucinations where according to clinical and psychopathological level acoustical hallucinations differed with their stereotype, defining a plot of insane designs. The prevalence of MPD depended on duration of frustration for less than 3 years replacement 0. 086 ($P<0.01$), negation 0. 086 ($P<0.01$) for more than 3 years, hyper indemnification 0.183 ($P<0.01$), and rationalization 0.279 ($P<0.01$).

Conclusion: Acoustical hallucinations with a duration over 5 years with the diagnosis of the paranoid schizophrenia make (57%). Duration of disease till 3 years and till one year 26% and 17% relatively, probably cause presence, first of all, prevalence of analarm component, as one of basic, defining synchronization and resistance of acoustical hallucinations. Prevalence of moderate depression of 50%, easy depression of 32%, it display of personal reaction it promote the process of activation specific MPD. At term of disease for less than 3 years there is replacement of 0.086 ($P<0.01$) and negation of 0.086 ($P<0.01$). For more than 3 years, hyper indemnification of 0.183 ($P<0.01$) and rationalization of 0,279 ($P<0.01$) become more active, and more than 5 years the projection of 0,36 ($P<0.01$) prevails. Interdependence of affective frustrations and mechanisms of psychological protection at acoustical hallucinations, are the system for formation of stereotype of clinical and psychopathological frustrations.

P-08-018 Comparision of atypical and typical antipsychotic on quantitative EEG measures in a glutamatergic animal model of psychosis

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Objective: Schizophrenia has been associated with dysfunctional integration of different cortical areas. These abnormalities can be documented by the changes in quantitative EEG (qEEG). On the other hand, neuroleptic agents produce beneficial effects on some of the symptoms of psychosis and induce specific alternations in qEEG. While many changes in qEEG have been found in people with schizophrenia, only limited information is available in animal models. Many authors describe EEG spectra in animals using 1–4 electrodes, and no data on coherence exists. Therefore, the aim of this study is to evaluate the effect of typical and atypical antipsychotic in an NMDA antagonist's model of psychosis using qEEG measures.

Methods: Seven days before EEG recording, 14 electrodes were stereotactically implanted bilaterally in frontal, parietal and temporal regions. On the day of the experiment, male Wistar rats were treated with MK 801 mg/kg 0.3 mg/kg i.p. and either clozapine 10 mg/kg i.p. or haloperidol 0.1 mg/kg s.c.. The signal was recorded homolaterally from six electrode pairs, while the animal's behaviour was continuously observed. Subsequent power spectral analysis and the EEG coherences were assessed congruently with the observed passive behaviour.

Results: In EEG spectral analysis, MK801 caused an increase of the power in gamma band and a decrease in slow wave bands. In EEG coherences, a decrease occurred interhemispherally in high beta and gamma bands and intrahemispherally in theta, delta, alpha and beta bands. Clozapine restored the MK801-induced slow wave band changes seen in power spectra. In EEG coherence, alpha and theta frequency bands were completely restored by haloperidol while clozapine partially restored most of the changes induced by MK801.

Conclusion: MK801 produced EEG abnormalities that correlate to its schizophrenia-like potential. Our results show that clozapine might be more effective in restoring some of these changes.

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P-08-019 Increased 5HT2A receptor binding in frontal cortex of schizophrenic subjects: Effect of aging and antipsychotic drug treatment

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Objective: Neuroimaging and postmortem studies have reported alterations of the 5HT2A receptor (5HT2AR) in brain of schizophrenic subjects. However, striking differences have been obtained in relation to the different methodologies and intrinsic confounding factors. The aim of the present study was to assess the 5HT2AR mRNA (qRT-PCR) and protein expression (western blot and [3H]ketanserin binding (10 nM)) in prefrontal brain cortex (BA9) of schizophrenics ($n=45$) and matched controls ($n=45$).

Methods: Displacement curves of [3H]ketanserin binding (2 nM) by the agonist DOI were performed in order to delineate the high affinity state of 5HT2AR. Subjects who gave negative results for antipsychotic drugs in the postmortem toxicological screening were considered antipsychotic (AP)free. To control the effect of suicidal behaviour, suicide victims ($n=13$) with other psychiatric diagnosis were also included. Controls were individually matched by gender, age and postmortem delay.

Results: Decreased 5HT2AR mRNA expression was observed in APtreated schizophrenics($-37\pm9\%$; $n=9$; $p<0.05$) compared to matched controls, without changes in APfree subjects ($n=18$). Immunodetection of 5HT2AR protein was unchanged. [3H]Ketanserin binding was increased in APfree schizophrenics ($+23\pm11\%$; $n=29$; $p<0.05$), but not in APtreated subjects ($n=16$) and suicide victims. Notably, an increase in the fraction of high-affinity sites for DOI displacing [3H]ketanserin was found in APfree schizophrenics ($12.4\pm1.4\%$ vs. $6.2\pm0.8\%$; $p<0.001$). [3H]Ketanserin binding correlated negatively with age in schizophrenic, suicide and control subjects. This effect of aging was more pronounced in APtreated (slope $=-7.4\pm3.1$) than in APfree (slope $=-3.6\pm2.6$) or control subjects (slope $=-2.3\pm0.8$).

Conclusion: These results suggest that the active conformation of 5HT2AR is upregulated in schizophrenia, a modulation that tends to be reversed by chronic treatment with antipsychotic drugs. Progressive aging makes the identification of the upregulation more difficult in schizophrenic subjects under treatment. The lower expression of 5HT2AR in older subjects may also underlie an association between fewer positive symptoms and increased age.

P-08-020 Social cognition and functioning in delusional disorder and schizophrenia. Differences between oral and long-term atypical antipsychotics

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Objective: Recent research has showed that there is a relationship among social cognition, neurocognition and psychosocial functioning in schizophrenia. Little information exists regarding the role of social cognition in delusional disorder and its assessment as a measure of treatment efficacy. We aimed to compare functioning and social cognition outcomes in delusional disorder and schizophrenia outpatients treated with oral or long-term atypical antipsychotics.

Methods: We included 36 outpatients with chronic psychotic disorders. Sociodemographic data, current age, age at onset in years and age at first psychiatric consultation were recorded. GEOPTE scale on social cognition and neurocognitive perception deficits, and GAF

scale for global functioning were assessed. The sample was divided into two groups according to the treatment received: oral vs. long-term atypical antipsychotics. For comparisons, Mann-Whitney U-test and Chi-square test were used.

Results: 18 delusional disorder (DD) patients and 18 patients on schizophrenia were included. Mean age (SD) at onset of illness was higher in delusional disorder compared to schizophrenia [45(9.65) years vs. 27.91(9.21); $p = 0.03$] and patients with schizophrenia started follow-up earlier ($p < 0.001$). No statistically significant differences were found between delusional disorder and schizophrenia patients attending to educational level, marital status, number of children and cohabiters. Mean (SD) score in GEOPTE scale was similar in schizophrenia than in DD [34.70(7.65) vs. 30.29(7.20); $p = 0.082$]. Patients receiving oral antipsychotic treatment displayed more deficits in social cognition compared to those treated with long-acting atypical antipsychotics, according to GEOPTE scale score [34.43 (8.08) vs. 29.47 (6.02)] but this result was not statistical significant. General functioning was similar between the two treatment groups.

Conclusion: Social cognition may be an important target in the pharmacological treatment of DD and schizophrenia. Long-term atypical antipsychotics could improve social cognition in patients with chronic psychotic disorder.

P-08-021 Pharmacological characterization and exploration of novel transcripts of a developmentally regulated and phencyclidine-inducible gene, SAP97, in mammalian brains

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Objective: Recently accumulated evidence supports that the disturbed N-methyl-D-aspartate (NMDA) receptor-mediated glutamate neurotransmission is involved in the pathophysiology of schizophrenia. We have explored the transcripts induced by phencyclidine (PCP), an NMDA receptor antagonist, in the mammalian cerebral cortex.

Methods: Using differential screening, and quantitative RT-PCR methods, we isolated the neocortical transcript that was up-regulated in the adult but unchanged in infant rats, after a systemic administration of PCP. We further examined the expression and characterization of SAP97 in both rat and human specimens. All studies were approved by the ethics committees of the University.

Results: We have identified the synapse-associated protein-97 (SAP97)/discs large (DLG1) mRNA as a PCP-responsive transcript. The up-regulation of the SAP97 transcript in the adult neocortex after the acute PCP injection was mimicked by another NMDA antagonist, dizocilpine, but not by the indirect dopamine agonists, methamphetamine and cocaine, a selective D1 receptor antagonist SCH23390, a D2 receptor-preferring antagonist haloperidol and a GABAergic anesthetic pentobarbital. The pretreatment with a typical antipsychotic haloperidol failed to antagonize the increased neocortical SAP97 gene expression by PCP.

Conclusion: SAP97 gene encodes the synaptic scaffolding PDZ proteins that interact with ionotropic glutamate receptors. By using single nucleotide polymorphism (SNP) analyses, we have found a significant association between the human SAP97 gene and schizophrenia (Yamamoto et al., 2012 CINP abstract). These findings together suggest that SAP97 might be involved in the molecular basis of the development-dependent onset of the non-dopaminergic symptoms seen in schizophrenia and the schizophrenia-like psychosis induced by NMDA receptor blocking. Currently, we are further examining the expression of novel splicing variants of SAP97 in the human brain and their possible functional relationship with the symptoms.

P-08-022 The p250GAP gene is associated with risk for schizophrenia and schizotypal personality trait

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Objective: Hypo-function of glutamate N-Methyl-d-aspartate (NMDA) receptor is implicated in the pathophysiology of schizophrenia. p250GAP is a brain-enriched NMDA receptor-interacting RhoGAP. p250GAP is involved in spine morphology, which has been shown to be altered in post-mortem brains of schizophrenia. Schizotypal personality disorder has a strong familial relationship with schizophrenia. Several susceptibility genes for schizophrenia have been related to schizotypal traits.

Methods: We first investigated the association of eight linkage disequilibrium-tagging SNPs that cover the p250GAP gene with schizophrenia in a Japanese sample of 431 schizophrenia patients and 572 controls. We then investigated impact of the risk genetic variant in the p250GAP gene on schizotypal personality traits in 180 healthy subjects using the Schizotypal Personality Questionnaire.

Results: We found a significant difference in genotype frequency between patients and controls in rs2298599 ($\kappa 2 = 17.6$, $p = 0.00015$). The minor A/A genotype frequency of rs2298599 was higher in patients (18%) than in controls (9%) ($\kappa 2 = 15.5$, $p = 0.000083$). Moreover, we found that subjects with the risk A/A genotype of rs2298599 showed higher scores on schizotypal traits ($F1,178 = 4.08$, $p = 0.045$), particularly interpersonal factor ($F1,178 = 5.85$, $p = 0.017$), compared with G allele carriers.

Conclusion: These results suggest that the genetic variation in the p250GAP might increase susceptibility not only for schizophrenia but also for schizotypal personality traits. We concluded that the p250GAP might be a new candidate gene for susceptibility to schizophrenia.

P-08-023 Influence of psychiatric comorbidity on rehospitalization of patients with first-episode schizophrenia

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Objective: The problem of rehospitalization of patients after the first episode of schizophrenia is one of the major problems influencing the course and outcome of the treatment as well as treatment expenses. The aim of the study was to determine the influence of psychiatric comorbidity on the one-year rehospitalization rate for first-episode schizophrenia patients.

Methods: The study was conducted at University Psychiatric Hospital Vrapce among 123 patients with first-episode schizophrenia who were treated between January 1, 2007 and January 1, 2008. The patients were prospectively followed-up for rehospitalization during one year after hospital discharge, i.e., until January 1, 2009. Descriptive statistics was used to describe demographic and clinical data, whereas time to rehospitalization was analyzed with Kaplan-Meier survival analysis.

Results: There was a significant difference between the rehospitalized and non-rehospitalized patients in the presence of psychiatric comorbidity ($p = 0.046$).

Conclusion: Among other rehospitalization risk factors, the psychiatric comorbidity was found to increase the rehospitalization rate. Psychiatric comorbidity that showed the greatest influence on the rehospitalization rate was alcohol and opiate abuse.

P-08-024 Partial agonism at trace amine-associated receptor 1 (TAAR1) reveals a novel paradigm for neuropsychiatric therapeutics

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Objective: Trace amines, endogenous compounds structurally related to classical biogenic amines, represent endogenous ligands of the trace amine-associated receptor 1 (TAAR1). Because trace amines also influence the activity of other targets, selective ligands are needed for the functional elucidation of TAAR1. Here we report on the identification and electrophysiological and behavioral characterization of the first selective and potent TAAR1 partial agonist. Furthermore, the suitability of TAAR1 as a drug target for various neuropsychiatric indications will be discussed.

Methods: The TAAR1 partial agonist was evaluated for its binding affinity and functional activity at rodent and primate TAAR1 receptors stably expressed in HEK293 cells, for its physicochemical and pharmacokinetic properties, for its effects on the firing frequency of monoaminergic neurons ex vivo, and for its properties in vivo using genetic and pharmacological models of CNS disorders.

Results: The TAAR1 partial agonist shows high affinity for TAAR1, has potent functional activity with selectivity over other molecular targets and has good pharmacokinetic properties. In mouse brain slices, the TAAR1 partial agonist increased the firing frequency of dopaminergic and serotonergic neurons in Taar1 expressing regions, the ventral tegmental area and the dorsal raphe nucleus, respectively. In vivo, examining the consequences of activating TAAR1 selectively on various behavioral paradigms in rodents and monkeys, the TAAR1 partial agonist demonstrates antipsychotic-, anxiolytic- and antidepressant-like activities. Furthermore, it attenuates drug-taking behavior and is highly effective in promoting attention, cognitive performance and wakefulness.

Conclusion: Using the first potent and selective TAAR1 partial agonist we show that TAAR1 is implicated in a broad range of relevant physiological, behavioral and cognitive neuropsychiatric dimensions. Collectively, these data uncover important neuromodulatory roles for TAAR1 and demonstrate its therapeutic potential in psychiatric disorders such as psychosis, depression and substance abuse.

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P-08-025 Significance of elevated brain kynurenic acid following neonatal influenza A infection

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Objective: Neonatal virus infection induces the mouse brain kynurenine pathway, including kynurenic acid (KYNA) – an end-metabolite that has previously been implicated in schizophrenia pathophysiology. The objective of the present study was to investigate the long-term behavioral effect of such neonatal infection, and the link to elevated KYNA during neurodevelopment.

Methods: Male C57BL/6 mice were i.p injected with the neurotropic influenza virus A/WSN/33 or vehicle at P3. Another set of male C57BL/6 mice were i.p injected with L-kynurenine or vehicle at P7–16. In adult life, horizontal activity was analyzed. Following a 60 min habituation period, D-amphetamine or saline was administered i.p., and horizontal activity was recorded for 90 min. Whole brain KYNA concentrations was analyzed using a HPLC system and a fluorescence detector.

Results: Administration of D-amphetamine in adult mice increased horizontal activity in both infected and uninfected mice. Mice infected with influenza virus showed a more pronounced increase in horizontal activity. Similarly, D-amphetamine administration to adult mice increased horizontal activity in both L-kynurenine treated mice and vehicle controls. The D-amphetamine induced increase in horizontal activity tended to be more pronounced in the L-kynurenine treated mice. Basal horizontal activity did not differ between infected and uninfected mice or between L-kynurenine treated mice and vehicle controls. Brain KYNA levels did not differ between the comparison groups at time of locomotor assessment.

Conclusion: Present study confirms that a neonatal virus infection targeting the brain is associated with behavioral disturbances in adult life. Our results are in line with the enhanced striatal dopamine release by amphetamine, as observed by brain imaging studies in patients with schizophrenia. Notably, subchronic elevations of brain KYNA in adult rats enhance amphetamine-induced increase in brain dopamine release. The present study adds support to the hypothesis of brain KYNA as an important mediator in the development of neuropsychiatric symptoms.

P-08-026 Association study of catechol-O-methyltransferase gene polymorphisms with schizophrenia and psychopathological symptoms in Han Chinese

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Objective: Although dysfunction of catechol-O-methyltransferase (COMT)-mediated dopamine transmission is implicated in the etiology of schizophrenia, the human COMT gene has not been associated consistently with schizophrenia. The purpose of this study was to investigate whether the COMT gene is associated with the development of schizophrenia and whether polymorphisms of this gene influence psychopathological symptoms in patients with schizophrenia.

Methods: Fourteen polymorphisms of the COMT gene were analyzed in a case–control study of 876 Han Chinese individuals (434 patients and 442 controls). All participants were screened using a Chinese version of the modified Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) and all patients met the criteria for schizophrenia. Furthermore, pretreatment psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) in a subset of 224 hospitalized schizophrenia patients that were drug naïve or drug free, to examine the association between clinical symptomatology and COMT polymorphisms.

Results: No significant differences in allele or genotype frequencies were observed between schizophrenia patients and controls, for all variants investigated. Haplotype analysis revealed that three haplotype blocks of the COMT gene were not associated with the development of schizophrenia. Moreover, these COMT polymorphisms did not influence the PANSS scores of schizophrenia patients.

Conclusion: This study suggests that the COMT gene may not contribute to the risk of schizophrenia and to the psychopathological symptoms of schizophrenia among Han Chinese.

P-08-027 Repetitive transcranial magnetic stimulation-induced cumulative pattern of serum brain-derived neurotrophic factor as a biomarker of rehabilitation in patients with chronic schizophrenia: Optimism or pessimism for psychiatric rehabilitation

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Objective: The aim of this study is to investigate the role of serum Brain-Derived Neurotrophic Factor (sBDNF) as a biomarker of neuroplasticity for psychiatric rehabilitation through the evaluation of

the response of sBDNF to the quantified stimuli applied with repetitive Transcranial Magnetic Stimulation (rTMS).

Methods: Right-handed twenty inpatients, with chronic schizophrenia, on stable medication whose minimum duration of illness was 10 years were recruited. The handedness was assessed using Edinburgh Handedness Inventory. Consecutive 10 weekday sessions with 20 Hz rTMS (a total of 20,000 stimuli) were applied over the left dorsolateral prefrontal cortex at 100% of motor threshold. There was no change in the medication for at least 2 week before enrollment and 4 weeks thereafter. Primary outcome measure was the change in the mean concentration of duplicated sBDNF(pg/ml). Clinical severity or change was measured using the Clinical Global Impression scale (CGI) and the Positive and Negative Symptom Scale (PANSS).

Results: Eighteen participants (male, 10; female, 8) completed the study and were analyzed. The mean (SD) of chlorpromazine equivalent (CPZE) of antipsychotics were 1,325.69 (761.58)mg. The mean (SD) of baseline CGI-severity and total PANSS score were 4.61 (0.50) and 68.44 (6.05), respectively. The differences from baseline, in the level of sBDNF, just after the completion of rTMS sessions were statistically significant (paired t-test: $t=2.245$, $df=17$, $p=0.038$). At 2 weeks after the completion of rTMS sessions, however, the significance in the level of sBDNF was not manifest ($t=1.381$, $df=17$, $p=0.185$).

Conclusion: The findings of this study suggest that in patients with chronic schizophrenia, sBDNF may serve as a biomarker of neuroplasticity, but the change pattern of sBDNF might manifest both positive and negative implications on psychiatric rehabilitation.

P-08-028 D-neuron-trace amine hypothesis of schizophrenia

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Objective: Dopamine (DA) dysfunction, glutamate hypofunction, neurodevelopmental deficits, and neural stem cell hypofunction are widely accepted hypotheses for etiology of schizophrenia. Nevertheless, molecular mechanisms of mesolimbic DA hyperactivity have not yet been clarified. The author intended to examine whether mesolimbic DA hyperactivity might be explained by some mechanisms, in which D-neurons, i.e., trace-amine-producing neurons, and trace amine-associated receptor, type 1 (TAAR1) are involved.

Methods: The author's previous reports on post-mortem brains of schizophrenia, using immunohistochemistry with antibodies against amine-related neural substances, such as aromatic L-amino acid decarboxylase, and literatures on TAAR1 and neural stem cells, were referred.

Results: In brains of schizophrenia, hypofunction of neural stem cells in the subventricular zone of lateral ventricle must cause decrease of D-neurons in the nucleus accumbens and striatum, and resulting decrease of the amounts of trace amines in the nucleus. The reduction of trace amine signals to TAAR1 on DA terminals of ventral tegmental area (VTA) DA neurons may increase the firing frequency of VTA DA neurons, and leads to increase of DA release in the nucleus accumbens. DA hyperactivity in the nucleus accumbens and striatum may inhibit forebrain neural stem cell proliferation, via DA D2 receptors, and causes additional decrease of D-neurons, which may induce additional hyperactivity of mesolimbic DA system.

Conclusion: The innovate ''D-neuron-trace amine hypothesis'' may explain the molecular mechanism of mesolimbic DA hyperactivity of schizophrenia.

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P-08-029 Finally we are on the begin: Real causes of some psychotic disorders

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Objective: The detection of possible real etiological factors by some psychotic disorders is the best opportunity to introduce more etiological targeted and more effective therapy of some Schizophrenia-like and other psychotic disturbances.

Methods: Clinical study with targeted investigations to detect all possible etiological factors and comorbidity in sample of 100 patients by acute psychotic disorders. Clinical, biochemical, bacteriological, virusological, neurophysiological investigations and targeted neuroimageing (MRI, MR angiography – arteriography and venography).

Results: The most frequent etiology in our sample of 100 patients with psychotic future were: psychoactive drugs (29%), respiratory tract and other infections (25%), endocrine and metabolic disturbances (16%), cerebrovascular disorders (12%), brain disorders (11%) and neurodevelopmental disorders (7%). Between patients with infectious/inflammatory etiological factors and events involved in clinical picture acute of psychotic disorders: sinusitis by 5 of patients, cerebral venous thrombosis 2, tonsillopharyngitis 3, otitis media 2, dental focuses 3, bronchitis – bronchopneumonia 4, urogenital infection 1, syphilis 1, neuroboreliosis 1, infectious mononucleosis 2, thrombophlebitis cruris 1.

Conclusion: The relative clear etiology or commorbidity by acute psychotic disorders is the best way to targeted effective therapy and further prophylaxis of some mental disorders. The recovery can be very good, the possibility to relapse is very small and the stigmatization of mentally ill patients in these cases is practically diminished.

P-08-030 Disrupted-in-schizophrenia 1 (DISC1) regulates oligodendrocyte differentiation

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Objective: Multiple lines of evidence obtained by brain imaging, studies in postmortem brains and genetic association studies, have implicated oligodendrocytes (OL) and myelin dysfunction in schizophrenia (SZ). We addressed the possibility of glial expression of DISC1, a key susceptibility gene for major psychiatric disorders including SZ. In addition, we clarified the role of DISC1 in OL differentiation.

Methods: Glial expression of DISC1 was examined both in vivo and in vitro. Effect of manipulating DISC1 expression on OL differentiation was assessed by using primary culture of oligodendrocyte precursor cells (OPC).

Results: DISC1 mRNA expression was detected not only in neurons but also in glial cells and especially abundant in OPC where DISC1 localized in cell body, nucleus and process. In an in vitro OL differentiation system, myelin related markers such as CNPase, MAG and MBP increased and cells with matured morphology increased when endogenous DISC1 was knockdowned by RNA interference. Furthermore, overexpression of truncated DISC1, supposedly by functioning in a dominant negative fashion, resulted in an increase of myelin related proteins. On the contrary, both expression of myelin related proteins and number of cells with matured morphology were decreased upon overexpression of full length DISC1. We also show a possible involvement of Sox10 and Nkx2.2, well known transcription factors regulating the expression of myelin genes, in the regulatory pathway of OL differentiation by DISC1.

Conclusion: Mammalian DISC1 endogenously expressed in OL lineage negatively regulates OL differentiation by regulating Sox10 and Nkx2.2 expression.

P-08-031 Effects of zonisamide on tardive dyskinesia: A preliminary open-label trial

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Objective: Once developed, tardive dyskinesia (TD) is a challenging condition to treat. The recent evidence has demonstrated that zonisamide, an antiepileptic drug indicated for partial-onset seizures, may also have beneficial effects for ameliorating dyskinesia in Parkinson's disease. However, this finding has not systematically been tested in patients with TD associated with antipsychotic treatment. The objective of this study was to examine the efficacy, tolerability, and safety of zonisamide against TD in these patients.

Methods: In this 4-week open-label study, subjects who suffered TD were given 50–100 mg/day of zonisamide. Severity of TD was evaluated at the baseline and endpoint, using the Abnormal Involuntary Movement Scale (AIMS).

Results: Eleven subjects (6 females; mean ± SD age, 75.5±4.7 years; schizophrenia [N=6], bipolar affective disorder [N=2], schizoaffective disorder [N=1], mental retardation [N=1], mental retardation with epilepsy [N=1]) participated in this study. The AIMS total score (mean ± SD) was significantly decreased from 24.1±5.5 to 19.5±5.9, with 36.4% of the subjects (N=4) demonstrating a >20% decrease in the AIMS total score.

Conclusion: Treatment with zonisamide was well-tolerated and no participants dropped out prematurely. Zonisamide may be safe and effective for the treatment of TD in a subgroup of patients. These preliminary findings need to be further explored by larger well-designed trials.

P-08-032 Optimal D2 receptor occupancy rate of antipsychotics for the treatment of dopamine supersensitivity psychosis and late-onset psychosis

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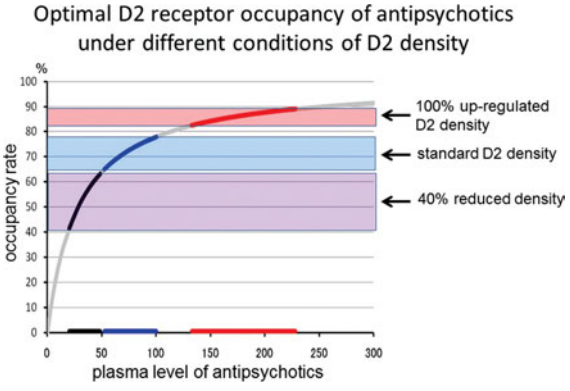
Objective: Our aim is to estimate optimal D2 receptor occupancy rate of antipsychotics for the treatment of treatment-resistant schizophrenia, especially for patients with dopamine supersensitivity psychosis.

Methods: Under assumptions that there is an optimal range of the number of D2 receptors available for dopamine binding, which is constant under different D2 receptor density, we estimated optimal D2 receptor occupancy with different D2 density.

Results: The results showed that the optimal occupancy rate and optimal plasma level of antipsychotics increase with an increase in the D2 density, but decrease with a decrease in the D2 density.

Conclusion: Optimal D2 receptor occupancy of antipsychotics may change with D2 receptor density of each patient with schizophrenia. Patients with up-regulated D2 density may need higher doses of antipsychotics for the treatment..



P-08-033 Efficacy of aripiprazole-IM-depot for long-term maintenance treatment of schizophrenia

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Objective: To evaluate the efficacy and tolerability of once-monthly aripiprazole intramuscular depot (ARI-IMD) for maintenance treatment in adult schizophrenia.

Methods: Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) during a 4–6-week oral conversion phase (Phase 1). Phase 2 was a 4–12-week oral aripiprazole stabilisation phase. Subjects meeting stability criteria (4 weeks) entered an ARI-IMD stabilisation (400 mg/injection) phase with co-administration of oral aripiprazole for 2 weeks (Phase 3). Subjects meeting stability criteria (12 weeks) were randomised (2:1) to ARI-IMD or placebo (52-week: Phase 4). Primary endpoint was time to impending relapse. Safety and tolerability were assessed.

Results: 710 patients entered Phase 2, 576 progressed to Phase 3 and 403 were randomised to Phase 4. The study stopped early because efficacy was demonstrated by pre-planned interim analysis. Time-to-impending relapse was significantly delayed in ARI-IMD compared with placebo in interim and final analyses ($p<0.0001$, log-rank test). Rate of impending relapse was significantly lower with ARI-IMD than placebo at endpoint (10.0%, n=27/269 vs. 39.6%, n=53/134; HR: 5.0; 95% CI: 3.15–8.02; $p<0.0001$). Improvements in PANSS Total score were maintained with ARI-IMD, but showed significant worsening with placebo (mean change at Week 52: ARI-IMD=1.4, placebo=11.6, $p<0.0001$). CGI-S scores showed significant differences favouring ARI-IMD ($p<0.0001$). Most common treatment-emergent AEs (≥5% of aripiprazole-treated patients and greater than placebo) were insomnia (10.0% vs. 9.0%), tremor (5.9% vs. 1.5%) and headache (5.9% vs. 5.2%), respectively. Most AEs were mild or moderate. Incidence of injection site pain in Phase 3 was 5.9%, while in Phase 4 was 3.0% vs. 3.7% for ARI-IMD compared with placebo.

Conclusion: ARI-IMD significantly delayed time to impending relapse compared with placebo and was a well-tolerated maintenance treatment option in schizophrenia.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Pamela Perry, Na Jin, Brian Johnson, Robert A Forbes, Robert D McQuade and William H Carson are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

sP-08-034 Medication prescribing patterns for patients with schizophrenia and related psychosis in a university psychiatric hospital

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Objective: Despite multiple therapeutic advances, especially in psychopharmacology, the treatment of schizophrenia has remained a major challenge. Surveys of prescribing in psychiatric services internationally have identified the relatively frequent and consistent use of antipsychotics polypharmacy (AP) with a prevalence of up to 50% in some clinical settings. The purpose of this study was to examine trends in the use of antipsychotic medications in an inpatient unit at a university mental health hospital in Korea.

Methods: This retrospective study was conducted in Severance Mental health Hospital (SMH), a part of the unit of psychiatry, Yonsei University College of Medicine, which is a representative psychiatric facility offering comprehensive treatment to institutionalized patients

with severe and persistent mental illness, in Korea. We reviewed all the psychotropic medications prescribed to inpatients SMH, diagnosed as having schizophrenia or schizoaffective disorder (DSM-IV-TR, 4th edition) at time of discharge and 60days after discharge in the year 2010.

Results: Of the 264 studied patients, 260 cases were treated with antipsychotics (Mean dose = 723 mg ± 519) chlorpromazine equivalent) and 47.3% were discharged under AP treatment. The most prevalent combination of drugs was risperidone plus quetiapine (N = 20). Quetiapine was the most frequently used antipsychotic as adjuvant treatment (N = 64). Fifty-six cases (21.5%) received mood stabilizer 22 case received anticholinergics, 157cases (60.3%) received benzodiazepines and 149 cases (57.3%) were prescribed anticholinergics.

Conclusion: Although, the controlled evidence for its efficacy and safety as a strategy remains inconclusive, AP is a common pharmacological strategy as it is shown in our study. Because of severe and patients in SMH, and using low dose quetiapine for sleep make the ratio of antipsychotic polypharmacy higher. And at some cases, polypharmacy was only used for short-term period (less than 60 days), the definition of antipsychotics polypharmacy. Clearly more controlled research is needed to evaluate the short-term and long-term effects of antipsychotic polypharmacy.

P-08-035 Correlation between the left temporal lobe volume and the duration of untreated prodromal state in ultra-high risk for psychosis

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Objective: A longer duration of untreated psychosis (DUP) in schizophrenia is well-reported to lead to a poorer clinical outcome, in relation to smaller gray matter volume in the left planum temporale, possibly reflecting a neurodegenerative process after the onset of overt psychosis. However, the effect of duration of untreated period of prodromal syndrome (DUPS) on brain morphometry is not clearly understood. This study aimed to investigate the relationship between the DUPS of ultra-high risk group (UHR) and the regional brain volume.

Methods: DUPS was defined as the duration in months from the first fulfilment of UHR criteria to the UHR screening. It was measured retrospectively by careful interview at the time of screening just before the MRI scan. The voxel based analysis tested the gray matter volume differences between the UHR and the control groups, and the regression analysis was conducted to examine if there was any gray matter region correlated with DUPS in UHR group with age and gender as covariates.

Results: The mean DUPS was 23.27 months (standard deviation: 22.45 months) in 34 ultra-high risk subjects. The left superior temporal lobe volume appeared to be negatively correlated with DUPS at the level of uncorrected $p = 0.001$, cluster size = 100.

Conclusion: These findings conformed to the previous reports of DUP in the first episode schizophrenia and may reflect that the pathological process of schizophrenia would progress in the left temporal lobe during the prodromal state, in continuum to the overt illness course. The results also supported the requirement of the early detection and treatment of UHR individuals.

P-08-036 Genome-wide DNA methylation analysis using peripheral blood samples derived from unmedicated patients with schizophrenia

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Objective: Schizophrenia is a common and complex psychiatric disease with a lifetime morbidity rate of 0.5–1.0%. The pathophysiology of schizophrenia still remains unclear. DNA methylation is known to play a critical role in gene expression without altering DNA sequence. To gain further insight into the molecular mechanisms underlying schizophrenia, a genome-wide DNA methylation profiling (485,764 CpG dinucleotides) of the human peripheral blood was conducted (n = 47, 24 unmedicated schizophrenia and 23 matched controls).

Methods: For DNA methylation analysis, Infinium® humanmethylation450 Beadchip was used. Surrogate variable analysis was used after background and color-balance corrections. False discovery rate correction was applied at the 0.05 level for multiple testing. Furthermore, a cluster analysis was performed to determine whether we could distinguish schizophrenic samples from controls based on the selected markers.

Results: Significant diagnostic differences in methylation were observed at 10,747 CpG sites. Of these CpG sites, 9,765 sites (90.9%) demonstrated higher methylation level in schizophrenia cases compared with controls. According to the CpG content, 28.7% were located in CpG islands, 17.7% were in CpG shores, and 14.8% were in CpG shelves. From the genomic distribution, 35.7% were located in the promoter regions, 32.4% were in gene bodies, and 3% were in 3′-untranslated regions. All the schizophrenic and control samples were separated into two distinguished groups using a clustering based on the methylation profiles of the 7 selected markers (significant change in absolute mehtylation level > 0.2).

Conclusion: This is the first genome-wide methylation study using unmedicated samples with schizophrenia. Although previous studies have focused on methylation differences in schizophrenia at CpG sites within CpG islands around gene promoter regions, we demonstrated that aberrant DNA methylation in schizophrenia occurred across the genes. Our results also indicate that DNA methylation profiles can be used as a potential diagnostic biomarker for schizophrenia.

P-08-037 Aripiprazole and valproate for acute schizophrenia patients

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Objective: It is very important to clarify the effect of combind therapy of aripiprazple (ARP) and valproic acid (VPA) for acute phase of patients with schizophrenia.

Methods: 38 schizophrenics (F2 on ICD10 criteria), M/F:19/19, 39.8 ± 15.6 y.o., were treated with ARP 12–30 mg/day and VPA 600–1200 mg/day for 8-week.

Results: The therapy showed the reduction were PANSS 13.8%, PANSS-EC 21.1% and CGI-S (clinical Global impression severity) 39.1% and the increment of GAF 18.2%. There was no significant changes on EPS, HbA1c, serum lipids, PRL, and body weight.

Conclusion: The combined therapy of ARP and VPA is very effective and tolerant for acute schizophrenia patients.

P-08-038 Effects of tapering of long-term benzodiazepines on cognitive function in patients with schizophrenia receiving a second-generation antipsychotic

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Objective: The high use of long-term benzodiazepines (BZDs) with second-generation antipsychotics (SGAs) has been identified as an important issue in the treatment of schizophrenia in Japan. BZDs can cause various adverse effects such as dependence and cognitive impairment. The aim of this study was to evaluate the effects of gradual reduction or discontinuation of daytime BZD use on cognitive function and quality of life (QOL) in patients with chronic schizophrenia receiving an SGA.

Methods: Thirty schizophrenic patients who had received an SGA with concomitant BZDs for at least 3 months were enrolled. Before and 4 weeks after tapering of daytime BZDs, the Brief Assessment of Cognition in Schizophrenia Japanese-language version (BACS-J) and the Schizophrenia Quality of Life Scale Japanese-language version (SQLS-J) were administered. Other clinical evaluations also included

the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity of Illness Scale (CGI-S) and the Drug Induced Extrapyramidal Symptoms Scale (DIEPSS). To compare for practice effects on the BACS-J, 10 patients with chronic schizophrenia were assessed without tapering BZDs.

Results: BZDs were reduced or discontinued safely in most patients, and no emergent withdrawal symptoms were observed. Of 20 patients, 9 (45.0%) successfully discontinued daytime BZD and remained daytime BZD-free for at least 4 weeks. Significant improvements were shown in verbal memory, working memory, and composite score, as measured by the BACS-J without practice effects. In addition, the motivation/energy score on the SQLS-J, the negative symptoms and total scores on the PANSS significantly improved after tapering BZDs. There were no significant changes in the CGI-S score or the DIEPSS total score.

Conclusion: Reduction or discontinuation of long-term daytime use of BZDs may be warranted in patients with schizophrenia treated with SGAs, as it may improve cognitive function, subjective QOL, and psychiatric symptoms with no significant adverse effects.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-08-039 Subtype-specific effect of NMDA receptor blockade on cortical gamma oscillations

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Objective: NMDA receptor (NMDA-R) hypofunction is a key component of the pathomechanism of cognitive impairment in schizophrenia. NMDA-R antagonists elicit psychotic symptoms in human and schizophrenia-relevant signs in rodents, including a strong increase in gamma activity in different cortical areas. NMDA-Rs are composed of several subunits and the major differences in the distribution and dynamical properties of NMDA-Rs containing the NR2A and NR2B subunits indicate that they may play different roles in cortical network activity, and that hypofunction of these receptors may differently affect gamma synchrony, critical for a number of cognitive functions. The goal of the present study was to test this hypothesis.

Methods: Gamma power were measured in freely behaving rats before and after administration of NMDA-R antagonists with different subunit selectivity.

Results: We found that the strong aberrant gamma activity induced by NMDA-R blockade primarily depends on NMDA-Rs containing the NR2A subunit whereas blockade of NR2B/C/D subunit-containing receptors do not have such effect. We also demonstrate a second type of gamma enhancement elicited in a state-dependent fashion during REM sleep by selective blockade of NR2B subunit-containing NMDA-Rs, at short latency. This pattern was also present after full NMDA-R blockade but only at a later stage when the aberrant gamma oscillations and other psychotic-like symptoms ceased and the periodic alternation of sleep-wake states returned.

Conclusion: Alteration of gamma oscillations due to subtype-specific changes in NMDA-R function may have serious implications for the pathomechanism and treatment of cognitive impairment. Thus, pathologic neuronal synchronization due to NR2A receptor deficiency may contribute to cognitive deficits in schizophrenia where the number of interneurons co-expressing NR2A and parvalbumin is selectively reduced. In contrast, the characteristics of the oscillations induced by NR2B-dependent mechanisms are in agreement with its demonstrated higher tolerability and the possibility of minimizing psychotomimetic side effects in therapeutic applications of NMDA receptor antagonists.

P-08-040 First cases of the treatment with paliperidone ER in Albania

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Objective: The aim of this work was to explore tolerability and treatment response of flexible doses of paliperidone ER (3,6,9,12 mg/day) in adults suffering from resistant paranoid schizophrenia.

Methods: Four patients with resistant paranoid schizophrenia were included in this study. The patients were male, on the average 39.8 years old, diagnosed according to DSM-IV with schizophrenia from on the average 15.7 years, which had presented therapeutic resistance to some antipsychotics (haloperidol, clopixol, rispolepidone, olanzapine, clozapine). All subjects were treated with 3–12 mg paliperidone ER, according to the severity of symptoms. Patient's Positive and Negative Syndrome Scale (PANSS), Clincal Global Impression-Severity (CGI-S), Adverse Events (AEs) were assessed at five time points: baseline, 1st, 2nd, 3rd, month of treatment. Personal and Social Performance (PSP) scale was assessed at every three month of treatment.

Results: Three patients completed the four month trial of paliperidone ER and one of them interrupted the medication (3 mg/day) after one month because of the noncompliance. One patient started and finished the treatment with paliperidone XR 6 mg/day, two patients started the treatment with 9 mg/day, but during the last month they received 12 mg/day for better improvement. The PANSS, CGI-S, AEs and PSP scales indicated that the treatment with paliperidone XR of three schizophrenic patients was effective and paliperidone did not produce adverse events. The treatment with this medication was noneffective only for one patient.

Conclusion: These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics. Backround: Paliperidone is a second generation antipsychotic medication approved for the treatment of schizophrenia. It is a useful option in the treatment of the acute symptoms of schizophrenia and may also be used in patients previously unsuccessfully treated with other antipsychotics.

P-08-041 Association of antipsychotic dose with memory performance in chronic schizophrenia

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Objective: The examination of the effect of antipsychotic dosage on cognition and in particular memory in schizophrenia has produced contradictory findings. The aim of this study was to investigate the association of antipsychotic dose with memory performance in chronic schizophrenia using a cross-sectional design.

Methods: 107 patients (age = 42.3 years, SD = 10.12, range 18–64) with chronic schizophrenia from a psychiatric hospital were assessed with the Cambridge Automated Neuropsychological Test Battery (CANTAB) in tasks of pattern, spatial recognition and spatial working memory (PRM, SRM: per cent correct responses and SWM: between-search errors and strategy score). The Positive and Negative Syndrome Scale (PANSS) was used to measure symptomatology. Regression modeling was carried out to assess the effect of antipsychotic dose in chlorpromazine equivalents on memory performance, controlling for symptoms (PANSS), age, education and anticholinergic use.

Results: The patients' mean antipsychotic dose was 895.55 and their mean years of education 11.05 (SD = 3.46). Increased antipsychotic dose was significantly associated with worse PRM and SRM performance ($B = -0.01$, C.I. $= -0.02, -0.004$, $t = -3.29$, $df = 93$, $p = 0.001$ and $B = -0.006$, C.I. $= -0.01, -0.002$, $t = -2.66$, $df = 93$, $p = 0.009$, respectively). The correlations of antipsychotic dose with SWM measures SWM were not significant. The above results did not change after adjusting for atypical antipsychotic administration.

Conclusion: In conclusion, antipsychotic dose negatively correlated with recognition memory but not working memory performance in schizophrenia. Future prospective trials should further clarify the relationship of antipsychotic dose with specific memory deficits in patients with schizophrenia.

P-08-042 Cost-effectiveness of asenapine in the treatment of schizophrenia and bipolar disorder in Canada

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Objective: Asenapine is a new antipsychotic approved in Canada for the treatment of schizophrenia and bipolar disorder (SCZ and BPD). Asenapine has shown a comparable efficacy profile to atypical antipsychotics. However, in contrast to most atypical antipsychotics, it is associated with a favourable (metabolic) profile. The objective of this study was to assess the economic impact of asenapine compared to atypical antipsychotics in the treatment of SCZ and BPD in Canada.

Methods: A combined decision tree and Markov model was constructed to assess the cost-utility of asenapine compared with atypical antipsychotics. The decision tree takes into account the occurrence of extrapyramidal symptoms (EPS), the probability of switching treatment due to EPS, and the probability of gaining weight. The Markov model comprises the following states: long-term metabolic complications (diabetes, hypertension, CHDs (Coronary heart Disease), and stroke), fatal stroke, fatal CHD, and death by suicide or other causes. For SCZ, asenapine was also compared with olanzapine, quetiapine, ziprazidone and aripiprazole. For BPD, due to limited data on other antipisychotics, asenapine was compared with olanzapine only. Analyses were conducted from both a Canadian Ministry of Health (MoH) and a societal perspective over a five-year time horizon with yearly cycles.

Results: For both indications, asenapine is a dominant strategy (meaning more effective and less expensive) over olanzapine from both a MoH and a societal perspective. Compared to quetiapine, asenapine is also a dominant strategy in SCZ. Furthermore, asenapine has a favourable economic impact compared to ziprazidone and aripripazole in SCZ.

Conclusion: This economic evaluation demonstrates that asenapine is a cost-effective strategy compared to olanzapine and to most atypical antipsychotics used in Canada.

Policy of full disclosure: Jean Lachaine received research funds from Lundbeck. Dominque Gilbert, Maud Beillat and Helene Corson are employees at Lundbeck.

P-08-043 Glutamate levels in the associative striatum decrease with antipsychotic treatment in first-episode of psychosis

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Objective: Schizophrenia is a mental illness in which both glutamatergic and dopaminergic systems are thought to be involved. Using proton magnetic resonance spectroscopy (1H-MRS), our group has demonstrated an increase of glutamate levels in the associative-striatum (dopamine rich-region) of first-episode of psychosis (FEP) subjects. Nevertheless, it is unclear whether this increase persists after antipsychotic treatment. The aim was to compare glutamate levels in FEP patients, before and after antipsychotic treatment, with appropriate controls in the associative-striatum and the cerebellar cortex as a control region (negligible for dopamine).

Methods: Twenty-one antipsychotic-naïve FEP patients (age: 26.1 + −8.5, 12-males), and 18 age and gender similar controls (age: 24.5 + −5.1, 8-males) were included. Patients were treated with risperidone (3.45 + −1.27 mg/day) for 4-weeks with doses adjusted based on clinical judgment (PANSS pre-treatment = 94.7 + −13.3; post-treatment = 57.6 + −9.1, $p < 0.001$). Participants underwent two 1H-MRS studies in a GE-3T scanner (PRESS TE = 30 ms, TR = 2000 ms, 128 averages, voxels = 8 ml) centred in the right dorsal caudate and right cerebellar cortex in all subjects. Concentrations were estimated with LCmodel and corrected for cerebrospinal fluid proportion.

Results: Patients showed higher levels of glutamate during the antipsychotic-naïve condition versus controls in the associative-striatum ($T = -2.62$, $p = 0.01$). After antipsychotic treatment, patients showed a decrease in glutamate levels ($T = 2.18$, $p = 0.04$) and no differences with controls. There were no differences in glutamate cerebellar levels between all groups.

Conclusion: Our results indicate an increase of glutamate in the associative-striatum in FEP patients, showing a decrease after clinically effective antipsychotic treatment. These preliminary results suggest that higher glutamate levels in the associative striatum can be reversed with appropriate antipsychotic treatment. Moreover, the lack of change in the cerebellum suggests that the increase of glutamate in psychosis is not ubiquitous within the brain and may be associated with dopamine rich regions.

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P-08-044 A splitting mind: Imbalanced internal and external worlds in schizophrenia

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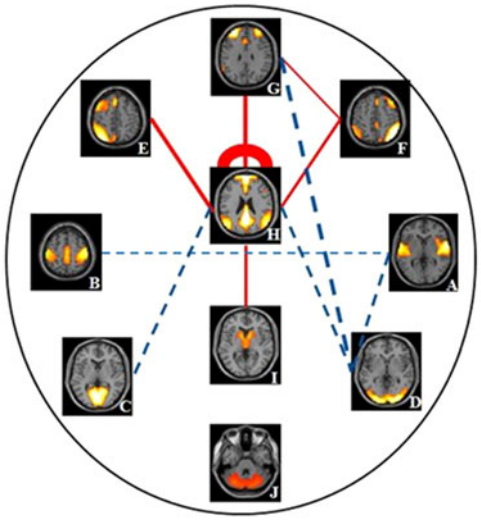
Objective: Brain dysconnection has been hypothesized to underlie the pathophysiology of schizophrenia. This study explores the pattern of functional dysconnections across whole-brain neural networks in a sample of 121 first-episode, treatment-naïve patients with schizophrenia by comparing to 103 healthy controls.

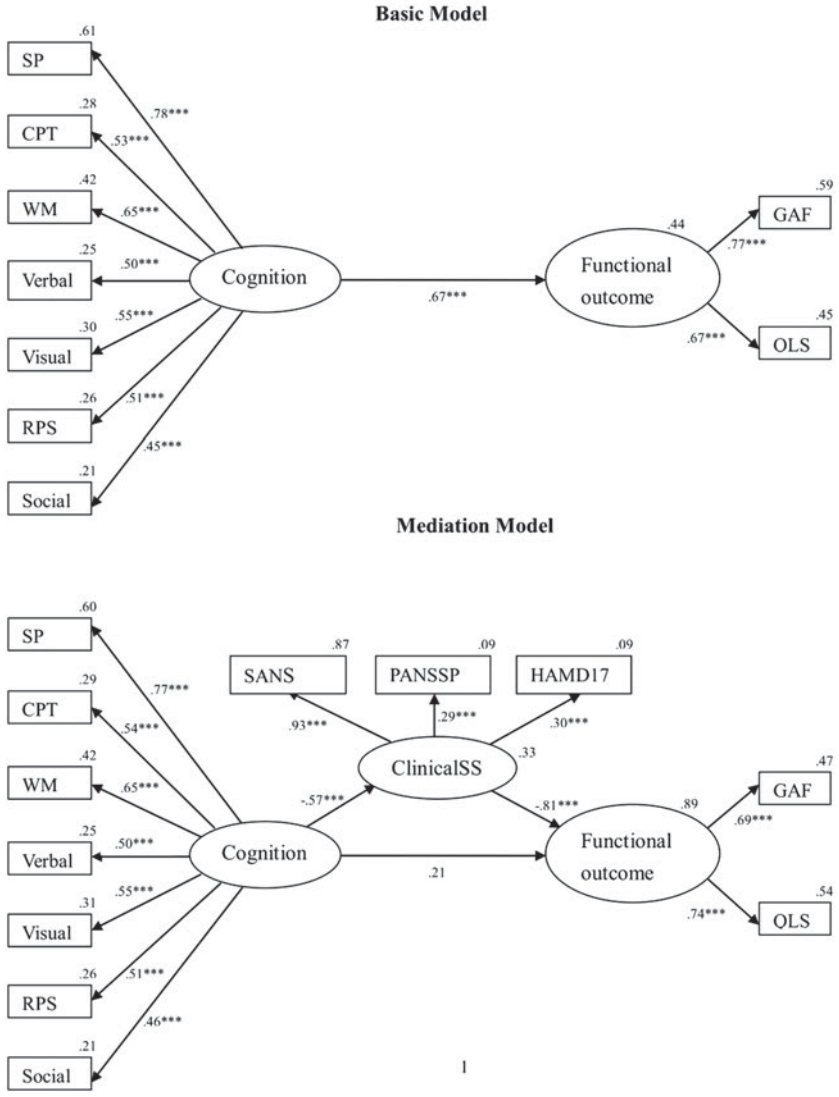
Methods: Resting-state functional connectivity was measured by using functional magnetic resonance imaging (fMRI). Group independent component analysis was applied to resting-state fMRI data to extract elementary functional clusters of the brain and the connectional relationships between these clusters were then evaluated. In the



Red: Increased functional connectivity in schizophrenia;
Blue: Decreased functional connectivity in schizophrenia

A: Auditory Network; B: Somatomotor Network; C: Primary Visual Network;
D: Extrastriate Visual Network; E: Left Dorsal Attention Network;
F: Right Dorsal Attention Network; G: Executive control and Salience Network;
H: Default mode Network; I: Thalamostrial System; J: Cerebellum

Fig. 1. Basic model and mediation model. Note: ***P < .001. Circles represent unobserved latent variables. Rectangles represent observed measured variables. Values are standardized path coefficients. The squared multiple correlation (R^2) value for the dependent variable appears above its circle or rectangle. SP: Speed of processing, CPT: Continuous Performance Test, WM: Working memory, Verbal: Verbal learning and memory, Visual: Visual learning and memory, RPS: Reasoning and problem solving, Social: Social cognition, GAF: Global Assessment of Functioning Scale, QLS: Quality of Life Scale, ClinicalSS: Clinical symptoms, SANS: Scale for the Assessment of Negative Symptoms, PANSSP: Positive score of the Positive and Negative Syndrome Scale, HAMD17: 17-item Hamilton Depression Rating Scale.



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patient group we found 29 abnormal functional connections, including 19 hyper-connections and 10 hypo-connections. To interpret these aberrant functional connections in terms of brain functionalities, we divided the whole brain into ten functional networks/areas and ascribed each functional cluster to one of these networks. Changed connections between functional clusters were thereby interpreted to abnormal connections between functional networks.

Results: Hyperconnectivity was observed within the default mode network (DMN) and between the DMN and other cognitive networks, whereas hypoconnectivity was predominantly associated with sensory networks. The data collectively suggest that information processing related to the external world (i.e. connectivity involving sensory networks) is compromised in company with increased connectivity related to the internal world (i.e. connectivity involving the DMN), and communications between the internal and external worlds are impaired in schizophrenia.

Conclusion: These findings imply distorted sensory perceptions and undermined coordination between perception and cognitive functions in the patient, and should provide a new angle to understand several core features of schizophrenia such as sensory processing deficits and positive symptoms like hallucination.

P-08-045 Ahi1 gene expression levels in mutant mice are directly correlated with levels of state anxiety and threat detection: Translational relevance to schizophrenia and autism

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Objective: Schizophrenia is characterized by substantial genetic contribution to its etiology. The Abelson helper integration site (AHI1) gene was previously shown by our group to be associated with schizophrenia in humans, with evidence for changes in its expression as the possible causative mechanism. Association with autism has also been reported. Therefore, we studied the behavioral consequences of expression alterations of this gene in various paradigms modeling different facets of schizophrenia, employing mice heterozygous (HET) for an Ahi1 knockout mutation.

Methods: Open field (OFT), elevated plus maze (EPMT), social interaction in pairs (SIIPT) and light dark box (LDT) tests were conducted on HET mice compared to littermates wild type (WT) mice.

Results: A consistent finding of our experiments was significantly reduced levels of situational anxiety in HET mice compared to WT mice. In the OFT, HET mice spent significantly more time in the arena center compared to WT mice ($p=0.02$). In the EPMT, HET mice, compared to WT mice, spent significantly more time in the maze open arms ($p=0.006$) and less time in the closed arms ($p=0.009$). In the SIIPT, pairs of unfamiliar HET mice spent significantly more time interacting with each other than corresponding pairs of unfamiliar WT mice, in the first, anxiety provoking encounter ($p=0.01$). This finding probably reflects less anxiety in the HET mice when encountering a potentially hazardous situation such as an unknown animal. Finally, in the LDT, HET mice spent significantly more time in the open lightened zone ($p=0.02$) than WT mice.

Conclusion: Our findings indicate that reduced expression of the Ahi1 gene in mice is associated with a decrease in perception of threatening situations, which may arise from reduced connectivity between the amygdala and other forebrain areas, including the cortex. This finding has been reported in several psychiatric disorders, including schizophrenia and autism.

P-08-046 G72 protein expression in peripheral blood as a diagnostic biomarker of schizophrenia

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Objective: To date, there is no peripheral biomarker for schizophrenia. NMDA hypofunction is implicated in the pathophysiology of schizophrenia. D-serine, a potent NMDA co-agonist, is metabolized by D-amino acid oxidase (DAAO), which is activated by DAAO activator (DAOA, or named G72). Theoretically, DAOA overactivation leads to NMDA hypofunction. This study examined whether peripheral G72 protein expression is characteristic of schizophrenia.

Methods: G72 protein level was measured in peripheral plasma in patients with schizophrenia, patients with bipolar I disorder, and healthy controls. Receiver operating characteristic (ROC) curve was conducted to determine the optimal cutoff values of G72 protein level for schizophrenia patients vs. healthy controls and vs. bipolar patients.

Results: Among all subjects, the G72 protein level was higher in schizophrenia ($\text{mean}=2.726\pm1.411$, $n=119$) when compared with healthy individuals (0.892 ± 0.415, $p<0.001$, $(n=42)$, but lower when compared with bipolar I patients (3.896 ± 2.103, $p=0.001$, $(n=51)$. The optimal cutoff value, 1.564, between schizophrenia and healthy subjects generated a sensitivity of 0.77 and specificity of 0.98 (area under curve [AUC] of ROC = 0.894). A cutoff of 4.318 differentiated all schizophrenia from bipolar I patients with a sensitivity of 0.41 and specificity of 0.87 (AUC = 0.659).

Conclusion: These findings provide the first peripheral diagnostic tool for schizophrenia. NMDA hypofunction as evident by over-activated G72 protein expression may serve as a common pathway for vulnerability of schizophrenia.

P-08-047 Influences of neurocognition and social cognition on functional outcome in patients with chronically stable schizophrenia: Mediated by positive, negative, and depressive symptoms

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Objective: The functional outcome of schizophrenia is affected by multiple factors, among which cognition and clinical symptoms are regarded as important determinants suggested by previous studies that link cognition to outcome. The relationship between cognitions (both neuro- and social- cognitions) and outcome in the existence of clinical symptoms remains unclear. The current study employed structural equation modeling to examine more directly whether clinical symptoms mediate the relationship between cognition and functional outcome in patients with schizophrenia.

Methods: Three hundred and two patients with chronically stable schizophrenia received evaluation of cognition (using MATRICS Consensus Cognitive Battery, including 7 domains covering neurocognition and social cognition), clinical symptoms (including positive, negative and depressive symptoms), and functional outcome assessed by Global Assessment of Functioning Scale and Quality of Life Scale.

Results: Structural equation modeling identified clinical symptoms as a mediator of the relationship between cognition (including all 7 domains of MATRICS) and functional outcome in schizophrenia. The relationship between cognition and functional outcome was significant in the basic model, but was not significant in the mediation model that included clinical symptoms. The mediation model demonstrated that the link between cognition and functional outcome was mediated by clinical symptoms, mainly negative symptoms.

Conclusion: The present study suggests that clinical symptoms mediate the influence of neurocognition and social cognition on functional outcome in schizophrenia. Future studies should also consider the interaction with other potential mediators to increase the predictive power.

P-08-048 Effect of lurasidone on weight and metabolic parameters: Results from pooled short-term placebo-controlled trials in schizophrenia

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Objective: To evaluate the effect of lurasidone treatment of subjects with schizophrenia on weight and metabolic parameters.

Methods: Data were pooled from 7 DB, placebo-controlled trials, including 4 with active comparators, of subjects who met DSM-IV criteria for schizophrenia with an acute exacerbation. The analysis sample consisted of subjects treated with lurasidone (dose range, 20–160 mg, total $N=1508$); haloperidol 10 mg ($N=72$); olanzapine 15 mg ($N=122$); risperidone 4 mg ($N=65$); quetiapine XR ($N=119$); and placebo ($N=708$).

Results: During 6 weeks of treatment, the mean change in weight, in kg at LOCF-endpoint, was +0.43 for lurasidone (pooled), +0.02 for haloperidol, +4.15 for olanzapine, +2.09 for quetiapine-XR, +0.20 for risperidone, and −0.02 for placebo. The proportion of patients experiencing ⩾7% weight gain was 3.3% for placebo, 4.2% for haloperidol, 4.8% for lurasidone, 6.2% for risperidone, 15.3% for quetiapine XR, and 34.4% for olanzapine. Median endpoint changes in lipids were as follows: triglycerides (mg/dL), −4.0 for lurasidone, −3.0 for haloperidol, +25.0 for olanzapine, +4.0 for risperidone, +9.5 for quetiapine XR, and −6.0 for placebo; and total cholesterol (mg/dL), −5.0 for lurasidone, −8.0 for haloperidol, +9.0 for olanzapine, +6.5 for risperidone, +6.0 for quetiapine XR, and −5.0 for placebo. Median LOCF-endpoint change in glucose (mg/dL) were similar for combined lurasidone (0.0) and placebo (0.0), and somewhat higher for haloperidol (+2.0), olanzapine (+4.0), risperidone (+3.0), and quetiapine XR (+3.0).

Conclusion: In these pooled analyses of short-term studies, treatment with lurasidone was associated with minimal increases in weight and BMI. Decreases in median total cholesterol and triglycerides were also observed.

Policy of full disclosure: Dr. Pikalov, Silva, Cucchiaro, Hsu, Xu, and Loebel are full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-049 Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind study

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Objective: To evaluate the efficacy and safety of lurasidone (LUR) vs. quetiapine XR (QXR) in preventing relapse in subjects with schizophrenia.

Methods: After completing an initial DB, 6 week trial with LUR (80 mg; 160 mg) or QXR (600 mg), subjects received 12 months of DB, flexible once-daily doses of LUR (40–160 mg) vs. QXR (200–800 mg). The primary a priori time-to-relapse comparison was between subjects treated with LUR (n = 139) and QXR (n = 79) who were clinical responders after acute treatment, using a Cox proportional hazards model, with a pre-specified non-inferiority margin for the risk of relapse hazard ratio of 1.93.

Results: LUR was non-inferior to QXR in risk for relapse over the 12 month treatment period (hazard ratio 0.728, 95% CI [0.410, 1.295]). Risk of relapse in LUR treated subjects was reduced by 27.2% (hazard ratio 0.728) compared with QXR. The Kaplan-Meier estimate of the probability of relapse was lower for LUR vs. QXR (0.237 vs. 0.336). Rates of adverse events ⩾5% in the LUR group were akathisia (12.6%), headache (10.6%), insomnia (7.9%), anxiety (6.0%), parkinsonism (6.0%), and weight increased (6.0%). At 12 months, treatment with LUR and QXR, respectively, resulted in a mean change in weight of +0.7 vs. +1.2 kg; a median change in cholesterol of 0.0 vs. +4.0 mg/dL; and a median change in triglycerides of −18.0 vs. −7.0 mg/dL. There were no clinically meaningful changes in other laboratory or ECG parameters on either drug.

Conclusion: This DB study demonstrated non-inferiority of lurasidone to QXR in prevention of relapse over a 12 month period, with a 27.2% reduction in relapse risk compared with QXR. Lurasidone was associated with minimal adverse effects on weight and metabolic parameters.

Policy of full disclosure: Dr. Loebel is a full-time employee of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-050 Efficacy of lurasidone in schizophrenia: Factor analysis of pooled short-term trials

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Objective: To evaluate the efficacy of lurasidone across five previously validated PANSS factors (positive, negative, disorganized thought, hostility, and depression/anxiety).

Methods: A post-hoc factor analysis was performed on pooled data from 5 positive six-week, double-blind, placebo-controlled trials of subjects hospitalized with an acute exacerbation of schizophrenia who were randomly assigned to fixed, once-daily doses of lurasidone 40 mg (n = 290), 80 mg (n = 334), 120 mg (n = 290), 160 mg (n = 121), or placebo (n = 497). Data were analyzed using a mixed model repeated measures (MMRM) model with an unstructured covariance matrix. Effect sizes (ES) were calculated from an ANCOVA analysis (LOCF-endpoint) as the between-treatment group difference in LS mean change scores divided by the pooled standard deviation of the change scores.

Results: Baseline characteristics were highly similar in the pooled lurasidone (n = 1035; mean PANSS total score, 96.1) and placebo (n = 497; mean PANSS total score, 96.1) groups. At endpoint, treatment with lurasidone was associated with significantly greater improvement in the PANSS total score compared with placebo (−22.6 vs. −12.8; $P < 0.001$; ES, 0.42). Significantly greater endpoint improvement ($P < 0.001$ for all comparisons) was observed for lurasidone versus placebo across all five PANSS factors. Changes for lurasidone vs. placebo were −8.4 vs. −6.0 (ES, 0.35) in the PANSS positive factor; −5.2 vs. −3.3 (ES, 0.32) in the PANSS negative; −4.9 vs. −2.8 (ES, 0.40) for disorganized thought; −2.7 vs. −1.6 (ES, 0.34) for hostility; and −3.2 vs. −2.3 (ES, 0.29) on depression/anxiety factors. Lurasidone160 mg dose was consistently associated with the highest effect size for each factor.

Conclusion: In this pooled, post hoc factor analysis of placebo-controlled trials, treatment with lurasidone across the daily dosing range of 40–160 mg, was effective in improving all 5 PANSS factors, suggesting efficacy across the full spectrum of symptoms associated with schizophrenia.

Policy of full disclosure: Drs. Cucchiaro, Silva, Mao, Pikalov, and Loebel are all full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-051 An in vitro analysis of disintegration times of different formulations of orally disintegrating olanzapine

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Objective: Orally disintegrating tablet (ODT) forms of medication are sometimes used as alternatives to standard oral tablets for patients who have difficulty swallowing, those who need to have ingestion verified, and those who may resist other drug product forms (e.g. injection). ODTs are a tablet or wafer form of medication that disintegrate in the mouth, aided only by saliva. ODTs can disperse in as little as 1 to 2 seconds or as long as 2 to 3 minutes, depending on the different fast dissolve/disintegration technologies used to manufacture the tablets. Orally disintegrating olanzapine (ODO) is manufactured by several different companies, using different formulations and processes. The objective of the study is to investigate differences in disintegration time of these tablets which may potentially impact clinical parameters such as patient acceptance and adherence to treatment.

Methods: Six types of ODO, along with Risperdal M-Tab as an external comparator, were evaluated for formulation composition, manufacturing method, disintegration and dissolution characteristics, expiration dates, packaging and formulation differences in comparison with the freeze-dried Zydis/Velotab formulation of ODO. Automated dissolution test equipment, DISTEK DISBA0045 and DISBA0046 with an Opt-Diss UV fiber optic SPEC0088 attachment, was used to capture the various ODT dissolution rates by measuring real time release of the active ingredient. Additionally, a high speed video camera was used to capture disintegration times of ODO products in simulated saliva held at 37 °C.

Results: Time required for initial and complete disintegration, with 95% confidence intervals, will be presented.

Conclusion: The in vitro disintegration test is a proxy for the disintegration process in a patient's mouth. Differences found in formulation and manufacturing process of ODO may be associated with different disintegration times which may potentially impact their use in clinical practice.

Policy of full disclosure: Dr. McDonnell is a full-time employee of Eli Lilly and Company. Research reported was sponsored/funded by Eli Lilly and Company.

P-08-052 Patient satisfaction and caregiver burden related to olanzapine long-acting injection

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Objective: To assess patients' attitudes toward and satisfaction with olanzapine long-acting injection (LAI) and determine effects on caregiver burden.

Methods: Data were analyzed from 2 long-term, open-label studies. Study 1 (N = 931) assessed long-term safety up to 6.5 years. Study 2 was a 2-year randomized study comparing the effectiveness of olanzapine LAI (N = 264) and oral olanzapine (N = 260). Measures included the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ) in both studies and the Drug Attitude Inventory (DAI-10) and Burden Assessment Scale (BAS; a caregiver self-report measure) in Study 2, with assessments at 6- to 12-month intervals.

Results: In Study 1, 73% of patients were satisfied with olanzapine LAI at first assessment, 87% at 6 years, and 73% at patient's endpoint.

In Study 2, 75% were satisfied at first assessment, 88% at 2 years, and 73% at patient's endpoint (similar to oral-treated patients). On the DAI-10, >80% of LAI-treated patients endorsed positive statements at each time point, including 90% stating that ''the good things about the medication outweigh the bad'' at 2 years. On the BAS, caregivers reported statistically significant improvement in their overall burden at 2 years (p values < 0.001).

Conclusion: Results suggest that olanzapine LAI is viewed positively by patients and caregivers.

Policy of full disclosure: Dr. McDonnell is a full-time employee of Eli Lilly and Company.

P-08-053 Polypharmacy to counteract antipsychotic-induced non-motor side effects: A systematic review

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Objective: In contrast to antipsychotic-induced extrapyramidal side effects, the data are still limited on concomitant medications to counteract non-motor side effects in schizophrenia. We therefore carried out a systematic review to synthesize the evidence on the management of antipsychotic-induced non-motor adverse effects with polypharmacy.

Methods: The following terms were included in a systematic search of EMBASE, MEDLINE, PubMED, PsycINFO and the Cochrane Library: (schizophrenia and adjunctive) or (schizophrenia and augmentation) or (schizophrenia and combination) or (schizophrenia and polypharmacy) or (schizophrenia and polytherapy). As a final term for each search, the following adverse effects were added as potential targets of polypharmacy: diabetes, dyslipidemia, metabolic, obesity, weight gain, sexual dysfunction, prolactin, hypotension, and sedation (last search: December 2011). Studies were included if (1) they targeted subjects with a diagnosis of schizophrenia or related psychotic disorders, and (2) they reported on the reduction of antipsychotic-related non-motor adverse effects using concomitant medications as a primary outcome. Cross-referencing of the identified articles was also performed.

Results: From the initial list of 2051 articles, 113 studies met the inclusion criteria. Of these, nine, five, two, two, and two double-blind randomized controlled trials (DBRCTs) showed the efficacy of adjunctive metformin, topiramate, aripiprazole, reboxetine, and sibutramine to counter metabolic side effects of antipsychotics, respectively. These studies lasted for 6–16 (mean, 11) weeks with the number of participants of 15–207 (mean, 56). One DBRCT and three open-label trials demonstrated that concomitant aripiprazole was efficacious for hyperprolactinemia induced by other antipsychotics. Sildenafil has been reported to improve sexual dysfunction in one DBRCT and one open-label trial.

Conclusion: Although additional drug costs, drug interactions, and side effects of concomitant drugs themselves need to be carefully taken into account and more studies are indicated, polypharmacy aiming for the reduction of antipsychotic-induced non-motor adverse effects may warrant an individualized clinical consideration.

P-08-054 Descriptive study of antipsychotic drugs use in psychiatry outpatients

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Objective: The goal of this study is to know in the current real clinical practice how is the prescription of antipsychotic drugs in outpatients with psychotic disorders.

Methods: An observational and descriptive cross-sectional study, with a CRF developed to collect the specific data which was administered during the period from February to May 2011 in 4 differents Psychiatry Mental Health Clinic of Balearic Island in Spain (Manacor, Emili Darder, Pere Garau and Menorca) to patients with psychotic disorders who were prescribed antipsychotic drugs.

Results: The sample obtained were 205 patients with the following profile: a man (62%) 43.2 + 11.9 years old, with paranoid schizophrenia (61.1%) over 5 years evolution (77%) with no substance use disorder (83.7%) and treated with atypical antipsychotics (99.5% of cases). The 38% of patients had oral more long acting injection antipsychotic. The patients under 34 years old were the most frequently performed treatment with antipsychotic long-acting injection ($p < 0.05$). Risperidone, paliperidone and olanzapine were the most frequent oral antipsychotics used.

Conclusion: 1. The use of oral antipsychotics in combination with intramuscular antipsychotics is common in current clinical practice, 2. The age group between 25 and 34 years old is having more problems with adherence to treatment and more frequently receiving intramuscular antipsychotic medication as long-term outpatient treatment, 3. Male patients have a percentage of adherence slightly lower than women and tend to receive more often antipsychotic injectable long-term, 4. 76% of patients had a good compliance and were satisfied with their treatment in both gluteal or deltoid administration.

P-08-055 Benefits of switching schizophrenic patients from olanzapine to aripiprazole

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Objective: It is well-known that olanzapine easily cannot be used in schizophrenic patients with hyperglycemia and is contraindicated for patients with diabetes in Japan. Aripiprazole has advantages compared to other antipsychotics regarding side-effects. Schizophrenic patients switching from an agent with an anticholinergic profile to another could have risk of cholinergic rebound symptoms. Therefore, longer taper of the anticholinergic agent may be necessary because of their different receptor-affinity profiles. The purpose of the present study was to evaluate if switching could be successful after switching from olanzapine to aripiprazole concomitantly with diphenhydramine, an antihistaminergic agent.

Methods: Patients, diagnosed with schizophrenia (DSM-IV criteria) and required a change in olanzapine therapy because of persistent symptoms and troublesome side-effects, were included for the study. Aripiprazole was given at a dose of 6 to 12 mg/day in addition to olanzapine, and then olanzapine was tapered down at a rate not exceeding 2.5 mg/week and aripiprazole was up-titrated over switching, after which aripiprazole was maintaned between 6 and 24 mg/day through the evaluation period. Diphenhydramine was used between 0 and 150 mg/day. Clinical efficacy was assessed with PANSS, CGI-S, CGI-I and GAF at weeks 4 and 8 after switching. Continuation rate of aripiprazole use was investigated. Serum fasting glucose, HbA1C level, and fasting triglyceride were also evaluated.

Results: Of 14 patients, 9 patients (64.3%) successfully completed the switch and continued aripiprazole treatment to 8-week after switching. Although 1 patient showed exacerbation in symptoms caused by rebound, discontinuations due to adverse events of aripiprazole were not observed.

Conclusion: Switching from olanzapine to aripiprazole generally resulted in retention of efficacy and improvements in tolerability across the evaluation period. Most notably, management of rebound effects by switching was achieved. This would be due to gradual discontinuation of the pre-switch medication and concomitant use of diphenhydramine to avoid rebound symptoms.

Policy of full disclosure: Speakers': Otsuka, Eli Lilly, GSK, Ds-pharma.

P-08-056 Altered levels of endocannabinoids in postmortem human brain of schizophrenic subjects

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Objective: Numerous studies have implicated the endocannabinoid (EC) system in the pathophysiology of schizophrenia. Some ECs have been measured in blood and cerebrospinal fluid of schizophrenic

subjects but to the date, there is no information about the status of EC levels in schizophrenics' brain tissue. The aim of this study was to evaluate the EC levels in postmortem cerebellum (CB), hippocampus (HC) and prefrontal cortex (PFC) of schizophrenics and matched controls. To investigate the effect of the antipsychotic (AP) treatment, schizophrenics who gave negative results for antipsychotics in the postmortem toxicologicology were considered AP-free.

Methods: Brains from 19 patients with diagnosis of schizophrenia (DSM-IV), and 19 controls matched by age, gender and postmortem delay were used. The ECs were determined in brain homogenates lipid fraction by quantitative liquid chromatography with tandem mass spectrometric detection. The levels of the two main ECs, 2-arachidonoylglycerol (2AG) and arachidonoylethanolamide (anandamide, AEA) were measured.

Results: Increased levels of 2AG were observed in schizophrenics compared to controls in all brain areas, reaching significant values in HC (2375 ± 395 vs. 1415 ± 237 pmol/g; $p = 0.04$) and PFC (1230 ± 233 vs. 519 ± 89 pmol/g; $p = 0.01$). 2AG levels remained increased in HC and PFC of AP-free schizophrenics, while reversed to control values in the HC of AP-treated subjects. AEA levels were lower in schizophrenics when compared to controls in all brain areas. This decrease was statistically significant in CB (297 ± 31 vs. 451 ± 45 pmol/g; $p = 0.009$) and HC (265 ± 31 vs. 400 ± 31 pmol/g; $p = 0.004$). When the schizophrenic group was subdivided, a decrease in AEA levels was found in the PFC of AP-treated schizophrenics (219 ± 36 vs. 346 ± 31 pmol/g; $p = 0.02$) but not in AP-free subjects (310 ± 49 pmol/g).

Conclusion: These results demonstrate that AEA and 2AG levels are altered in some brain areas in schizophrenia. Moreover, these data provide further evidence that the chronic antipsychotic treatment is able to modulate the EC brain levels.

P-08-057 Aripiprazole treatment and plasma levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, and catecholamine metabolites in first-episode untreated Japanese schizophrenia patients

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Objective: We investigated the effects of aripiprazole on plasma levels of brain-derived neurotrophic factor (BDNF) and catecholamine metabolites in first-episode untreated schizophrenia patients.

Methods: The subjects were 50 Japanese first-episode untreated schizophrenia patients who met the DSM-IV-TR criteria and were treated with aripiprazole monotherapy. Twenty-nine were male and 21 were female. The age was ranged from 21 to 42 yr (mean ± S.D.; 30.8 ± 5.3 yr). The plasma levels of catecholamine metabolites were measured by HPLC-ECD. The plasma BDNF levels were measured by ELISA. The genotyping (BDNF Val/Met) was determined by direct sequence around the region. The study was approved by the Ethical Committee of the UOEH.

Results: Treatment with aripiprazole for 8 weeks significantly increased plasma BDNF levels. It also changed plasma levels of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG). A negative correlation was also observed between duration of psychosis (DUP) and plasma BDNF levels. No correlation was however observed between plasma BDNF levels and the dose of aripiprazole. In addition, twelve of 50 patients were longitudinally measured plasma levels of catecholamine metabolites and BDNF. Plasma HVA increased at week 2, and decreased at week 8 comparing with baseline. Plasma MHPG increased at week 8.

Conclusion: To the best of our knowledge, this is the first report showing that aripiprazole increases plasma levels of BDNF and MHPG in first-episode untreated schizophrenia patients, which might be related to the improvement of negative symptoms of schizophrenia and cognitive functions. Furthermore, the BDNF Val66Met polymorphism was independent of the response to aripiprazole.

P-08-058 Assessment of subjective well-being and safety in patients with antipsychotic-naïve first-episode schizophrenia treated with blonanserin: One-year open-label trial

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Objective: Blonanserin is a novel atypical antipsychotic that exhibits a potent antagonistic activity at dopamine D2, 3 and serotonin 5-HT2A receptors. The purpose of this study was to assess the subjective well-being and safety in patients with antipsychotic-naïve first-episode schizophrenia treated with blonanserin for one year.

Methods: Twenty-four antipsychotic-naïve patients with first-episode schizophrenia participated in this study. Blonanserin (2–24 mg/day) was given in an open label design for 12 months. Psychopathology, subjective well-being, and safety were evaluated at baseline, 2, 6, and 12 months. Psychopathology was assessed by Positive and Negative Syndrome Scale (PANSS). Subjective well-being was evaluated by the Subjective Well-being Under Neuroleptic Treatment Scale Short form-Japanese version (SWNS-J). Safety assessments included laboratory tests, body weight, Body Mass Index (BMI), and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS). This study was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Thirteen patients (6 males and 7 females; mean age, 28.2 ± 5.6 years) completed the study. The mean blonanserin dose was 4.2 ± 3.0 mg/day at 12 months. Significant improvements from baseline to endpoint were reported for all items on the PANSS ($p < 0.01$) and SWNS-J ($p < 0.05$). In the laboratory tests, the values of alkaline phosphatase significantly increased from baseline ($p < 0.05$). In addition, high density lipoprotein cholesterol and fasting blood sugar significantly decreased ($p < 0.05$), but all of these data remained within the normal range. Although mean body weight and BMI increased from baseline, the rate of weight gain was only 6.1%. There was no significant change in the DIEPSS score.

Conclusion: Blonanserin produced favorable long-term outcomes and good safety profiles in patients with antipsychotic-naïve first-episode schizophrenia. The results suggest that blonanserin may be useful in the management of first-episode schizophrenia.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-08-059 Antidepressant and anxiolytic effects of quetiapine strongly correlate to neuropeptide Y increase and corticotropin-releasing hormone decrease in CSF from schizophrenic patients

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Objective: NPY and CRH play a role in the CNS physiology/pathophysiology and in the mechanisms of action of antidepressant/antipsychotic drugs. Early data showed increased NPY in CSF from schizophrenic patients and NPY changes by antipsychotics in rodent brain. In depression, NPY is decreased in CNS from depressed patients and animal models of depression, chronic stress and PTSD. Conversely, ECT, lithium and antidepressants increase NPY. In view of these findings we investigated if (1) quetiapine, an antipsychotic efficient also in affective disorders would modify NPY and CRH in CSF of schizophrenic patients, and (2) the effects on NPY and CRH will correlate to changes in depression and anxiety, symptoms that are common both in schizophrenia and affective disorders.

Methods: Twenty-two DSM-IV schizophrenics(age 35.9 ± 7.4 y; illness duration 20.3 ± 24.8 m), diagnosis confirmed with Structured Clinical Interview participated. Patients were assessed with PANSS at baseline and weekly thereafter. Lumbar puncture was performed at

baseline and after 4 weeks of 600 mg/day quetiapine. NPY-like immunoreactivity (-LI) and CRH-LI were determined by RIA.

Results: PANSS total score decreased > 20%. Quetiapine treatment was associated with an NPY-LI increase and CRH-LI decrease (ps < 0.01). Stepwise multiple regression analysis revealed that Δ NPY-LI and Δ CRH-LI levels and their ratios predicted 63% ($p < 0.001$) of the Δ PANSS total score variability; Δ NPY-LI 42% of the Δ PANSS anxiety items ($p < 0.05$) and Δ CRH-LI 40% of the Δ PANSS depression items ($p < 0.05$).

Conclusion: Quetiapine effects on NPY and CRH correlated strongly with the decrease in the depression and anxiety PANSS items. Since psychiatric diagnoses are generally clusters of symptoms of various durations and there are hardly any pathognomonic signs, our approach to focus on specific symptoms, regardless of diagnosis, would seem to be a more fruitful approach to elucidate the underlying neurobiology.

P-08-060 Effects of discontinuation of long-term biperiden use on cognitive function and quality of life in schizophrenia

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Objective: The high use of long-term antiparkinsonian anticholinergic drugs with antipsychotics has been identified as an important issue in the treatment of schizophrenia in Japan. The aim of this study was to evaluate the effects of gradual discontinuation of biperiden, an anticholinergic drug, on cognitive function and quality of life (QOL) in schizophrenia.

Methods: Thirty-nine schizophrenic patients who had received one or two kinds of second-generation antipsychotics (SGAs) with concomitant biperiden for at least 3 months were enrolled. Before and 4 weeks after discontinuation of biperiden, the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) and the Schizophrenia Quality of Life Scale (SQLS-J) were administered. Clinical evaluation also included the Positive and Negative Syndrome Scale (PANSS). To compare the practice effect on BACS-J, 10 chronic patients with schizophrenia were assessed without tapering biperiden.

Results: Biperiden was discontinued safely in most patients receiving an SGA (N = 24), and no emergent extrapyramidal symptoms (EPS) were observed. Significant improvements were shown in attention, processing speed, and composite score, as measured by the BACS-J without practice effect. In addition, the psychosocial condition score on the SQLS-J and the general psychopathology score on the PANSS significantly improved after biperiden discontinuation. However, exacerbation in clinical symptoms and emergent EPS were observed in patients taking more than two kinds of SGAs (N = 5).

Conclusion: Discontinuation of long-term biperiden use may be warranted in patients with schizophrenia treated with a single SGA, as it may improve cognitive function, subjective QOL, and psychiatric symptoms with no significant adverse effects. However, caution should be paid when tapering biperiden in patients treated with more than two kinds of SGAs, since it may worsen psychotic symptoms or motor function.

P-08-062 Multiple behavioral deficits reminiscent of schizophrenia in mice deficient in DISC-M (disrupted in schizophrenia matsuzawa), a gene encoding a transcriptional regulator

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Objective: We have recently reported a schizophrenic patient with a de novo mutation, a balanced chromosome translocation [t (4; 13)(p16.1; q21.31)]. We attempted to determine the break point within chromosome 4 and found that it locates at the upstream region of a gene encoding a putative transcriptional regulator protein, and we named the gene DISC-M (Disrupted_In_Schizophrenia, Matsuzawa). However, it remains unknown whether and how the functional loss of the gene really impacts on the etiology of schizophrenia in the patient.

Methods: To get insights into the question, we analyzed mice lacking the corresponding gene using multifaceted approaches in the current study. In addition, we have conducted a comprehensive gene expression analysis of the brain from the KO mice.

Results: The homozygous mice were born in a mendelian ratio by the cross between heterozygous mice. Behavioral assessments showed that they are hyperactive in the open field test and other tests, and that they are highly sensitive to MK801, an NMDA antagonist. In addition, the mice have a severe impairment in auditory fear conditioning test, suggesting deficits in learning/memory abilities. In contrast, we have found abnormalities in neither prepulse inhibition nor social interaction. Of interest, but neurogenesis in hippocampal dentate gyrus of the young adult mice was significantly decreased, although the tissue architecture seemed to be not different from the control mice. Furthermore, we identified DISC-M-regulated genes, many of which are related to neuronal function or development.

Conclusion: In conclusion, some of phenotypes of the mice seem to be reminiscent of schizophrenia. Since biological functions of the gene are still largely unknown, further investigation will be needed to reveal the mechanism of the abnormalities and the relationship between schizophrenia and this gene.

P-08-063 Kynurenic acid in cerebrospinal fluid, plasma and urine of healthy male volunteers

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Objective: Kynurenic acid (KYNA) is a neuroactive tryptophan end-metabolite, produced both in peripheral and brain tissues, with poor blood-brain crossing properties. Its precursor kynurenine however easily crosses the blood-brain barrier. KYNA is elevated in the brain and cerebrospinal fluid (CSF) of patients with schizophrenia and is currently being investigated for its possible role in schizophrenia pathophysiology. In the present study we compare the levels of KYNA in CSF, plasma and urine of healthy male volunteers and correlate these levels to putative confounders.

Methods: Plasma (collected at five time points over 24 hours starting/ending at 08:00 am), urine (24-hour) and CSF (collected at the end-point 08:00 am) from 30 healthy male volunteers were analyzed for KYNA content using HPLC with fluorescence detection.

Results: The mean 24-hour plasma and urine KYNA levels were positively correlated ($r = 0.41$, $p = 0.03$). No correlations were observed between CSF and plasma levels of KYNA. A trend towards significance was observed between CSF and urine KYNA levels ($r = 0.33$, $p = 0.08$). We found no correlations between the CSF, plasma or urine levels of KYNA and age, weight, height, body mass index or coffee consumption. However, there were negative associations between nicotine use and the urine ($r = -0.45$, $p = 0.02$) and CSF ($r = -0.47$, $p = 0.01$) levels of KYNA.

Conclusion: The plasma and urine levels of KYNA were positively correlated, while CSF KYNA levels did not correlate to plasma or urine KYNA content in healthy male volunteers. Interestingly, the use of nicotine was negatively associated with both CSF and urine levels of KYNA. In line with this, chronic exposure to nicotine reduces KYNA content in the rodent brain [1]. Nicotine use might thus be an important confounding factor in clinical studies investigating kynurenine metabolism.

1. Zielinska et al. 2009. PMID: 19616570.

P-08-064 Endogenous kynurenic acid induces a reduction in parvalbumin immunoreactivity in the rat frontal cortex

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Objective: Reduced expression of GABAergic parvalbumin interneurons and GAD67, a GABA synthesizing enzyme, is one of the most replicated and consistent findings in schizophrenia. Recent studies also confirm that kynurenic acid (KYNA), an endogenous antagonist

of N-methyl-D-aspartate and β7 nicotinic (NMDA) receptors, is elevated in the cerebrospinal fluid and post mortem brain of these patients. Experimental studies report that blockade of NMDA receptor with phencyclidine or ketamine leads to similar dysregulations in GABAergic circuits and are thus, suggested to be a core feature of the illness.

Methods: The aim of this study was to investigate if pharmacological sub-chronic elevation of endogenous KYNA levels decreases brain expression of GAD67 and GABAergic parvalbumin interneurons. For this purpose, western blotting was used to quantify tissue levels of GAD67 and parvalbumin proteins in brain tissue. Localization of protein changes was visualized by immunohistochemistry.

Results: Rats were treated twice daily (12-h interval) for 6 days with saline or kynurenine (s.c.), the immediate precursor of KYNA, in a dose (100 mg/kg) known to induce a 2-fold increase in brain KYNA levels. Rats with subchronically elevated KYNA levels displayed reduced levels of parvalbumin protein in the cingulate and piriform cortices.

Conclusion: These data suggest that the dysfunction of parvalbumin interneurons observed in patients with schizophrenia might be a direct consequence of elevated levels of KYNA in these patients. In addition, present results support subchronic elevation of brain KYNA as a valid animal model of schizophrenia.

P-08-065 Anhedonia as an influencing factor to social functioning and quality of life at patients with schizophrenia

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Objective: study the role of anhedonia in negative affect to social functioning and quality of life in patients with schizophrenia and postpsychotic depression.

Methods: scale for anhedonia assessment Snaith-Hamilthon (1995), GAF (2002), Sheehan Disability Scale (1983).

Results: 205 patients were divided into comparable groups. 115 patients with negative syndrome of paranoid schizophrenia (NSH), 90 patients with postpsychotyc depression (PPD). Men – 63.9%, women – 36.1%. The average age was 32.85 ($\pm$0.66) years. 58.53% of patients had anhedonia. NSH group anhedonia observed in 60 patients (52.17%), PPD group – in 60 patients (66.66%). The anhedonia level in all groups reached moderate (22.16 $\pm$ 0.38). In all groups the disability level reached of severe. NSH-A group the disability level was significant ($p \leqslant 0.05$). NSH-A group observed significant disturbances of cognitive functioning and ''communication'' ($p < 0.05$; $r = 0.329$), ''family life'' ($p < 0.01$; $r = 0.385$) compared with patients without anhedonia. PPD-A group the cognitive functioning was a considerable. In the ''communication'' ($p < 0.01$; $r = 0.428$) and ''family life'' ($p < 0.01$; $r = 0.598$) revealed moderate disturbance, but these disturbances were significant against groups of patients without anhedonia. In PPD and NSH groups observed a significant reduction of cognitive functions with respect to education and socioeconomic status. Was heavy cognitive impairment that interferes with activities in various areas of social and professional activities or teaching. Was found poor quality of life in patients with anhedonia in all groups of study. NSH-A group the quality of life was significantly ($p \leqslant 0.05$; $r = -0.282$). In patients without anhedonia in all groups was satisfactory quality of life.

Conclusion: anhedonia presence in the clinical picture of schizophrenia makes a favorable foundation for the impairment of cognitive performance, breach of communication and inability to perform their household and family responsibilities, and degrades the quality of life of patients.

P-08-066 The psychopharmacology algorithm project at the Harvard South shore program: An update on schizophrenia

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Objective: This is an update of the algorithm for schizophrenia from the Psychopharmacology Algorithm Project at the Harvard South Shore Program.

Methods: A literature review was conducted focusing on new data since the last published versions (1999–2001).

Results: For new-onset schizophrenia, the first-line antipsychotics, recommended with very slight preference, are amisulpride, aripiprazole, risperidone, or ziprasidone. If the trial of the first antipsychotic cannot be completed due to intolerance, try another until one of the four is tolerated and given an adequate trial of 4–6 weeks. There should be evidence of bioavailability. If there is an unsatisfactory response to this adequate trial, try a second monotherapy with any antipsychotic. If there is another unsatisfactory response, and at least one of the first two trials was with risperidone, olanzapine, or a first-generation antipsychotic (FGA), then clozapine is recommended for the third trial. If neither trial was with one of these three possibly slightly more effective antipsychotics, a third trial prior to clozapine should occur, using one of these options. If there is an unsatisfactory response to monotherapy with clozapine (with dose adjusted using plasma levels), consider adding risperidone, lamotrigine, or electroconvulsive therapy. If one of these augmentations is unsuccessful, possible options are to try another, try adding memantine or omega-3-fatty acid to clozapine, switch from clozapine to another antipsychotic not yet tried (especially aripiprazole), combine an FGA with mirtazapine, or combine risperidone with celecoxib. Finally, combinations of antipsychotics not including clozapine may be tried.

Conclusion: Though all recent major guidelines for the pharmacotherapy of schizophrenia propose that two monotherapy antipsychotic trials should occur followed by a trial of clozapine, there is variation in the manner in which clinicians are encouragned to accomplish these steps. The authors argue that the above is an evidence-supported approach.

Policy of full disclosure: Osser – no financial conflict of interest Jalali-Roudsari – no financial conflict of interest Manschreck – received research support from Pfizer in the past year.

P-08-067 Relationship between serum L-serine level and symptoms of schizophrenia

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Objective: We previously reported a schizophrenia case with low serum L-serine and L-glutamate levels. This case had a chromosomal translocation with breakpoints localized to 3q13.12 and 9q21.2. In this patient, expression of the phosphoserine aminotransferase 1 gene, which is located adjacent to the breakpoint and encodes an enzyme in the L-serine synthesis pathway, was reduced. Therefore, we hypothesized that serine metabolism may be related to the symptoms of schizophrenia. Here, we compared severity of schizophrenia and levels of amino acids that are related to serine metabolism.

Methods: Twenty-nine schizophrenic patients were included in this study (17 males and 12 females). The mean age of participants was 59.9 (SD: 9.6) years. Severity of symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS). Furthermore, cognitive functions were assessed using Japanese-language version of the Brief Assessment of Cognition for Schizophrenia (BACS-J). Serum concentrations of L-serine, D-serine, glutamate, and glutamine were measured by high-performance liquid chromatography.

Results: Multiple regression analysis revealed that the PANSS positive score was positively correlated with serum L-serine levels ($p < 0.01$) and L-glutamine levels ($p < 0.05$). The BACS score showed a tendency for correlation with the serum level of L-glutamate ($p < 0.05$). These results were corrected by age and sex.

Conclusion: Our results indicate the importance of studying serine metabolism in schizophrenic symptoms. However, the number of participants was relatively small, and confirmation of these results in a larger cohort is required. Furthermore, functions of enzymes within the serine metabolism should be investigated in order to elucidate the role of serine metabolism in schizophrenia pathophysiology.

P-08-068 Dopamine D1 receptor involvement in EGF receptor transactivation to ERK signaling induced by clozapine

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Objective: Treatment of the positive psychotic symptoms of schizophrenia with standard antipsychotic drugs (APDs) is ineffective in about one third of cases. For these treatment resistant patients the alternative is the APD clozapine which is superior to other agents but carries serious side-effects. Why clozapine is uniquely effective is unknown, but we have postulated may involve G-protein coupled receptor (GPCR) and epidermal growth factor (EGF) receptor (ErbB1) transactivation signaling to the MAPK-ERK cascade. This was based upon clozapine-induced initial down-regulation and delayed ErbB1 mediated activation of the cortical and striatal ERK response in-vivo distinct from other APDs. The GPCR to which clozapine binds to induce EGF receptor (EGFR) phosphorylation is unidentified and thus we examined the dopamine D1 receptor (D1R) as a candidate given its association with dopaminergic transmission in the prefrontal cortex and regulation of locomotor activity and cognitive function.

Methods: The effects of the selective D1R agonist SKF38393, antagonist SCH23390 and EGFR inhibitor, AG1478 on clozapine-mediated EGFR-ERK phosphorylation in CHO-K1 cells stably expressing the EGFR and transiently transfected with the D1R were examined to assess GPCR involvement.

Results: Clozapine induced significant inhibition of ERK1/2 phosphorylation within 10 minutes of exposure to CHO-K1-EGFR D1R transfected cells, followed by a delayed maximal increase in ERK phosphorylation at 90 minutes which normalized by 120 minutes, a profile similar to that described in cortical neuronal cells. SKF38393 caused reversal of clozapine-induced ERK1/2 inhibition at 10 minutes; SCH23390 plus clozapine elevated ERK1/2 phosphorylation above clozapine treatment alone at 90 minutes whilst AG1478 dose-dependently inhibited clozapine-mediated ERK1/2 phosphorylation seen at 90 minutes. Parallel detection of EGFR (Tyr1068) phosphorylation indicated a time disconnect with ERK phosphorylation.

Conclusion: These data highlight complexity in the clozapine-induced D1R-EGFR transactivation mechanism that initiates downstream ERK effects and advocate disturbed D1R-EGF system signaling in refractory schizophrenia.

P-08-069 Does repetitive transcranial magnetic stimulation have a positive effect on working memory and neuronal activation in treatment of negative symptoms of schizophrenia?

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Objective: Repetitive transcranial magnetic stimulation represents a promising therapeutic method for influencing negative symptoms of schizophrenia, thanks to its unique ability to modulate the neuronal activity of the cortical cerebral areas and neuronal spheres that are included in the pathophysiology of schizophrenia.

Methods: The Aim of Study to find out whether, under conditions of a double-blind, placebo coil controlled study, high frequency rTMS over the left DLPFC would have a positive effect on working memory, as assessed by means of the Verbal Fluency Test (VFT), an important parameter of cognitive schizophrenia deficit with simultaneous fMRI examination of the respective changes of neuronal activation.

Results: The evaluated group included in total 30 patients (males). Real rTMS group included 19 patients and the sham rTMS group 11 patients. A statistically significant increase in the mean VFT score and statistically significant reduction of severity of the negative, general and total symptoms of schizophrenia occurred in the real rTMS group. The rate of positive symptoms of schizophrenia remained unchanged. A statistically significant increase in the mean VFT score and statistically significant reduction of severity of the general and total symptoms of schizophrenia occurred in the sham rTMS group. The intensity of the negative symptoms of schizophrenia was not statistically significantly reduced. The rate of positive symptoms of schizophrenia remained unchanged. Compared to the sham rTMS, the real rTMS caused a statistically significantly higher reduction of severity of the negative, affective and total symptoms of schizophrenia. On the contrary, no difference was found with respect to the positive and common symptoms of schizophrenia.

Conclusion: (1) No positive impact of high frequency rTMS, administered over the left DLPFC area, on working memory parameters and the respective changes of neuronal activation detected by fMRI was found. (2) rTMS seems to be a very well tolerated neurostimulation method for treatment of negative schizophrenia symptoms from the point of view of the effect on cognitive functions.

P-08-070 Impairment of magnocellular pathway in visual processing among patients with schizophrenia

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Objective: Schizophrenia is associated with deficits in higher order processing of visual information, steady state visual evoked potential responses recorded over the occipital cortex in patients with schizophrenia suggest a dysfunction of lower level visual pathways, which was more prominent for magnocellular than parvocellular biased stimuli. The magnocellular pathway helps in orienting towards salient stimuli. A magnocellular pathwad deficit could contribute to higher level visual cognitive deficits in schizophrenia dysfunction of the magnocellular pathway may also account for other well described aspects of neurophysiological dysfunction in schizophrenia, for example, the magnocellular pathway projects predominantly to dorsal cortical stream (i.e. parietal lobe), which codes motion perception and spatial localization. Our work aims at assessing the magnocellular pathway by VEP.

Methods: 30 schizophrenic patients were recruited randomly from Alexandria University Hosiptal. They scored 4 or higher on the Clinical Global Impression Scale for Severity CGI-S. Visual Evoked Potential VEP was done to them and compared to healthy control group.

Results: In the right eye the mean P100 was 104.55 ± 5.62 and 95 ± 5.27 msec in schizophrenic and healthy control group respectively with statistical significant difference. A finding that has been replicated in the left eye where the mean P100 was 105.8 ± 5.41 and 95.85 ± 5.4 msec in the same respective groups.

Conclusion: P100 in both right and left eyes are more prolonged in schizophrenic patients compared to healthy control groups.

P-08-071 Comparison of the effects of quetiapine XR and IR on cognitive performance and alertness in patients with schizophrenia – the extra study

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Objective: To assess daytime cognitive performance and overall sedation in patients receiving quetiapine extended release (XR) versus quetiapine immediate release (IR).

Methods: Phase IV prospective, double-blind, crossover study (NCT01213836). Patients with stable schizophrenia were treated with XR or IR before enrolment. Study design comprised 2 stages; Periods 1 and 2 (10–18 days each). Patients were randomized to 2 groups: XR once-daily evening dose (Period 1), followed by IR dosed twice-daily (Period 2); IR twice-daily (Period 1), followed by XR once-daily evening dose (Period 2). Doses corresponded to quetiapine dose before enrolment (400–750 mg). Assessments from 3 post-dose visits ($\geqslant$5 days following treatment in each Period), were analysed according to quetiapine formulation received. Daytime cognitive performance was measured by standardized Attentional Composite score, combining Detection and Identification domains of the CogState Battery Task. Sedation was assessed with the 0–100-point Bond-Lader VAS and 1–7-point Stanford Sleepiness Scale.

Results: 65 patients were randomised (69.2% male; mean age 38.6 years); 51 included in per protocol analysis. Averaged across

3 post-dose assessments, adjusted mean difference in Attentional Composite score in XR and IR patients was 0.005 ($p = 0.907$). Patients receiving XR were more alert than those receiving IR, (Bond-Lader VAS score, mean [SD]: 23.5 [19.0] vs. 28.6 [21.4]); estimated overall treatment difference: 5.2 [95% CI: 2.3; 8.2] ($p < 0.0009$). Patients receiving XR also reported feeling less sedated than those on IR (Stanford Sleepiness Scale, mean [SD]: 2.4 [0.9] vs. 2.6 [1.0]); estimated overall treatment difference: 0.28 [95% CI: 0.12; 0.43] ($p < 0.0008$).

Conclusion: Daytime cognitive performance was similar for the quetiapine IR and XR treatment groups. XR was associated with less daytime sedation than IR at approved doses for this indication.

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P-08-072 Is it possible to improve the prediction of the psychotic chronic patients? An extension study after 60 months

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Objective: To evaluate the clinical and functional progression of patients that having been treated with conventional antipsychotic medication in a previous comparative study vs. Risperidone Long Acting Inyectable(RLAI), accepted RLAI as a treatment choice for their illness.

Methods: We conducted the study with an initial sample consisting of 26 schizophrenic patients, treated with conventional antipsychotic treatment in the previous main study, and 14 of them voluntarily accepted the change to RLAI treatment. During a period of 12 months, follow-up visits were performed at 3, 6 and 12 months for all patients included in both treatment groups. The following scales and questionnaires were used for assessment and measurement: Global Illness Severity (Global Clinical Impression GCI), Treatment Satisfaction Scale, Insight (G12 PANSS), Remission Criteria (Andreassen Criteria), Global Activity Evaluation Scale (GAES). Personal and Social Performance (PSP). Also the following information was collected: hospitalization rates, treatment discontinuation and concomitant antipsychotic.

Results: We found statistical differences among patients treated with long acting atypical and typical antipsychotic. The RLAI group showed significantly higher remission rates and treatment satisfaction scores. Also an improvement in patient Insight, GCI, GAES, PSP and an increase of patients treated with antipsychotic monotherapy was observed. Regarding hospitalization and treatment discontinuation rates, no statistical differences were found in both groups at baseline and at endpoint.

Conclusion: Clinical and functional improvements observed following treatment with RLAI for one year in patients previously treated with conventional antipsychotic treatment, were similar to those showed in the main study, which this study is its extension.

P-08-073 Physical condintion, functionality and cognicion in patients with schizophrenia

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Objective: To evaluate the association between physical condition, mental cognition and functionality in patients with schizophrenia.

Methods: We conducted a epidemiological, retrospective and transversal study including a total sample of 90 patients diagnosed with schizophrenia, according to CIE 10. Patients were divided into 2 groups regarding the antipsychotic treatment received: conventional (typical) or atypical ones. Physical condition was assessed by evaluating the anthropometric, biochemical and clinical parameters and also by the analysis of the presence of metabolic syndrome (defined according to WHO) and cardiovascular risk (as determined by Framingham and waist/triglycerides scores). Cognitive impairment was assessed by the Screen for Cognitive Impairment scale in Psychosis (SCIP) and functionality was evaluated with the Personal and Social Performance Scale (PSP). Clinical data also included years in the disease evolution and number of hospital admissions in the previous year.

Results: The following significant correlations were observed, all of them measured by the Pearson correlation coefficient; Inverse correlations: PSP endpoint score and SCIP total score, $p < 0.05$. PSP endpoint score and cardiovascular risk (Framingham), $p < 0.05$. PSP endpoint score and number of hospital admissions, $p < 0.01$. Direct correlation: SCIP total score and number of hospital admissions, $p < 0.05$. Cardiovascular risk (Framingham) and disease progression years, $p < 0.05$. The group of patients treated with atypical antipsychotics have better functionality, less deterioration cognitive and lower cardiovascular risk when compared to those patients treated with typical antipsychotics.

Conclusion: Lower functionality has been observed in patients with greater cognitive impairment and it is related to increased cognitive impairment, cardiovascular risk and number of hospital admissions. The group of patients treated with atypical antipsychotics demonstrated better functionality, less deterioration cognitive and lower cardiovascular risk when compared to those patients treated with typical antipsychotics.

P-08-074 Clinical outcome in outpatients with schizophrenia who switched their antipsychotic treatment due to suboptimal efficacy: Results from the ETOS study

A. Roussidis[1], C. Kalkavoura[2], I. Vlachos[3], A. Chaidemenos[4], I. Ioannidou[5], E. Mellos[6], A. Theodorou[7]. [1]*AstraZeneca Hellas, Athens, Greece*; [2]*Psychiatric Department, Sismanoglio General Hospital, Athens, Greece*; [3]*Private Practice, Patras, Greece*; [4]*8th Psychiatric Clinic, Psychiatric Hospital, Athens, Greece*; [5]*Private Practive, Nafplio, Greece*; [6]*Aiginition Hospital-OKANA, Athens, Greece*; [7]*Private Practice, Athens, Greece*

Objective: Schizophrenia is a chronic, severely disabling illness associated with poor treatment adherence and frequent treatment modifications. The ETOS study aimed to identify the reasons and evaluate the outcome of switching antipsychotic treatment in outpatients with schizophrenia.

Methods: ETOS was an observational 18-week study in outpatients, diagnosed with schizophrenia according to DSM-IV, who were initiated on a new antipsychotic monotherapy within the preceding two weeks. A total of 574 patients were enrolled. Ethical approval was obtained prior to study initiation (NCT00999895).

Results: The final analysis included 568 patients, 53% male and 47% female and mean disease duration of 11.7 ($\pm$12.3) years. In total 249 patients (43.8%) switched due to lack of efficacy and 50 patients (8.8%) switched due to the lack of both tolerability and efficacy. Patients who switched due to lack of efficacy were mainly (>10%) switched from aripiprazole (22.1%), risperidone (21.3%), olanzapine (16.5%) and ziprasidone (12.9%). PANSS and CGI-S scores at baseline were 92.9 ($\pm$28.2) and 4.1 ($\pm$1.1) respectively. Following treatment switch, 86.9% of patients who switched due to efficacy reasons experienced meaningful clinical benefit by achieving a CGI–CB score of $\leqslant 4$ at final visit [clinical benefit in all patients was 87.9% ($n = 499$)]. Total PANSS, CGI-I and CGI-S scores were significantly improved by the end of study, showing a mean decrease of 31.69, 0.70 and 1.14 respectively (all $p < 0.0001$). BARS was also significantly improved by the end of the study with a mean change of 9.73 ($p < 0.0001$).

Conclusion: Antipsychotic monotherapy switch due to lack of efficacy was shown to be beneficial in outpatients with schizophrenia, associated with significantly improved clinical benefit and significant increase of patients' adherence to treatment in daily clinical practice.

Policy of full disclosure: Andreas Roussidis is an employee of AstraZeneca Hellas. This study was funded from AZ Hellas.

P-08-075 Reasons for switching antipsychotic treatment in outpatients with schizophrenia: Results from the ETOS study with focus on tolerability

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Objective: The ETOS study aimed to identify the reasons and evaluate the outcome of switching antipsychotic treatment in outpatients with schizophrenia.

Methods: ETOS was an observational 18-week study in outpatients, diagnosed with schizophrenia according to DSM-IV, who were initiated on a new antipsychotic monotherapy within the preceding two weeks. A total of 574 patients were recruited. Ethical approval was obtained prior to study initiation (NCT00999895).

Results: The final analysis included 568 patients. 53% of participants were male and 47% female. The main reason for switching antipsychotic treatment was lack of tolerability (n = 369, 65.0%), followed by lack of efficacy (n = 249, 43.8%), while 8.8% of patients switched due to lack of both tolerability and efficacy. The main tolerability reasons (>5%) in descending order of prevalence were weight gain (40.4%), extrapyramidal symptoms (30.1%), lack of tolerance (11.4%), hyperprolactinaemia (10.6%), hyperlipidaemia and/or hyperglycaemia (6.5%). Patients who changed treatment for tolerability reasons (n = 369) were mainly (>10%) switched from olanzapine (37.4%) and risperidone (24.7%). Of those patients switching due to lack of tolerability, 58.5% were switched to quetiapine/quetiapine XR, 10.8% to aripiprazole, 9.8% to olanzapine, 6.2% to paliperidone, 5.4% to ziprasidone, followed by other antipsychotics (<5%). A CGI–CB score of $\leqslant 4$ was achieved by 89.0% of patients switching due to tolerability reasons. In patients switching due to weight gain (n = 149), extrapyramidal symptoms (n = 111) or hyperprolactinaemia (n = 39), weight, SAS scores and prolactin levels were significantly decreased by 6.85 kg, 11.30 and 62.30 ng/ml respectively (all $p < 0.0001$).

Conclusion: The ETOS study identified lack of tolerability to be the main reason for switching antipsychotic treatment in outpatients with schizophrenia. Switching to antipsychotic monotherapy was accompanied by significantly improved tolerability for specific measures in daily clinical practice.

Policy of full disclosure: This study was funded from AstraZeneca Hellas. Andreas Roussidis is an employee of AZ Hellas.

P-08-076 Effect of aripiprazole, risperidone and olanzapine, on the acoustic startle response in recent episodes of schizophrenia

G. Rubio[1], R. Jurado[1], I. Morales[1], I. Martínez-Gras[1], G. Ponce[1], R. Rodríguez-Jiménez[1], M.-A. Jiménez-Arriero[1]. [1]*Hospital 12 de Octubre, Madrid, Spain*

Objective: Studies have also shown that differences in the kind of the antipsychotics influenced disruption of the sensorimotor gating system, including prepulse inhibition of the startle reflex (PPI). Atypical antipsychotics improve PPI more than typical, but little is known about the effects of aripiprazole on PPI. Aripiprazole, an atypical antipsychotic drug, is a D2 dopamine–receptor partial agonist, but also has affinity to several serotonin receptors (5-HT1A,2A,2C,7). We hypothesized that patients taking aripiprazole would show greater impairment in PPI than those patients with risperidone or with olanzapine.

Methods: In the present study we investigated the influence on startle response in recent episodes of schizophrenia in 15 patients taking aripiprazole, 15 taking risperidone and 14 patients with olanzapine. Participants were on maintenance therapy with only one antipsychotic drug for 12 weeks. The startle measures used were prepulse inhibition percentages at 30, 60 and 120 milliseconds (% PPI-30, % PPI-60 and % PPI-120, respectively), and % habituation.

Results: Aripiprazole improved PPI more than risperidone and than olanzapine at 30 and 60 milliseconds but not at 120 ($p < 0.01$). Risperidone improved %PPI-60 more than olanzapine ($p < 0.01$).

Conclusion: Aripiprazole, in subjects with recent episodes of schizophrenia improved PPI disruption more than risperidone and olanzapine at early attentional stages. These data suggest the role of the D2 Dopamine –receptor partial antagonist on sensoriomotor gating system of patients with schizophrenia.

P-08-077 First-episode psychosis: Factors influencing relapse over 1-year follow-up

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Objective: Describe which variables are related with relapse in patients diagnosed of first-episode psychosis over one-year follow-up.

Methods: Consecutive 129 first-episode patients treated in Institut de Neuropsiquiatria i Addicions from Barcelona from 2007 to 2011 were evaluated over 1-year follow up. We assessed sociodemographic and clinical variables, including cannabis use, duration of untreated psychosis (DUP), relapses, and several scales (PANSS, SUMD, GAF), at different timepoints: baseline, at 1-month, 6-months and 1-year follow-up. We performed a multiple regression analysis. Number of relapses was the dependent variable, and DUP, gender, age, cannabis use over follow-up, PANSS positive and negative subscale, GAF, and SUMD at one-month follow-up were the independent variables.

Results: Gender ($p = 0.014$), PANSS positive symptoms at 1-month follow-up ($p = 0.027$), and cannabis use ($p < 0.001$), are associated with relapse in our sample.

Conclusion: Male gender, persistent positive symptoms at one-month follow-up and cannabis use, may predict independently relapse in first- episode psychosis.

P-08-078 Dopamine D2 receptor occupancy and cognition in schizophrenia: Analysis of the CATIE data

H. Sakurai[1], R. Bies[2], S. Stroup[3], R. Keefe[4], T. Rajji[2], T. Suzuki[5], D. Mamo[2], B. Pollock[2], K. Watanabe[5], M. Mimura[5], H. Uchida[5]. [1]*Keio University, School of Medicine, Tokyo, Japan*; [2]*Toronto, Canada*; [3]*New York, USA*; [4]*Durham, USA*; [5]*Tokyo, Japan*

Objective: Antipsychotic drugs exert antipsychotic effects by blocking dopamine D2 receptors in the treatment of schizophrenia. However, effects of D2 receptor blockade on neurocognitive function still remain to be elucidated. The objective of this analysis was to evaluate impacts of estimated dopamine D2 receptor occupancy with antipsychotic drugs on several domains of neurocognitive function in patients with schizophrenia in the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial.

Methods: The dataset from the CATIE trial was used in the present analysis. Data were extracted from 410 subjects who were treated with risperidone, olanzapine, or ziprasidone, received assessments for neurocognitive functions (verbal memory, vigilance, processing speed, reasoning, and working memory) and psychopathology, and provided plasma samples for the measurement of plasma antipsychotic concentrations. D2 receptor occupancy levels on the day of neurocognitive assessment were estimated from plasma antipsychotic concentrations, using population pharmacokinetic analysis and our recently developed model. A multivariate general linear model was used to examine effects of clinical and demographic characteristics, including estimated D2 occupancy levels, on neurocognitive functions.

Results: D2 occupancy levels showed significant associations with the vigilance and the summary scores. Neurocognitive functions, including vigilance, were especially impaired in subjects who showed D2 receptor occupancy level of >77%.

Conclusion: These findings suggest a non-linear relationship between prescribed antipsychotic doses and overall neurocognitive function and vigilance, which has an important clinical implication and may endorse the upper limit of the established antipsychotic therapeutic window of D2 occupancy (i.e., 80%) from the standpoint of cognition as well.

Policy of full disclosure: Dr. Bies has received NIH, CAMH, Lilly and Indiana University based grant funding. Dr. Stroup has received grants from NIMH and the Foundation for the National Institutes of Health. He has received consulting income from Janssen and Lilly.

Dr. Richard Keefe currently or in the past 5+ years has received investigator-initiated research funding support from the Allon, AstraZeneca, Department of Veteran's Affair, Eli Lilly, GlaxoSmithKline, National Institute of Mental Health, Novartis, Organon Pharmaceuticals, Pfizer, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. He currently or in the past 5+ years has received honoraria, served as a consultant, or advisory board member for Abbott, Acadia, Astellas, Astra-Zeneca, BiolineRx, BrainCells, Bristol-Myers-Squibb, Cephalon, CHDI, Cortex, Cypress Bioscience, Eli Lilly, EnVivo, Johnson & Johnson, Lundbeck, Memory Pharmaceuticals, Merck, NeuroSearch, Orexigen, Oganon Pharmaceuticals, Orion, Otsuka, Pfizer, Roche, Sanofi-Aventis, Shering-Plough, Shire, Solvay, Sunovion, Takeda, Wyeth, and Xenoport. Dr. Keefe receives royalties from the BACS testing battery and the MATRICS Battery (BACS Symbol Coding). He is also a shareholder in NeuroCog Trials, Inc., Durham NC. Duke University holds the copyright for the SCoRS, and licenses are issued by NeuroCog Trials, Inc. There is currently no license fee to use the SCoRS. Dr. Rajji has received Brain and Behavior Research Foundation (NARSAD), CFI, CIHR, NIH, Ontario Ministry for Health and Long-Term Facilities, and Ontario Ministry for Innovation. Dr. Mamo has received investigator-initiated grant support from Pfizer within the past 5 years. Dr. Suzuki has received fellowship grants from the Japanese Society of Clinical Neuropsychopharmacology, Government of Canada Post-Doctoral Research Fellowships, Kanae Foundation, and Mochida Memorial Foundation, and manuscript fees from Kyowa Hakko Kirin and Dainippon Sumitomo Pharma within the past 5 years. Dr. Pollock receives research support from the National Institute of Health and the Canadian Institutes of Health Research. Within the past five years he has been a member of the advisory board of Lundbeck Canada (final meeting was May 2009) and Forest Laboratories (final meeting was March 2008). Dr. Pollock has served one time as a consultant for Wyeth (October 2008) and Takeda (July 2007). He was also a faculty member of the Lundbeck International Neuroscience Foundation (LINF) (final meeting was April 2010). Dr. Watanabe has received grants, or consultant fees from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, and Pfizer, and received speaker's honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years. Dr. Mimura has received grants, or consultant fees from Eisai, Astellas Pharma, GlaxoSmithKline and Meiji, and received speaker's honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomiyakuhin within the past 5 years. Dr. Uchida has received grants from Pfizer, speaker's honoraria from Otsuka Pharmaceutical, Janssen Pharmaceutical, and Shionogi, and manuscript fees from Dainippon Sumitomo Pharma within the past 5 years. Dr. Sakurai has nothing to disclose.

P-08-079 Patient-reported outcomes (PROs) with aripiprazole intramuscular depot (ARI-IMD) for maintenance treatment in schizophrenia

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Objective: To characterise the adherence profile of ARI-IMD by examining PROs from long-term treatment.

Methods: Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) during a 4–6-week oral conversion phase (Phase 1). Phase 2 was a 4–12-week oral aripiprazole stabilisation phase. Subjects meeting stability criteria (4 weeks) entered an IMD stabilisation phase (400 mg/injection) with co-administration of oral aripiprazole the first 2 weeks (Phase 3). Subjects meeting stability criteria (12 weeks) were randomised (2:1) to ARI-IMD or placebo (52-week: Phase 4). Mean changes in PROs were assessed from baseline to last visit in Phases 2–4 using the DAI, MAQ and PSMQ modified.

Results: 710 subjects entered Phase 2 (633 were titrated to oral aripiprazole in Phase 1); 576 Phase 3 and 403 Phase 4. The study stopped early because efficacy was demonstrated by pre-planned interim analysis. Between Phases 2–4, mean DAI scores remained similar (Phase 2: 21.5; Phase 3: 21.4; Phase 4: 21.1 ARI-IM-depot vs. 22.2 placebo) indicating adherence to medication. Mean MAQ scores = 0–1 indicated high adherence behaviour. PSMQ scale scores at last visit showed subjects had high levels of treatment satisfaction (Phase 3: 92.8%; Phase 4 ARI-IMD: 92.7%; Phase 4 placebo: 85.0%). A high percentage of subjects preferred their current medication at last visit (Phase 3: 89.1; Phase 4 ARI-IMD: 86.2%; Phase 4 placebo: 85.7%). There were a sustained percentage of subjects reporting less to no side-effects at last visit (Phase 3: 86.9%; Phase 4 ARI-IMD: 88.9%; Phase 4 placebo: 89.0%).

Conclusion: ARI-IMD offers a new treatment option for the long-term management of schizophrenia with the potential to improve adherence to medication resulting from improved PROs and medication satisfaction.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Brian Johnson, Na Jin, Robert A Forbes, William H Carson and Robert D McQuade are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

P-08-080 NMDAR-mediated dysfunctional connectivity predicts cognitive impairments

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Objective: Disordered brain connectivity is a central pathophysiological hallmark of schizophrenia. The key mechanism for dysconnectivity is thought to be disrupted N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity. However, no study has yet experimentally investigated the contribution of NMDAR-mediated synaptic plasticity to psychotic symptom formation. The mismatch negativity (MMN) is an event-related potential (ERP) and has recently been interpreted as a prediction error (PE) signal during perceptual learning and has been shown to depend critically on NMDAR-dependent synaptic plasticity. Specifically, the NMDAR antagonist S-ketamine, which induces schizophrenia-like symptoms, reduces the MMN in healthy subjects comparable to those observed in schizophrenia. The MMN is generated within a neuronal hierarchy, where each level provides predictions about the state of the level below and evaluates the discrepancy with the actual inputs from the lower level (i.e. PE). Within this Bayesian framework, PEs are conveyed via synaptic connections, which will be adjusted during learning and inference in order to minimize PE at all levels of the hierarchy.

Methods: We combined conventional statistical parametric mapping (SPM) with DCM modeling of ERP data to investigate effective connectivity within the MMN network in order to examine whether the known reduction of MMN under S-ketamine can be explained by changes in the plasticity of glutamatergic long-range connections among hierarchically related auditory areas, and if so, where these changes would be expressed.

Results: DCM analyses revealed that S-ketamine significantly perturbed bottom-up effective connectivity, the extent of which predicted significant S-ketamine-induced cognitive impairments.

Conclusion: Based on empirical data, we have described for the first time a pathophysiological mechanism underlying dysfunctional connectivity, which gives rise to specific symptom formation, namely to cognitive impairments. Our model-based characterization of NMDAR-mediated effects on synaptic plasticity thus connects pharmacological, physiological and computational approaches in relation to the formation of a specific psychotic symptom, suggesting high relevance for pathophysiological theories of schizophrenia.

P-08-081 Central interleukin-6 activation in patients with chronic schizophrenia

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Objective: Accumulating studies during the last decade indicate that schizophrenia is associated with immunological processes in the brain. For this reason, studies have been directed towards cytokines, proteins that directly initiate and control immunological responses. One of the most frequently reported cytokine in schizophrenia is interleukin (IL)-6, a cytokine involved in brain development, synaptic plasticity and behavior. The purpose of the present study is to analyze cytokine concentration in the cerebrospinal fluid (CSF) from well-characterized patients with respect to antipsychotic treatment and symptoms.

Methods: CSF cytokine concentrations were analyzed by an electrochemiluminescence biosensor assay (Meso Scale Discovery, Gaithersburg, MD, USA). Patients were stable, chronically outpatients with schizophrenia (17 males and 9 females). Diagnosis was based on clinical interviews by an experienced psychiatrist and the severity of symptoms was rated with Brief Psychiatric Rating scale (BPRS) and global assessment of functioning (GAF). All patients were medicated with olanzapine for at least one month before lumbar puncture. CSF concentrations of IL-6 from patients were compared with those of 37 healthy age matched volunteers (23 males and 14 females).

Results: Our results show that patients with schizophrenia display significant increased levels of IL-6 in CSF (3.2 ± 0.4 pg/ml) compared with healthy volunteers (1.8 ± 0.2 pg/ml). No correlation between IL-6 and symptoms rated with BPRS or GAF were found. Further, treatment with olanzapine did not influence IL-6 concentrations as no correlation between IL-6 and treatment with respect to prescribed dose, time of treatment or concentration of olanzapine in CSF were found.

Conclusion: Present data confirm that IL-6 is increased in the brain of chronic patients with schizophrenia and strengthen the idea that the disease is associated with brain immune activation. Cytokines, in particular IL-6 may hence serve as biomarkers of chronic schizophrenia.

P-08-082 The enhancing properties of modafinil in schizophrenia and early psychosis

L. Scoriels[1], B. Sahakian[1], P. Jones[1]. [1]*University of Cambridge, United Kingdom*

Objective: Modafinil is a central nervous system compound that has vigilance promoting properties as well as beneficial effects on cognitive and emotional functions in the healthy and diseased population. Our group showed that modafinil improved working memory, planning abilities, cognitive flexibility and emotional recognition in chronic schizophrenia and first episode psychosis. It is still unclear how modafinil affects these functions. We aimed at reviewing the literature that tested the neuropathways of modafinil in different areas of the brain. We also targeted the cognitive and emotional effects of modafinil in all the studies that tested the compound in patients with schizophrenia.

Methods: Two systematic reviews were carried out. One reviewed the neuropathways taken by modafinil and categorised studies according to the animal models used, the neurotransmitter systems and the brain regions activated by the compound. The other was a Cochrane review protocol that aims at meta-analysing the effects of modafinil in schizophrenia.

Results: Preliminary results from these two reviews show that modafinil acts mainly by inhibiting the GABAergic system, where as it activates the glutamatergic, dopaminergic, noradrenergic and serotonergic systems. These patterns of action have been shown particularly in the prefrontal cortex, hippocampus, hypothalamus, thalamus, striatum and substantia nigra both in animals and humans. These neuropharmacological effects of modafinil induce improvements in working memory, fluency, cognitive flexibility and problem solving in patients with schizophrenia.

Conclusion: These original findings allow us to better understand the neuromechanisms of modafinil and although the interaction between modafinil and antipsychotics – the most commonly prescribed medication in psychosis – has yet to be tested, results from these two reviews suggest that modafinil may be an adequate adjuvant treatment for psychosis. It may help patients cope with their cognitive impairments and improve their functional outcomes and quality of life.

P-08-083 Catalytic activity of abzyms in patients with schizophrenia with tardive dyskinesia

L. Smirnova[1], N. Fattakhov[2], E. Odintsova[3], V. Buneva[3], N. Krotenko[4], E. Rudikov[1], S. Ivanova[5]. [1]*Mental Health Research Institute, Tomsk, Russia*; [2]*Siberian State Medical University, Medico-Biological Faculty, Tomsk, Russia*; [3]*Chemical Biology and Basic, Medicine SB RASci, Novosibirsk, Russia*; [4]*Siberian State Medical Univers, Tomsk, Russia*; [5]*Institute of Mental Health, Tomsk, Russia*

Objective: Research objective is studying DNase activity of IgG allocated from the serum of patients with paranoid schizophrenia.

Methods: An antibodies of G group was allocated from the blood of 35 donors, including control group of 15 healthy persons. Patients with schizophrenia have been divided on 2 groups: 6 patients with tardive dyskinesia (TD) and 15 patients without TD. All patients were treated in department of endogenous disorders of Mental Health Research Institute SB RAMSci, Tomsk. The diagnosis of schizophrenia was based on criteria the ICD-10. The severity of TD was assessed using the abnormal involuntary movement scale (AIMS). DNase activity defined on level of hydrolysis of DNA plasmids pBluescript, proteolytic activity defined on level of hydrolysis of myelin basic protein and its peptides. The concentration of antibodies to DNA defined by the ELISA method.

Results: It was established that IgG of schizophrenic patients has higher specific DNase activity (0.392 ± 0.190 pmol DNA/mg antibody/hour), than in healthy persons (0.029 ± 0.061 pmol DNA/mg antibody/hour). It has been defined that specific DNase activity is own property of antibodies. It has been defined that specific DNase activity of antibodies in patients with TD in 2 times higher (0.740 ± 0.300 pmol DNA/mg antibody/hour), than in group without TD (0.300 ± 0.130 pmol DNA/mg antibody/hour). The level of specific DNase activity of antibodies in healthy controls was 0.029 ± 0.060 pmol DNA/mg antibody/hour. The hydrolysis of myelin basic protein by antibodies in group of the patients with TD also was maximum 58.6%, unlike patients without TD 12.7%. In group of control hydrolysis level was 1.5%.

Conclusion: High values of the catalytic activity of IgG in patients with tardive dyskinesia suggest their involvement in the development of this complication.

P-08-084 Neurocognitive deficit correction in patients with schizophrenia

A. Spikina. *St Petersburg Medical Academy, Russia*

Objective: To study the influence of neurocognitive training as well as long-term use of psychopharmacological drugs with serotoninergic mechanism of action (serdolect, fluvoxamine) on higher cortical function in patients with schizophrenia and to evaluate their effectiveness in the treatment of schizophrenia.

Methods: For revealing the symptoms of neurocognitive deficits, we used standard tests such as learning the 10 words (test of Luria), Benton Test (Benton Visual Retention Test), Stroop Test – Stroop Color interference Test, Test ''Encryption''. To assess the attention: The test for the visual and motor coordination (parts A and B) – Trail Making Test A & B. To assess executive functions-test ''Mazes''.

Results: After training the cognitive processes in schizophrenia patients were obtained by increasing the tempo of the performance, improving the concentration, the adequacy of long-term thinking and memory have been identified trend towards an increase in operational short-term memory, the maximum improvement falls on visual memory, and minimal attention to the function. Patients receiving serdolect and fluvoxamine have shown significant improvement in neurocognitive profile in comparison with the control group, and, better indicators such as verbal associative productivity, selective attention, working memory and motor coordination was significantly higher in patients treated with serdolect.

Conclusion: The neurocognitive training showed itself as an effective method of correcting neurocognitive deficits. Using drugs with serotoninergic mechanism showed significant improvement in neurocognitive profile of schizophrenia patients. Serdolect showed statistically significant improvement in the basic neurocognitive parameters in comparison with Fevarin.

P-08-085 Service delivery improvement project for clozapine monitoring in assertive outreach team

S. Sreenivas[1], S. Davies[2]. [1]*NHS, Halifax, United Kingdom;* [2]*Southwest Yorkshire PFT, Halifax, United Kingdom*

Objective: Clozapine plasma levels are broadly related to daily dosing. Despite different estimates of response thresholds, plasma levels can be useful in optimizing treatment. It has been observed that there needs to be a high quality service system, to aid the effective monitoring of the Clozapine levels in the Assertive Outreach Team, Halifax. Objectives: (1) To develop additional indications for Clozapine level monitoring in the Southwest Yorkshire Partnership Foundation Trust Policy (2007). (2) To develop Clozapine monitoring from the date of first initiation of Clozapine medication.

Methods: Clozapine monitoring form has been designed. Clozapine levels collected from the clinical notes/Kings pathology online system. Communication made with pharmacists of the Southwest Yorkshire Partnership Foundation Trust and Clozapine monitoring Policy discussed in Drug and Therapeutics Sub Committee Meeting in July 2011.

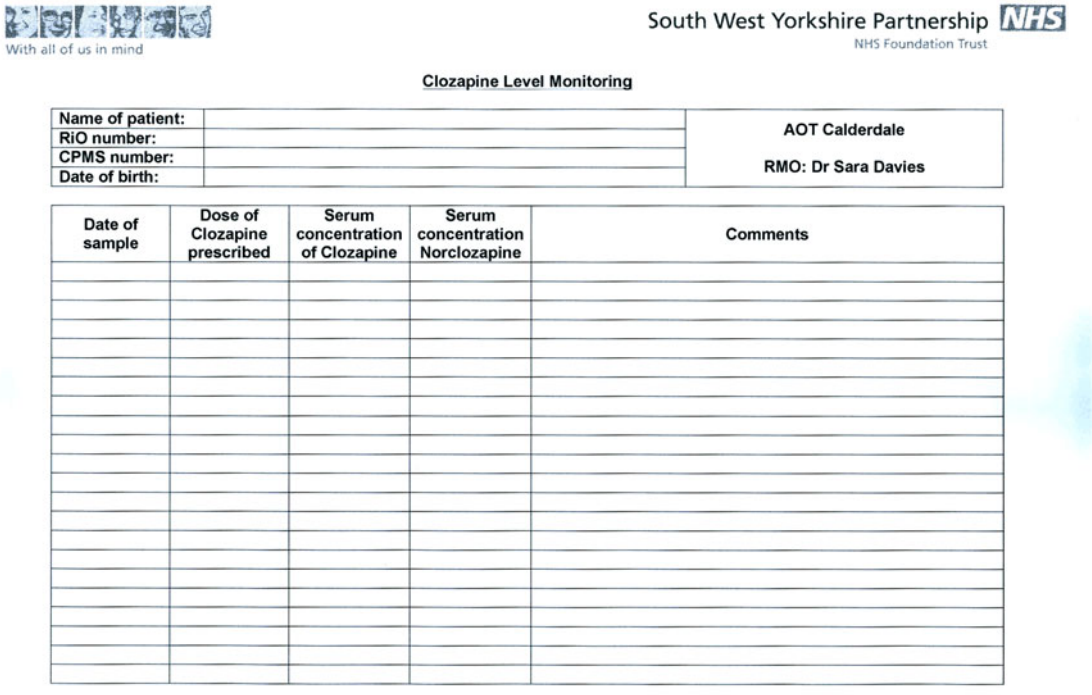
Results: The Policy now Includes additional indications for clozapine level monitoring: ''To monitor concordance with treatment particularly if there is a history of non-concordance with medication, which is linked with previous or likely hospital admission. Adherence can be measured over time with serial Clozapine assays, particularly when adherence is a critical part of the care plan, for example for maintenance of mental health that is essential for the patient's safety, adherence to a Community Treatment Order or other Section of the Mental Health Act 1983 (Amended 2007)''. Clozapine monitoring form is designed and is available to the AOT.

Conclusion: The current system would help in a longitudinal analysis of the variation of levels with doses of Clozapine, also giving an opportunity to determine possible reasons for changes in clozapine levels. Clozapine levels can help monitor concordance with treatment for service users with a history of enduring mental illness and low compliance, including support with adherence to requirements for Community Treatment Orders. A Clinical Audit Project can be conductedin 1 year to make sure that the policy is being adhered to and Clozapine monitoring forms are being completed.

P-08-086 Effects of aripiprazole on autonomic nervous system activity in schizophrenia

A. Suda[1], I. Kishida[2], M. Fujibayashi[3], C. Kawanishi[2], Y. Iwamoto[2], T. Furuno[2], C. Ishii[4], N. Ishii[5], N. Sugiyama[1], T. Moritani[6], Y. Hirayasu[2]. [1]*Numazu Chuo Hospital, Numazu City, Shizuoka, Japan;* [2]*Department of Psychiatry, Yokohama City University, Yokohama City, Kanagawa, Japan;* [3]*The Division of Physical and Health Education, Neyagawa City, Osaka, Japan;* [4]*Fujisawa Hospital, Fujisawa City, Kanagawa, Japan;* [5]*Fujisawa Hospital, Fujisawa City, Kanagawa, Japan;* [6]*Graduate School of Human and Environmental Studies, Kyoto City, Kyoto, Japan*

Objective: Schizophrenic patients have been reported to have an increased prevalence of cardiovascular diseases. Although treatment with second-generation antipsychotics (SGAs) have effects on positive and negative symptoms of schizophrenia, they also promote weight gain, may lead to metabolic syndrome that increases the risk of cardiovascular diseases. On the other hand, aripiprazole displays low affinity for H1-histaminergic, muscarinic, cholinergic, and adrenergic receptors. This profile is predictive of low propensity to weight-gain, metabolic disruption. We reported reduced autonomic nervous system (ANS) activity in schizophrenia. In the present study, we sought to replicate the reported positive association between low ANS activity and schizophrenia in a larger number of patients, and we



With all of us in mind

South West Yorkshire Partnership NHS
NHS Foundation Trust

Clozapine Level Monitoring

Name of patient:		AOT Calderdale
RiO number:		
CPMS number:		RMO: Dr Sara Davies
Date of birth:		

Date of sample	Dose of Clozapine prescribed	Serum concentration of Clozapine	Serum concentration Norclozapine	Comments

investigated the influence of aripiprazole on ANS activity and compared with other antipsychotic drugs.

Methods: Subjects were 211 Japanese patients with schizophrenia and 44 healthy controls. All subjects received an explanation of our study and written informed consent was obtained. ANS activity was assessed by means of heart-rate variability power spectral analysis, which enables us to identify separate frequency components, i.e., total power (TP: overall ANS), low-frequency (LF: sympatho-vagal) power, and high-frequency (HF: vagal) power, during a resting condition. Statistical analyses were performed using t-tests to determine the presence of differences in the ANS activity.

Results: We found significantly lower ANS activity in schizophrenic patients than controls (TP; $p<0.001$, LF; $p<0.001$, HF; $p<0.001$). Patients receiving aripiprazole ($n=11$) have higher ANS activity than the other patients ($n=196$).

Conclusion: Our findings suggest that schizophrenic patients possess reduced ANS activity, which might be associated with increased cardiovascular mortality, and aripiprazole have less adverse effects on ANS activity compared with other antipsychotic drugs.

P-08-087 Prevalence of metabolic syndrome among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia

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Objective: The objective of this study was to determine the prevalence of metabolic syndrome(MetS), hypertension and diabetes mellitus (DM) among schizophrenia patients treated with monotherapy atypical antipsychotics.

Methods: The study was conducted at 4 mental institutions and 4 general hospitals in Malaysia. 527 patients were screened during study period and 485 patients fulfilled the DSM-IV criteria for schizophrenia. 325 schizophrenia patients agreed to be interviewed but only 274 consented for fasting blood investigations and metabolic syndrome profile. The definition of MetS was based on Modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with Asians values for waist circumference.

Results: Out of 325 patients, 186 patients (57.2%) received monotherapy atypical antipsychotics. 64/186 on risperidone, 61/186 patients were on olanzapine, 28/186 patients were on paliperidone, 14/186 were on clozapine, 8/186 on aripiprazole, 7/186 on quetiapine and 4/186 on amisulpride. The prevalence of hypertension and DM among schizophrenia patients after initiation of monotherapy antipsychotics was 5.7% (95% CI 1.9–15.4) and 5.7% (95% CI 1.9–15.4) in olanzapine, 7.5% (95% CI 3.0–17.9) and 5.5% (95% CI 1.9–14.9) in risperidone, 7.1% (95% CI 2.0–22.7) and 11.5% (95% CI 4.0–29.0) in paliperidone, 16.7% (95% CI 3.0–56.4) of DM in quetiapine and 14.3% (95% CI 2.6–51.3) of DM in aripiprazole. None of amisulpride patients developed hypertension and DM. 53.2% of overall patients had MetS. While 83.3% in clozapine, 66.7% in quetiapine, 53.8% in paliperidone, 52.8% in olanzapine, 43.4% in risperidone and 14.3% in aripiprazole developed MetS. None of patients on amisupride has MetS.

Conclusion: The prevalence of MetS was high among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia. Urgent measures are needed to address the issue.

P-08-088 Defining treatment-resistant schizophrenia and treatment response: A pragmatic proposal

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Objective: To propose a pragmatic definition on treatment-resistant schizophrenia (TRS) and treatment response that was originated from a critical appraisal of the currently available evidence.

Methods: The authors previously presented comprehensive reviews on TRS and response status thereafter in TRS. They formed the basis of our proposal, with an updated literature search.

Results: Previous studies defined TRS with a failure to respond to adequate trials with antipsychotics. Treatment response has been defined mainly with improvements in the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS). Other factors were somewhat variable, and the resultant response rates differed substantially across the TRS studies. Integrating past evidence and real-world feasibility, we propose that TRS be defined by $\geqslant 2$ failed adequate trials with different antipsychotics (at chlorpromazine equivalent doses of $\geqslant 600$ mg/day for $\geqslant 6$ consecutive weeks) that could be retrospective or preferably include prospective failure to respond to $\geqslant 1$ antipsychotic trials. In addition, our proposed criteria require both a score of $\geqslant 4$ on the Clinical Global Impression (CGI)–Severity subscale and a score of $\leqslant 49$ on the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) or $\leqslant 50$ on the Global Assessment of Functioning (GAF) scales to define TRS. Once TRS is established, we propose that subsequent treatment response be defined based on a CGI–Change score of $\leqslant 2$, a $\geqslant 20\%$ decrease on the total PANSS or BPRS scores, and an increase of $\geqslant 20$ points on the FACT-Sz or GAF.

Conclusion: Defining TRS, although challenging, is highly relevant given its personal and societal consequences and an agreement is desirable for the field. We propose an adoption of the CGI (global impression), PANSS/BPRS (classical psychopathology) and GAF/FACT-Sz (global functioning) for this purpose. These definitions should be further tested for reliability/validity and practicality.

P-08-089 Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia

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Objective: Schnurri-2 (Shn-2), an NF-kB site-binding protein, tightly binds to the enhancers of major histocompatibility complex (MHC) class I genes and inflammatory cytokines, which have been shown to harbor common variant single nucleotide polymorphisms associated with schizophrenia. Although genes related to immunity are implicated in schizophrenia, there has been no study showing that their mutation or knock-out results in schizophrenia.

Methods: As a course of our large scale screening to identify animal models of psychiatric disorders, Shn-2 KO mice were subjected to a comprehensive behavioral test battery.

Results: Here, we show that Shn-2 knockout mice have behavioral abnormalities that strongly resemble those of schizophrenics. The mutant brain demonstrated numerous schizophrenia-related phenotypes, including transcriptome/proteome changes remarkably similar to those of postmortem schizophrenia patients, decreased parvalbumin and GAD67 levels, increased theta power on electroencephalograms, and a thinner cortex. Dentate gyrus granule cells failed to mature in Shn-2 knockout mice, a previously proposed endophenotype of schizophrenia. Shn-2 mice also exhibited mild chronic inflammation of the brain.

Conclusion: These results suggest that genetically-induced changes in immune system may be a predisposing factor in schizophrenia.

Policy of full disclosure: NW and MM are employees of Astellas Research Institute of America, a subsidiary of Astellas Pharmaceuticals, which designs pharmaceuticals for a wide variety od diseases that may be related to this research.

P-08-090 Effects of chronic exposure of cariprazine on dopamine receptor subtypes

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Objective: Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist in development for the treatment of schizophrenia and

bipolar mania. Long-term effects of cariprazine on expression of dopamine (DA) receptor subtypes in adult rat brain regions were quantified to determine regionally selective changes in tissue levels of DA receptors.

Methods: Rats (n = 8) received vehicle control (1 ml/kg/d) or cariprazine (0.06, 0.2, or 0.6 mg/kg) administered intraperitoneally for 28 days. Brains were collected and dopamine receptor autoradiographic assays were performed on tissues from multiple regions. Mean values of nonspecific binding in each region were subtracted from the corresponding mean total binding to determine specific radioligand binding expressed as fmol bound/mg tissue; 2-way analysis of variance (ANOVA) analyzed overall changes across treatments and brain regions.

Results: Repeated treatment with cariprazine failed to alter levels of DA D1 receptors in all brain regions examined. Cariprazine 0.2 and 0.6 mg/kg dose-dependently increased D2 receptor concentrations in medial prefrontal cortex (27% and 43%, respectively), nucleus accumbens (40% and 45%), medial (41% and 53%) and lateral caudate putamen (52% and 63%); 0.06 mg/kg had no effect. Quantification of D3 receptors using [3H]7-OH-DPAT showed that cariprazine 0.06, 0.2, and 0.6 mg/kg increased D3 receptor binding in olfactory tubercle (27%, 49%, and 67%) and Islands of Calleja (32%, 41%, and 57%); more increases in D3 receptor levels were also detected using the D3-preferring radioligand [3H]PHNO particularly in nucleus accumbens. Cariprazine (0.06, 0.2, and 0.6 mg/kg) increased D4 receptors in hippocampus (38%, 71%, and 98%).

Conclusion: Long-term administration of cariprazine induced regional and dose-dependent changes in DA receptor subtypes in different rat forebrain regions. Most changes were similar to other second generation antipsychotics; only cariprazine, and not any other antipsychotic agent, increased abundance of forebrain D3 receptors. These findings support the unique psychopharmacological properties of cariprazine.

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P-08-091 Effect of blonanserin on cognitive function in antipsychotic-naïve first-episode schizophrenia

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Objective: Cognitive impairment is a core feature of schizophrenia and is present early in the course of the illness. The purpose of this study was to evaluate the short-term effects of blonanserin, a novel second-generation antipsychotic drug developed in Japan in 2008, on cognitive function in first-episode schizophrenia.

Methods: Twenty-four antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Blonanserin (2–24 mg/day) was given in an open label design for 8 weeks. The Brief Assessment of Cognition in Schizophrenia (BACS-J) was administered as the primary outcome measure at baseline and 8 weeks. Clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Quality of Life Scale (SQLS-J), and the Clinical Global Impression-Severity of Illness Scale (CGI-S). To exclude the possibility of retest effects on the BACS-J, 10 age-matched patients with chronic schizophrenia treated with blonanserin were tested at baseline and after an 8-week interval. This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Twenty first-episode patients (10 males and 10 females) completed the study. The mean daily dose of blonanserin was 7.2 ± 4.0 mg/day at 8 weeks. At the 8-week endpoint, repeated measures analysis of covariance revealed a significant group-by-time interaction effect on the letter fluency task due to better performance in the first-episode group, but not in the control group. Main effect of time or group-by-time interaction effect on the Tower of London task was not significant; however, the first-episode group, but not control group showed substantial improvement with a moderate effect size. All items on the PANSS, SQLS-J, and CGI-S significantly improved after 8 weeks of treatment.

Conclusion: These results suggest that blonanserin improves some types of cognitive function associated with prefrontal cortical function.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-08-092 Cuprizone early deficits accompanied by specific glial activation implicate pathophysiological changes in schizophrenia

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Objective: Despite an apparent lack of demyelination, a growing body of clinical evidence suggests that abnormalities in white matter are involved in pathophysiology of schizophrenia. A copper chelator, cuprizone, is known to induce damage on rodent oligodendrocytes when it is ingested with food for several weeks. Here we exposed mice to cuprizone for only one week to model the mild glial damage observed in schizophrenia.

Methods: C57BL/6J mice were given a diet containing 0.2% cuprizone for one week and examined for behavioral and molecular consequences. In addition to locomotor response to psychotomimetic, Y-maze and novel object recognition tests were performed as behavioral readouts. Expression levels of glial markers and cytokines were investigated by immunohistochemical staining, in situ hybridization and quantitative RT-PCR.

Results: Surprisingly, such short-term exposure to cuprizone was enough to augment responsiveness to both methamphetamine and MK-801, and also impaired memory function. In the cuprizone mice, mRNA expression levels of astroglial (Glial fibrillary acidic protein, GFAP) and microglial (ionized calcium binding adaptor molecule 1, Iba1) markers were elevated, while the one-week cuprizone treatment substantially reduced mRNA expression of the oligodendrocyte marker (myelin basic protein, MBP) without any apparent change in MBP immunohistochemical staining. Interestingly, a proinflammatory cytokine, Interleukin 6 (IL6), was prominently induced in the hippocampus, and the induction was almost exclusively in astrocytes.

Conclusion: The behavioral deficits elicited by short-term cuprizone exposure showed similarities to schizophrenia and were accompanied by specific glial activation predominantly in the hippocampus.

P-08-093 Medication in schizophrenia with frequent relapses

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Objective: A significant percentage of people with mental health disorders need a long-standing care in psychiatric and social institutions, or else they are relapsing and have increased number of hospital admissions. Ten per cent of the patients with schizophrenia have frequent relapses and long hospitalizations. The aim of the present work was to study patients with a history of multiple hospitalizations, to find possible aggravating factors and to study the antipsychotic therapy they received (monotherapy or polypharmacy).

Methods: The participants (305 patients) were randomly selected among the hospitalized patients of the 9 acute admission departments of PHA (Psyhiatric Hospital of Attica). For the statistical analysis, the program SPSS was used.

Results: The participants (305 patients): average age of 44.3 years old (SD = 13.2), 68.2% men, 74.8% involuntary hospitalized, 7.9% on first episode, age onset of the disease 27.2 years old (SD = 10.9), 18.7% with illegal substance abuse, cessation of drug therapy before

admission in 64.3%, and 89.8% showed thought disorder and only 54.8% perception disorder, 70.1% showed aggression, 25.2% were administered more than one antipsychotic at admission with 7.2% receiving long acting medications. After 3 weeks, 41.5% were on more than one antipsychotic. There was no statistically significant difference regarding the use of multiple drugs in patients with multiple admissions (over 5) compared to the rest of them.

Conclusion: Antipsychotic polypharmacy has been found to reduce the treatment compliance and to increase the relapses and the mortality compared to antipsychotic monotherapy, but it remains a usual practice which persists despite the doubtful clinical outcomes.

P-08-094 The effect of antipsychotics on GABAergic interneurogenesis in adult brain

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Objective: Patients with schizophrenia display cognitive, behavioral disturbances and morphological abnormalities which might be caused by the progressive neurodegeneration. Although the mechanism of neurodegeneration in schizophrenia is still unclear, one of the current hypothesis focused on the relation to the altered GABA neurotransmitter system and density of GABA interneurons. In the previous study, we investigated the effect of recently developed atypical antipsychotics on the neural stem cell (NSC) function change especially focusing on the neuronal differentiation prepared from rat embryos. The atypical antipsychotics have shown the suppressive effects on the non competitive NMDA receptor antagonist MK-801-induced inhibition of NSC differentiation to neurons, indicating that atypical antipsychotic-induced alteration of neurogenesis could contribute to the neural network repair impaired in the schizophrenic brain.

Methods: In the present work, we examined the effect of atypical antipsychotics against MK-801/GABAA antagonist-induced impairment of NSC differentiation to neurons those considered parallel observations in the pathophysiology of schizophrenia, using cultured adult hippocampal and subventricular zone (SVZ)-derived NSCs, and analyzed its differentiation of GABAergic interneuron subtypes, such as somatostation, parvalbumin, and calretinin.

Results: Several antipsychotics suppressed the MK-801/GABAA antagonist-induced inhibition of neuronal differentiation of adult NSCs. Their promotions of each GABAergic subtype differentiation was different among tested antipsychotics.

Conclusion: The results suggested that the increase of adult interneurogenesis by antipsychotic might be involved in the mechanism of recovering of the neural network change in schizophrenia and the different proportion of each antipsychotic-induced cell phenotype differentiation of NSCs might relate to its characteristic of clinical efficacy in the treatment of schizophrenia.

P-08-095 Amineptine treatment of chronic catatonia: A controlled study

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Objective: Data on the treatment response of catatonic phenomena accompanying chronic schizophrenia are limited. The objective of this study was to explore the therapeutic effects of add-on amineptine, a dopamine agonist antidepressant in chronic catatonic schizophrenia.

Methods: Fifteen subjects with DSM-IV schizophrenia with persistent catatonic features underwent a 15-week, double-blind, placebo-controlled cross-over trial; 6 weeks each for amineptine and placebo with a 3-week wash-out period in-between. The primary outcome measure was the sum score of the Bush-Francis Catatonia Rating Scale. Changes in psychopathology and extrapyramidal side effects (EPS) constituted the secondary outcome measures.

Results: Amineptine augmentation of pre-existing antipsychotic treatment had no appreciable effect on catatonia ratings. Apart form a statistically significant but clinically negligible improvement of negative symptoms scores, there were no changes in the psychopathology and EPS ratings.

Conclusion: The lack of therapeutic effects of the dopamine agonist amineptine on persistent catatonia suggests that the dopaminergic system may not have a decisive role in the pathophysiology of catatonic syndrome associated with chronic schizophrenia.

P-08-096 Survey of prescription for 2nd generation antipsychotics in inpatients with schizophrenia in Japan: A nationwide multiple-center survey on prescriptions in 2010

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Objective: Comprised mainly of pharmacists engaged in psychiatric care in Japan, the Psychiatric Clinical Pharmacy Research Group (PCP Research Group) has been conducting nationwide studies on survey of prescription drugs on a continual basis since 2005, in order to understand the current state of pharmaceutical therapy in inpatients with schizophrenia. This article reports the study results of 2010 (n=25.346) from a view point of prescription 2nd generation antipsychotics (SGAs).

Methods: Among the schizophrenic patients (ICD-10: F20) hospitalized at one of the psychiatric clinics to which members of the PCP Research Group belonged, the names of drugs and doses were studied for the prescription given on the day of October in 2010, for the following types of drugs: antipsychotics, antiparkinsonians, anxiolytics/hypnotics, and mood stabilizers.

Results: The mean number and dose of drugs prescribed per day were 2.0 drugs at 802.8 mg/day (CP equivalents) for antipsychotics, 0.7 drugs and 1.9 mg/day (BP equivalents) for antiparkinsonians, and 1.5 drugs at 15.0 mg/day (DAP equivalents) for anxiolytics/hypnotics. The rates of prescriptions of 1st generation antipsychotics (FGAs) were 58.2%, and that of SGAs were 84.0%, and the rates of monotherapy of each were 6.1% and 30.4%, respectively. The rates of concomitant therapy with SGAs were 33.7% for antiparkinsonians, 70.5% for anxiolytics/hypnotics, and 28.3% for mood stabilizers, respectively.

Conclusion: While the rates of prescription of SGAs have reached 84.0% of all prescriptions, the rates of monotherapy are limited in 30.4% and they are often used in combination with FGAs. It is suggested that pharmacists engaged in psychiatric care should actively commit themselves as a professional of drugs to ensuring appropriate prescriptions in order to get maximum merits of SGAs, and hence improved adherence in patients.

P-08-097 Pharmacological treatment of schizophrenia and schizoaffective disorder – focused on combinations of antipsychotics

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Objective: Acute treatment of schizophrenia and schizoaffective disorder is often carried out during hospitalization and its most important role is based on psychopharmacs, especially antipsychotics of the second generation. The most convenient is monotherapy but in clinical practice it is sometimes not possible.

Methods: The aim of our retrospective study was to focuse on pharmacotherapy, especially combinations of antipsychotics, in our inpatients treated for schizophrenia or schizoaffective disorder during one-year period. Data were collected from medical records of inpatients treated for schizophrenia or schizoaffetive disorder at the Department of Psychiatry in Brno, Czech Republic, during one-year period. We focused on therapy before patientśdischarge.

Results: During one-year period we treated 87 inpatients with schizophrenia (F20 according to ICD-10) and 35 inpatients with schizoaffective disorder (F25). One antipsychotic drug was used for

the treatment of 58.6% patients with schizophrenia and 74.29% patients with schizoaffective disorder. Two antipsychotic drugs were used in the treatment of 36.78% patients with schizophrenia and 17.14% with schizoaffective disorder. Three antipsychotic drugs were used in the treatment of 4.60% patients with schizophrenia nad 2.86% with schizoaffetive disorder. Remaining 5.71% patients with schizoaffetive disorder were without antipsychotic medication, but no patient with schizophrenia. The most often combinations were: clozapine + amisulpride, clozapine + haloperidol and clozapine + aripiprazole. Mood stabilizers were used in 13.79% patients with schizophrenia and 45.71% patients with schizoaffective disorder. Antidepressants were used in 4.60% patients with schizophrenia and 17.14% patients with schizoaffective disorder.

Conclusion: In our retrospective study we found out, that most patients with schizophrenia and schizoaffective disorder are treated with one antipsychotic. Combinations were especially used in patients with treatment resistance, who are even resistant to monotherapy with clozapine. Just clozapine was very often combined with other antipsychotics, especially with amisulpride, haloperidol or aripiprazole.

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P-08-098 Cognitive effects of an anticholinergic challenge in healthy volunteers and drug-free patients with schizophrenia

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Objective: The importance of the cholinergic neurotransmission for cognitive processes is very well established. However, its role in the pathogenesis of schizophrenia is still not sufficiently explored. The purpose of this study was to investigate the effects of an anticholinergic challenge on cognition and attention in unmedicated patients with schizophrenia and healthy controls.

Methods: 12 medication-free patients with schizophrenia (29.3 ± 8.8 years) and 12 healthy controls (29.8 ± 9.6 years) were included. Psychopathology and cognitive performance were assessed twice: at baseline and after administration of a single dose of the subtype-nonselective acetylcholine receptor antagonist biperiden (5 mg intravenously). The following scales/tests were used: PANSS, Trail Making Test A and B (TMT-A/B), Regensburg Verbal Fluency Task (RWT), Digit Span from the Wechsler Memory Scale, Letter-Number Span, Digit-Symbol-Substitution Task and Continous Performance Task- Identical Pairs version (CPT-IP).

Results: In almost all tests patients performed worse than controls in both conditions. Biperiden impaired the performance in the majority of the tests in both groups. Using a repeated measures ANOVA we found a statistically significant time*group interaction concerning the TMT-B ($p = 0.03$), indicating a more pronounced impairment in patients than in controls. Analyzing the parameters verbal and spatial d-prime from the CPT-IP we found an effect that did not achieved statistical significance ($p = 0.078$ resp. $p = 0.074$). These results point to a slight improvement in attentional capacity in controls but not in patients. In the RWT the number of generated words after biperiden challenge increased in controls but not in patients (time*group interaction in phonemic category change: $p = 0.016$). The score increase showed a significant positive correlation with the observed increase in PANSS score in controls ($r = 0.688$, $p = 0.019$).

Conclusion: Our results indicate a complex influence of anticholinergic intervention on different cognitive domains. The differences between controls and patients point to alternations in cholinergic systems in schizophrenia.

Policy of full disclosure: Dr. Veselinovic has received grant support from Bristol-Myers Squibb. Dr. Vernaleken has served on the speakers' bureau of Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline. Dr. Gründer has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Cheplapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka,and Servier. He has served on the speakers' bureau of Astra Zeneca,Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, and Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH, Düsseldorf, Germany. Dr. Janouschek declares no conflicts of interest.

P-08-099 Needs and QoL in schizophrenic hospitalized patients treated with risperidone or haloperidol

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Objective: Objective of this research is a discovery of the difference in most common needs and the QoL between groups of male paranoid schizophrenic hospitalized patients treated with risperidone or haloperidol.

Methods: Patients are classified in accordance with the diagnostic criteria of ICD X classification. First group of 20 patients was treated with risperidone in a dose of 2 mg to 6 mg. Second group of 20 patients was treated with haloperidol in a dose of 5 mg to 15 mg. Sample of paranoid schizophrenic patients were evaluated with the Camberwell Assessment of Need and the Lancashire Quality of Life Profile two months after admission to hospital treatment. Brief Psychiatric Rating Scale was used to assess the strength of psychopathological phenomena at the time of application of CAN and LQOLP questionnaires. Research results obtained are processed using standard statistical methods.

Results: Patients treated with risperidone showed significantly higher subjective and objective quality of life in section of leisure & community participation and section of social relations. The same group of patients showed not significantly higher subjective quality of life in section of religion and section of family relations. Most often detected needs in the areas of accommodation, daytime activities, company, intimate relationships and sexual expression. Patients treated with haloperidol showed significantly higher mean number of unmet needs.

Conclusion: The results of this study indicate that risperidone may contribute to the socialization of male paranoid schizophrenic patients two months after admission to hospital treatment. Risperidone may also contribute to reducing unmet needs.

P-08-100 Daytime sleepiness and activity-rest rhythms in patients with schizophrenia during treatment with sedative and non-sedative antipsychotics

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Objective: Antipsychotics have variable effects on sleep and daytime sleepiness. The study was aimed to assess daytime sleepiness, sleep quality, and activity-rest rhythms in patients with schizophrenia during treatment with sedative and non-sedative antipsychotics.

Methods: Hundred seventeen patients with paranoid schizophrenia (67 males, 50 females, mean age 27.4 ± 6.9) were assessed with the use of the wrist actigraphy (Cambridge Neurotechnology AW4) throughout seven consecutive days. Daytime sleepiness was assessed with Epworth Sleepiness Scale (ESS), Athens insomnia scale (AIS), and sleep diaries were used for assessment of sleep quality. Analysis of variance (ANOVA) was used to test the differences between the patients and 40 healthy controls (HC) (20 males, 20 females, mean age 28.5 ± 7.4) and between groups of patients with following monotherapy treatment options: aripiprazole n = 13, olanzapine n = 40, risperidone n = 20, sertindole n = 17. As the groups were not matched for gender the differences are reported separately for males and females.

Results: Male patients had longer time in bed (TIB) ($p < 0.001$), longer total sleep time (TST) ($p < 0.001$), lower average 24 h-activity ($p < 0.005$) and lower daytime activity ($p < 0.05$) than male HC. Female patients showed longer TIB ($p < 0.001$), longer sleep latency ($p < 0.01$), longer TST ($p < 0.001$), lower 24 h-activity ($p < 0.001$), and lower daytime activity ($p < 0.001$) than female HC. Treatment with olanzapine and risperidone was related to longer TIB, longer TST, and higher sleep efficiency than treatment with aripiprazole and sertindole ($p < 0.05$). The kind of antipsychotic treatment did not have significant

effects on average 24 h-activity and daytime activity. No significant differences were also found in AIS and ESS.

Conclusion: Patients with schizophrenia differed from HC in numerous parameters assessed with wrist actigraphy. The treatment with sedative antipsychotics prolonged TIB and TST, but the physical activity of the patients was low both during treatment with sedative and non-sedative antipsychotics in comparison to the HC.

P-08-101 Valproic acid normalizes abnormal cellular proliferation, transcriptional changes and schizophrenia-related behaviors in Disc1 mutant mice

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Objective: Disrupted-In-Schizophrenia-1 (DISC1) is an established risk gene for schizophrenia. We sought to test potential preventative treatments in Disc1-L100P mutant mice, an animal model with schizophrenia-related behaviours.

Methods: We tested whether early valproate treatment would prevent behavioral abnormalities in Disc1-L100P mutants by counteracting aberrant expression of some genes, thereby normalizing brain development.

Results: Treatment with valproate before the onset of behavioral impairments in Disc1-L100P mutants corrected hyperactivity, and deficits in prepulse inhibition and latent inhibition. Disc1-L100P mutants also had increased glial cell proliferation in the subventricular zone, which was normalized by valproate pre-treatment. Genome-wide transcription profiling showed that the Disc1-L100P mutation induced the largest changes in hippocampus, and some transcript changes were reversed by valproate.

Conclusion: Valproate treatment in adolescence may represent a type of preventative intervention for patients at risk for schizophrenia.

P-08-102 Association study of phencyclidine-responsive synapse-associated protein 97 (SAP97) gene in schizophrenia

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Objective: Disturbed neurotransmission via NMDA type glutamate receptor is thought to be involved in some molecular mechanisms of positive, negative and cognitive symptoms of schizophrenia. The synapse-associated protein 97 (SAP97)/discs large (DLG1) gene encodes the synaptic scaffolding PDZ protein, which interacts with ionotropic glutamate receptors including the AMPA and NMDA receptors, and has been suggested to relate to the neural basis of the puberty-associated onset of schizophrenia and the NMDA antagonist psychosis: SAP97 mRNA expression is upregulated by phencyclidine (PCP) in the neocortex only after a critical period for the development of a PCP-induced animal model for these psychoses in the rat. Human SAP97 gene is located in chromosome 3q29. In this study, we aimed to investigate possible association between the SAP97 gene and schizophrenia.

Methods: We genotyped total 23 SNPs capturing the known common haplotype variations of the SAP97 gene in the samples from schizophrenic patients and healthy controls. The study was approved by the ethics committees of the institutes. All participants gave informed and written consent to participate in the study.

Results: In a single marker analysis, ten SNPs displayed nominally significant association with schizophrenia, although the p-values of these SNPs were not significant after the Bonferroni correction. We also compared haplotype estimates based on case-control genotypes and observed significant association of eight two- and three- SNP haplotypes with schizophrenia following permutation-based correction. Further examination of the above series of SNPs or haplotypes in each gender revealed significant associations between some of these SNPs or haplotypes and the disorder only in males.

Conclusion: The present findings suggest that the SAP97 gene may be a susceptibility factor in male schizophrenics. The modification of the glutamate receptors-SAP97 protein signaling and/or the receptor trafficking might be involved in some of the etiology of schizophrenia and other psychoses.

P-08-103 The satisfaction improved after switching to pariperidone ER mono-therapy among Japanese patients with schizophrenia

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Objective: Medication adherence is an important thing for continuation of schizophrenia medical treatment. The patient itself has satisfaction is important, in order to continue medical treatment and prevent a recurrence. The Pariperidone ER which put on the market in Japan in 2010 is expected stable blood concentration by OLOS system. This may affect to reduce the instability of symptoms or side effects, therefor may improve adherence. We investigated the patients' satisfaction by switching to Pariperidone ER mono therapy in Japanese patients with schizophrenia.

Methods: Design: A 24-weeks, open trial. This study approved by ethical committee in Fujita Health University. Setting: Inpatient (N = 34) and outpatient (N = 87) at eleven hospitals in Japan. Participants: Written informed consent patients with schizophrenia (N = 121) age 20–78. Investigations: Switching to Pariperidone ER mono therapy and assessed GAF, CGI, side effects and satisfaction scale (POM) from patient and family in 0, 4, 12 and 24 week.

Results: Former antipsychotics were Risperidone (N = 82), Olanzapine (N = 11), Aripiprazole (N = 9) and others (N = 19). 109 patients completed 24 weeks. The median of CGI score changed from 4 to 3, the average GAF score changed from 42.7 to 59.9 and the median of patients' POM changed from ''little well'' to ''well''. And the EPS decreased among the study period.

Conclusion: We confirmed the Pariperidone ER mono therapy improved not only patients' symptoms but also satisfaction. This therapy expected to improve patients' QOL and reduce the distress among the life with schizophrenia.

Policy of full disclosure: Janssen Pharmaceutical K.K.

P-08-104 Cigarette smoking in male patients with chronic schizophrenia in a chinese population: Prevalence and relationship to clinical phenotypes

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Objective: A significantly high prevalence of smoking in schizophrenia may be linked to reduced clinical symptoms and side effects in subjects of European background. The aims of the present study were to examine the prevalence of smoking and its associations with clinical phenotypes in Chinese patients with schizophrenia, who were less well characterized than other populations.

Methods: The smoking prevalence and behaviors were evaluated by clinician-administered questionnaires and the Fagerstrom Test for Nicotine Dependence (FTND) in 776 male patients with schizophrenia and 560 control subjects. Patients also were rated on the Positive and Negative Symptom Scale (PANSS), the Simpson and Angus Extrapyramidal Symptom Rating Scale (SAES), and the Abnormal Involuntary Movement Scale (AIMS).

Results: Our results showed that compared to normal controls, patients had higher lifetime incidence of smoking (79% vs. 63%), and were more likely to be heavy smokers (61% vs. 31%), but had lower smoking cessation rates (4% vs. 9%) (all $p < 0.0001$). In schizophrenia patients, the prevalence of smoking increased with age, with the particularly greater prevalence than controls in age cohorts of 55–75 years: 75% vs. 46% ($p < 0.0001$). Of the smokers with schizophrenia, 73% started to smoke an average of 7.6 years before the onset of their illness. Current smokers scored significantly lower on the PANSS negative symptom subscore ($p < 0.005$), and on the SAES symptom scale ($p < 0.04$; Bonferroni corrected $p > 0.05$), compared to non-smokers in patients.

Conclusion: These results suggest that male schizophrenia patients of Chinese descent smoke more frequently than the general population. Further, smokers with schizophrenia may display fewer negative symptoms and, possibly less parkinsonism than non-smokers with schizophrenia.

P-08-105 Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls

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Objective: Studies suggest that the functional polymorphism of brain-derived neurotrophic factor gene (BDNF Val66Met) may mediate hippocampal-dependent cognitive functions. Few studies have reported its role in cognitive deficits in schizophrenia and whether peripheral BDNF levels may be useful to assess cognitive measures in schizophrenia.

Methods: Six hundred and fifty-seven schizophrenic inpatients and 445 healthy controls were included in this study. Performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), presence of the BDNF Val66Met polymorphism and serum BDNF levels were compared between groups. Patient psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS).

Results: Our results showed that visuospatial/constructional abilities significantly differed by genotype but not genotype × diagnosis, and the Val allele was associated with better visuospatial/constructional performance in both schizophrenia patients and healthy controls. On attention performance, there were significant genotype and genotype by diagnosis effects. Met allele-associated attention impairment was specific to schizophrenia patients but not healthy controls. In patient group, partial correlation analysis showed a significantly positive correlation between serum BDNF and the RBANS total score. Furthermore, BDNF levels × genotype interaction on RBANS total score was statistically significant.

Conclusion: Our findings demonstrate the association between the BDNF Met variant and poor visuospatial/constructional performance. Furthermore, the BDNF Met variant may be specific to attentional decrements in schizophrenic patients. The association between decreased BDNF serum levels and cognitive impairment in schizophrenia is dependent on the BDNF Val66Met polymorphism.

P-09. Antidepressants

P-09-001 Antidepressant-like activity of water-soluble curcumin formulations in behavioral paradigms of despair

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Objective: Curcumin is the active principle of Curcuma longa, one of the widely used components in traditional system of medicine in India. Despite its efficacy in experimental studies aiming neuronal disorders like depression, curcumin's poor water solubility challenges its therapeutic formulations. This study investigates the antidepressant-like activity of novel water soluble curcumin formulations, dispensed in three different concentration levels. Further, the study comparatively evaluates St. John's Wort (SJW), another herbal preparation.

Methods: These compounds were evaluated in the forced swimming test in mice and the corresponding changes in the neurotransmitter levels were measured.

Results: Three water soluble curcumin formulations, C-5, C-20, C-50 (50–200 mg/kg, p.o.) decreased the immobility period, increased serotonin and dopamine levels in the brain tissues. A sub-effective dose (50 mg/kg) of these formulations enhanced the antidepressant-like effect of various antidepressant drugs like desipramine (tricyclic antidepressant), fluoxetine (selective serotonin reuptake inhibitor (SSRI)] or venlafaxine [dual (5-HT and NE) reuptake inhibitor (SNRI)]. However, no significant change in the anti-immobility effect with tranylcypromine (non-selective MAO inhibitor) was observed. In addition, 25 mg/kg dose of SJW showed significant antidepressant-like effect in all the behavioral studies and also significantly increased brain neurotransmitter levels, especially that of serotonin.

Conclusion: The effects produced by C-5 were comparable with that of SJW and fluoxetine, respectively. Besides, in all these observations the water soluble formulation, C-5 showed significant antidepressant-like effect, including enhancement of neurotransmitter levels as compared to the similar dose of conventional curcumin preparation. Thus, this formulation may be a novel treatment option in the management of mental depression.

P-09-002 Transcriptional modulation of serotonin transporter as a new antidepressant strategy

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Objective: Identifying the factors contributing to the etiology of anxiety and depression is critical for the development of more efficacious therapies. Serotonin (5-HT) is linked to both disorders. Current antidepressants, which block the serotonin transporter (SERT), show limited efficacy and slow onset of action. Here, we used a small interference RNA (siRNA) strategy to examine the biological consequences of reducing SERT expression, as previously reported for 5-HT1A-autoreceptors.

Methods: Adult mice were locally infused with vehicle, nonsense-siRNA and SERT-siRNA into dorsal raphe nucleus (DR). The functional effects of SERT-siRNA knockdown were compared with those produced by chronic fluoxetine treatment.

Results: Local SERT-siRNA infusion for 4-days decreased SERT expression in the DR (40%). This was accompanied by a widespread reduction of SERT-binding sites throughout the brain. Moreover, a 4-day regimen with intra-DR SERT-siRNA modified brain variables considered to be key markers of antidepressant action, such as: (a) reduced expression and sensitivity of 5-HT1A-autoreceptors, (b) augmented extracellular 5-HT in DR-projecting areas such as striatum and hippocampus, (c) increased hippocampal neurogenesis, and (d) increased expression of plasticity-associated genes (BDNF, VEGF and ARC). In contrast, a 4-day regimen with fluoxetine did not alter any of these variables and only started to modify them after 15-day treatments.

Conclusion: These findings highlight the critical role of SERT in the control of serotonergic function, including neural plasticity. They also support the use of siRNA targeting serotonergic genes (SERT, 5-HT1A autoreceptors) as a new generation of antidepressant therapies with a potential greater efficacy faster onset of action than current treatments.

P-09-003 Prevalence and pattern of sexual dysfunction in females receiving antidepressants

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Objective: To study the prevalence and pattern of sexual dysfunction in female patients receiving antidepressants.

Methods: Eighty married female patients with a diagnosis of depressive disorder, currently in remission, and receiving a single antidepressant at least for 3 months, were assessed for sexual dysfunction on Female Sexual Function Index (FSFI) scale.

Results: It was found that 95% of patients had decreased desire, 60% had decreased arousal, 37.5% had decreased lubrication, 63.8 had decreased orgasm, 55% had decreased satisfaction and 25% had pain during sexual activity.

Conclusion: Sexual dysfunction is quite prevalent in married female patients receiving antidepressants and all the domains of sexual functioning are impaired by antidepressants.

P-09-004 Antidepressant activity of curcumin: Involvement of serotonin and dopamine system

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Objective: Curcumin is a major active principle of Curcuma longa, one of the widely used preparations in the Indian system of medicine. It is known for its diverse biological actions. The present study was designed to investigate the involvement of monoaminergic system(s) in the antidepressant activity of curcumin and the effect of piperine, a bioavailability enhancer, on the bioavailability and biological effects of curcumin.

Methods: Behavioral (forced swim test), biochemical (monoamine oxidase (MAO) enzyme inhibitory activity), and neurochemical (neurotransmitter levels estimation) tests were carried out.

Results: Curcumin (10–80 mg/kg, i.p.) dose dependently inhibited the immobility period, increased serotonin (5-hydroxytryptamine, 5-HT) as well as dopamine levels (at higher doses), and inhibited the monoamine oxidase enzymes (both MAO-A and MAO-B, higher doses) in mice. Curcumin (20 mg/kg, i.p.) enhanced the anti-immobility effect of subthreshold doses of various antidepressant drugs like fluoxetine, venlafaxine, or bupropion. However, no significant change in the anti-immobility effect of imipramine and desipramine was observed. Furthermore, combination of subthreshold dose of curcumin and various antidepressant drugs resulted in synergistic increase in serotonin (5-HT) levels as compared to their effect per se. There was no change in the norepinephrine levels. The co-administration of piperine (2.5 mg/kg, i.p.), a bioavailability enhancing agent, with curcumin (20 and 40 mg/kg, i.p.) resulted in potentiation of pharmacological, biochemical, and neurochemical activities.

Conclusion: The study provides evidences for mechanism-based antidepressant actions of curcumin. The co-administration of curcumin along with piperine may prove to be a useful and potent natural antidepressant approach in the management of depression.

P-09-005 Abuse antidepressant use

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Objective: The number of antidepressants has grown exponentially and its indication has been changing over time. Initially mainly used as a treatment for mood disorders, while in recent decades, used to treat anxiety, eating disorders, obsessive-compulsive disorder, substance abuse, personality disorders, schizoaffective disorder, chronic neuropathic pain, etc. No conclusive data on long-term risks of these drugs, but they continue to prescribe indiscriminately by the firm belief of its safety. OBJECTIVE: Conduct a descriptive study to reflect how many patients started antidepressant treatment on admission to a Brief Hospitalization Unit (UHB) of Psychiatry during 2000. After 10 years of monitoring, evaluating the effectiveness-ineffectiveness, continuity-discontinuation of it.

Methods: Select medical records of patients who are discharged with an antidepressant medication. Collect the following data: age, sex, diagnosis and previous antidepressant treatments, family history of antidepressant treatment, reason for admission and establishment of antidepressant treatment, type of antidepressant, average stay, discharge diagnosis, continuity of treatment/discontinued (reason discontinuation), current clinical status.

Results: After 10 years found that 40% patients continue antidepressant treatment. ● Most did not have the diagnosis of Mood Disorder.

Conclusion: ● Antidepressants have a clear potential for abuse and dependence that is attributed to its anticholinergic action. ● The reasons for treatment discontinuation: clinical stability, abandonment, powerlessness, turn, side effects.

P-09-006 Low-trapping NMDA channel blocker AZD6765 increases gamma-band EEG without dissociative side-effects: A comparison with ketamine in healthy volunteers

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Objective: Ketamine has demonstrated robust antidepressant activity in small clinical trials. However, ketamine's side-effects may limit its therapeutic utility. AZD6765, a low-trapping NMDA channel blocker in development for major depression, is predicted to have an improved tolerability profile compared to ketamine. Preclinically, NMDA channel blockers increase gamma-band EEG – a potential therapeutic biomarker of cortical disinhibition. The object of this study was to use quantitative EEG to determine whether AZD6765 in humans causes electrophysiological changes comparable to ketamine without the occurrence of dissociative side-effects.

Methods: A four-way, placebo-controlled, crossover study in healthy volunteers compared i.v. infusion of AZD6765 (75 and 150 mg) with an antidepressant dose of ketamine (0.5 mg/kg). Baseline and post-drug EEGs were obtained under controlled conditions and composite brain EEG maps were analyzed using Standard Decision Tree methods. Changes in gamma (35–55 Hz) band power served as the primary endpoint. Secondary endpoints included Clinician Administered Dissociative Status Scale (CADSS), electronystagmography, and pupil size.

Results: Significant increases in gamma-band EEG were observed at 1 hour for ketamine and AZD6765, and baseline-corrected gamma-band EEG following AZD6765 150 mg was statistically indistinguishable from that observed following ketamine. In contrast, AZD6765 caused no dissociative symptoms, whereas ketamine produced a moderate yet significant increase in CADSS and was associated with an increase in supine systolic blood pressure. No significant changes in nystagmus or pupil size were observed with AZD6765.

Conclusion: Consistent with preclinical findings, this study supports the utility of gamma-band EEG as a biomarker for NMDA channel blockade and provides evidence that differentiates ketamine from AZD6765 across multiple tolerability endpoints including cardiovascular and psychotomimetic liability. AZD6765 demonstrated NMDA channel blockade and an improved tolerability profile compared to ketamine.

Policy of full disclosure: Author is employed by Forenap, the CROI conducting the study on behalf of AstraZeneca.

P-09-007 Clinical predictors of antidepressant response and remission in treatment resistant depression

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Objective: Few studies investigated clinical predictors of antidepressant response-remission in treatment resistant depression (TRD). The present has been performed in the context of a European multicenter project. Its aim was to identify predictors of antidepressant response/remission in a sample of TRD prospectively assessed patients and to compare results to ones obtained on another sample of TRD patients retrospectively assessed.

Methods: 414 patients who failed to respond to a previous antidepressant were firstly included in a 6-week treatment with venlafaxine; secondly, those who failed to respond were treated for a 6-week treatment with escitalopram. MINI was administered at baseline. HRSD, MADRS, CGI-S and CGI-I scales were administered from baseline to week 12. Other information has been collected at baseline.

Results: Completers have been included in the analyses. In the first phase, non responders and non remitters to venlafaxine reported lower rate of inpatients, higher rate of psychiatric antecedents, lower benzodiazepine use at baseline, higher rate of side effects, higher CGI-S and lower CGI-I scores, and higher treatment doses. Moreover, non responders showed lower age and lower episode number while non remitters showed higher current suicidal risk level. In the second

phase, non responders and non remitters to escitalopram reported higher duration of current episode, higher treatment dose, and higher CGI-S and lower CGI-I scores. Moreover, non remitters showed higher rate of current suicidal risk and higher current suicidal risk level, higher rate of comorbid anxiety disorders, in particular panic disorder and generalized anxiety disorder, and higher rate of antecedents of second degree affected by bipolar disorder.

Conclusion: Some clinical variables have been identified as associated with treatment non response/non remission in TRD. Specifically, current suicidal risk and comorbid anxiety disorders, in particular panic disorder, seem to be predictors of treatment non remission/resistance in two sample of TRD patients. Further clarification of the role of other clinical variables should be explored.

P-09-008 Effects of pharmacodynamic properties of antidepressants on central autonomic regulation in young women with recurrent depression

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Objective: Recurrent depression is often associated with alterations of central autonomic regulation. Pharmacodynamic properties of antidepressants may cause changes in central autonomic function. We examined the relationship between autonomic status of women with recurrent depression and pharmacodynamic properties of antidepressants.

Methods: Resting RR intervals and respiratory signals were simultaneously obtained from 38 euthymic women with recurrent depression receiving escitalopram (n = 19) or venlafaxine monotherapy (n = 19) and 38 matched and healthy women. Linear measures of heart rate variability were extracted to assess cardiac autonomic control. Sample Entropy (SampEn) was computed to assess the complexity of heart rate and respiratory signal, and Cross-SampEn were calculated to measure a nonlinear interaction of both signals.

Results: Women with recurrent depression receiving venlafaxine showed significant decreases in cardiac vagal activity and interaction between heart rate and respiration when compared to women with recurrent depression receiving escitalopram or healthy controls. Effect sizes for these differences in autonomic control were large between women receiving venlafaxine and healthy controls. Compared with healthy controls, women with recurrent depression receiving escitalopram showed tendencies toward decreased cardiovagal tone and reduced cardiorespiratory coupling. A significant association between cardiorespiratory decoupling and venlafaxine dose was observed.

Conclusion: In addition to a substantial link between depression and autonomic dysregulation, the current study suggests that altered autonomic modulation in euthymic women with recurrent depression may be associated with pharmacological properties of antidepressants.

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P-09-009 Tianeptine in treatment of depression in cancer with deep vein thrombosis on anticoagulant medication

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Objective: Patients undergoing major abdominal surgery for malignancy are at particularly high risk of developing deep vein thrombosis (DVT). Studies show that half of all cancer patients have a psychiatric disorder, usually a depression. The anticoagulant given to prevent recurrent risk for DVT can cause bleeding but this adverse event was reported also at more antidepressants classes like selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitor. The aim of this study was to investigate the tianeptine effect, used for treatment of depression, on overanticoagulation during the anticoagulant medication in patient with cancer and DVT.

Methods: We included 11 patients, 7 women and 3 men with age between 30–42 years, with diagnosis of depression by DSM IV criteria, who were suffered DVT $\geqslant 1$ times during the last month after a surgery intervention for cancer. All patients received anticoagulants daily with high intensity of international normalized ratio (INR) settings (around 3.7–4.0 INR) and tianeptine 12.5 mg three times on day. The combination of tianeptine with anticoagulants was monitored by measurements of INR to avoid overanticoagulation. For measurement the depressive symptoms we used Hamilton Depression Rating Scale (HDRS)- 17 items. Period of study it was 3 month, with one visit per week in the first month and at 2 weeks to the endpoint.

Results: We didn't found risk for overanticoagulation during anticoagulant treatment in combination with tianeptine. The patients tolerated very well the treatment and at the endpoint we obtained the remission of depressive symptoms. It wasn't necessary to adjustment the doses of anticoagulant on the period of the study.

Conclusion: There was no increase in risk for overanticoagulation in subjects treated with tianeptine and anticoagulants. This medication can be take in consideration in treatment of depression at patients with recurrent DVT on anticoagulant medication.

P-09-010 Antidepressant usage after bariatric surgery

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Objective: To examine antidepressant medication usage in a retrospective study of 439 patients who had Roux-en-Y gastric bypass surgery for weight loss.

Methods: A retrospective chart review identified 170 patients on antidepressant mediations presurgery and 180 patients not on antidepressant medications presurgery. Average age of the sample was 47 years old, most were female, and average BMI was 47.

Results: Of the 170 patients who were on antidepressant medications presurgery, 40% had no change in their antidepressant medications, 23% had an increase in antidepressant medications, 18% changed antidepressants, and only 16% decreased or stopped their antidepressant medications.

Conclusion: Many patients seeking to have bariatric surgery are prescribed antidepressant medications, but there is little documentation regarding antidepressant usage after having bariatric surgery. In this retrospective medical chart review few patients were able to reduce or discontinue their antidepressant medications after having bariatric surgery. These results highlight the need for careful monitoring of mood after having bariatric surgery. These results have been accepted for publication: Cunningham, JL, Merrell, CC, Sarr, MG, Somers, KJ, McAlpine, D, Reese, M, Stevens, SR, & Clark, MM. Investigation of Antidepressant Medication Usage after Bariatric Surgery, Obesity Surgery, ''in press''.

P-09-011 Agomelatine treatment normalized anxiety behaviour, Period 1 and Period 2 expression in a rat model of posttraumatic stress disorder

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Objective: Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder defined by the co-existence of three clusters of symptoms: re-experiencing (flash-backs, recurrent and distressing recollections and dreams, intense physiological reactivity after reminders exposure), avoidance/numbing (persistent avoidance of trauma's reminders) and hyperarousal (anxiety, insomnia, concentration difficulties, exaggerated startle response, irritability). Moreover, abnormal circadian rhythms are observed in PTSD patients. Agomelatine is a melatonergic agonist (MT1/MT2) and 5HT2C antagonist with antidepressant, anxiolytic and re-synchronizing effects in animals and humans. Here, we evaluated the effect of agomelatine on behavior and clock genes Period1 and Period2 expression in the predator scent stress (PSS) rat PTSD model.

Methods: Adult male Sprague-Dawley rats were exposed to PSS for 10 min, and 1 h later treated for 3 days with vehicle or agomelatine (50 mg/kg i.p.). Rats were assessed in the Elevated Plus Maze (EPM)

and acoustic startle response (ASR) on Day8 and sacrificed 24 h after (ZT19) for Per1 and Per2 immunohistochemistry evaluation.

Results: In the EPM, agomelatine antagonised ($p < 0.035$) the time spent in the open arms decrease observed in PPS vehicle-treated rats. In the ASR, agomelatine ($p < 0.002$) reversed the mean startle amplitude increase observed in PSS vehicle-treated rats. Moreover agomelatine induced decreases in the prevalence rates of individuals displaying extreme behavioural responses (EBR) (PTSD-like). As regards clock genes expression, agomelatine normalized Per1 increases observed in the CA3 ($p < 0.05$), DG ($p < 0.015$) and SCN ($p < 0.0002$) of PPS rats. Agomelatine also normalized the Per2 increases observed in the CA1 ($p < 0.00025$), CA3 ($p < 0.0008$), DG ($p < 0.05$) and SCN ($p < 0.0035$) of PPS rats.

Conclusion: These results suggest that agomelatine normalized anxiety behavior in this animal model of PTSD and normalized the Per1 and Per2 clock genes expression changes observed in this model suggesting that these clock genes are involved in the neurobiological response to anxiety in this PTSD model.

P-09-012 The use of agomelatine in the current psychiatric clinic: A naturalistic study

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Objective: Agomelatine has been shown to be effective and well-tolerated in several Clinical Trials, under strict methodological limits, for the treatment of Major Depression. Its use to treat depressive symptoms in other mental disorders is less known. The present study wass aimed to evaluate the clinical response to agomelatine and its safety in an outpatient adult psychiatric facility.

Methods: 25 mg/day of agomelatine was prescribed according to clinical judgment. MADRS assessed the intensity of symptoms before (W0) and after at least 8 weeks of treatment (W8). CGI was used at W8 for self-assessment. Monotherapy or association with other psychotropics were both used.

Results: 23 men (mean age = 52.8 years, MADRS mean score at W0 = 23.7) and 87 women (mean age = 48.8 years, MADRS mean score at W0 = 25.2) were included. The distribution of patient according to ICD-10 was: F0 = 15; F1 = 2; F2 = 2; F3 = 71; F4 = 14; F5 = 3; F6 = 3). 105 patients completed the minimum 8 weeks of treatment (5 abandoned it). Cost (n = 10) and side effects (n = 15) caused the interruption of treatment at W8. Other 7 patients reported side effects without needing any further action. Mean MADRS scores were: W0 = 25.3; W8 = 15.1 ($p < 0.001$). 79% of patients were improved on W8: 6% very much improved, 46% much improved, 27% little improved ($p < 0.001$). The most significant side effects were nausea/vomiting (n = 9) and overall discomfort (n = 8).

Conclusion: Agomelatine has demonstrated to be useful in current psychiatric clinical practice with high response level in 8 weeks of treatment. Side effects can be related to the (i) possible drug interactions, (ii) the context of the mental disorder, (iii) the intrinsic pharmacological properties of the drug.

Policy of full disclosure: Servier suported the inscription and travel fees to this congress.

P-09-013 PharmacoMRI and cognitive effects of the low-trapping NMDA channel blocker AZD6765 compared with ketamine in untreated major depressive disorder

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Objective: To determine the immediate effects of AZD6765 and ketamine on neural activity in the subgenual cingulate cortex (SGC) and its relationship with subsequent change in depressive symptoms and emotion processing using pharmaco- and functional magnetic resonance imaging (phMRI, fMRI).

Methods: Sixty treatment-naïve males or females aged 18 to 45 years with major depressive disorder were randomly assigned to three groups to receive (i.v.) ketamine, AZD6765, or placebo during a 60 min phMRI scan. Twenty-four hours later, behavioural and fMRI responses to emotional stimuli were recorded. Baseline and follow-up Montgomery-Asberg Depression Rating Scale (MADRS) scores were recorded.

Results: Both AZD6765 and ketamine increased SGC BOLD signal responses; no decreases were seen in any brain region. The SGC responses correlated with improvement in MADRS scores 24 hours and 7 days post-infusion. Following administration of AZD6765, interviewer-rated psychotic and dissociative symptoms were minimal and not statistically significant. In contrast, ketamine produced a moderate statistically significant increase in dissociative symptoms. Both drugs reduced amygdala responses to fear and sadness in the emotional faces task 24 hours post-infusion.

Conclusion: Activation of the SGC was seen following both drugs and this effect was associated with improvement in depressive symptoms 24 hours and 7 days post-infusion. The results suggest that AZ6765 and ketamine both have antidepressant-like effects on emotion processing in the brain and that diminished NMDA glutamate neurotransmission in the SGC is a likely proximal mechanism.

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P-09-014 Antidepressant activity of 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-YL)-cyclohexanol, a β-substituted phenylethylamine in mice

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Objective: Trace amines are known to play an important role in the pathophysiology of major depression. The present study is an attempt to evaluate one of newly discovered putative trace amine modulator, 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol (NME), in animal models of depression.

Methods: Various behavioral and biochemical paradigms of despair were used in the present study.

Results: The molecule (4–16 mg/kg., i.p.) dose-dependently inhibited the immobility period in mouse forced swim test, the effect comparable to venlafaxine. The ED50 values of this NME and venlafaxine in mouse forced swim test were found to be 5.27 [4.38–6.35] mg/kg., i.p. and 4.66 [3.48–6.25] mg/kg., i.p., respectively. Further, NME at 4–16 mg/kg., i.p. reversed the immobility period in mouse tail-suspension test. Additionally, the molecule at 8 mg/kg., i.p. reversed reserpine-induced behavioral despair in mouse forced swim test. When administered simultaneously, it enhanced the antidepressant activity of sub-effective doses of imipramine or fluoxetine in the mouse forced swim test. Neurochemical analysis revealed that the molecule at 8 mg/kg., i.p. increased the levels of norepinephrine (21% increase) without affecting serotonin in the mouse brain. However, at higher dose (16 mg/kg., i.p.), it increased the levels of norepinephrine (13% increase), serotonin (37% increase), and dopamine (42% increase). The molecule enhanced the locomotor activity in mice only at higher doses. The molecule, unlike venlafaxine, which potentiated barbiturate-induced hypnosis, was devoid of any sedative activity.

Conclusion: In conclusion, the novel trace amine possess antidepressant-like activity in animal models of depression by modulating the neurotransmitter levels in the brain. Such an activity might be due to the modulating action of this novel molecule on trace amine receptors. Such a molecule may be the future drugs of choice for the treatment of major depression.

P-09-015 Serotonergic antidepressants and hyponatraemia in aged psychiatry

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Objective: To investigate the incidence and risk factors for antidepressant induced hyponatraemia in elderly people treated with serotonergic antidepressants.

Methods: In a retrospective chart analysis depressed patients aged > 63 years were investigated for change in serum sodium levels in two samples separated by a median period of 45.5 days and with the first specimen taken prior to treatment. Patients were grouped into three cohorts; treated with an SSRI or SNRI (n = 77), treated with an antidepressant other than an SSRI or SNRI (n = 54) and not treated with an antidepressant (n = 128).

Results: For change in sodium level between measurements and total number of patients with hyponatraemia, there was no significant difference between cohorts. However, the rate of reduction of serum sodium levels between time points was significantly greater for SSRI and SNRI treated patients ($p < 0.001$) and patients treated with other antidepressants ($p = 0.03$) compared to patients not treated with antidepressants. Moreover, the distribution of values of change in serum sodium was skewed towards reduced serum sodium in patient treated with SSRI or SNRIs (skew −0.43) and patients treated with other antidepressants (skew −0.09) but not for patients not treated with antidepressants (skew 0.25).

Conclusion: These data suggest that hyponatraemia is associated with antidepressant treatment that effects some individuals only. Generalized linear modelling showed that the risk of hyponatraemia increases with increased age, female gender, and particularly the antidepressant agents sertraline and escitalopram. The findings are of clinical significance as they demonstrate that hyponatraemia can occur rapidly in patients treated with these antidepressants.

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P-09-016 Difference between morning and evening thyrotropin response (delta delta TSH) and prediction of antidepressant treatment outcome in major depresion

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Objective: About 50% of major depressed patients have inadequate response to an individual antidepressant trial. Early predictors of response are needed to improve effectiveness of antidepressant treatment. This study sought to determine whether the thyroid function evaluation at baseline and after 2 weeks of treatment could predict antidepressant response in hospitalized patients.

Methods: Serum levels of thyrotropin (TSH), free triiodothyronine (FT3), free thyroxine (FT4) were measured before and after 08.00 h and 23.00 h protirelin challenges (thyrotropin-releasing hormone [TRH]; 200 μg intravenously), on the same day, in 30 medication-free DSM-IV euthyroid major depressed inpatients and 30 healthy hospitalized controls. After 2 weeks of antidepressant treatment (tianeptine, n = 15; extended-release venlafaxine, n = 15) the same TRH tests were repeated in all inpatients. Antidepressant response was evaluated after 6 weeks of treatment.

Results: At baseline, serum 23.00 h-TSH basal values, 23.00 h maximum increment in TSH level (delta TSH) and the difference between 11 PM-delta TSH and 8 AM-delta TSH (delta delta TSH) were significantly lower in patients compared to controls ($p = 0.03$, $p = 0.0001$, and $p < 0.0001$, respectively). Twenty patients showed reduced delta delta TSH values (i.e. ≤ 2.5 mIU/l; sensitivity, 67%; specificity, 97%). Pretreatment thyroid function tests were not associated with clinical outcome (full response rate 57%). After 2 weeks of treatment, patients with reduced delta delta TSH values (n = 14 [47%]) showed poor clinical outcome, while those with normal delta delta TSH values showed full response on day 42 ($p < 0.0006$). A logistic regression on delta delta TSH values on day 14 predicted endpoint clinical response (odds ratio, 3.30; 95% confidence interval, 1.35–8.08; $p = 0.009$).

Conclusion: Our results suggest that the delta delta TSH test performed early during antidepressant treatment could be used to predict eventual outcome and guide treatment decision.

P-09-017 Pharmacodynamics of Org 26576, an AMPA positive allosteric modulator, in patients with major depression: an exploratory, randomized, double-blind, placebo-controlled Phase 1b trial

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Objective: This study explored the safety, tolerability, pharmacokinetics, and pharmacodynamics(PD) of Org 26576 in depressed patients; PD included QEEG endpoints, cognition, and treatment response on the MADRS.

Methods: Part I (N = 24) evaluated maximum tolerated dose (MTD) and optimal titration schedule using a 10 to 16-day multiple rising dose paradigm in depressed subjects. Part II (N = 30) followed a parallel-groups design, in which subjects received either 100 or 400 mg BID of Org 26576 or placebo for 28 days. The QEEG-based endpoint Antidepressant Treatment Response (ATR; Covidien) was assessed at baseline and Week 1. MADRS and a computerized cognitive battery were administered at baseline and endpoint.

Results: Part I: The MTD study determined a safe starting dose of 200 mg BID with an MTD of 450 mg BID. Part II: Both doses of Org 26576 showed a small numeric advantage over placebo on the MADRS at Day 28 [Change from baseline 100 mg BID: −15.40 (±6.40); 400 mg BID: −14.78 (±11.72); placebo −12.67 (±9.35); and Org 26576 was associated with improvements on computerized tests of executive functioning (Effect size 100 mg BID vs. placebo: 1.01; 400 mg BID vs. placebo: 0.77) and speed of processing (Effect size 100 mg BID vs. placebo: 0.88). The ATR at Week 1 was able to significantly predict symptomatic response at endpoint in the active treatment group, as was early improvement in social acuity, as measured by a face emotion recognition task (POET; CNS-Vital Signs).

Conclusion: Org 26576 was well tolerated in patients. Exploratory pharmacodynamic endpoints suggested that it may show promise as an antidepressant in future well-controlled, adequately powered proof of concept trials. Further study is also warranted to assess the use of markers such as ATR and social acuity as response surrogates in small Phase I patient studies.

Policy of full disclosure: Ereshefsky, Gertsik, Kim, and Unabia are employees of PAREXEL, recipient of grant support from Merck, USA. Nations was an employee of Merck. Dogterom, Bursi, and Schipper were employees of Merck Sharpe and Dohme, The Netherlands. Greenwald and Zraket are employees of Covidien recipients of grant support from Merck.

P-09-018 Lymphoblastoid cell lines as models for pharmacogenomics in psychopharmacology

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Objective: Epstein-Barr virus (EBV) immortalized human lymphoblastoid cell lines (LCL) serve as models in personalized medicine to understand the genetic variability underlying drug effects. Different cohorts of LCLs are existing that so far have been mainly used to study genomic influences on the phenotype of cytotoxic drug effects in cancer therapy. Recently, other than anticancer drugs have been used to study transcriptomic variability in modulation of drug effects. We use this method to study the genetics of antidepressant drug effects and see if this method may serve as a surrogate parameter for antidepressant drug response. The aim of this project was first, to study if the cell toxic effects of different antidepressant drugs are specific to the drug class, and second, to correlate the findings of drug induced cell-toxicity with clinical data.

Methods: We used LCLs from patients who have been treated with antidepressant drugs and characterized for the clinical course of drug response in the context of the Munich Antidepressant Response Signature (MARS) study by the Max Planck Institute of Psychiatry. We examined the effects of mirtazapine, imipramine and paroxetine in different concentrations and epigallocatechin gallate (EGCG), the main component of green tea that has known antiproliferative effects as a control for a different antiproliferative substance class. The experiments were repeated three-times in each cell line.

Results: The drug concentration that inhibited the cell growth by 50% (IC50: imipramine 80 μM, paroxetine 15 μM, mirtazapine 300 μM, EGCG 15 μM) correlated significantly between the three antidepressant drugs (imipramine versus paroxetine $r=0.55$, $p=0.017$; imipramine versus mirtazapine $r=0.48$, $p=0.045$). EGCG also inhibited cell growth but it did not correlate with the cell toxicity of the antidepressant drugs ($r=0.13$, $p=0.47$ for imipramine, $r=0.23$, $p=0.23$ for paroxetine, $r=0.11$, $p=0.57$ for mirtazapine).

Conclusion: Correlations between cell growth inhibition and clinical antidepressant therapy outcome will then be tested in these patient cohorts from Munich.

P-09-019 Differential regulation of FADD protein content by electroconvulsive seizure and classic antidepressants in rat brain

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Objective: Major depression has been linked with genetic abnormalities of Apaf1, suggesting a role for enhanced cell death or apoptosis. Light deprivation in rats, a behavioral model of depression-like behavior, was recently shown to increase apoptosis and apoptosis-related markers. Conversely, the antidepressant drugs desipramine and tianeptine induced antiapoptotic effects in an animal model of depression. Fas-Associated protein with Death Domain (FADD), the adaptor protein of the extrinsic apoptotic pathway, is essential in Fas receptor-induced apoptosis. Moreover, FADD is a unique regulator of cell life and death and plays a critical role in many essential cellular processes. In fact, phosphorylated FADD (pSer191 FADD) mediates non-apoptotic actions such as cell growth and differentiation.

Methods: The current study investigated the effects of acute and chronic electroconvulsive seizure (ECS) and classic antidepressant treatments (desipramine and fluoxetine) on total FADD and pFADD protein contents in brain regions associated with depression in the rat.

Results: A single session of ECS (95 mA, 0.6 s, 0.6 ms, 100 pulses/s) increased FADD in the hippocampus (22%, $p<0.01$) and cortex (30%, $p>0.05$), without altering pFADD content. Repeated sessions of ECS (5 days) were not associated with alterations in FADD (induction of tolerance) or pFADD in the hippocampus and cortex. Contrarily, desipramine (10–30 mg/kg, 2–4 h) and fluoxetine (10 mg/kg, 2 h) decreased FADD in cortex (20–30%, $p<0.05$; 10–15%, $p>0.05$; respectively), without altering pFADD content. Notably, two weeks treatment with desipramine (10 mg/kg) or fluoxetine (3 mg/kg) stimulated pFADD in the cortex (desipramine: 23%, $p<0.05$; fluoxetine: 59%, $p<0.01$). These chronic treatments were not associated with alterations in FADD content.

Conclusion: The results uncover novel differential effects of diverse antidepressant treatments over FADD protein in the rat brain. Future experiments will aim at better understanding FADD-mediated cell fate regulation, which might be relevant in the therapeutic context of major depression.

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P-09-020 Potential benefits of slow titration of paroxetine treatment in elderly population

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Objective: Approximately 15% among over 65-years individuals suffers from depression. Particularly in this population, SSRIs could lead to an early exacerbation of anxiety and a very gradual titration is usual in clinical practice. The aim of this study is to compare efficacy and tolerability of gradual versus rapid titration of paroxetine in the elderly.

Methods: 50 non-demented elderly (⩾60 years old) outpatients with Major Depression or Anxiety disorders (⩾13 total score at Hamilton Depression Rating Scale – HAM-D – or Hamilton Anxiety Rating Scale -HAM-A) were randomized to paroxetine 10 mg or to gradual tapering (2.5 mg on alternate days up to 10 mg in 7 days). Then dosage could be adjusted according to clinical response.

Results: During the first 3 days of treatment a significant worsening in psychic anxiety was observed in patients treated abruptly with 10 mg of paroxetine (difference in HAM-D psychic anxiety subscale from baseline: 110.61% vs. 89.38% with rapid and slow titration respectively; $p=0.03$). Overall a significantly greater improvement in depressive and anxious symptoms favored gradual titration (HAM-D Core cluster and HAM-D psychic anxiety cluster respectively repeated misure ANOVA $p=0.014$ and $p<0.001$, also when controlling for confounders). At 8th week slightly higher drop outs in patients administered with abrupt dosage was observed (15.38% vs. 39.13%, $p=0.06$; respectively for slow and rapid titration).

Conclusion: Our results suggest that a gradual titration of paroxetine could avoid the initial treatment anxiety worsening and drop out at the beginning of the treatment. Open issues are possible concomitant somatic treatments and difference in long-term tolerance.

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P-09-021 Fluvoxamine boosts duloxetine plasma levels in depressed patients

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Objective: Duloxetine (DLX) is a serotonin-norepinephrine reuptake inhibitor (SNRI) that is effective for major depressive disorder and generalized anxiety disorder (GAD). The drug is metabolized by CYP1A2 and to a lesser extent by CYP2D6. Fluvoxamine (FLX) is a serotonin reuptake inhibitor (SSRI) and known to be a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2. It should therefore not be co-administered with DLX in the first place. There are nevertheless rare clinical situations when a combination might be advantageous, for example in cases when plasma levels of DLX remain low despite individuals taking high dosages.

Methods: In this study the plasma levels of DLX as well as the clinical and adverse effects were retrospectively analyzed in thirteen patients treated with a combination of the two substances. Steady state DLX levels were measured in patients before taking FLX and under different daily doses of FLX within the same subjects.

Results: Adding 25 mg of FLX per day to a steady-state treatment with 30 mg of DLX in 8 patients led to an average increase of DLX plasma levels that was 3-fold with a magnitude of 50–506%.

Conclusion: Our findings indicate that DLX plasma levels can be boosted by the potent CYP1A2 inhibitor FLX. However, the co-administration of duloxetine with potent CYP1A2 inhibitors should not be used in clinical routine without extreme precaution and under continuous control of plasma-levels.

P-09-022 Progesterone withdrawal-induced depression-like behavior is differentially sensitive to the effects of direct serotonin receptor modulation in comparison to selective serotonin reuptake inhibition

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Objective: Background: Long-term progesterone administration followed by abrupt withdrawal induces depression-like and anxiety-like behavior in female rats, similar to symptoms in women with premenstrual dysphoric disorder (PMDD). However, few studies have compared efficacy of antidepressants with different mechanisms of action in women, or in animal models of hormonally induced depression-like behavior. Objective: The progesterone withdrawal (PWD) model was used to compare the efficacy of an SSRI (fluoxetine), specific serotonin (5-HT) receptor modulators, and a novel multimodal antidepressant, LuAA21004. LuAA21004 is a 5-HT3 and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist and an inhibitor of the 5-HT transporter in vitro.

Methods: PWD was induced in a multiple withdrawal paradigm by i.p. injection of progesterone in oil (30 mg/kg) for 3 weeks. Depression-like behavior was assessed using forced swim test, and brain 5-HT levels were measured using HPLC.

Results: Fluoxetine did not reduce depression-like behavior when administered either chronically (2 weeks) or acutely (2 days). In contrast, LuAA21004 reduced depression-like behavior after both acute and chronic administration. Acute administration of 5-HT3 receptor antagonist ondansetron or 5-HT1A receptor agonist flesinoxan also reduced depression-like behavior. However, these effects were not additive in combination with fluoxetine. Brain serotonin levels were not altered after PWD.

Conclusion: These data indicate that antidepressants with 5-HT3 antagonist and/or 5-HT1A agonist activity are more efficacious than an SSRI after PWD in female rats. Furthermore, 5-HT receptor modulation is not additive with SSRI administration, consistent with data indicating no primary deficit in serotonin levels in this model.

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P-09-023 Effect of the multimodal antidepressant LU AA21004 on rat hippocampal plasticity and recognition memory

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Objective: Many depressed patients have cognitive disturbances [Gotlib IH, Joormann J. Annu Rev Clin Psychol 2010; 6: 285–312.]. The multimodal antidepressant Lu AA21004 is a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and 5-HT transporter inhibitor in vitro [Mørk A, et al., J Pharmacol Exp Ther 2011. jpet.111.189068.]. Here we report its preclinical effects on parameters involved in cognitive processing.

Methods: Field excitatory postsynaptic potentials were recorded in the CA1 area of dorsal hippocampus before and after high frequency stimulation (HFS) of the Schaffer's collaterals in 5-HT-depleted rats (with PCPA), stressed rats placed on an elevated platform, and controls. The novel object recognition (NOR) test (24 h retention) in a Y-maze was used to evaluate episodic memory. Hippocampal cell proliferation was measured by immunohistochemistry.

Results: In controls, HFS provoked a stable long-term potentiation (LTP) of ~30%. Lu AA21004 (10 mg/kg i.p.) reduced LTP to ~10%. Lu AA21004 pre-treatment prevented the suppressant effect of stress, but not of 5-HT depletion. In the NOR test, Lu AA21004 increased the time spent exploring the novel object during the retention test (index of recognition: ~40% versus ~10% for controls); this effect was partly prevented by the selective 5-HT3 receptor agonist SR57227 and the selective 5-HT7 receptor agonist AS19. Finally, LuAA21004 induced an increase in cell proliferation in the dentate gyrus after 1, 3 and 14 days of treatment.

Conclusion: Lu AA21004 produced an effect on LTP similar to that of serotonergic antidepressants, but prevented the suppressant effect of acute stress. Lu AA21004 also enhanced episodic memory, an effect mediated, at least partly, by its 5-HT3/7 receptor antagonism. Finally, Lu AA21004 induced a surprisingly rapid increase of hippocampal cell proliferation. Together, these preclinical data suggest that the antidepressant, Lu AA21004, may have a beneficial effect on cognitive processes.

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P-09-024 The efficacy of paroxetine in treating chronic subjective dizziness

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Objective: To investigate the antidepressant paroxetine in the treatment of chronic subjective dizziness efficacy and indications.

Methods: 53 cases of chronic subjective dizziness were divided into two groups, integrated treatment group received Paroxetine (Seroxat 20~40 mg/d), the control group received conventional medical treatment (strong Dingxuan films, etc.), both groups with supportive psychotherapy, the treatment period of 4 weeks. Before treatment, after Hamilton Depression Scale respectively (HAMD), Hamilton Anxiety Scale (HAMA), 90 Symptom Checklist (SCL-90) and self-vertigo symptom questionnaire score.

Results: 33 patients with chronic subjective dizziness with HAMD, HAMA score and the SCL-90 part of the factor scores were significantly higher than the norm, the difference was significant ($P < 0.05$). After 4 weeks of integrated group therapy HAMD, HAMA and SCL-90 score was significantly lower than the control group, the difference was significant ($P < 0.05$). Patients with chronic subjective dizziness antidepressants (paroxetine) reduce vertigo symptoms after treatment was significantly greater than the control sub-consolidated group, the difference was significant ($P < 0.05$).

Conclusion: The prevalence of chronic subjective dizziness in patients with emotional problems, antidepressants for the treatment of patients with chronic subjective dizziness, vertigo can improve symptoms but also improve mood symptoms. Keywords: chronic subjective dizziness, anxiety, depression, paroxetine, treatment.

P-09-025 Efficacy of agomelatine in elderly patients with major depressive disorder (MDD). Arandomised, double-blind study vs. placebo

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Objective: This 8 weeks multiethnic international double-blind randomized study evaluated the efficacy of the antidepressant agomelatine, a MT1/MT2 receptor agonist and a 5HT2c receptor antagonist, in elderly patients suffering from MDD compared to placebo using the Hamilton Depression Rating Scale 17 items (HAM-D-17).

Methods: 222 out-patients MDD aged of at least 65 years were randomised to receive agomelatine 25–50 mg (151) or placebo (71) for 8 weeks.

Results: In the total population, the mean HAM-D total score significantly decreased from baseline to endpoint with agomelatine (from 26.9 ± 2.8 to 13.4 ± 7.5) vs. placebo (from 26.8 ± 3.2 to 16.1 ± 7.6) with a significant difference in favor of agomelatine of 2.67 ($SE = 1.06$), $p = 0.013$. In the more severe patients (HAM-D total score $>= 25$ and CGI-S $>= 5$ at baseline), the clinical benefit was reinforced with a significant difference in favor of agomelatine of 3.79 ($SE = 1.37$), $p = 0.007$. The response rate to treatment (decrease in HAM-D total score from baseline of at least 50%) was significantly higher with agomelatine than with placebo: 59.46% vs. 38.57% respectively in the total population ($p = 0.004$) and 64.95% vs. 36.59% respectively in the more severe patients ($p = 0.002$) The proportion of patients with at least one Emergent Adverse Event (EAE) related to treatment was of 28.5% in the agomelatine group and 19.7% in the placebo group. A similar proportion of patients discontinued the treatment due to EAE

in the agomelatine group (7.9%) and in the placebo group (8.5%). Most common reported adverse events and more frequent on agomelatine were somnolence, diarrhoea, dry mouth and constipation.

Conclusion: This study shows that agomelatine is an efficient antidepressant treatment in the elderly patients.

Policy of full disclosure: I received speaker honoraria from AstraZeneka, Bayer, BMS, Eisai, Pfizer, Janssen-Cilag, Novartis and Servier, and was international scientific coordinator of the study.

P-09-026 The combination of cognitive-behaviour therapy and antidepressants in the treatment of depression

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Objective: Cognitive Behavioral Psychotherapy constitutes a major treatment for Depression. Nevertheless, there are forms of severe depression that resist treatment, both with cognitive-behavioral therapy in monotherapy, and with a combination of antidepressants. Cognitive Behavioral anti-depression Treatment requires 20–25 sessions and is mainly based on the principles of Collaborative Empiricism, as well as on the doctrines of the ancient Greek philosopher Epictetus.

Methods: 15 patients (9 female, and 6 male) were studied. The patients were selected among the patients treated in the inpatient facility and the outpatient setting of the Psychiatric Department of ''Konstatopouleio'' General Hospital, Nea Ionia, during the years 2009 and 2010. All patients, without exception, were taking a combination of antidepressants. Furthermore, the above patients were given the MADRS (Montgomery-Asberg Depression Rating Scale) for Depression, and CGI-S (Clinical Global Impression of Severity) Scales. The cut-off value for Depression in MADRS scale is 12. All 15 patients were treated with a cognitive-behavioral treatment of 25–30 sessions, along with medication treatment.

Results: From 15 patients, 2 (male) abandoned cognitive behavioral treatment due to a lack of motivation, and free time. The 13 patients (7 female, and 6 male) that remained in treatment received a combination of antidepressant medication and cognitive behavioral therapy, and showed a significant improvement at their MADRS and CGI-S scores, proving that their depressive symptomology improved. It should be noted that all 15 patients suffered from moderate to severe depression. Anyhow, all 13 patients submitted to Cognitive Behavioral Therapy did not satisfactorily respond to the antidepressant medication combination.

Conclusion: Cognitive Behavioral Therapy, combined with antidepressant treatment, the latter being adequate in dosage and with a low side-effect profile, helps to treat treatment-resisting Depression. Research shall extend beyond the completion of Cognitive Behavioral Therapy, with a follow-up of these particular patients every six months, for a period of two years.

P-09-027 Efficacy and tolerability of paroxetine, fluvoxamine and milnacipran in depression: A result of two pooled open label randomized controlled trial

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Objective: To compare efficacy and tolerability of paroxetine(PAX), fluvoxamine(FLV) and milnacipran(MIL) in Japanese patient with major depressive disorder.

Methods: A total of 200 Japanese patients suffering from major depression were allocated to flexible dosage of PAX (n = 100), FLV (n = 50) or MIL (n = 50) in two randomized 6-week study. The clinical response was evaluated using the Hamilton Rating Scale for Depression (HAM-D) assessed at each visit. Tolerability was assessed by dropout rate caused by side effect. Involvement of anxious or delusional depression in treatment efficacy or tolerability was also evaluated. A repeated measures analysis of variance, analysis of covariance and Cox regression analysis were applied.

Results: HAM-D percent change among three treatment group was significantly different ($p = 0.005$, endpoint HAM-D % changes; PAX; 63.8%, FLV; 60.2% and Mil; 44.6%) by LOCF procedure (n = 168). Subsequent analysis between two treatment groups showed significantly better improvement in PAX compare to MIL ($p = 0.004$) and no significant differences were seen between PAX and FLV and also FLV and MIL. While in per protocol analysis (n = 143), PAX showed significantly better improvement than FLV ($p = 0.033$) and MIL ($p = 0.012$). Cox regression analysis showed significantly difference of side effect induced dropout rate among three antidepressants ($p = 0.029$, MIL; 29.4% > PAX:18.8%, FLV; 6.1%). In both anxious depression and delusional depression subgroup, FLV showed significantly greater improvement than MIL. Anxious depression was also associated with high side effect-induced dropout rate ($p = 0.026$).

Conclusion: PAX showed greater improvement than MIL and FLV with moderate risk of drop out. FLV showed lower dropout risk and subsequent favorable improvement only in LOCF procedure, in which fewer side effects medication tends to produce better result also in treatment efficacy. Grater efficacy of FLV in anxious and delusional depression might be related to its sigma1 receptor affinity. Higher anxiety should be also considered as the important factor of dropout.

Policy of full disclosure: This study was supported by Glaxo SmithKline, Meiji Seika Kaisha Ltd., Asahi Kasei Pharma Corporation.

P-09-028 Antidepressant selective gynecomastia

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Objective: Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) indirectly result in decreased dopamine neurotransmission. Adverse effects (AE) associated with dopamine blocking agents have been reported with both SSRIs and SNRIs, including movement disorders and galactorrhea. Further, mammoplasia and gynecomastia have been reported which may be associated with altered dopamine neurotransmission or perturbations in sexual hormones. Whereas movement disorders can be objectively noted by the treating psychiatrist and galactorrhea is an AE which the patient readily volunteers, increased breast mass is less frequently directly reported by patients and rarely directly questioned of patients receiving antidepressants. This case report addresses selective gynecomastia in a patient having received multiple antidepressants.

Methods: Case analysis with literature review.

Results: A 67-year-old male with major depression, dysthymia, obsessive-compulsive disorder, social anxiety, hypertension, diabetes, and hyperlipidemia presented with new onset gynecomastia and breast tenderness. Mammography revealed bilateral gynecomastia without suspicious mass, cluster of calcification, or other abnormalities. These new symptoms developed after sertraline was added to his stable medication regimen (duloxetine, alprazolam, rosuvastatin, metoprolol, hydrochlorothiazide, sitagliptin). When sertraline was discontinued, gynecomastia and breast tenderness rapidly resolved. Though the patient had been treated with multiple psychotropics during 13 years (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, mirtazapine, duloxetine, desvenlafaxine, bupropion, nortriptyline, alprazolam, buspirone, pregabalin and modafinil), gynecomastia and breast tenderness only occurred when sertraline was combined with duloxetine.

Conclusion: Gynecomastia is an AE associated with antidepressants but is rarely addressed. Gynecomastia can be antidepressant selective. Clinicians are advised to question patients regarding this potential AE.

P-09-029 Effect of duloxetine on chronic tension-type headache in patients with major depressive disorder

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Objective: A wide variety of antidepressants have been used to treat tension headache in patients with major depressive episode. Alterations in noradrenergic and serotonergic neurotransmitter systems have been implicated in the pathophysiology of major depressive disorder and chronic pain. So the newer antidepressant, duloxetine acting on both noradrenergic and serotonergic neurotransmitter systems is expected to be more effective in pain management in major depressive disorder than selective serotonin reuptake

inhibitors(SSRIs) and tricyclic antidepressants(TCAs). The purpose of this study was to investigate the clinical therapeutic effects of duloxetine treating tension-type headache in major depressive disorder patients.

Methods: 33 outpatients diagnosed with major depressive disorder according to the Diagnostic and Statistical manual version IV (DSM-IV) diagnostic criteria, complaining of tension-type headache were included in this study. The duloxetine dose was adjusted when required. The dose range was 30–60 mg/day. Simple self-rating questionnaire about somatic pains including headache, Hamilton Depression Rating Scale (HDRS), Mongomery-Asberg Depression Rating Scale (MADRS), and Beck Depression Inventory (BDI) were administerd at baseline and repeated after eight weeks of duloxetine trial.

Results: 33 patients had fulfilled this clinical trials. 18 were female and 15 subjects were male. Their mean age (±SD) of this group was 37.50±8.50. Mean duration of their current depressive episode (±SD) at baseline was 2.78±1.42 months. After 8 weeks of duloxetine trial, twenty seven patients (81.8%) reported that their daily headache was absent or improved and twenty five patients (75.8%) remained free of analgesics. All patients who reported improvement in headache, also showed improvement in depressive symptoms. The remaining six patients (18.2%) reported no improvement in headache. However, two of them showed some improvement in mood states, both subjectively and objectively.

Conclusion: These data suggest that duloxetine may be effective in reducing tension-type headache in patients with major depressive disorder.

P-09-030 Measuring work productivity with depression treatment: A novel methodology

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Objective: It is well recognized that major depressive disorder (MDD) is associated with significant impairment in occupational functioning. However, there is still little information about gains in work productivity with effective treatment of MDD, in part because the intensive nature of standard clinical trials makes it difficult for working patients to participate. In this study, we used a novel clinical trials methodology (telephone raters, telephone administered psychotherapy, on-line questionnaires) to examine work productivity outcomes in treatment of MDD.

Methods: The WORKER Study was a 12-week randomized controlled trial of escitalopram plus cognitive-behaviour therapy (CBT) in employed patients with MDD. Patients were randomized to open-label treatment with escitalopram 10–20 mg with 8 sessions of a validated CBT program administered by trained therapists over the telephone (Tel-CBT), or to escitalopram with adherence reminder telephone calls. Outcome assessments included several work productivity questionnaires (e.g., Lam Employment Absence and Productivity Scale [LEAPS], Sheehan Disability Scale [SDS], Health and Work Performance Questionnaire [HPQ]) completed on-line over a secure web site.

Results: A total of 98 evaluable patients were randomized to treatment. There were significant gains for both conditions on all work productivity measures after 12 weeks of treatment. However, some measures showed greater sensitivity to change and larger effect sizes than others.

Conclusion: The novel methodology used in this study may provide better demonstration of productivity gains in clinical trials of depression treatment. Sensitivity to improvement in productivity varies by scale, so productivity scales must be validated in clinical trials.

Policy of full disclosure: Funding for this study was provided by an investigator-initiated trials grant from Lundbeck Canada. CTRN: NCT00702598. Dr. Lam is on ad hoc Speaker/Advisory Boards for, or has received research funds from: Aquaceutica, AstraZeneca, Biovail, Bristol-Myers Squibb, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association Foundation, Eli Lilly, Litebook Company, Lundbeck, Lundbeck Institute, Pfizer, Servier, St. Jude's Medical, Takeda, and UBC Institute of Mental Health/Coast Capital Savings. Dr. Parikh has received honoraria for speaking from AstraZeneca, Lilly, Pfizer, and Bristol Myers-Squibb, the Canadian Psychiatric Association, and the Canadian Network for Mood and Anxiety Treatments; has served as a consultant to AstraZeneca, Lilly, Pfizer, Lundbeck, and Bristol Myers-Squibb; and received educational or research grants from AstraZeneca, Lilly, Pfizer, Lundbeck, and Bristol Myers-Squibb.

P-09-031 The antidepressant effectiveness of agomelatine in severely depressed and depressed elderly patients: Subgroups of the non-interventional study VIVALDI

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Objective: The antidepressant efficacy of agomelatine, a melatonergic agonist and 5-HT2C antagonist, has been demonstrated in clinical trials. The aim of this non-interventional study was to evaluate the effectiveness of agomelatine on depressive symptoms, sleep-wake rhythm and its acceptability in routine practice. Data of 2 subgroups, severely depressed and elderly depressed patients, are presented.

Methods: Within the VIVALDI study 3317 outpatients with MDD were treated by 665 German psychiatrists over 12 weeks. Patients received 25 mg agomelatine once daily (od) at bedtime, with possible dose increase to 50 mg od if needed. Antidepressant effects were evaluated by short-version MADRS (svMADRS) and CGI, the effects on sleep and daytime functioning by a patient questionnaire (modified CircScreen). Adverse drug reactions (ADR) were documented at weeks 2, 6 and 12. Subgroups with severely depressed (svMADRS $\geqslant 30$; $n=1882$) and elderly patients $\geqslant 65$ years ($n=446$) were analysed.

Results: In the total population, svMADRS total score decreased from 30.6 at baseline to 12.8 at final visit, in severely depressed from 36.7 to 14.7, in elderly depressed patients from 29.0 to 12.2. In total 65.8% of patients could be classified as responders ($\geqslant 50\%$ decrease in svMADRS) and 54.8% as remitters (svMADRS $\leqslant 12$). In the subgroups of severely depressed and elderly depressed patients 67.8% and 65.0% were responders, 47.8% and 59.3% were in remission, respectively. Daytime sleepiness was ameliorated in 78.2% of total population, 80.6% of the severely ill and in 68.0% of the elderly depressed patients. Agomelatine was well tolerated in all groups. ADR were reported for 10.0%, 8.9% and 10.1% of patients in total population, severely ill and elderly depressed patients, respectively.

Conclusion: In this study agomelatine demonstrated the antidepressant effects, improvement of daytime functioning and good tolerability in unselected depressed patients, including multimorbid elderly and severely depressed patients in daily practice.

Policy of full disclosure: Georg Thieme Verlag, Springer Verlag Heidelberg/Berlin, Springer Verlag Wien, Urban & Fischer/Elsevier München, Astra Zeneca, Bayer, Boehringer Ingelheim, Jannsen-Cilag, Lilly, Lundbeck, Merz, Novartis, Organon, Pfizer, Servier, Steigerwald, Teva, Wyeth.

P-09-033 Investigating nitric oxide synthase as an up-stream mediator of the antidepressant action of ketamine

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Objective: Excessive glutamate transmission at N-methyl-D-aspartate receptors (NMDA-R's) may underlie a primary mechanism in the physiology that leads to depression, and ketamine, an NMDA-R antagonist, rapidly alleviates depression in humans. Several downstream mechanisms are suggested to mediate the antidepressant action of ketamine, including the activation of extracellular-signal-regulated kinases 1/2 (ERK1/2), protein kinase B (or Akt) and the mammalian target of rapamycin (mTOR). However, the mechanism(s) that are affected immediately downstream of NMDA-R's remain unclear. Neuronal nitric oxide synthase (nNOS) couples to and is activated by NMDA-R's, and the uncoupling of the nNOS-NMDA-R complex prevents NMDA-R-mediated excitotoxicity. Therefore, we investigated whether the antidepressant mechanism of ketamine involves the inhibition of nitric oxide (NO) signalling.

Methods: We used a genetic rat model of depression, the Flinders Sensitive Line (FSL) rats, and their control, the Flinders Resistant Line (FRL) rats, to investigate whether l-arginine, a precursor of NO, attenuates the behavioural antidepressant-like effect of ketamine in FSL rats in the forced swim test (FST), and whether l-arginine can prevent the phosphorylation of ERK1/2, Akt and mTOR by ketamine in the frontal cortex in these rats. We also measured the activity of nNOS activity in this region. Four groups of FSL rats received vehicle (saline, i.p.), ketamine (15 mg/kg, i.p.), l-arginine (250 mg/kg, i.p.) or ketamine + l-arginine, and assessed in the FST 1 hour later, whereafter their brains were dissected for molecular assays. One vehicle-treated group of FRL rats was used as validation.

Results: Behavioural results showed that l-arginine significantly attenuated the antidepressant-like action of ketamine in the FST. Western blotting and nNOS activity experiments are on going and these results are imminent.

Conclusion: Results from the FST suggest that ketamine's antidepressant activity may involve a reduction in NO signalling.

P-09-034 Regulation of biological rhythms with agomelatine in patients with major depression

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Objective: Dysruption of circadian function is a cause of neuropsychiatric disorder. Ageing and stress are also associatied with a weakened responsiveness of the circadian clock to environmental stimuli. Agomelatine shows chronobiotic effects, it has resincronization properties. Agomelatine is an agonist of MT1 and MT2 and antagonist 5HT2c receptors, it desinhibits the release of noradrenalin and dopamine in the prefrontal cortex via GABA interneurons. Agomelatine promotes slow sleep wave, increases hippocampal neurogenesis, cell survival, neurotrophic factors BDNF, neuroplasticity and cell survival. It decreases stress induced glutamate release. Activates intracellular signaling involving kinases Erk, GSK3 beta, and Akt. The objective is to regulate the altered circadian rhythms with Agomelatine and also to evaluate its efficacy in the treatment of depression.

Methods: We administered to 150 patients, with moderate major depression, Agomelatine 25 mg, 1 hour before bedtime, during a period of 6 months. We evaluated Ham-D score, HAD for anxiety, Epworth for sleep.

Results: Experienced at least 50% reduction in HAM depression score and improvement in the other parameters. There was decreased depression, prevented relapse, adverse and discontinuation symptoms.

Conclusion: Agomelatine potentiates the effects of melatonin. It restores the circadian rhythm, resetting the suprachiasmatic nucleus, starts a new reorganization of neurotransmitters and hormones. It has the potencial to balance all the biological rhythms of hormones producing an improvement in general health,because it helps to reinstall the balance of the PNIE system. It demonstrated efficacy in the management of major depression, anxiety and in the re-synchronization of circadian rhythms.

P-09-035 Blood microRNA longitudinal changes in depressed patients during antidepressant treatment

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Objective: Major depression (MD) is a severe mental disorder that represents one of the major causes of disability worldwide. Less than 50% of all the patients treated with the currently available antidepressants (ADs) shows full remission. Recent efforts to develop novel ADs have been relatively unsuccessful, mainly because of deficits in basic knowledge about the pathogenesis of MD and the mechanisms behind ADs efficacy. Current research supports the hypothesis that this disorder is driven by abnormalities in biological pathways contributing to synaptic plasticity. MicroRNAs (miRNAs) are potent modulators of protein expression that play key roles in brain pathways regulating neurogenesis and synaptic plasticity. These small RNAs may be critical for the pathophysiology of mental disorders and may influence the effectiveness of psychotropic drugs. In this work, we wanted to investigate a possible involvement of miRNAs in the mechanism of action of the AD escitalopram (SSRI).

Methods: We conducted a whole-miRNome quantitative analysis with qRT-PCR of the changes in the blood of 10 depressed subjects after 12 weeks of treatment with escitalopram. To get a global interpretation of the possible biological functions of the modulated miRNAs, we conducted a bioinformatic analysis of the 3'UTRs human sequences for the prediction of target genes and a functional survey of the KEGG pathways involved.

Results: Thirty miRNAs were significantly differentially expressed after the treatment: 28 were up-regulated and 2 were strongly down-regulated. The analysis of target genes and related KEGG terms showed a significant enrichment in several pathways associated with neuronal brain functions.

Conclusion: The results of this study represent the first evidence in the blood of MD patients of a possible involvement of miRNAs in AD action. The 12 weeks treatment with escitalopram modified the expression profiles of miRNAs that potentially target a multitude of genes implicated in outstanding neuronal functions in the adult brain.

P-09-036 A 6 month cross sectional study of antidepressants use in the first visits in our center for mental health between July and December 2011

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Objective: To evaluate the characteristics of the first 150 new patients and to determine the use of antidepressants in our Center for Mental Health between July and December 2011 and to determine the characteristics of the patients that were prescribed the use of antidepressants.

Methods: Subjects: The population study were one hundred and fifty patients that were first time visited in ou Center for Mental Health between July and December 2011. Procedure: This is a cross-sectional study -Independent variable were sex and age. Patients were diagnosed according to DSM's criteria-IV of Unipolar disorder, Bipolar affective disorder/Psychotic disorders/Substance use disorder/or comorbidity among axis II.

Results: From the selected sample of 150 patients 58 were male and 92 were female. The 82% were treated with antidepressants in the first visit. The 59% of the selected sample were diagnosed of Unipolar Depression disorder, the 21.3% of Anxiety disorders and only a 6% of Psychotic disorder and 5.3% of substances abuse disorder. The mean age of patients treated with antidepressants was 46 years old. The 18% of the patients that were treated with antidepressants had diagnosis of personality disorders. To be women aged between 24th-55th years old were the main variables associated to be prescribed the use of antidepressants ($p\text{-value} < 0.005$).

Conclusion: From our selected one hundred and fifty patients visited from the first time in our Adults Center for Mental Health 123 were treated with antidepressant, the 70% of these patients were diagnosed of unipolar depressive disorder (86 patients) and the 22% of the patients treated with antidepressants were diagnosed of anxiety disorders. Antidepressants were most frequently used in that time period by people between 24 and 55 years old. The study shows that 80% of patients visited in our Cente between 24 and 55 years old take antidepressants, more than in any other age-sex group.

P-09-037 Dysthymia treatment with agomelatine

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Objective: Use of agomelatine in patients with dysthymia (DSM-IV-R), to evaluate efficacy and tolerance.

Methods: In 21 patients with dysthymia (14 women and 7 men) we have used for three months agomelatine as basic medication. 7 patients were treated with adjunctive benzodiazepines. We have Assessed the effectiveness of treatment by HAM-D (17 items) on days 0 and 90, also a complete haemathological analysis was performed on

all patients, including liver enzymes, and recorded the presence of side effects when reported by patients. In 11 patients we tappered of previous antidepressant treatment because of insufficient therapeutic response, and 10 were new patients, being agomelatine their first treatment.

Results: The mean baseline HAM-D was 14 points and decreased at 3 months to 8 points, almost normal. There were no notable side effects, being Agomelatine well tolerated. The patients improvement was quite rapid.

Conclusion: We believe that agomelatine due to its special mechanism of action (melatonergic receptor agonist MT1 and MT2, and antagonist of 5HT2C receptors), and in the regulation of biological clock, as well as depressed mood, should occupy a notable place in the treatment of dystymic Depression.

P-09-038 Comparison of the effects of agomelatine and the 5ht2c antagonists sb242084 and s32006 on suprachiasmatic nucleus cell firing rates in vitro

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Objective: Agomelatine is a melatonergic agonist and a 5HT2C antagonist with antidepressant activity in animal models and humans. Several preclinical studies have demonstrated that its antidepressant activity depends on synergy between its melatonergic agonist and 5HT2C antagonist properties. We previously showed that both agomelatine and melatonin can cause dose-dependent suppressionof firing rates of suprachiasmatic nucleus (SCN) cells in Syrian hamsters in vivo. The aim of this study was to investigate in vitro the mechanism by witch agomelatine decreases SCN neuronal activity by comparing its effects to those of two 5HT2C antagonists (SB242084, a neutral antagonist, and S32006, an inverse agonist).

Methods: Coronal slices 500 μm thick containing the SCN were prepared from male Wistar rats, and single-unit recordings of SCN neurons were made using glass microelectrodes. After establishment of baseline firing rates, slices were perfused with vehicle (DMSO) or agomelatine (3.75 mg/100 ml) in one study, or with vehicle (DMSO), SB242084, or S32006 (0.3 mM) in another study.

Results: For agomelatine, 90% of SCN neurons showed $>$ or $=20\%$ suppression of firing rates, with decreases averaging $37.3 \pm 32.3\%$ (SEM) ($n=23$, $p<0.001$. For SB242084, 73.8% of neurons showed $>$ or $=20\%$ suppression of firing rates, with average decreases of $32.1 \pm 8.9\%$ ($n=45$, $p<0.01$). For S32006, 66.7% showed $>$ or $=20\%$ suppression of firing rates, with average decreases of $31.0 \pm 8.0\%$ ($n=26$, $p<0.01$).

Conclusion: These results demonstrate that the two 5HT2C antagonists decrease spontaneous firing rates of SCN neurons in vitro and that their effects are somewhat weaker than those observed with agomelatine. The findings suggest that the melatoninergic agonist properties of agomelatine in synergy with its 5HT2C antagonist properties could be involved in inmediating its effects on SCN neurons. Studies using a melatonergic antagonist (S22153) are ongoing to further clarify agomelatine's mechanism of action.

P-09-039 Pioglitazone as an adjunct to citalopram for moderate to severe major depressive disorder: Randomized double blind placebo-controlled trial

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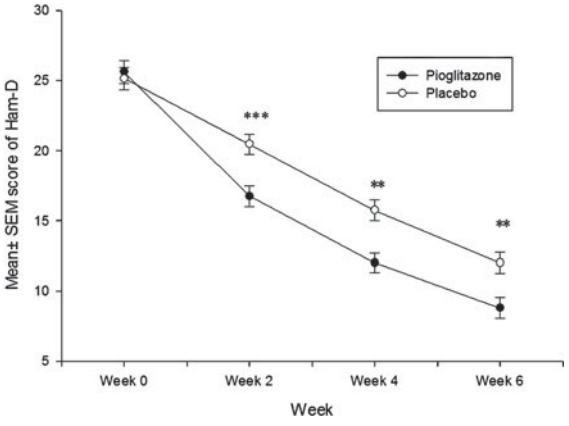
Objective: Major depressive disorder (MDD) is associated with immune and metabolic disturbances, neuroinflammation, and impaired neuroprotection. Thiazolidinedions(including pioglitazone) have important immunoregulatory, neuroprotective, anti-excitotoxic, and anti-neuroinflammatory properties. Moreover, these drugs have shown antidepressant effect in animal models of depression as well as open-label human studies of concurrent MDD and metabolic syndrome. We aimed to evaluate the antidepressant effect of add-on pioglitazone in patients with MDD in the absence of metabolic syndrome and diabetes.

Methods: This was a randomized double-blind placebo-controlled study (NCT01109030). Forty patients with MDD (DSM-IV-TR) who had Hamilton depression rating scale-17 (Ham-D) score $\geqslant 22$, were randomized to pioglitazone (15 mg every 12 hours) ($n=20$) or placebo ($n=20$) in addition to citalopram for six weeks. Evaluation was done using Ham-D at baseline and, second, fourth and sixth weeks. Fisher's exact test was used for comparison of early improvement ($\geqslant 20\%$ score reduction by second week), treatment response ($\geqslant 50\%$ score reduction), and remission(score $\leqslant 7$) between the two groups. Two-factor analysis of variance (ANOVA) with repeated measures, and analysis of covariance were used for comparison of scores between placebo and pioglitazone groups.

Results: More patients in pioglitazone group achieved early improvement, response at sixth week, and remission than placebo group. (95%,95%,45% in pioglitazone group versus 30%, 40%, 15% in placebo group, $P<0.001$, <0.001, 0.04 respectively). Repeated measure ANOVA showed significantly better results in pioglitazone than placebo group during the course of the study[$F(1,38)=9.483$, $p=0.004$] [Figure 1]. Subjects in pioglitazone group showed significantly lower scores at all time-points(except baseline) than placebo group ($P<0.01$). Frequency of side effects was similar between the two groups.

Conclusion: Pioglitazone is an effective and safe add-on treatment in patients with moderate to severe MDD, even when metabolic syndrome and diabetes are not present.



P-09-040 Risk factors of drug interaction between warfarin and antidepressant in a clinical setting

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Objective: Patients with cardiovascular or cerebrovascular diseases are at increased risk of developing depression and when depression develops, vascular risk is exacerbated further (Lett H., 2004; Frasure-Smith N., 2009). Patients with treatment-resistant depression after an acute coronary syndrome are at an even greater risk for cardiovascular accidents (Carney R., 2009). Treatment of depression in these patients should be emphasized not only to improve quality of life but also to acquire a better prognosis of vascular disease. Information concerning antidepressant use concurrently with warfarin is scarce. A study evaluating the risk factors for INR change in respect with warfarin and antidepressants would be very helpful.

Methods: In this study, we evaluated the risk factors for INR increase after addition of an antidepressant in a total of 312 patients who used warfarin. Patients' sex, age, BMI, AST, ALT) creatinine, indication of warfarin use, dose of warfarin, type of added antidepressant were assessed for investigating possible risk factors with INR increase $\geqslant 15\%$ after adding an antidepressant.

Results: Among 312 patients, 106 patients (34.0%) showed an elevation of $\geqslant 15\%$ after adding an antidepressant. We selected 12 antidepressants which were used in more than 5 patients. These 12 antidepressants were used in 300 patients. Univariate analysis showed level of creatinine, indication of warfarin use, dose of warfarin, type of used antidepressants are potential risk factors for INR increase in respect to antidepressant and warfarin interaction.

Among the antidepressants, imipramine showed statistically significant increase of INR in warfarin users.

Conclusion: The results of this study suggest that level of creatinine, indication of warfarin use, dose of warfarin, adding imipramine are risk factors for INR increase with respect to the interaction of antidepressant and warfarin. The small number of patients is a limitation of this study. A large-scale study comparing multiple antidepressants will be needed.

P-09-041 Effect of a single dose SSRI on serotonin levels in the non-human and human primate brain

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Objective: Despite widespread use of selective serotonin reuptake inhibitors (SSRIs) for treatment of depression and anxiety disorders, the exact mechanism underlying the clinical effect remain unclear. We previously demonstrated that the newly developed 5-HT1B-receptor specific radioligand [11C]AZ10419369 is sensitive to changes in endogenous serotonin concentrations in monkey. The primary aim of the present study was to examine whether a single dose of a SSRI (escitalopram) affects endogenous serotonin levels in serotonergic projection areas.

Methods: The study was performed in 3 monkeys and 9 human subjects. All subjects were examined with PET and [11C]AZ10419369 at baseline and post-dose conditions (monkey n=7, human n=9). Escitalopram was administered intravenously (2 mg/kg) to monkeys and per orally (20 mg) to humans. The binding potential (BPND) of [11C]AZ10419369 in serotonergic projection areas (e.g. cortical regions, caudate nucleus, putamen and thalamus) were defined by means of the simplified reference tissue model (SRTM) and an equilibrium method (monkeys only). The difference in BPND between pre- and post-dose PET measurements was the primary outcome.

Results: In monkeys the BPND decreased post-dose in all examined brain regions.The decrease reached statistical significance in occipital cortex, midbrain, dorsolateral prefrontal cortex and thalamus ($p < 0.05$). In humans, there was on the contrary no decrease in BPND post-dose. Across examined areas there was rather a small increase in BPND, which reached statistical significance in occipital cortex ($5 \pm 5\%$; $p < 0.05$).

Conclusion: A single dose of escitalopram generated a small, but significant, decrease in BPND in monkey, consistent with elevated serotonin levels. In humans, no evident effect was found at a 7-fold lower dose level. The study does not support a major effect on serotonin levels after administration of a single dose escitalopram in clinically relevant doses in either species.

Policy of full disclosure: The radioligand [11C]AZ10419369 has been developed in a cooperation between Karolinska Institutet and AstraZeneca. Lars Farde also holds a position as Chief Scientist, iMed CNS/Pain, AstraZeneca, Sweden.

P-09-042 Chronic fluoxetine treatment increases neurogenesis in the cortex of adult mice

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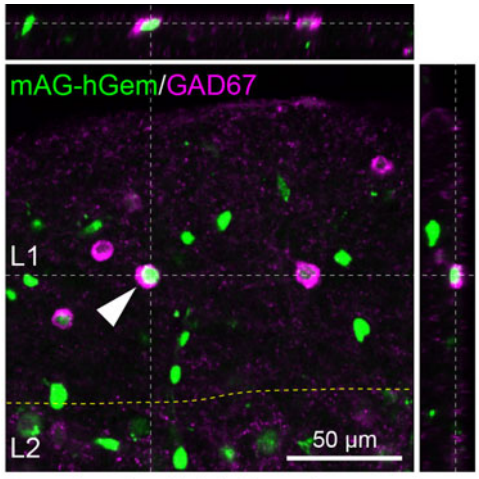
Objective: Adult neurogenesis in the hippocampal subgranular zone (SGZ) and the anterior subventricular zone (SVZ) is regulated by various factors including neurotransmitters, hormones, stress, aging, voluntary exercise, environmental enrichment, learning, and ischemia. Chronic treatment with selective serotonin reuptake inhibitors (SSRIs) modulates adult neurogenesis in the SGZ, which is hypothesized to mediate the antidepressant effect of these substances. Layer 1 inhibitory neuron progenitor cells (L1-INP cells) were recently identified in the adult cortex, but it remains unclear what factors other than ischemia affect the neurogenesis of L1-INP cells.

Methods: FLX solution was intraperitoneally injected into mice at a certain dose per day for 3 weeks. FLX concentrations were determined for individual mice. For FLX pellet treatment, the mice were subcutaneously administered either FLX or control pellets (Innovative Research of America) in the dorsal interscapular region. To label L1-INP cells and new neurons with the retrovirus vectors that express a fluorescence protein Venus under the enhanced synapsin I promoter, the virus solution was stereotaxically injected into the cortical layer 1 of mice.

Results: Immunofluorescence and genetic analyses revealed that FLX treatments increased the number of L1-INP cells in all examined cortical regions in a dose-dependent manner. The virus labeling showed that Venus-expressing GABAergic interneurons were generated from retrovirus vector-labeled L1-INP cells.

Conclusion: This study indicates that FLX treatment can control the production of GABAergic interneurons in the cortex. The cortical neurogenesis of L1-INP cells would also account for some of the therapeutic effects of antidepressants.



Green signals, which indicate the expression of mAG-hGem, are derived from the Fucci-S/G2/M marker, while magenta signals indicate GAD67+ structures. L1-INP cells are detected as double-positive cells (indicated by arrowheads). The cell images were taken from the frontal cortex 3 weeks after FLX treatments.

P-09-043 Compliance of depressed patients treated with specific serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)

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Objective: Current data confirms previous estimates that depression will become in the next years one of the most important causes of social disability. Given the importance of the problem, patient adherence to an antidepressant treatment that has clinical efficacy, tolerability and functional rehabilitation is essential in the management of depression. The objective of this comparative study between the two classes of antidepressants was to evaluate the dynamic predictors that might influence the therapeutic adherence.

Methods: As a working method we carefully selected two groups of patients so that were no significant differences in the demographic, socio-professional, economic and family status. The study was designed with six evaluation visits at significant intervals, thus allowing us to obtain statistically significant data. Instruments used : MADRS to assess the severity of depression, Sheehan Disability Scale (SDS) as a global functionality scale, tolerability evaluation through direct interview and by spontaneous reporting of adverse reactions.

Results: The dynamics in MADRS score for the two groups of patients treated with two classes of antidepressants was comparable. Both classes proved to be effective as of 3 months and there were no statistically significant differences between the two classes in terms of therapeutic remission. Patients in both groups showed improvement in quality of life already noticeable at first evaluation (probably due to a lower acute depressive simptomatology), the patients treated with SSRIs having a better socio-occupational functioning ($p = 0.001$). There was a significant difference between the percentages of patients who

abandoned the study because of side effects, a significantly higher proportion of patients in the group treated with TCAs presenting side effects severe enough to warrant withdrawal from research.

Conclusion: Although part of different generations of antidepressants, both SSRIs and TCAs are effective and retain the long-term effectiveness, the only obvious difference being therapy discontinuation due to adverse reactions.

P-09-044 Experimental medicine model shows no depressogenic effects of varenicline

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Objective: To assess the effects of varenicline on emotional and non-emotional cognition. Varenicline is a partial agonist at α4β2 nicotinic acetylcholine receptors (nAChRs) and also binds at several other nAChRs; the drug is used clinically as an aid to smoking cessation. Post marketing data suggested an association between varenicline and depression and suicide, leading to a black box warning. By contrast, animal studies indicated a potential antidepressant effect. There is also evidence to suggest that varenicline may benefit non-emotional cognition, in particular working memory. Healthy volunteer models of emotional processing have the potential to detect both antidepressant and depressogenic effects of drugs (e.g. Horder et al., 2012).

Methods: We randomized 41 non-smoking healthy volunteers to receive varenicline (final dose 1 mg) or placebo for seven days. On the seventh day emotional processing (facial expression recognition, emotional memory and dot probe) and non emotional cognition (working and declarative memory) were assessed.

Results: 38 volunteers were included in the analysis. Varenicline did not affect subjective ratings of mood. There were no specific effects of the drug on facial expression recognition or the dot probe. Varenicline did, however, speed responses ($p = 0.02$) to positive words in the emotional recognition memory test. Varenicline also affected non-emotional memory with positive effects on recall memory ($p = 0.02$) and working memory ($p = 0.03$).

Conclusion: These results suggest that varenicline does not have a depressogenic effect in a healthy volunteer model, in fact the emotional recognition memory finding is more in keeping with the preclinical data in suggesting an antidepressant-like effect of the drug. These data also provide further evidence to support the involvement of nAChRs in non-emotional memory. Horder et al. (2012) J Psychopharm 26: 125–32.

Policy of full disclosure: CJH has acted as a consultant for the following companies: Servier, GSK, Astra-Zeneca. Lundbeck and P1vital. She also holds shares in P1vital and is on the advisory board. PJC has been a paid member of advisory boards of Eli Lilly, Lundbeck, Servier and Wyeth and has been a paid lecturer for Eli Lilly, Servier, and GlaxoSmithKline. He has received remuneration for scientific advice given to legal representatives of GlaxoSmithKline AP, EP, RJM, CPP and SFMcT report no conflicts of interest.

P-09-045 Effects of low-trapping NMDA channel blocker AZD6765 on gamma-band EEG and psychotomimetic liability: A comparison to ketamine in freely behaving rats

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Objective: NMDA channel blockers increase gamma-band (~40 Hz) EEG – a potential biomarker of cortical disinhibition. Cortical disinhibition is believed to contribute to the antidepressant properties of the NMDA antagonist, ketamine. However, changes in spontaneous gamma-band EEG have been hypothetically linked to ketamine's psychotomimetic adverse effects. Based on in vitro and behavioural studies, AZD6765, a low-trapping NMDA channel blocker, in clinical development for major depression, is predicted to have an improved tolerability profile compared with ketamine. The object of the current study was to test the hypotheses that gamma-band EEG activity can be separated from preclinical measures of psychotomimetic liability and evaluate the adverse effect profile of AZD6765 relative to ketamine.

Methods: EEG and behaviour were monitored simultaneously following administration of AZD6765 or ketamine to rats chronically implanted with skull surface electrodes and trained to perform an auditory detection task for food reward. Pharmacokinetic-pharmacodynamic modeling related EEG power within the gamma-frequency band (35–55 Hz) to free plasma and brain concentrations.

Results: Both ketamine and AZD6765 produced concentration-dependent elevations in gamma-EEG. Based on free brain exposures, the in vivo potency of AZD6765 (relative to in vitro MK-801 site-binding affinity) was greater than that of ketamine. At high plasma concentrations and high gamma-EEG, ketamine and AZD6765 produced transient reductions in attention; however, for comparable levels of gamma-band EEG, AZD6765 produced significantly less performance impairment and less hyper-locomotion than ketamine.

Conclusion: This study explored gamma-band EEG measurement as a translational, pharmacodynamic biomarker of NMDA channel blockade. Based on its ability to elevate gamma-band EEG without producing the same degree of behavioural disruption as ketamine, AZD6765 may deliver antidepressant benefits comparable with ketamine but with reduced psychotomimetic liability.

Policy of full disclosure: Full-time employee of AstraZeneca.

P-09-046 Mode of action of agomelatine: Synergy between melatonergic and 5-HT2C receptors

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Objective: Agomelatine is a novel and clinical effective antidepressant drug with melatonergic (MT1/MT2) agonist and 5-HT2C receptor antagonist properties. Both receptorial components are widely expressed in the central nervous system and, although the role of the different receptor activities of agomelatine in relation to its antidepressant action has not been fully elucidated, it seems that this compound could act synergistically on both the melatonergic and the 5-HT2C receptors. Aim of this poster is to highlight the available preclinical evidence suggesting that the molecular/cellular effects of agomelatine and, in turn its antidepressant activity, are the result of a synergic action between its agonism at MT1/MT2 and antagonism at 5-HT2C receptors.

Results: Indeed, it was found that survival of newborn hippocampal cells is stimulated only when both receptorial actions of agomelatine are present. In the same way, only agomelatine but not the two individual components attenuated the circadian rhythm of BDNF transcript in prefrontal cortex, resulting in significantly higher expression level in the morning, and increased Arc expression. Moreover, agomelatine showed a typical effect of antidepressants, blockade of acute stress-induced increase of glutamate release in cortical areas, which was not replicated by treatments with either melatonin or a selective 5-HT2C receptor antagonist. This synergic action was shown to be responsible for agomelatine effects on neurogenesis, BDNF, Arc and glutamate release. Even if traditional antidepressants also modulate these parameters, this effect is not optimized as in the case of agomelatine, which is able to resynchronize these effectors at distinct circuital and intracellular levels.

Conclusion: Taken together, these findings strongly suggest that agomelatine effects at the cellular level result from a synergistic interaction between its action on MT1/MT2 and 5-HT2C receptors. This interaction underlies the efficacy of agomelatine in terms of restoring circadian rhythms and relieving depressive symptoms.

Policy of full disclosure: GR has scientific collaboration with and is member of scientific board for Eli Lilly, Innova Pharma, and Servier. MAR has received honoraria or research support from AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma Co. Ltd, Eli Lilly, Innova Pharma, Merck Sharp & Dohme, Servier and Takeda. MP has received research support and/or has been consultant for Abiogen, GlaxoSmith-Kline, MerckSharp & Dohme, Servier and Fidia. The other Authors declare no conflict of interest. All authors did not receive any support for this paper from Servier.

P-09-047 Treatment of major depressive disorder in epilepsy

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Objective: In epileptic subjects offten apperars Major depressive disorder. Clinically experience sugest that low doses of SSRI are much beather than other antidepresants agents. In this study we confirm the findings in controlled design.

Methods: The total of 67 adult patients of both genders (28 females) with Grand-mall epilepsy (clinically and EEG verified) and depression was treated either with sertraline p.o. 50 mg qd ($n=35$) or with psychotherapy, particularly supportive approach ($n=32$). Diagnosis of epilepsy was confirmed cllinicaly and by EEG. Diagnosis of depression was established with DSM-IV criteria and severity of illness was assessed with the use of HAM-D scale at baseline, after 2, 4, 6 and 8 weeks.

Results: The total HAM-D scores for sertraline group at baseline, 2, 4, 6, and 8 weeks were 22.36 ± 5.35, 16.89 ± 4.64, 13.97 ± 3.12, 11.99 ± 3.05 and 9.02 ± 1.64, respectively ($p<0.05$). The total HAM-D scores for control group at baseline, 2, 4, 6, and 8 weeks were 22.96 ± 5.11, 19.65 ± 4.03, 19.12 ± 4.07, 17.81 ± 4.14 and 17.23 ± 4.76, respectively ($p<0.05$). HAM-D scores of sertraline group was significantly lower than that ones in supportive psychotherapy group ($p<0.05$). There were no differences in number of seizure episodes in study groups (1 vs. 1, $p>0.05$).

Conclusion: Sertraline was significantly effective in ameliorating of Major depressive episode in epilepsy, with no additional risk for seizures.

P-09-048 Aripiprazole adjunctive pharmacotherapy in depression: Probable drug-drug interaction

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Objective: Aripiprazole is a third generation antipsychotic with partial dopaminergic activity. In addition to its proven antipsychotic effects, it has become more widely accepted at the clinical level. It is FDA-approved as an adjunctive therapy for depression with or without psychotic features. This case report concerns the development of severe Parkinsonian features in a depressed psychotic patient following the addition of aripiprazole to his sertraline treatment.

Methods: Irrelevant (case report).

Results: Irrelevant (case report).

Conclusion: The occurrence of extrapyramidal side effects of aripiprazole in the case reported here is likely attributable to multiple drug interaction. This may be explained by hepatic cytochrome P450-dependent metabolism of aripiprazole, in particular the enzyme subtypes 2D6 and 3A4, both of which have been shown to be inhibited by sertraline. Sertraline-inhibited metabolism of aripiprazole would cause serum aripiprazole levels to become elevated, resulting in greater occupancy of striatal D2 receptors and producing the observed extrapyramidal side effects.

P-09-049 Augmenting ssris with an alpha4beta2nachr partial agonist: Lack of efficay on major depressive disorder with insufficient response

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Objective: An $\alpha4\beta2$nAChR Partial Agonist (PA) was tested in a proof-of-concept study to investigate its efficacy, safety, and tolerability in the augmentation of SSRIs therapy in MDD with insufficient clinical response.

Methods: An OL 8 week SSRIs treatment was followed by a 6-week, DB phase where subjects were randomized to adjunctive $\alpha4\beta2$nAChR PA or placebo, while continuing on ADT. The primary efficacy endpoint was the change from DB baseline (week 8) in the MADRS total score at week 14. Independent remote interviews were utilized to confirm eligibility at screening and at week 8.

Results: In the OL phase, 297 subjects were treated with SSRIs, of whom 162 (54.5%) subjects were qualified to be randomized in the DB phase. When 113 of 198 planned subjects in double-blind phase (57%) either completed or discontinued the study, a Sponsor unblinded interim analysis for efficacy and safety was conducted. The stopping rule for futility was met and the study was terminated early. In the final analysis, the treatment difference presented in LS mean$\pm$S.E. of the $\beta4\beta2$nAChR PA vs. PBO was -1.30 ± 1.565 with 2-sided 80% confidence interval (-3.32, 0.71), (2-sided $p=0.4062$). Placebo response rate (MADRS change from DB baseline at Week 6 of the DB phase; LS mean$\pm$S.E$=-8.30\pm1.088$) was not a factor in the lack of drug effect. Exploratory post-hoc analyses are currently ongoing.

Conclusion: The lack of a treatment effect of $\alpha4\beta2$ nAChR PA vs. placebo was demonstrated. Interim analysis with a futility rule allowed for early termination. Placebo response rate was not a factor in the lack of drug effect. The drug was safe and well tolerated in this study.

Policy of full disclosure: Pfizer, Inc.

P-09-050 Combined use of selective serotonin reuptake inhibitor drugs with other CNS active drugs during early pregnancy. Consequence on congenital malformation risk

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Objective: Many studies have shown that pregnant women who use selective serotonin receptor inhibitors (SSRI) also use several other drugs in excess compared with other pregnant women. The present study aimed to identify women with combined use of SSRIs and other CNS-active drugs in early pregnancy and to study the possible impact of such combinations on teratogenicity. It has been suggested that the combined use of SSRI and benzodiazepines should represent a higher teratogenic risk than either of the two drug categories.

Methods: Data from the Swedish Medical Birth Registry was used. Women giving birth between July 1, 1995 and December 31, 2008 ($n=1{,}290{,}672$) were interviewed in early pregnancy by midwives. Use of any CNS active drug was reported by 26,511 and 12,050 of them reported the use of SSRI. Data was adjusted for year of birth, maternal age, parity, smoking in early pregnancy, number of previous miscarriages, and body mass index. The teratogenicity risk analyzes were performed in two steps: (1) for each single category of drugs: Opioids (except dextropropoxyphene and codeine), Dextropropoxyphene or codeine, Anticonvulsants, Antipsychotics (except lithium, dixyrasine and proclorperazine), Lithium, Benzodiazepines, Hypnotic benzodiazepine receptor agonists, and Other sedatives or hypnotics, and (2) for concomitant use of an SSRI and one or more of the listed drug categories.

Results: Use of anticonvulsants, antipsychotics, or lithium alone was associated with an increased risk for any relatively severe congenital malformation and the use of opioids with an increased risk for a cardiovascular defect. The most common drug combination was SSRI and a benzodiazepines; $n=509$. No risk increase for any congenital malformation or for a cardiovascular defect was found.

Conclusion: The suggested synergistic action of SSRI drugs and benzodiazepines with respect to teratogenesis could not be supported.

P-09-051 Effect of antidepressants on serum sodium levels – a prospective study

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Objective: Antidepressants especially Selective Serotonin Reuptake Inhibitors have been associated with hyponatremia, though literature is mainly in the form of case reports. Considering paucity of literature this study aims to establish the incidence, risk factors, time of detection of hyponatremia complicating treatment with antidepressant therapy. Also, to objectively assess the causality, severity and preventability of hyponatremia.

Methods: A Prospective study with 74 patients in the Psychiatric outpatient setting. All patients evaluated by Psychiatrist, initiated on antidepressant therapy, with normal serum sodium concentration at

baseline and meeting eligibility criteria were inducted into the study with a follow up of more than 6 months.

Results: Overall incidence of hyponatremia [<135mEq/L] was 32.4% [24/72]. Time to detection of hyponatremia was 224.71±117.79 days [Mean±SD]. We found a moderately strong positive correlation between the use of mirtazapine (p value of 0.089) and venlafaxine (p value of 0.097) with hyponatremia. Though not statistically significant we identified 3 cases of hyponatremia with use of Milnacipran which has not been reported so far. No risk factors could be isolated as significant on multivariate regression analysis. Of the cases 87.5% were identified as ''probable'' with Naranjo's Algorithm of causality assessment, 91.7% were identified as ''moderate severity – level 3'' on Hartwig and Siegel's scale and all the cases were ''probably preventable'' on Schumock and Thornton scale.

Conclusion: Hyponatremia is an under-recognized and potentially serious complication of antidepressant therapy. There is a need for awareness and routine monitoring especially during the initial weeks of therapy and stratification of patients based on risk factors such as co morbid medical conditions and concomitant medications. Our results provide the foundation of a model for prevention, early detection and treatment of hyponatremia there by reducing the mortality, morbidity and health care costs associated with preventable adverse medical events.

P-09-052 Similarities in the biochemical modulation of DARPP-32, CREB, CamKII and AMPA receptors by lurasidone and fluoxetine

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Objective: Some atypical antipsychotics have antidepressant properties and are used as adjuvant therapies in depression. Lurasidone, a novel atypical antipsychotic, acts as an antagonist at D2, 5-HT2A and 5-HT7 receptors, but agonist at 5-HT1A receptors, a binding profile indicative of antidepressant properties. This study therefore aimed at comparing the biochemical actions of lurasidone with that of the fluoxetine, risperidone and the selective 5-HT7 receptor antagonist, SB-258741.

Methods: Male adult C57Bl6 mice received daily oral gavage for 3 weeks with vehicle, lurasidone (3 mg/kg), fluoxetine (20 mg/kg), risperidone (1 mg/kg) or SB-258741 (10 mg/kg). One hour after the last drug administration, mice were killed by decapitation and their brains were rapidily snap frozen. Cortices, hippocampi and ventral striata were processed for immunoblotting to measure the phosphorylation states of proteins implicated in actions of antidepressants.

Results: Fluoxetine and lurasidone, but not risperidone and SB-258741, shared the ability to decrease P-Ser845-GluR1 and P-Ser133-CREB in hippocampus. Previous work has indicated that fluoxetine increases the phosphorylation states of GluR1 and CREB. This discprepancy is likely due to differences in administration (oral vs. subcutaneous or intraperitoneal) and/or treatment duration between studies. Fluoxetine and lurasidone, but not risperidone and SB-258741, also increased P-Thr286-CamKIIbeta in ventral striatum. Finally, fluoxetine and lurasidone decreased P-Thr34-DARPP-32 in ventral striatum, an effect shared with risperidone and SB-258741.

Conclusion: These data demonstrate similarities in the biochemical modulation of several important signaling molecules by lurasidone and fluoxetine. Future studies will evaluate whether co-adminstration of lurasidone will augment biochemical effects of fluoxetine and study behavioral paradigms of antidepressant efficacy.

Policy of full disclosure: Dainippon Sumitumo.

P-09-053 Enhanced memory for reward cues following acute buprenorphine administration in humans

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Objective: The mu-opioid system has been implicated in the preferential processing of reward cues in rodents, but no such data are available in humans. The happy facial expression is a pivotal reward cue in humans, and it has been shown that impaired memory for facial happiness is associated with self-reported and hormonal measures of depression. We investigated whether a single 2 mg administration of the mu-opioid agonist, buprenorphine, would change short-term memory for happy, angry or fearful expressions relative to neutral faces.

Methods: Healthy human subjects participated in a randomized placebo-controlled within-subject design, in which they performed an emotional face relocation task after administration of buprenorphine and placebo.

Results: Compared to placebo, buprenorphine resulted in a significant enhancement of the memory for happy faces relative to neutral faces.

Conclusion: Our data demonstrate, for the first time in humans, that acute up-regulation of the mu-opioid system increases the processing of reward cues, and thus points at potential antidepressant properties of mu-opioid agonists in humans.

P-09-054 SERT and NET occupancy by serotonin and norepinephrine reuptake inhibitors in non-human primates in vivo

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Objective: The monoamine systems are key targets for antidepressant drugs. The combined serotonin and norepinephrine reuptake inhibitors (SNRIs), a subgroup of antidepressants, have been reported to show a large variability in relative affinity in vitro for the serotonin transporter (SERT) and norepinephrine transporter (NET), respectively. For instance, the calculated affinity ratio is about 30 for venlafaxine, and 1.6 for milnacipran. However, in vitro data do not completely predict in vivo conditions. In this study in nonhuman primates, the in vivo occupancy of SERT and NET of the two SNRIs, venlafaxine and milnacipran was examined by PET.

Methods: PET measurements with [11C]MADAM, a PET radioligand for SERT, and [18F]FMeNER-D2, a PET radioligand for NET, were performed in two female cynomolgus monkeys using the High Resolution Research Tomograph (HRRT) system at baseline conditions and after intravenous administration of venlafaxine or milnacipran, respectively. The relationship between dose, plasma concentration and transporter occupancy was examined by using the hyperbolic function developed for saturation analysis and a binding affinity (Kd) was expressed by the dose or plasma concentration corresponding to 50% occupancy of the transporter.

Results: After administration of venlafaxine and milnacipran SERT and NET were occupied in a dose and plasma concentration dependent manner. The affinity ratio between SERT and NET was 1.9 for venlafaxine and 0.6 for milnacipran.

Conclusion: In this PET study in nonhuman primates, the affinity in vivo was similar at SERT and NET after administration of any of the two test-drugs venlafaxine and milnacipran. This observation is not consistent with in vitro data in the literature and illustrates the need for in vivo studies when characterizing antidepressants.

P-09-055 Antidepressants as putative seizure-precipitating factors in taylor's dysplasia

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Objective: This is a case report of a patient with depressive symptoms and a history of Taylor's dysplasia (an epileptogenic cerebral cortical dysplasia) who demonstrated late-onset epilepsy.

Methods: We reviewed the patient's case notes and the literature on Taylor's dysplasia and the association of antidepressants with epileptic seizures.

Results: The patient is a 42 year old Greek woman who presented at the Emergency Department following a suicide attempt by drug overdosing and coexisting depressive symptoms. The patient had a history of Taylor's dysplasia, which is associated with epilepsy, but had not experienced seizures until 5 years ago. At that time she

was first prescribed mirtazapine for the treatment of anxiety and depressive symptoms. Following mirtazapine administration she developed focal seizures associated with aura. Thereafter, she experienced 5–6 seizures per year and was treated with oxcarbazepine. Depressive symptoms proved resistant to mirtazapine and she sequentially received venlafaxine and several specific serotonin reuptake inhibitors with moderate results. Since the first appearance of seizures she has always been under treatment with antidepressants. At psychiatric assessment she exhibited depressive mood, fatigue, loss of energy, inability to cope with stress but was free from active suicidal ideation. Her medication comprised Paroxetine 20 mg, oxcarbazepine 600 mg and lorazepam 5 mg daily. Following admission to psychiatric ward and due to the potential association of paroxetine with seizures, paroxetine was discontinued and oxcarbazepine was increased to 900 mg daily. Despite paroxetine discontinuation, her psychiatric symptoms improved. After three months of follow up she remains free of seizures and no longer demonstrates depressive symptoms.

Conclusion: This case report suggests that antidepressants could precipitate seizures in a patient with depressive symptoms and Taylor's dysplasia. We conclude that antidepressants should be used with caution in patients suffering from brain disorders predisposing to epilepsy.

P-09-056 Efficacy of paroxetine compare to fluoxetine in the elderly patient with major depressive disorder

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Objective: Depression is a common problem in older adults. The symptoms of depression affect every aspect of your life, including energy, appetite, sleep, and interest in work, hobbies, and relationships. There are many antidepressants for the effective treatment of depression in elderly people. To compare fluoxetine vs. paroxetine in terms of efficacy and time of starting effect.

Methods: The efficacy of paroxetine and fluoxetine and their effects on cognitive and behavioural function were compared in a 6 week, randomized study of 60 elderly depressed patients (aged 61 to 75 years). Antidepressant efficacy was assessed using the Hamilton Depression Rating Scale (HAMD), Beck Depression Inventary and Clinical Global Impression (CGI) scale. The Mini-Mental State Examination (MMSE), and HAMD cognitive factor scores were used to assess cognitive and behavioural function.

Results: Paroxetine demonstrated comparable efficacy to fluoxetine in the treatment of elderly depressed patients, but at the end of treatment, there was a significantly higher proportion of responders to paroxetine than to fluoxetine. Both treatments produced improvements in all measures of cognitive and behavioral function.

Conclusion: Paroxetine was significantly superior to fluoxetine from Week 3, indicating a possible early effect. There was no difference between the two agents in either the tolerability or safety of treatment.

P-09-057 Polypharmacy in major depressive disorder

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Objective: Major Depressive Disorder (MDD) is a disorder, that causes interpersonal disfunctioning. Although monotherapy is usually recommended in the initial phase of treatment, the results of STAR*D show, that <30% of the patients gain remission with monotherapy. The goal of this study is to investigate the incidence of antidepressant combination therapy against monotherapy between patients with severe depression, who are hospitalized in acute treatment departments in the Psychiatric Hospital of Attica.

Methods: The participants (47 patients) were randomly selected among the patients of the 9 acute treatment departments in Psychiatric Hospital of Attica. Statistic program SPSS was used in the analysis.

Results: The participants (47 patients) had average age of 51.3 years (SD=13.7). 44.7% of them were men, 10.6% were in involuntarily admitted in hospital, 66% had suicidal ideation or/and attempted suicide, only 23.4% had their first episode, 25.5% used also illegal substances. The average age of onset for their disorder was 35.7 years (SD=16.6). 34% of these patients were treated with only one antidepressant, while the rest of them were treated with a combination of antipsychotics or/and mood stabilizers. After 3 weeks of treatment 23.4% of them were treated with only one antidepressant, when combination therapy with more than 3 medications was more complex and frequent. We were not able to find any statistically significant differences between the beginning of involuntary admission and the discharge in terms of combination treatment.

Conclusion: Due to development study of psychopharmacology treatment for Major Depressive Disorder a new tendency has appeared: increased polypharmacy – the concurrent use of many medications – for the treatment of depression.

P-09-058 Selective serotonin reuptake inhibitors inhibit glycoprotein vi-mediated platelet aggregation through the influence of the interaction between FCRY and syk

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Objective: Platelets are recognized as a peripheral model for central serotonergic neurons because thy share similarity in the reuptake, storage and metabolism of serotonin. The antidepressants selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin through serotonin transporter in neurons as well as platelets. We currently reported that an SSRI, citalopram, exerts an agonist-dependent role in inhibiting the aggregation in response to collagen and convulxin, indicating that the transport of serotonin regulates the activation of glycoprotein (GP) VI-mediated pathways. Therefore, we further clarify the mechanism of the inhibitory effect of SSRIs on GPVI-mediated pathway of platelet aggregation.

Methods: Blood from healthy donors was collected by venipuncture into sodium citrate (9:1) and centrifuged to prepare platelet-rich plasma. The antiplatelet effect of SSRIs was determined by platelet aggregometer. The expression of GPIIb/IIIa and P-selection on platelets was examined by flow cytometry. The influence of SSRIs on the molecules of GPVI-dependent signal transduction pathways was determined by Western immunoblot.

Results: SSRIs inhibited convulxin-induced platelet aggregation in a concentration-dependent manner. SSRIs inhibited the expression of GPIIb/IIIa and P-selection induced by convulxin. In addition, SSRIs concentration-dependently inhibited the phosphorylation of signaling molecules including Akt and Syk, but there was no inhibitory effect on the phosphorylation of FcRγ, indicating that the target site of SSRIs in the inhibition the GPVI dependent activation pathway is downstream of FcRγ and upstream of Syk. FcRδ was co-immunoprecipitated with Syk under the stimulation of convulxin. Pretreatment of platelets with SSRIs reduced the amount of FcRγ co-immunoprecipitated by Syk.

Conclusion: In platelets, the transport of serotonin through serotonin transporter during GPVI stimulation regulated the interaction or the recruitment of Syk to FcRγ. This study partially explains the mechanism of the antiplatelet effect of SSRIs.

P-09-059 Comparative analysis of agomelatine and selective serotoninergic reuptake inhibitors in major depressive disorder with severe anxiety features

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Objective: To evaluate the comparative medium term efficacy and tolerability of agomelatine versus selective serotoninergic reuptake inhibitors (SSRIs) in patients diagnosed with major depressive disorder and significant anxiety symptoms.

Methods: We included in our study 42 patients, 28 female and 14 male, mean age 41.5, diagnosed with major depressive disorder, according to DSM IV TR criteria, who also presented a Hamilton Anxiety Rating Scale (HAMA) score of at least 25, corresponding to

severe anxiety. Mean duration of hospitalization was 12.7 days and both the depressive and anxiety symptoms were treated using either agomelatine 25–50 mg daily, flexible dose or an SSRI (fluoxetine 20–40 mg daily, paroxetine 20–40 mg daily or escitalopram 10–20 mg daily). Patients were monitored every 4 weeks for 6 months with psychometric instruments- Hamilton Depression Rating Scale (HAMD) 17 items, HAMA, Clinical Global Impressions- Severity/Improvement (CGI-S/I), Global Assessment of Functioning (GAF).

Results: Depressive symptoms responded well to agomelatine (mean endpoint HAMD value was 12.1) and SSRIs (mean endpoint HAMD value 10.7), without significant inter-group difference ($p = 0.332$) and both psychological and somatic components of the anxiety decreased significantly during the agomelatine administration (overall HAMA decrease 77.6% – somatic 68.3% and psychological 86.9% at endpoint). Patients treated with SSRIs showed a similar evolution, with a 78.9% overall HAMA decrease (somatic 77.1% and psychological 80.7%). CGI-S/I and GAF decreased significantly in both groups, without significant differences. Agomelatine was better tolerated than SSRIs (6 mild and moderate adverse events reported in the first group versus 11 in the second group). No drop out was recorded throughout the study due to adverse events.

Conclusion: Agomelatine has a similar efficacy to the SSRIs in the treatment of major depression associated with severe anxiety features. Agomelatine was better tolerated than SSRIs during the 6 months of this study.

P-09-060 Quality of life assessment in fibromyalgia during duloxetine treatment

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Objective: To assess the quality of life in patients diagnosed with fibromyalgia during medium-term treatment with duloxetine.

Methods: A group of 25 patients, 16 female and 9 male, mean age 53.2, diagnosed with fibromyalgia were evaluated for physical symptoms severity, depressive and anxiety symptoms, daily functioning and quality of life, using Hamilton Depression Rating Scale-17 items (HAMD), Hamilton Anxiety Rating Scale (HAMA), Fibromyalgia Impact Questionnaire (FIQ), Clinical Global Impressions-Severity/Improvement (CGI-S/I) and Quality of Life Inventory (QOLI). Patients included in this trail received duloxetine 60–90 mg daily, flexible dose, for 24 weeks and were monitored every 4 weeks. Inclusion criteria: age between 18 and 65, no personal history of major depressive disorder. Exclusion criteria: other severe organic diseases, comorbid axis I or II diagnosis, HAMD over 14, HAM over 18.

Results: Patients responded well to duloxetine therapy, as the final normalized FIQ score decreased with 3.4 points ($p < 0.01$). Also, the HAMA scores improved significantly (-71.3%, $p < 0.001$), with insomnia and psychological anxiety being more responsive than other items (-82.2% and -75% at week 24). Reduction of insomnia correlated highly with improvement in life quality (.51), followed by decreased lombar pain (.43) and overall HAMD score (.40). The CGI-I scores improved, from mean baseline values of 4.8 to 2.1 at week 24. The quality of life scales regarding health, family relations and social relations from the QOLI registered significant improvement compared to baseline ($+25.3\%$, $+39.2\%$ and $+26.5\%$ respectively, $p < 0.01$). Patients who had the higher response rate to the treatment also had the higher rate of life quality improvement ($r = 0.63$). There were 4 drop-outs registered, due to adverse events (nausea, sedation, $n = 2$) or non-compliance ($n = 2$).

Conclusion: Treatment of fibromyalgia with duloxetine determined improvements in pain, anxiety and depressive symptoms and, consequently, improved patients quality of life.

P-09-061 Serotonin transporter gene-linked polymorphic region influences discontinuation of pharmacotherapy with paroxetine

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Objective: Discontinuation of antidepressant is critical for the outcome of pharmacotherapy for depression and anxiety disorders, however, factors affecting discontinuation of antidepressants have been unknown. We investigated the association between discontinuation of selective serotonin reuptake inhibitor, paroxetine (PAX) and genetic variants of serotonin (5-HT) transporter gene-linked polymorphic region (5-HTTLPR), −1019C/G promoter polymorphism of the 5-HT1A receptor in Japanese patients with panic disorder.

Methods: Subjects were 65 patients who fulfilled DSM-IV-TR criteria for a diagnosis of panic disorder. Subjects were administered PAX 10 mg/day for 2 weeks. Plasma concentration of PAX after the initiation of pharmacotherapy was determined by high performance liquid chromatography, and the patients were identified as being non-adherent for pharmacotherapy when their plasma levels were under the lowest limit of detection (0.5 ng/ml). 5-HTTLPR and −1019C/G 5-HT1A genotypes were determined by polymerase chain reaction techniques. A multiple logistic regression was performed to analyze the relationships between gender, comorbid of agoraphobia, comorbid major depressive disorder, comorbid physical illness, smoking, habitual use of alcohol, use of drugs for internal medicine, 5-HTTLPR and −1019C/G gene variants (independent variables) and total discontinuation rate, discontinuation rate due to non-adherence, discontinuation rate due to adverse effects (dependent variables).

Results: Multiple logistic regression revealed significant relationship between 5-HTTLPR genotype (L/L, L/S vs. S/S) and total discontinuation rate (46.2% vs. 21.1%, $p = 0.034$). There were not significant relationships between independent variables and discontinuation rate due to non-adherence (26.9% vs. 10.5%), and due to adverse effects (19.2% vs. 10.5%). The odds ratio for L allele carrier subjects who discontinued medication was 3.21 (95% confidence interval, 1.07 to 9.62).

Conclusion: L allele carrier of 5-HTTLPR might predict discontinuation of pharmacotherapy with PAX.

P-09-062 The importance of rigor in post-baseline assessments in CNS clinical trials

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Objective: Inappropriate subjects may be enrolled in a study when enrollment pressures cause inflated baseline severity scores. An increasing number of studies now include methods such as blinded independent centralized ratings (CR) to ensure that appropriate subjects are entered into the trial. Post-baseline factors such as functional unblinding, expectation bias and rater drift can also affect outcomes. Independent raters, blind to study visit, can minimize functional unblinding and expectation bias. Continuous calibration of CR can minimize rater drift.

Methods: Studies with both site ratings (SR) and CR can be evaluated to determine how critical post-baseline blinding and continuous calibration are. A trial of acute schizophrenia used CR for the PANSS and SR for the BPRS on the same subjects. A Parkinson's psychosis study used CR in the US and SR ex-US to assess subjects using the SAPS. A GAD trial used CR of subjects enrolled by SRs' SIGH-A evaluations.

Results: In the schizophrenia trial, CR separated the active comparator and one of two test arms. SR separated the active comparator but neither test arm. In the Parkinson's psychosis study, pimavanserin showed greater separation with CR than SR. In the GAD trial, CR had lower placebo response than SR, independent of subject selection.

Conclusion: Data from several studies support the continued importance of rater blinding and independence, post subject selection. Results suggest that precision of ratings beyond baseline can increase the sensitivity of findings in a clinical trial, decrease placebo response rates and potentially eliminate Type II errors.

Policy of full disclosure: MedAvante, Inc.

P-09-063 The power of expectation bias

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Objective: Expectation bias occurs when an individual's expectations about an outcome influence perceptions of one's own or others' behavior. In clinical trials, both raters and subjects may enter trials with

expectations. Rater expectation bias occurs when raters expect that subjects will improve over the course of the trial. Subject expectation bias occurs when subjects themselves expect to get better. Rater and subject expectations can interact to create a therapeutic alliance. Any or all of these may result in increased placebo response and decreased drug-placebo separation. Double blind studies are designed to minimize bias by blinding subjects and raters to randomization assignment. However, other factors to which subjects and raters are typically unblinded, such as inclusion/exclusion criteria, adverse events and visit sequence may also affect placebo response.

Methods: We reviewed eight published studies that illustrate the problems of subject and rater expectation bias across several therapeutic areas including Major Depressive Disorder, Generalized Anxiety Disorder, psychosis, Parkinson's disease and dementia.

Results: Studies examining rater expectation bias suggest that rater expectations can affect diagnosis and decrease IRR when subjects do not behave according to expectations. Studies of subject expectation bias suggest subject expectations can increase placebo response and affect study outcome. Studies of the interaction of rater and subject expectations find placebo response increases linearly with number of follow-up visits, and having a different rater for baseline, endpoint, and sequential visits may decrease placebo response.

Conclusion: Patient expectations, rater expectations, and rater-patient relationships can increase placebo response and decrease signal detection. Blinding raters to protocol details, including entry criteria and visit number, reduces expectations of improvement. Using different raters at baseline, endpoint and consecutive visits reduces the possibility that relationship bias could influence ratings. Utilizing remote, independent raters is one means to adequately blind and vary raters.

Policy of full disclosure: MedAvante, Inc.

P-09-064 Early life stress prevents the antidepressant effect of carbamazepine in the rats

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Objective: The present study was undertaken to investigate the effects of early life stress (social isolation rearing from weaning) on the behavioral response produced by carbamazepine in the rat forced swimming test.

Methods: Isolation and socially reared rats were compared for their response in the two aversive situations, either without drug pretreatment or following sub-chronic administration of carbamazepine or vehicle (2% tween 80). Beginning at 21 days of age, male Wistar rats were raised either in social isolation (one rat/cage) or in groups of five or six rats/cage (social rearing) for six weeks before behavioral testing.

Results: The results demonstrated that untreated isolation reared rats showed significantly less immobility time and more struggling in the forced swimming test than socially reared rats. Sub-chronic administration of carbamzepine (10, 20 and 40 mg/kg i.p.) 24, 5 and 1 h to socially reared rats significantly induced the antidepressant effects (decreased immobility time and increased struggling time) compared to vehicle (2% tween 80) treated rats. However, these effects were not observed in carbamazepine treated isolation reared rats.

Conclusion: These results indicate early life stress such as social isolation rearing prevents the antidepressant effects of carbamazepine in the rat forced swimming test, but mechanisms of action remain unknown.

P-09-065 Potential antidepressant, but not antipsychotic, activity of new 2,3-dichlorophenylpiperazines containing quinoline- or isoquinoline-sulfonamide moieties in behavioral models in mice

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Objective: Affective disorders are highly debilitating diseases whose treatment is still unsatisfactory because of poor efficiency and unwanted effects of drugs. The most successful approaches in drug development are those that demonstrate preclinical antidepressant and/or antipsychotic activity and target the unmet clinical needs.

Methods: Continuing our research with long-chain arylpiperazines as mixed ligands of serotonergic and dopaminergic receptors, a new series of quinoline- and isoquinoline- sulfonamides with 2,3-dichlorophenylpiperazine moiety (PZ-380, PZ-381, PZ-387, PZ-394, PZ-508, PZ-547, PZ-548, PZ-549, PZ-599) were synthesized and evaluated in vitro for their affinity for dopamine D2 and serotonin 5-HT1A, 5-HT2A, 5-HT6, 5-HT7 receptors. Selected compounds with the most promising receptor profile, i.e. PZ-380, PZ-387, PZ-508, PZ-599, were examined in in vivo models towards their potential antidepressant and antipsychotic activity in mice.

Results: All compounds displayed high-to-moderate affinity for D2 (Ki = 8–54 nM), 5-HT1A (Ki = 13–88 nM), 5-HT2A (Ki = 57–200 nM) and 5-HT7 (Ki = 12–83 nM) and low affinity for 5-HT6 receptors (Ki = 121–13310 nM). The four selected to study compounds produced antidepressant-like effects in the forced swim test in mice with effective doses of 10 and/or 20 mg/kg. PZ-380 displayed antagonistic activity toward D2 receptors examined in the apomorphine-induced climbing model in mice. However, the remaining compounds proved to be partial agonists of these sites. None of the tested compounds attenuated locomotor hyperactivity induced by MK-801 in mice.

Conclusion: The obtained results indicate that new synthesized compounds targeting the aforementioned receptor systems could yield an effective antidepressant action. Unfortunately, in contrary to Aripiprazole containing 2,3-dichlorophenylpiperazine moiety, potential antipsychotic effects of evaluated compounds have not been proven in the hyperlocomotion induced by MK-801 in mice. Study supported by: MNiSW (No. N N405 378 437), Funds for Statutory Activity (UJCM), Polish-Norwegian Research Fund (No. PNRF-103-AI-1/07).

P-09-066 KNT-127 produces antidepressant-like effects in mice though the delta opioid receptors, without producing convulsions

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Objective: We have previously reported that a delta opioid receptor (DOP) agonist, SNC80, produces potent antidepressant-like effect in rodent. However, SNC80 also produced convulsions. Recently, we succeeded in synthesizing a novel DOP agonist called KNT-127. In this study, we have examined the antidepressant-like and the possible convulsive effects of KNT-127 in mice.

Methods: The forced swim test was performed using male ICR mice weighing 30–40 g. KNT-127 (1 mg/kg, s.c.) or imipramine (6 mg/kg, s.c.), a tricyclic antidepressant, was administered 30 min before the test session. Naltrindole (1 mg/kg, sc), a selective DOP antagonist, was administered 30 min before KNT-127 administration. Convulsive effects on mice were measured for 20 min after the drug treatment.

Results: In mice subjected to the forced swim test, KNT-127 significantly decreased the duration of immobility and increased the duration of swimming. These behavioral changes were similar to that observed for imipramine. The antidepressant-like effect of KNT-127 in mice was antagonized by pretreatment with naltrindole. On the other hand, KNT-127 produced no convulsions at doses of up to 100 mg/kg.

Conclusion: The present study demonstrated that a novel DOP agonist, KNT-127, induces antidepressant-like effects without producing convulsions in mice. We propose that KNT-127 should be considered as a candidate compound for the development of DOP-based antidepressants that have fewer undesired side effects.

P-09-067 Neuronal correlates of antidepressant effect in the forced swim test in mice

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Objective: The forced swim test (FST) has been widely used as a behavior test to evaluate antidepressant effects of drugs, while the relevant neuronal pathways remain elusive.

Methods: BALB/c mice, pretreated with imipramine (IMP; 10 mg/kg, i.p.) or saline, were subjected to single session of the FST (10 min). Mice were perfused 2 hours after onset of the FST, and the expression of c-Fos, a marker of neuronal activation, was examined through immunohistochemical method.

Results: Pretreatment with IMP significantly decreased the duration of immobility in FST. IMP pretreatment increased expression of c-Fos in a few subdivisions of the bed nucleus of the stria terminalis (BNST) and the retrochiasmatic area of the hypothalamus. The densities of the c-Fos immunoreactivity in some other regions showed positive or negative correlations with the duration of immobility in the FST.

Conclusion: The present result suggests that the BNST and hypothalamus are involved in antidepressant effect in the FST. Segregated networks of the neurons might regulate active and passive stress-coping behaviors.

P-10. Molecular Neurobiology/Pharmacology

P-10-001 Neuroprotective effect of novel low-molecular NGF mimetic GK-2 was completely blocked via PI3K/Akt pathways inhibition

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Objective: The neuroprotective action of nerve growth factor NGF are mediated by tyrosine kinase receptor and phosphatidylinositide 3 kinase (PI3K)/Akt pathways. The dimeric linear dipeptide mimetic of NGF loop 4, hexamethylenediamide bis-(N-succinyl-glutamyl-lysine), named GK-2 was synthesized in Zakusov's Institute of Pharmacology RAMN. We have previously shown that GK-2 had neuroprotective properties on cell models of oxidative stress, glutamate toxicity and MPTP-induced injury of neurons. HT-22 cells were pretreated with PI3 kinase inhibitor LY294002 in order to investigate signaling pathway mediating the neuroprotective action of GK-2 on model of oxidative stress.

Methods: Experiments were carried out on hippocampal cell culture line HT-22. Cells damages were provoked by 1.5 mM hydrogen peroxide for 30 min. After that, medium was changed to original medium without agents. HT-22 cells were pretreated with 100 mkM LY294002 for 30 min prior to GK-2 stimulation. Cell viability was measured by MTT-test.

Results: It was shown that LY294002 blocked the neuroprotective effects of GK-2 (10–5 and 10–8 M) and NGF (100 ng/ml) against hydrogen peroxide-induced cell death in all experimental time points.

Conclusion: PI3K/Akt pathways were shown to be involved in the neuroprotective effect of GK-2 as well as that of NGF.

P-10-002 Critical care in psychiatry

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Objective: Psychiatric medications are frequently an essential component of care for critically ill patients. Their use may lead to medical complications, however, as a result of direct toxicity from psychotropic medications, drug-drug interactions, or intoxication or withdrawal states. These complications may be a nuisance (e.g., dry mouth and nausea) or serious and life-threatening (e.g., neuroleptic malignant syndrome [NMS] and cardiac arrhythmias). This symposium addresses the most important medical complications of psychiatric treatment, in critical care set up.

Methods: The use of psychiatric medications in critically ill patients is an important component of comprehensive care. Many a times a psychiatrist is consulted by ICU Internists for alteration in behaviour, mood, thinking and perception of reality. Because the emergence of psychiatric symptoms may be precipitated and exacerbated by various medical conditions, proper evaluation and emergency management is of utmost importance. Many psychotropic drugs are notorious for causing sudden and life threatening physical complications needing ICU management, like Neuroleptic Malignant Syndrome, Serotonin Syndrome, Electrolyte imbalance, Cardiac Arrythmias etc.

Conclusion: Psychotropic drugs can cause toxicity, intoxication and withdrawl states, severe drug reactions like rashes, S-J Syndrome, drug interaction with several drugs used in general medical conditions etc, which need to be evaluated and managed. In this regard, it is essential to consider the potential complications of psychotropics while balancing the important role they serve in treatment of the medically ill.

P-10-003 Dopamine D2 and 5-hydroxytryptamine 5-HT2A receptors assemble into functionally interacting heteromers

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Objective: In view of the co-distribution of dopamine D2LR and 5-hydroxytryptamine 5-HT2A receptors (D2LR and 5-HT2AR, respectively) within inter alia regions of the dorsal and ventral striatum and their role as a target of antipsychotic drugs; in this study we assessed the potential existence of D2LR-5-HT2AR heteromers in living cells and the functional consequences of this interaction.

Methods: In the cellular and molecular work we have used BRET, biochemical binding, dual luciferase reporter assay, fluo-4 Non Wash Calcium Assay and a bioinformatic approach based on a set of amino acid triplet homologies.

Results: By means of a proximity-based bioluminescence resonance energy transfer (BRET) approach we demonstrated that the D2LR and the 5-HT2AR form stable and specific heteromers when expressed in HEK293T mammalian cells. Furthermore, when the D2LR-5-HT2AR heteromeric signaling was analyzed we found that the 5-HT2AR-mediated phospholipase C (PLC) activation was synergistically enhanced by the concomitant activation of the D2LR as shown in a NFAT-luciferase reporter gene assay and a specific and significant rise of the intracellular calcium levels were observed when both receptors were simultaneously activated. Conversely, when the D2LR-mediated adenylyl cyclase (AC) inhibition was assayed we showed that costimulation of D2LR and 5-HT2AR within the heteromer led to inhibition of the D2LR functioning, thus suggesting the existence of a 5-HT2AR-mediated D2LR trans-inhibition phenomenon. Finally, a bioinformatics study reveals that the triplet amino acid homologies LLT (Leu-Leu-Thr) and AIS (Ala-Ile-Ser) in TM1 and TM3, respectively of the D2R-5-HT2AR may be involved in the receptor interface.

Conclusion: Overall, the presence of the D2LR-5-HT2AR heteromer in discrete brain regions is postulated based on the existence of D2LR-5-HT2A receptor–receptor interactions in living cells and their codistribution inter alia in striatal regions. Possible novel therapeutic strategies for treatment of schizophrenia should be explored by targeting this heteromer.

P-10-004 Not all dopamine D2 receptor antagonists were created equal: Potential role of presynaptic versus postsynaptic dopamine D2 receptor blockade in early genes induction by antipsychotics

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Objective: Striatal dopamine D2 receptor (D2R) occupancy is related to antipsychotics efficacy and extra-pyramidal symptoms (EPS) occurrence. Low-dose amisulpride preferentially blocks presynaptic dopamine autoreceptors, whereas higher doses block postsynaptic D2Rs. Antipsychotics acting preferentially at presynaptic D2R appear

to have low propensity to induce EPS, although the molecular explanation is still elusive.

Methods: We investigated, using in situ hybridization, the expression pattern of genes involved in neural activity (c-fos and Zif-268) and synaptic rearrangements (Homer1a and Arc) after acute treatment with low (10 mg/kg) and high (35 mg/kg) dose Amisulpride (AMS10 and AMS35, respectively), Haloperidol 0.8 mg/kg (HAL), and vehicle (VEH), in rat forebrain regions relevant for psychosis pathophysiology and treatment.

Results: c-fos expression was found increased by AMS10, AMS35 and HAL in dorsomedial caudate-putamen (CP) compared to VEH and by HAL in lateral CP compared to other treatments ($p < 0.05$). Zif-268 expression was induced by AMS10 and AMS35 compared to VEH in all CP subregions and by HAL in lateral CP compared to other treatments and in medial CP and nucleus accumbens core compared to VEH and AMS10 ($p < 0.05$). Homer1a expression was increased by HAL in dorsolateral CP compared to other treatments, in ventrolateral CP compared to VEH and AMS35, and in dorsomedial CP compared to VEH, ($p < 0.05$). Arc expression was induced by HAL in lateral and ventromedial CP compared to other treatments and in dorsomedial CP compared to VEH and AMS10 ($p < 0.05$).

Conclusion: Amisulpride induced gene expression in a region-specific and dose-dependent manner. Despite haloperidol, that induced prominent gene expression in lateral CP – putatively involved in EPS occurrence, amisulpride preferentially modulated gene expression in limbic regions. These results suggest that other mechanisms behind D2R low-affinity and multireceptorial-profile of the atypical antispychotics may account for their ''atypicality'', probably involving a differential targeting of D2R antagonism in discrete brain regions.

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P-10-005 Efficacy, tolerability and critical issues of switch from quetiapine IR to XR in patients with affective disorders

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Objective: To date, few studies on the switch from Quetiapine Immediate Release (IR) to XR, in terms of efficacy, compliance, quality of life and other critical aspects have been published. The aim of the present study was to assess the aforementioned variables in patients with Affective Disorders.

Methods: Twenty-nine patients with Affective Disorders (9 with Major Depression, 20 with Bipolar Depression) switched from Quetiapine IR to XR were recruited. HAM-D, HAM-A, MADRS, YMRS, CGI, BARS, DISS were administered in order to assess efficacy, compliance and tolerability. Patients were assessed at T0 (switch), T1 (1 week after the switch) and T2 (6 weeks after the switch).

Results: The sample (13 = females, 16 = males) had a mean age of 51 ± 14 years and a mean age of onset of 34 ± 14 years. Patients' therapeutic regimen changed from a mean dose of 374 ± 255 mg of Quetiapine IR to 376 ± 243 mg of Quetiapine XR. Statistical analyses (paired t-test) showed a significant reduction of the total scores from T0 to T2 on HAM-D ($t = 2.03$; $p = 0.05$), HAM-A ($t = 2.9$; $p = 0.009$) and on CGI-S ($t = 2.82$; $p = 0.01$). The switch was well tolerated by the 65.2% of patients. Most reported side effects were early and central insomnia with daily drowsiness (17.4%), increased weight and appetite (4.3%), asthenia (4.3%) and constipation (4.3%). Seventy-one % of the sample scored 100 at BARS (maximum compliance).

Conclusion: Present results seem to support the switch from Quetiapine IR to XR in light of better outcome measures. However, more than one-third of the sample reported side effects that, in some cases, led to the drop-out from the study. Strategies to relieve most commonly reported side-effects (including gradual cross-switch) can facilitate the switch. Predictors of the above mentioned side effects need to be identified.

P-10-006 Modulating glutamate transmission in a rat model of depression

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Objective: Depression is a common disease characterized by cognitive and emotional symptoms, with high rate of treatment resistance, especially for cognitive symptoms. Depression has been linked to alterations in glutamate neurotransmission. We explored the hippocampal glutamatergic system in a rat model of depression (Flinders Sensitive line, FSL) to reveal mechanisms underlying the emotional and cognitive aspects of the disease.

Methods: To carry out this aim we combine electrophysiological, biochemical and behavioral approaches.

Results: We showed that FSL rats displayed hippocampal CA1 synaptic plasticity impairment and increased spontaneous excitatory post-synaptic currents (sEPSCs) in CA1 pyramidal cells compared to Sprague Dawley rats. Western blotting revealed hippocampal reduced levels of the glia glutamate transporter EAAT1 and the NMDA receptor subunit NR2A. Moreover, FSL exhibited recognition memory deficits in the novel object recognition test (NOR). We have used pharmacological treatments to target different mechanisms of glutamate regulation. D-serine bath application restored in vitro CA1-LTP by acting on NMDA receptors, while acute systemic administration restored the recognition memory deficit. Bath application of the mGlu2/3 receptor agonist LY354740 reduced CA1 sEPSCs and LY354740 chronic treatment was able to partially restore in vitro CA1-LTP (Gómez-Galán et al., 2012). At present, we have assessed the behavioral and physiological effects of the H3-receptor antagonist clobenpropit in FSL rats. Clobenpropit acutely restored memory impairments (in NOR and passive avoidance test), and had an antidepressant-like effect in the forced swim test. Clobenpropit bath application did not affect sEPSCs although acute systemic administration increased NR2A protein expression levels in the hippocampus of FSL rats.

Conclusion: Glutamatergic alterations associated to depression might require selective targeted modulation to exert both antidepressant and pro-cognitive effects. Understanding how to regulate the glutamatergic system directly or through the modulatory effect of monoamines would help in the development of new therapies in depression.

P-10-007 Fluvoxamine increased glutamate release by activating both 5-HT3 and sigma-1 receptors in prelimbic cortex of chronic restraint stress C57BL/6 mice

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Objective: Emerging evidence from therapeutic trials in humans and animal models suggests that in the treatment of depression, antidepressants play a role by targeting the glutamatergic system. Fluvoxamine is one of a widely-used SSRIs which has been considered to target monoamine neurotransmitter reuptake mechanisms. However, if fluvoxamine has an effect on the glutamate release is still unclear. The present experiment studied the effect of fluvoxamine on presynaptic glutamate release in prelimbic cortex, both in control C57BL/6 mice and chronic restraint stress C57BL/6 mice, and further investigated the mechanism underlying this effect.

Methods: The present experiment studied by using patch clamp, on-line fluorimetry, pharmacological approaches combined with other techniques.

Results: The results showed that fluvoxamine increased the glutamate release in the depression model mice but it had no effect on the glutamate release in the control mice. The mechanism underlying these effects in depression model mice was that, fluvoxamine firstly activated presynaptic 5-HT3 receptors, which transiently increased the $Ca2+$ concentration. The increase of $Ca2+$ concentration via 5-HT3 receptors caused the activation of sigma-1 receptors, which were activated by fluvoxamine. The activation of sigma-1 receptors increased the intrasynaptosomal $Ca2+$ concentration significantly

through the outflow of endoplasmic reticulum calcium and finally activated PKC.

Conclusion: These results suggested that fluvoxamine may have a selective effect and different mechanism based on the condition of animal.

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P-10-008 The cytochrome P450-mediated synthesis of serotonin in the brain: An in vitro study

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Objective: Brain cytochrome P450 (CYP) may be involved in the local metabolism of drugs and endogenous substrates such as neurosteroids or monoaminergic neurotransmitters. The CYP2D-mediated synthesis of dopamine and serotonin has been shown in vitro and in vivo; however, the formation of serotonin by this enzyme in the brain has not been demonstrated as yet. Therefore the aim of the present study was to demonstrate that the CYP2D-mediated synthesis of serotonin from 5-methoxytryptamine took place in the brain.

Methods: The experiment was carried out on male Wistar rats. The ability of CYP2D isoforms to O-demethylate 5-methoxytryptamine to serotonin was tested using rat recombinant CYP2D isoforms (CYP2D1/2/4/18) and human CYP2D6. The obtained results were compared with those concerning other CYP isoforms from the subfamilies CYP2A, 2B, 2C and 3A. Then O-demethylation of 5-methoxytryptamine was studied in brain microsomes in the absence or presence of the CYP2D inhibitor quinine or fluoxetine. Microsomes were prepared from the whole brain or from different brain structures including the brain stem (containing serotonergic raphe neurons) of control rats. The concentration of serotonin formed in vitro was measured using HPLC.

Results: Of the rat CYP isoforms studied, CYP2D isoforms (CYP2D2, CYP2D4 and CYP2D18) were the most effective in catalyzing the O-demethylation of 5-methoxytryptamine to serotonin; however, human CYP2D6 was more active than rat CYP2D isoforms in this respect. The formation of serotonin from 5-methoxytryptamine was demonstrated in microsomes derived from different brain structures. The reaction was inhibited by the two CYP2D inhibitors, quinine and fluoxetine.

Conclusion: In conclusion, brain CYP2D isoforms are able to catalyze the formation of serotonin from 5-methoxytryptamine, which may be of pharmacological importance to the treatment of psychiatric diseases. (Grant DeMeTer no. POIG.01.01.02–12-004/09 (European Union and the Ministry of Science and Higher Education, Warsaw, Poland) and statutory funds from the Institute of Pharmacology, PAS).

P-10-009 Dopaminergic signalling and associative learning in the nematode caenorhabditis elegans

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Objective: Introduction: Defective dopaminergic signalling has been implicated in the aetiology of a number of neuropsychiatric disorders. However, although the molecular mechanisms involved in the stimulus-reward pathway are relatively well characterised, their role in behavioural plasticity remains unclear. We use the nematode Caenorhabditis elegans (C.elegans) as a model to study behavioural plasticity as it has a simple nervous system, comprising just 302 neurons, whilst at the same time exhibiting relatively complex behavioural strategies.

Methods: Using a chemotaxis assay, we tested the role dopamine signaling played in olfactory associative learning. We compared olfactory chemotaxis in C. elegans wildtype (N2), the dopamine negative mutant (cat-2-), and the serotonin negative mutant (tph-1-). The Chemotaxis Index (CI), a measure of the strength of association between food and a volatile odour (benzaldehyde) was determined for each of the strains.

Results: As reported in previous work, the serotonin-deficient mutant tph-1- exhibited no olfactory chemotaxis. The dopamine-deficient mutant cat-2- exhibited a similar profile to the wildtype except for a raised CI 60 minutes after the end of the conditioning phase. This increase in CI could be reduced by exposing cat-2- mutants to exogenous dopamine.

Conclusion: The loss of the conditioning in the cat-2- mutants after 60 minutes and its reinstatement by exogenously applied dopamine suggests a complex balance exists between dopamine and other pathways involved in the maintenance of conditioning. One possible mechanism would involve the repression of an 'association signal' by dopamine. In the cat-2- mutant the 'association signal' is expressed and, in the presence of food-odour stimuli, association gradually returns reaching a maximum after 60 minutes. The subsequent decrease in the CI after 60 minutes in the cat-2- mutant can be explained by a negative feedback mechanism. We are working to identify this signal and testing whether there is a dopamine dose effect on this mechanism.

P-10-010 Temporal and spatial changes in tryptophan hydroxylase expression are associated with behaviour switching in caenorhabditis elegans

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Objective: Background: Tryptophan hydroxylase (tph) is a key enzyme in the biosynthesis of the neurotransmitter serotonin (5-HT). During the adult stage of development and in response to particular external conditions (presence of food), the nematode Caenorhabditis elegans switches behavior from feeding to egg laying. This behavior switching is controlled by serotonin but the mechanism remains unclear.

Methods: Wildtype C. elegans carrying a tph-1 promotor::gfp construct were live mounted on 5% agarose and changes in tph-gfp was documented via fluorescence microscopy as worms entered the egg-laying phase of their life cycle.

Results: We show that wildtype worms entering the egg laying phase upregulate tph expression in specific tissues including muscle tissue adjacent to the vulva. This pattern of expression is not seen in worms during the other stages of larval and adult development.

Conclusion: 5-HT has both a stimulatory (via a G protein-coupled receptor) and inhibitory (via a 5-HT-gated Cl- channel) effect on egg laying. Long term exposure to 5-HT attenuates this inhibitory response. The local actions of 5-HT include the stimulation of vulval contractions. Taken together, the changes in tph expression we observed are consistent with it playing a central role in egg laying behavior. We are now looking for potential candidates that might regulate tph transcription consistent with the expression patterns we observed.

P-10-011 Stress regulates the gene expression of neuronal PAS domain 4 (Npas4), via glucocorticoid receptor

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Objective: The expression levels of neuronal PAS domain 4 (NPAS4) mRNA are decreased in the hippocampus of socially-isolated or chronically restricted mice, which is accompanied by impairments of memory and emotional behavior with a reduced hippocampal neurogenesis. The reduction of NPAS4 expression induced by psychosocial stress may play a role in mental disorders, since NPAS4 has recently been shown to regulate the development of GABAergic inhibitory neurons. In this study, to investigate the transcriptional regulation of NPAS4 expression by stress, we focused on the effect of corticosterone (CS) on NPAS4 transcription.

Methods: Npas4 expression level in the hippocampus of ICR mice were measured 2 hours after the CS (10 mg/kg) injection or 1 week after the adrenalectomy. Effect of CS on Npas4 expression in restraint stressed mice was evaluated by using a glucocorticoid receptor (GR) antagonist, RU486. The effect of GR on the Npas4 promoter activity in Neuro2a cells was determined by a luciferase assay. Interaction of GR and Npas4 promoter was confirmed by a chromatin immunoprecipitation assay.

Results: Acute CS treatment significantly decreased the expression level of Npas4 mRNA in the hippocampus of mice, while the expression level was increased by adrenalectomy. The GR antagonist RU486 inhibited the reduction of NPAS4 expression induced by restraint stress. Reduced NPAS4 expression was also observed in CS-treated Neuro2a cells. Putative GREs were found at −2 kb to −1 kb upstream of the transcription initiation site of Npas4 promoter. The Npas4 promoter activity was increased by deletion of GREs rich sequence or treatment with RU486. Moreover, chromatin immunoprecipitation assay revealed the binding of ligand-bound GR to Npas4 promoter region.

Conclusion: These results suggest that psychosocial stress reduces the Npas4 gene expression via the binding of CS/GR complex to GREs located on the promoter region of the gene.

P-10-012 Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by aripiprazole

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Objective: Accumulating evidence suggests that neuronal plasticity plays a role in the mechanisms of action of atypical antipsychotic drugs. The atypical antipsychotic drug aripiprazole has been used as treatment of psychiatric diseases such as schizophrenia, major depression, bipolar disorder, and autism. In this study, we examined whether aripiprazole could affect nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells.

Methods: Twenty-four hours after plating, the medium was replaced with DMEM containing 0.5% FBS, 1% penicillin and 1% streptomycin with NGF (2.5 ng/ml), with or without aripiprazole, WAY-100635 (5-HT1A receptor antagonist), xestospongin C, 2-APB (IP3 receptor antagonists) or several specific inhibitors of cellular signaling pathways (PLC-γ, PI3K, Akt, p38 MAPK, and c-Jun N-terminal kinase (JNK), and the Ras/Raf/ERK/MAPK). Four days after incubation with NGF and test drugs, morphometric analysis on neurite outgrowth in PC12 cells was performed.

Results: Aripiprazole significantly potentiated NGF-induced neurite outgrowth, in a concentration dependent manner. Potentiation of NGF-induced neurite outgrowth mediated by aripiprazole was significantly antagonized by co-administration of the selective 5-HT1A receptor antagonist WAY-100635, but not the dopamine D2 receptor antagonist sulpiride. Furthermore, the potentiation of NGF-induced neurite outgrowth by aripiprazole was significantly blocked by IP3 receptor antagonists (xestospongin C and 2-APB). Moreover, selective inhibitors of several cellular signaling pathways significantly blocked the potentiation of NGF-induced neurite outgrowth by aripiprazole.

Conclusion: These findings suggest that aripiprazole could potentiate NGF-induced neurite outgrowth in PC12 cells, and that the beneficial effects of aripiprazole on neuronal plasticity may be involved in the mechanisms of it's action.

P-10-013 Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by ifenprodil: The role of sigma-1 and IP3 receptors

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Objective: Ifenprodil (Cerocral®) has been used as a cerebral vasodilator in a limited number of countries, including Japan and France. In addition to both the β1 adrenergic receptor and N-methyl-D-aspartate (NMDA) receptor antagonists, ifenprodil binds to the two subtypes (1 and 2) of sigma receptor. In this study, we examined the effects of ifenprodil on nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells. Furthermore, we examine the role of these receptors on the potentiation of NGF-induced neurite outgrowth by ifenprodil.

Methods: Twenty-four hours after plating, the medium was replaced with DMEM containing 0.5% FBS, 1% penicillin and 1% streptomycin with NGF (2.5 ng/ml), with or without ifenprodil, prazosin (α1 adrenergic receptor antagonist), Ro 25–6981 (NMDA receptor NR2B antagonist), NE-100 (sigma-1 receptor antagonist), SM-21 (sigma-2 receptor antagonist), xestospongin C (inositol 1,4,5-triphosphate (IP3) receptor antagonist) or 2-aminoethoxydiphenyl borate (2-APB) (IP3 receptor antagonist). Four days after incubation with NGF and test drugs, morphometric analysis on neurite outgrowth in PC12 cells was performed.

Results: Ifenprodil significantly potentiated NGF-induced neurite outgrowth, in a concentration-dependent manner. In contrast, prazosin and Ro 25–6981 did not alter NGF-induced neurite outgrowth. Potentiation of NGF-induced neurite outgrowth mediated by ifenprodil was significantly antagonized by co-administration of the selective sigma-1 receptor antagonist NE-100, but not the sigma-2 receptor antagonist SM-21. Furthermore, the potentiation of NGF-induced neurite outgrowth by ifenprodil was significantly blocked by treatment with the IP3 receptor antagonists, xestospongin C or 2-APB.

Conclusion: These findings suggest that activation at sigma-1 receptor and subsequent interaction with IP3 receptor may mediate the pharmacological effects of ifenprodil on neurite outgrowth.

P-10-014 Modulation of the extracellular D-serine contents by the a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate type glutamate receptor in the rat medial frontal cortex as revealed by in vivo microdialysis

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Objective: It has been widely accepted that D-serine plays a pivotal role in the control of the N-methyl-D-aspartate (NMDA) type glutamate receptor as its endogenous co-agonist in the mammalian brain. Abnormalities in the extracellular D-serine signal, which lead to the NMDA receptor dysfunction, have been implicated in the pathophysiology of a variety of neuropsychiatric disorders such as schizophrenia. The exact mechanisms underlying regulation of extracellular release of D-serine, however, await further elucidation. To get an insight into this issue, we have characterized the effects of agents acting at the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) type glutamate receptor on the extracellular contents of cortical D-serine in vivo, because in vitro experiments have suggested the involvement of the AMPA receptor in the control over the extracellular release of D-serine in the central nervous system although there is so far no in vivo evidence to for this interaction.

Methods: The present animal studies have been approved by the ethics committees of the Tokyo Medical and Dental University. We used an in vivo microdialysis technique in combination with high-performance liquid chromatography with fluorometric detection.

Results: We have shown that intra-medial frontal cortex infusion of the S-enantiomer of AMPA, an active enantiomer at the AMPA receptor causes a significant reduction in the extracellular contents of D-serine in the cortical area of the rat in a concentration-dependent, an AMPA/kainate receptor antagonist NBQX- and a calcium permeable AMPA receptor antagonist NASPM-reversible manner. The reducing effects of S-AMPA are augmented by co-infusion of an allosteric modulator of the AMPA receptor, cyclothiazide, which prevents AMPA receptor desensitization.

Conclusion: Our data support the view that the calcium permeable subtype of the AMPA receptor might exert a phasic inhibitory influence on the extracellular release of D-serine in the mammalian frontal cortical area in vivo.

P-10-016 Afobazole decrease menadione genotoxicity

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Objective: NRH quinone reductase 2 (NQO2) is a structural analog of well known phase-II biotransformation enzyme NAD(P)H quinone reductase 1 (NQO1). NQO2 catalyze two-electron reduction of o- and p-quinones. However, because of specifics in the tertiary structure it is capable for one-electron reduction of quinones, menadione for one, and generation of reactive oxygen species. Overexpression of NQO2 is associated with Alzheimer's disease and idiopathic Parkinson's disease, which pathogenesis is related to ROS generation due to products of catecholamine self-oxidation, dopa-quinone first of all. Our previous studies had revealed ligand properties of selective anxiolytic with neuroprotective activity afobazole towards to MT3 receptor, also known as regulatory site of NQO2 enzyme. In the next set of experiments we established that afobazole is NQO2 inhibitor with $Ki = 2.54 \times 10–4$ M (obtained for human recombinant NQO2).

The purpose of present study was to determine the influence of afobazole on NQO2-dependant quinone mediated genotoxicity as a marker of oxidative stress in the model of menadione toxicity in vitro.

Methods: Materials and methods: We have used the single cell gel electrophoresis assay (comet assay) as a marker of oxidative stress to investigate the model quinone compound menadione genotoxic effects in mice bone marrow cells.

Results: Our experiments on menadione genotoxicity have shown that incubation of mice bone marrow cells with dicoumarol in concentration of 10 μM, a potent selective NQO1 inhibitor, lead to 5,4-fold increase in the amount of DNA-strand breaks contrary to control group. Afobazole administration in concentration of 10 μM in same conditions lead to 1,7-fold decreased toxicity.

Conclusion: Afobazole decrease NQO2 mediated menadione genotoxicity. Obtained data assume one of the possible molecular mechanisms of neuroprotective activity of afobazole. Thus the further investigations are required.

P-10-017 Antidepressants enhance hippocampal dendritic outgrowth via mTOR signaling pathway

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Objective: A growing body of evidence has pointed to the rapid antidepressant effect of the subanesthetic dose of ketamine, N-methyl-D-aspartate (NMDA) receptor antagonist, via mammalian target of rapamycin (mTOR) signaling. mTOR signaling plays a fundamental role in axonal and dendritic growth. However, the mechanisms underlying this action of antidepressants have not been identified. We examined whether certain antidepressants (escitalopram, fluoxetine, paroxetine, sertraline, imipramine and tranylcypromine) promote neurite outgrowth via mTOR signaling in primary cultured hippocampal neurons.

Methods: Rat hippocampal cells were treated with ketamine or antidepressants for 5 days. Rapamycin, mTOR inhibitor, was added 30 min before drugs treatment. Using neurite assays, we measured changes in the dendritic morphology of hippocampal neurons.

Results: We found that ketamine (1–100 μM) and all antidepressants (1–50 μM escitalopram, 0.1–10 μM fluoxetine, 0.05–1 μM paroxetine, 0.05–1 μM sertraline, 0.1–10 μM imipramine and 1–50 μM tranylcypromine) significantly increased the total outgrowth of hippocampal dendrites in dose-dependently ($p < 0.01$). This effect of ketamine was blocked by mTOR inhibitor rapamycin (1 μM) ($p < 0.01$). The effects of escitalpram, paroxetine and tranylcypromine were also attenuated by rapamycin ($p < 0.05$). In contrast, fluoxetine, sertraline and imipramine did not affect this effect.

Conclusion: This study presents novel in vitro evidence that some antidepressants could promote neurite outgrowth through mTOR signaling pathway. This finding may provide new target protein for the mechanisms underlying neurotrophic properties of antidepressants.

P-10-018 Comparative study of hemantane and amantadine in rats with experimental intracerebral posttraumatic hematoma

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Objective: Hemantane (H.) (N-2(adamantyl)hexamethylenimine hydrochloride) is novel antiparkinsonian drug with complex mechanism of action including NMDA receptor antagonism and antiradical activity which allows to suppose the neuroprotective effect of H. The aim of the study was to assess the effects of H. in comparison with amantadine (AMA) in rats with intracerebral posttraumatic haematoma (IPH) which could be considered as a model of haemorragic stroke.

Methods: Sham-operated and rats with IPH were treated with saline (groups 1 and 2). H. (5 mg/kg, i.v.) or AMA (20 mg/kg, i.v.) (groups 3 and 4). Saline and drugs were administered first at 3, 5 hours after surgery and then for 4 consecutive days. On days 1, 3, 7 and 14 after surgery animals were placed in open field, elevated plus-maze, rotarod and passive avoidance tests.

Results: It was shown that both drugs significantly decreased mortality and improved motor activity and exploratory behavior in open field. AMA was little more effective in improving motor activity and exploratory behavior. In passive avoidance test no impairment of hole reflex in all groups of rats was registered. Impaired acquisition in animals with IPH was revealed in all retention trials. H. and AMA prevented these alterations. H. 5 mg/kg i.v. demonstrated more pronounced activity in restoring memory. There was no difference in retrieval testing between treated with H. and sham-operated animals in all days of testing sessions, while termination of AMA treatment caused decrease in retrieval of memory trace on day 7.

Conclusion: The results obtained testify for neuroprotective properties of the novel antiparkinsonian drug hemantane.

P-10-020 Serum pro-brain derived neurotrophic factor and remission in depressed patients after selective serotonin reuptake inhibitors treatment

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Objective: The role of brain-derived neurotrophic factor (BDNF) has been mainly known, implicating in the hippocampal neurogenesis after antidepressant administration. It have been reported that serum BDNF content is related to depression etiology and antidepressant treatment, but they are controversial. Recent studies found that proBDNF before processing is related to apoptosis by binding to p75 NTR (neurotrophin receptor) and may facilitate long–term depression. Our hypothesis is that the two forms of BDNF(pro- and total-) are related to depression susceptibility and remission after Selective Serotonin Reuptake Inhibitors(SSRI) treatment in elderly depressed patients.

Methods: Twenty-nine elderly patients, diagnosed as major depression according to criteria for depression of DSM-IV, entered a 6 week clinical trial with SSRIand documented the several clinical variables and plasma drug concentrations. Remission was defined as = <7 score of HAM-D. Patients and 29 normal volunteers were drawn venous blood between 9 ~ 12 a.m. Serum proBDNF immunoreactivity was determined by western blot and total BDNF(tBDNF) content by BDNF Emax Immunoassay System. Comparison between two groups was analyzed using t-test or Mann-Whitney test in SPSS ver.10.1.

Results: No serum proBDNF immunoreactivity and total BDNF contents was differed between normal volunteer and depressed patients. After 6 week of SSRI administration, proBDNF immunoreactivity was increased in remitted patients compared than in non-remitted patients ($p = 0.041$, by t test).

Conclusion: Our results suggest that serum proBDNF is possible to be candidate marker for remission after SSRI treatment. Further studies should elucidate the mechanism of the two types of BDNF in serum related to SSRI action.

P-10-021 Comparative receptor binding profile of lurasidone and other first and second generation antipsychotics

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Objective: To characterize the receptor binding profile of lurasidone compared to other first and second generation antipsychotics.

Methods: Binding affinities for lurasidone and other antipsychotics were determined in side-by-side assays using membrane preparations from non-human CNS or cell lines expressing cloned human receptors.

Results: Lurasidone displayed potent binding and full antagonism at dopamine D2 (Ki, 1.68 nM) and 5-HT7 (Ki, 0.49 nM) receptors; lurasidone had the highest affinity for the dopamine D2 receptor among antipsychotics tested, followed by risperidone and haloperidol. Lurasidone also showed full antagonism and high affinity at

serotonin 5-HT2A receptors (Ki, 2.03 nM). Lurasidone had nanomolar affinity (Ki = 6.75 nM) for serotonin 5-HT1A receptors, behaving as a weak-moderate partial agonist. Relative to dopamine D2 receptor binding, lurasidone showed higher affinity for 5-HT7, 5-HT2A, and 5-HT1A than the other antipsychotic agents tested. Lurasidone's binding to dopamine receptors was selective for dopamine D2 receptors: compared to its dopamine D2 receptor affinity, its Ki for D1 receptors was 156-fold higher, for D316-fold higher, and 30-fold higher for D4 receptors. Lurasidone had a favorable binding-profile at several receptors that are suspected of being associated with undesirable effects, with minimal affinity for 5-HT2C receptors (Ki, 415 nM), and no affinity for histamine H1 (IC50 > 1000 nM) and muscarinic [cholinergic] M1 (IC50 > 1000 nM) receptors. Lurasidone also displayed only moderate affinity for α2C adrenoceptors (Ki, 10.8 nM), and moderate-weak affinity for α1 adrenoceptors (Ki, 48 nM).

Conclusion: Lurasidone has potent and selective antagonist activity at the D2 receptor, coupled with equally potent antagonist activity at both 5-HT7 and 5-HT2A receptors. This profile is consistent with the expected antipsychotic efficacy, a moderate likelihood of EPS, a low potential for weight gain and related metabolic consequences, and the potential for beneficial impact on mood and impaired cognitive function.

Policy of full disclosure: Drs. Loebel, Cucchiaro, Werner and Pikalov are full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ. Dr. Ishiyama, Horisawa, Tokuda, Ogasa and Ishibashi are full-time employees of Dainippon Sumitomo Pharma, Osaka, Japan.

P-10-022 Low molecular weight dipeptide analogue of BDNF, GSB-106, prevents the hyperexpression of HO-1 acting via the TrkB receptors

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Objective: Brain-derived neurotrophic factor (BDNF) deficiency contributes a lot to the pathogenesis of most neurodegenerative diseases. The cellular actions of BDNF are mediated through the activation of the Trk receptors. The novel dipeptide analogue of BDNF, GSB-106, was synthesized in Zakusov Institute of Pharmacology RAMS. We have previously shown that GSB-106 had neuroprotective effects in different models of cell damages: oxidative stress, glutamate or 6-hydroxydopamine-induced toxicity. This study was undertaking in order to evaluate the possible mechanisms of this neuroprotective effect.

Methods: Experiments were performed on hippocampal neurons in culture HT-22. Oxidative stress was modeled by addition of H2O2 (1.5 mM) into the cell medium. GSB-106 (10–8 M) was added after damaging factor. BDNF (50 ng/ml) was added as a positive control. Western blot analysis was used for the detection of phosphorylated Trk-B level and synthesis of heme oxygenase-1 (HO-1).

Results: It is shown that GSB-106 caused a significant increase in phosphorylation of Trk-B; this effect appeared already in 30 sec interval. These data alow to suggest that GSB-106 similar to BDNF acts via the TrkB receptors. HO-1 is a stress-inducible enzyme involved in protection cell from oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. GSB-106, as well as BDNF (50 ng/ml), limited the overexpression of the protein HO-1, induced by oxidative stress.

Conclusion: (1) GSB-106 caused an increase of Trk-B phosphorylation; (2) the ability of GSB-106 to limit the hyperexpression of HO-1, induced by oxidative stress, proposed to be one of the mechanisms of its neuroprotective action; (3) according to both these parameters GSB-106 imitates the effects of BDNF.

P-10-023 Exposure to enriched environments during adolescence prevents abnormal behaviours associated with histone deacetylation inphencyclidine-treated mice

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Objective: Enriched environments (EEs) during development have been shown to influence adult behaviour. Environmental conditions during childhood may contribute to the onset and/or pathology of schizophrenia; however, it remains unclear whether EE might prevent the development of schizophrenia. Herein, we investigated the effects of EE during adolescence on phencyclidine (PCP)-induced abnormal behaviour, a proposed schizophrenic endophenotype.

Methods: Male ICR mice (3 wk old) were exposed to an EE for 4 wk and then treated with PCP for 2 wk.To investigate whether the histone modification during adolescence might be critical for the effect of EE, 3-wk-old mice were first treated with sodium butyrate (SB; an HDAC inhibitor) for 4 wk and then treated with PCP for 2 wk.

Results: The EE potentiated the acute PCP treatment-induced hyperlocomotion in the locomotor test and prevented chronic PCP treatment-induced impairments of social behaviour and recognition memory in the social interaction and novel object recognition tests. It also prevented the PCP-induced decrease of acetylated Lys9 in histone H3-positive cells and increase of the histone deacetylase (HDAC)5 level in the prefrontal cortex. Chronic SB treatment during adolescence mimicked the effects of EE, including potentiation of hyperlocomotion induced by acute PCP treatment and prevention of social and cognitive impairments, decrease of acetylated Lys9 in histone H3-positive cells and increase of the HDAC5 level in the prefrontal cortex associated with chronic PCP treatment.

Conclusion: Our results suggest that EEs prevent PCP-induced abnormal behaviour associated with histone deacetylation. EEs during childhood might prove to be a novel strategy for prophylaxis against schizophrenia.

P-10-024 Ultrastructural study of the stressed-glutamatergic synapse

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Objective: Dysfunction of the glutamatergic system has been associated with the pathophysiology of many stress-related disorders. Nevertheless, the mechanisms whereby stress and glucocorticoids affect the glutamatergic system are still unknown. In a previous study acute Foot-shock (FS)-stress was found to induce a marked increase of glutamate release from prefrontal and frontal cortex synaptosomes, which was completely prevented by chronic antidepressant treatment [1]. The aim of the present study was to evaluate if FS-stress induced increase in glutamate release is correlated with an increase in the number of vesicles anchored to the presynaptic membrane and ready for release and to evaluate if chronic antidepressant treatment modulates the effects of FS-stress on docked vesicles.

Methods: Medial prefrontal cortex (mPFC) was isolated based on its noticeable cytoarchitectural features. Asymmetric glutamatergic synapses were identified through electron microscopy and vesicles docked to the presynaptic membrane quantified.

Results: Overall vesicle redistribution after FS-stress and chronic antidepressant treatment was evaluated. Volumetric modifications within mPFC subareas were also investigated.

Conclusion: A better understanding of how behavioral stress and current antidepressants affect glutamatergic transmission will provide further knowledge in developing drugs directly targeting the glutamatergic system.

P-10-025 Synergistic or independent relationships of MAO B platelet avctivity, MAO B and COMT polymorphisms to impulsivity, aggression and novelty seeking?

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Objective: Low platelet MAO B activity and the COMT polymorphism genotype MetMet would result in higher DA levels and have been shown to be associated with Impulsivity, Novelty Seeking, Aggression and alcoholism. So far it is not clear, how the A/G intron 13 polymorphism of the MAO B gene relates to MAO B activity in platelets and personality traits, and if the three biomarkers act synergistically or independently on personality traits. This was investigated in the present study.

Methods: 60 male abstinent alcoholics participated in a reaction time task, filled in personality questionnaires and gave blood samples for genetic analyses and MAO B activity in platelets.

Results: Although platelet MAO B activity and MAO B genotype were not associated, interactions revealed that participants with low MAO B activity among G allele carriers scored highest on Aggression, A allele carriers in combination with the COMT ValVal genotype highest on Attentional Impulsivity, and A allele carriers in the MetMet group highest on Experience Seeking. Motor Impulsivity was only related to high MAO B activity, not to genetics, and faster reaction times were only observed in G allele carriers.

Conclusion: These results are compatible with the findings by Balciuniene et al. (2002) that the G allele indicates lower MAO B activity in brain than A, yielding higher DA levels and therefore perhaps higher speed and aggression which adds to the low MAO B activity in platelets. Data also suggest that low DA resulting from the ValVal genotype acts synergistically with the A allele in producing attention deficits. So the three biomarkers evidently differentially affect impulsivity, aggression, attention deficits and novelty seeking: The MAO B intron 13 A/G polymorphism is only one of several genetic polymorphisms for MAO B activity, but does indicate relevance as a behavioral marker.

P-10-026 Antibody-capture scintillation proximity assay/ [35S]GTPγS binding to Gaq functionally coupled with M1 acetylcholine receptors and 5-HT2A receptors in rat brain membranes

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Objective: To investigate receptor-mediated functional activation of heterotrimeric G proteins other than Gi/o subtypes.

Methods: Immuno-capture of Gα subunits with anti-Gα antibodies following [35S]GTPγS binding to rat brain membranes was combined with scintillation proximity assay (SPA) technology.

Results: Preliminary experiments using a series of agonists and commercially available anti-Gα antibodies indicated the increase in specific [35S]GTPγS binding to Gαq determined with anti-Gαq (E-17) (sc-393, Santa Cruz Biotechnology) evoked by carbamylcholine chloride (CCh) was pharmacologically relevant. Under the optimized conditions, CCh stimulated specific [35S]GTPγS binding to Gαq in a concentration-dependent and saturable manner with an EC50 of around 10 μM in all of the membranes prepared from rat hippocampus, cerebral cortex, and striatum. The addition of MT-7, a snake toxin with high selectivity for M1 over the other muscarinic acetylcholine receptors (mAChRs) (M2-M5), almost completely extinguished CCh-stimulated [35S]GTPγS binding to Gαq, even at a concentration as low as 1 nM, indicative of the exclusive involvement of M1 receptors in this response. The detailed pharmacological characterization was further investigated by means of a series of muscarinic agonists, antagonists, and allosteric modulators in hippocampal and cerebral cortical membranes. Under the same condition, 5-HT also stimulated specific [35S]GTPγS binding to Gαq in cortical membranes in a concentration-dependent manner. However, the stimulatory effects of 5-HT were not saturable and apparently biphasic. The inhibitory effects of ketanserin indicated that 5-HT2A receptor-mediated activation of Gαq might be detectable when lower concentrations (up to 10 μM) of 5-HT were used.

Conclusion: Both receptors are implicated in pathophysiology of several neuropsychiatric disorders as well as mechanisms of action of psychotropic drugs. The assay developed in the present study will be of help for the investigations in the field of biological psychiatry as well as drug discovery.

P-10-027 Changes in vascular endothelial growth factor (VEGF) induced by the morris water maze task

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Objective: The present study was undertaken to evaluate the effects on hippocampal vascular endothelial growth factor (VEGF) levels in rats when they experience hippocampal-dependent spatial learning via the Morris water maze (MWM) task.

Methods: After one day of intensive training, a highly sensitive enzyme-linked immunosorbent assay (ELISA) was used to measure VEGF protein levels in the hippocampus, cortex, and serum.

Results: Higher levels of VEGF were found in the trained group compared to a naive control group. VEGF levels also increased in rats that swam only for durations equal to the intensive training periods. In contrast, rats trained under the weaker MWM paradigm for five days showed a decrease in hippocampal VEGF protein level. Mimicking increases in neuronal VEGF in the hippocampus by direct infusion of VEGF into CA1 resulted in up-regulation of the phosphorylation of the cAMP response element-binding (CREB) protein and the Ca2+/calmodulin-dependent protein kinases II (CaMKII).

Conclusion: These results suggest that VEGF may be a physiological parameter involved in learning procedures that include physical activity.

P-10-028 Comparison of neurite outgrowth induced by erythropoietin (EPO) and carbamylated erythropoietin (CEPO) in cultured hippocampal neural progenitor cells

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Objective: A previous animal study has shown the effects of EPO and its non-erythropoietic carbamylated derivative (CEPO) on neurogenesis in the dentate gyrus. In the present study, we sought to investigate the effect of EPO on adult hippocampal neurogenesis, and to compare the ability of EPO and CEPO promoting dendrite elongation in cultured hippocampal neural progenitor cells.

Methods: Two-month-old male BALB/c mice were given daily injections of EPO (5 U/g) for seven days and were sacrificed 12 hours after the final injection. Proliferation assays demonstrated that EPO treatment increased the density of bromodeoxyuridine (BrdU)-labeled cells in the subgranular zone (SGZ) compared to that in vehicle-treated controls ($p < 0.05$).

Results: Functional differentiation studies using dissociated hippocampal cultures revealed that EPO treatment also increased the number of double-labeled BrdU/MAP2 (microtubule-associated protein 2) neurons compared to those in vehicle-treated controls ($p < 0.05$). Both EPO and CEPO treatment significantly increased the length of neurites extending from MAP2(+) cell soma, with CEPO ($p < 0.01$) having a better effect than EPO ($p < 0.05$).

Conclusion: In summary, these results provide strong evidences that EPO and CEPO promote adult hippocampal neurogenesis. We speculate that EPO and CEPO could be a good candidate for treating neuropsychiatric disorders such as depression and anxiety associated with reduced hippocampal neurogenesis.

P-10-029 Tianeptine treatment reverses increase on oxidative damage and decrease of antioxidant defense enzymes into the brain of rats submitted to the chronic mild stress model

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Objective: A growing body of evidence has suggested that reactive oxygen species may play an important role in the pathophysiology and treatment of depression. The present study was aimed to evaluate the effects of tianeptine (an antidepressant, which enhances the reuptake of serotonin) administration on the oxidative stress parameters in the brain of rats exposed to chronic mild stress (CMS) procedure.

Methods: To this aim, after 40 days of exposure to CMS Wistar rats were treated with tianeptine (15 mg/kg) or saline for 7 days. Then, the lipid and protein oxidation, and superoxide dismutase (SOD) and catalase (CAT) activities were evaluated in the rat brain.

Results: Our findings demonstrated that lipid oxidation was increased in stressed rats, and tianeptine reversed this effect in the prefrontal cortex and amygdala. In stressed rats there were an increase on the protein oxidation in the hippocampus and amygdala, but this effect was reversed only in the amygdala by tianeptine; in the nucleus accumbens there was a reduced on the protein oxidation in stressed rats treated with tianeptine, compared to stress group treated with saline. The SOD activity was reduced in all brain areas from stressed rats treated with saline, but treatment with tianeptine reversed these effects. The CAT activity decreased in stressed rats in the prefrontal cortex and amygdala, and treatment with tianeptine reversed these effects; in the hippocampus and nucleus accumbens there were an increase in the CAT activity in stressed rats treated with tianeptine, compared to control and stress group treated with saline.

Conclusion: Our data indicate that stress produces oxidants and impairment in the SOD and CAT activities, which could contributes to depression. In addition, tianeptine antidepressant exerted positive effects on the oxidative stress parameters, decreasing lipid and protein oxidation and increasing SOD and CAT activities in rats submitted to CMS.

P-10-030 The dopamine stabilizers ACR16 and (−)-OSU6162 display nanomolar affinities at the σ-1 receptor

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Objective: Converging in vivo evidence has advanced the σ-1 receptor as a pharmacological target for the treatment of neurological and psychiatric disorders such as L-DOPA-induced dyskinesia, schizophrenia, drug addiction, and depression. Considering their close structural resemblance to known σ-1 receptor ligands we investigated the ability of dopaminergic stabilizers, a new class of phenylpiperidine compounds, to bind σ-1 receptors.

Methods: σ-1 receptor ligand binding characteristics were determined by both saturation and competition assays using the specific σ-1 receptor agonist [3H](+)-pentazocine. Radioligand binding experiments were performed in membranes prepared from HEK293 cells that were transiently transfected with the human σ-1 receptor and in rat striatal membranes.

Results: Our results reveal that the dopaminergic stabilizers, (−)-OSU6162 and ACR16, display nanomolar affinity for the human σ-1 receptor heterologously expressed in HEK293 cells, as well as in rat striatal membranes. The affinity of ACR16 appears to be indistinguishable from that of the structurally related compound (+)-3-PPP; a ligand which has been widely used to study σ-1 receptors.

Conclusion: Dopaminergic stabilizers are a novel class of drug candidates that have shown clinical promise in the treatment of several severe neurological and neuropsychiatric disorders. While their exact mechanism of action is still under investigation, our data point to a previously overlooked aspect of their pharmacology. The present findings warrant further exploration of the relevance of σ-1 receptor binding for the in vivo actions of dopaminergic stabilizers.

P-10-031 Analysis of neuroadaptive changes following co-treatment of lurasidone and valproic acid in rats

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Objective: Combinatory therapy is widely used in psychiatry owing to the possibility that drugs with different mechanisms of action may synergize in order to improve specific functions, which are deteriorated in schizophrenia, bipolar disorders and major depression. While synaptic mechanisms may contribute to drug combination strategies, it should also be considered that, on the long-term, two drugs may 'cooperate' in modulating neuronal plasticity, which represents a downstream target crucial for functional recovery.

Methods: On this basis, in the present study we have investigated neuroadaptive changes set in motion upon chronic concomitant administration of the novel antipsychotic lurasidone (LUR) with the mood stabilizer valproate (VPA). The two agents were given to rats for 21 days and the animals were sacrificed 24 h after the last drug administration for the molecular analyses. We investigated the expression of the neurotrophin BDNF that represents a key marker of neuronal plasticity and cellular resiliency.

Results: The results emerging from these analyses suggest that co-administration of LUR and VPA produces a larger increase of BDNF expression in ventral hippocampus, through the regulation of specific neurotrophin transcripts, compared to each drug alone. We also found that the expression of HDAC-2 and DNMT1, two genes involved in the epigenetic machinery, were also significantly regulated by the combination LUR+VPA, suggesting that some of the transcriptional changes may be sustained by epigenetic mechanisms. Other genes important for neuronal adaptation, such Arc (Activity-regulated cytoskeletal associated protein), are significantly regulated by chronic treatment with LUR and VPA, although their combination does not provide any advantage over the drugs employed alone.

Conclusion: Our results suggest that the beneficial effects associated with combinatory treatment between a second-generation antipsychotic and a mood stabilizer could result from the ability to modulate neuroplastic molecules such as BDNF, whose expression and function is deteriorated in different psychiatric conditions.

Policy of full disclosure: This work was supported by funding from Sunovion Pharmaceuticals Inc.

P-10-032 Chronic lurasidone treatment restores functional and neuroplastic deficits in serotonin transporter knockout rats, an animal model of depression

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Objective: Lurasidone is a novel antipsychotic drug characterized by a multi-receptor signature. Some of these receptor mechanisms have been associated with antidepressant activity, including blockade of 5HT2a, 5HT7 as well as activation of 5HT1a. Furthermore, we have recently shown that chronic administration of lurasidone can increase the expression of BDNF, a marker of neuronal plasticity that has been associated with clinical antidepressant properties.

Methods: In the present work we specifically addressed the potential antidepressant activity of lurasidone by employing a genetic model of the disease, namely serotonin transporter knockout (SERT KO) rats, which are characterized by an anxious and depressive phenotype. To this purpose we chronically administered lurasidone to wild type or SERT KO rats and investigated behavioral and molecular changes produce by the drug.

Results: At behavioral level, we found that, chronic lurasidone treatment significantly increased fear extinction in SERT KO rats ($p < 0.01$), without affecting wild-type animals. At molecular level, lurasidone was able to normalize the reduced expression of the neurotrophin BDNF in the prefrontal cortex SERT KO rats. Such effect occurred through the regulation of specific neurotrophin transcripts, primarily of exon VI, and it was sustained by epigenetic mechanisms as demonstrated by the significant up-regulation of the DNA demethylating gene Gadd45γ. We also found that, when given to SERT KO rats, chronic lurasidone treatment was able to restore the reduced

expression of different GABAergic markers, including GAD67, parvalbumin and somatostatin.

Conclusion: Our results show that lurasidone can improve depression-related dysfunction of SERT KO rats, with a primary impact on prefrontal cortex, also through the modulation of the neurotrophin BDNF. The adaptive changes set in motion by repeated treatment with lurasidone may contribute to the amelioration of functional capacities, closely associated with neuronal plasticity, which are deteriorated in patients with schizophrenia, bipolar disease and major depression.

Policy of full disclosure: This work was supported by funding from Sunovion Pharmaceuticals Inc.

P-10-033 Antagonist dissociation from dopamine D2 receptors – dopamine stabilizers unbind faster than clozapine and quetiapine

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Objective: Medication with dopamine D2 antagonists is often associated with extrapyramidal symptoms and increased serum prolactin. The side-effect liability of antipsychotics correlates inversely with their rates of receptor dissociation. Recent studies indicate that the novel D2 receptor ligands, ACR16 (pridopidine) and (−)-OSU6162, initially described as ''dopamine stabilizers,'' act as antagonists with similarly high dissociation rates as clozapine and quetiapine. Those studies measured ligand dissociation from membrane preparations or used modified G proteins in functional assays. We aimed to examine antagonist dissociation in living cells, using an assay based on activation of G protein-coupled potassium (GIRK) channels. This assay uses native G proteins and has higher temporal resolution than previous studies.

Methods: GIRK current responses to dopamine receptor activation were recorded using two-electrode voltage clamp in Xenopus oocytes expressing dopamine D2L or D2S receptors, Regulator of G protein Signaling-4, and GIRK1/4 channels. First, dopamine (100 nM) was applied, eliciting a ''baseline'' response. Next, a maximally effective concentration of antagonist was washed in. After achieving steady-state inhibition the antagonist was washed out, still in the presence of dopamine. The time to half-maximal response recovery (T1/2) and the response recovery amplitude relative to baseline were taken as measures of antagonist dissociation.

Results: With clozapine and quetiapine, similar recovery time courses were observed ($T1/2 = 48 \pm 5.5$ s, and 60 ± 2.2 s, respectively). About 50% response recovery was observed. The dopamine stabilizers, ACR16 and (−)-OSU6162, lacked detectable efficacy in our assay. These compounds washed out faster than clozapine and quetiapine ($T1/2 = 8.2 \pm 1.8$ s, and 6.1 ± 0.44 s, respectively); and near-complete response recovery was observed.

Conclusion: The present data suggest that the ''dopamine stabilizers'' ACR16 and (−)-OSU6162 dissociate faster than clozapine and quetiapine. Such very rapid dissociation might be relevant to the low incidence of side-effects reported from clinical trials with these compounds.

P-10-034 Matrixmetalloproteinase-9 in schizophrenia and depression – is this the link within the hierarchical disease model?

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Objective: Recently it has been reported that the protein expression of the matrixmetalloproteinase-9 (MMP9), an extracellular protease, is similarly increased in patients suffering from schizophrenia and depression. Given the long discussed hypothesis that schizophrenia and affective disorder follow a hierarchical disease model and might have overlapping pathophysiological dysfunction processes MMP9 might mirror a biological link between schizophrenia and affective disorder.

Methods: Therefore, within this pilot study the blood concentration of MMP9 and its inhibitor TIMP1 (Tissue Inhibitors of Metalloproteinases) was examined in 37 patients with a DSM-IV diagnosis of a schizophrenia spectrum disorder, 78 patients with a DSM.-IV diagnosis of a major depression and 38 healthy controls. The Positive and Negative Syndrome Scale (PANSS) as well as the Hamilton Depression Rating Scale (HAMD-17) were applied Blood draws and clinical interviews were performed at baseline and every two weeks within the six weeks study period. ANOVA and univariate tests were calculated using the statistical program 2.11.1.

Results: The MMP9 concentration differed significantly between the patients and healthy controls (schizophrenia 143 ± 101 ng/ml, depression 135 ± 141 ng/ml, healthy controls 54 ± 48 ng/ml; ANOVA $F = 7.06$, $p = 0.001$). A significant positive correlation was found between illness severity of the depressed patients via the HAMD and the MMP9 concentration both at study entry (Pearson 0.234; $p = 0.040$) and also at endpoint (Pearson 0.302; $p = 0.0012$). Also, in the schizophrenia patients a significant positive association was found in terms of the severity of depressive symptoms measured via the depression item (Pearson 0.50; $p = 0.0111$) and the PANSS depression subscore (Pearson 0.44; $p = 0.0289$) at baseline.

Conclusion: These are the first preliminary results of MMP9 in the blood of patients with schizophrenia and depression. This suggests that both diseases might share more biological underpinnings than thought before. Future studies are warranted to replicate these first results.

P-10-035 High-throughput screening for allosteric modulators of the D2 dopamine receptor

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Objective: The D2 dopamine receptor (DAR) is central in the etiology and/or therapy of many neuropsychiatric disorders, however, truly specific drugs for this receptor have been difficult to obtain. A novel approach towards receptor-selective ligands is to identify allosteric modulators that bind to less conserved sites on the receptor and have the potential to be exquisitely selective. In order to identify allosteric modulators of the D2 DAR, we developed a high throughput-screening (HTS) platform to interrogate large chemical compound libraries.

Methods: The primary HTS assay utilizes a cell line expressing the D2 DAR coupled to a chimeric Gqi5 protein, thereby linking receptor activation to robust $Ca2+$ mobilization. Counter-screens against other DAR subtypes and radioligand binding studies were also carried out.

Results: Through the NIH Molecular Libraries Program, a 370,000+ small molecule library was screened to identify agonists (allosteric or orthosteric), positive allosteric modulators, or antagonists (allosteric or orthosteric). From this primary screen, 2,288 compounds with agonist activity, 1,408 compounds with potentiator activity, and 2,294 compounds with antagonist activity were cherry-picked. Upon further evaluation, none of the potentiators confirmed while 650 agonists and 858 antagonists did not confirm. The remaining confirmed agonist and antagonist ligands were subjected to orthogonal and counter-screening functional assays. On the basis of these analyses, 745 agonist and 499 antagonist compounds were evaluated using radioligand competition binding assays as a filter to separate orthosteric and allosteric ligands. These experiments resulted in the identification of 47 agonists and 48 antagonists that had insignificant effects on radioligand binding. These compounds would thus appear to be allosteric agonists and negative allosteric modulators of the D2 DAR.

Conclusion: We have conducted a high through-put screen of the NIH Molecular Libraries Program small molecule repository. Numerous lead compounds with agonist or antagonist activities were identified that appear to exert their functional effects via allosteric mechanisms. The most promising of these ligands are undergoing further characterization.

P-10-036 Compromising sigma-1 receptors at the ER renders cytotoxicity to physiologically relevant concentrations of dopamine in a NF-kB/Bcl-2-dependent mechanism: Potential relevance to Parkinson's disease

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Objective: To examine if the endoplasmic reticulum (ER) chaperone the sigma-1 receptor (Sig-1R) may play a role in Parkinsonism.

Methods: Dopamine (DA)-induced apoptosis was examined in wild type CHO cells and in Sig-1R knockout CHO cells.

Results: DA in physiological concentrations (e.g., lower than 10 μM) does not cause apoptosis. However, the same concentrations of DA cause apoptosis in Sig-1R knockdown CHO cells. In search for a mechanistic explanation, we found that unfolded protein response is not involved. Rather, the level of protective protein Bcl-2 is critically involved in this DA/Sig-1R knockdown-induced apoptosis. Specifically, the DA/Sig-1R knockdown causes a synergistic proteasomal conversion of NF-kB p105 to the active form of p50 which is known to downregulate the transcription of Bcl-2. Importantly, the DA/Sig-1R knockdown-induced apoptosis is blocked by the overexpression of Bcl-2.

Conclusion: Our results therefore indicate that DA is involved in the activation of NF-kB and suggest that endogenous Sig-1Rs are tonically inhibiting the proteasomal conversion/activation of NF-kB caused by physiologically relevant concentrations of DA which would otherwise cause apoptosis. Thus, Sig-1Rs and associated ligands may represent new therapeutic targets for the treatment of Parkinsonism.

P-10-037 Effects of a single and repeated lectroconvulsive seizure on hippocampal cell proliferation and spontaneous behaviors in the rat

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Objective: Electroconvulsive therapy (ECT) is known as a successful treatment for sever depression. However, the biological mechanism underlying the beneficial effects of ECT remains largely unknown. Thus, we investigated effects of electroconvulsive seizure (ECS) on hippocampal cell proliferation and behaviors in rats.

Methods: In this study, animals received a single or 10 repeated applications of ECS, and then cell proliferation and differentiation of new born cells (5-bromo-2-deoxyuridine (BrdU)-positive cells) in subgranular zone (SGZ) of the dentate gyrus were investigated. In addition, we investigated the effect of ECS on behavioral changes of animals by using a locomotor activity and spontaneous alteration behavior in a Y-maze test on 3, 14 and 28 days after ECS treatments.

Results: On three days after ECS, both a single and 10 repeated ECSs significantly increased BrdU-positive cells in the SGZ by +84% and +130% compared to each sham treatment, respectively. 10 On 14 days after the last ECS, both a single and 10 repeated ECSs showed significant decreases in cell proliferation by −52% and −62%, respectively compared to sham treatment. On the other hand, the locomotor activity and scores of spontatneous behavior of a Y-maze test did not show significant changes between the group with a single or 10 repeated ECSs and sham group on neither 3, 14 nor 28 days, regardless of increase or decrease in cell proliferation or differentiation of new born cells in SGZ after ECS.

Conclusion: These findings indicate that although ECT affects adult hippocampal neurogenesis, no obvious changes are observed in certain behavioral tests. We need further investigation of how adult hippocampal neurogenasis may involve in animal behavior after ECS treatments.

P-10-038 Effect of N-acetylcysteine on L-buthionine-SR-sulfoximine-induced reduction of cell viability in a-synuclein-transfected SH-SY5Y cells

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Objective: It is well known that α-synuclein (α-syn) plays an important role in the pathogenesis of Parkinson's disease (PD). Moreover, oxidative stress is also thought to be an important factor in PD due to dopaminergic neuronal cell death by free radicals and enhancement of α-syn fibrillation by oxidized stress.

Methods: In the present study, we examined the effects of L-buthionine-SR-sulfoximine (BSO), a GSH synthase inhibitor, with or without N-acetylcysteine (NAC), a source of GSH, on α-syn-induced cell injury in human neuroblastoma SH-SY5Y cells, to clarify the role of GSH, an intracellular antioxidant, on the molecular mechanism of α-syn-induced cell injury.

Results: Treatment with BSO significantly reduced cell viability of both empty-vector- and α-syn-transfected SH-SY5Y cells in a dose-dependent manner, although the ratio of α-syn-induced reduction of cell viability in α-syn-transfected cells was much greater than that in empty-vector-transfected cells. Moreover, BSO significantly reduced the intracellular total GSH level in both types of transformant cells. However, NAC significantly prevented BSO-induced reduction of both cell viability and GSH level in the α-syn-transfected cells.

Conclusion: Thus, these findings suggest that GSH plays an important role in α-syn-induced cell injury by reducing cell viability, although further study is needed to clarify the molecular basis of α-syn-induced cell injury.

P-10-039 The Sigma-1 receptor chaperone plays an essential role in neural circuits

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Objective: The endoplasmic reticular protein sigma-1 receptor (Sig-1R) is a novel chaperone and has been implicated in CNS diseases such as Alzheimer's disease, depression, and drug abuse. It is known that Sig-1Rs are particularly enriched in the mitochondrial associate ER membrane, MAM; however, little is known about how Sig-1R regulate neuronal mitochondria. We previously showed that Sig-1R promote the process of neuritogenesis and dendritogenesis in hippocampal neurons via the regulation of Rho GTP signaling pathways. In this study, we further examined the effects of Sig-1R siRNA on axon elongation and synaptic mitochondrial activities.

Methods: Neurons were transfected at DIV 1 and axon lengths were measured on both DIV 3 and DIV 7 by using tau immunostaining. We also examined synaptosomal mitochondrial mass and membrane potentials by using flow cytometry analysis. Rhodamine 123 and 10-N-nonyl acridine orange (NAO) were used as membrane potential- or mass- dependent fluorescent dyes, respectively.

Results: Knocking down of Sig-1Rs impaired axon elongation significantly. The lengths of axon of the Sig-1R-knockdown neurons were as short as 40% of the controls at DIV 3. The difference in axon lengths became more noteworthy as neuron culture extended. Although Sig-1R siRNA-transfected neurons were able to extend axon gradually in time, they showed a slower extension rate. Knocking down of Sig-1R caused aberrant axon extension was also associated with hyperphosphoylation of tau as indicated by MC1 antibody that recognized an early conformational change in tau. Our data showed that Sig-1R siRNA transduced neurons possessed significantly less mitochondrial mass and lower membrane potentials in the synaptosome. Mitochondrial movement in the growth cone areas was less active in Sig-1R siRNA neurons as well.

Conclusion: The observed changes in axon extension and synaptic mitochondrial activities in Sig-1R knockdown neurons indicted the importance of Sig-1R in maintaining synaptic functions and their significance in averting CNS diseases.

P-10-040 GABAergic regulation of extracellular D-serine concentrations in the rat medial frontal cortex of the rat as revealed by in vivo microdialysis

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Objective: It has now been well accepted that D-serine may be an intrinsic coagonist for the N-methyl-D-aspartate (NMDA) type glutamate receptor in the mammalian brain. Thus, D-serine facilitates various functions of the NMDA receptor by stereospecifically stimulating its glycine site and is present in the tissue and extracellular fluid at high contents throughout life with a GRIN2B subunit-like distribution. Moreover, selective elimination of D-serine by D-amino acid oxidase or D-serine deaminase has been shown to reduce the NMDA receptor functioning such as cGMP production and long-term potentiation formation in the rat brain. Although these findings suggest that the synaptic and/or extra-synaptic D-serine may play an crucial role in the regulation of the NMDA receptors, the molecular and cellular mechanisms of the physiological control of the extracellular D-serine concentrations are still unclear.

Methods: Therefore, we have investigated by using an in vivo microdialysis technique and a HPLC with fluorometric detection method the effects of GABAergic agents on the extracellular contents of D-serine in the medial frontal cortex of the freely moving rats. The present animal experiments have been approved by the ethics committees of the Tokyo Medical and Dental University.

Results: We found that the local perfusion of a selective GABAA receptor antagonist, bicuculline or picrotoxinin into the medial frontal cortex lowered significantly the cortical extracellular contents of D-serine. The decreasing effects of bicuculline was completely reversed by the local co-infusion of a selective GABAA receptor agonist muscimol. Neither GABAB nor GABAC selective antagonist failed to change the extracellular D-serine levels.

Conclusion: The present data are consistent with the seem the view that the extracellular D-serine release may be under a tonic facilitatory control by GABAergic transmission via the GABAA receptor at least in the rat medial frontal cortex.

P-10-041 Intravenous hemantane improves levodopa-induced dyskinesias in in 6-hydroxydopamine-lesioned rats

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Objective: Levodopa-induced dyskinesia (LID) becomes an extremely common and debilitating problem. An overactive glutamate transmission in the basal ganglia has been suggested to play a key role in the pathophysiology of Parkinson's disease (PD) and LID. NMDA receptor antagonist amantadine (AMA) is widely used to improve levodopa induced motor complications. Hemantane (H.) (N-2(adamantyl)hexamethylenimine hydrochloride) is effective in animal models and in patients with early stages of PD. H. has complex mechanism of action, including properties of uncompetitive, low-affinity NMDA receptor open-channel blocker. The aim of the study was to assess the effects of H. in parkinsonian rats with LID.

Methods: To induce parkinsonian syndrome 6-OHDA (12 μg) was injected into the left medial forebrain bundle (MFB). Levodopa (10 mg/kg) with benserazide (15 mg/kg) was administered starting 3 weeks after lesion daily during next 4 weeks. The dyskinetic effects of levodopa were evaluated using a validated rat AIMs scale, where axial, limb, orolingual and rotation AIMs represent the rodent equivalent of peak-dose dyskinesia in PD. Rats with LID were selected and divided in 2 groups. For 5 following days levodopa administration was preceded by injection of H. (5 mg/kg, i.v.) or AMA (20 mg/kg, i.v.). AIMs were registered 35 min after evodopa administration 4 times during 140 min.

Results: Co-administration of levodopa with H. or AMA resulted in significantly less dyskinesia than levodopa alone. Effects of acute injection of H. were less pronounced than of AMA. After 5 days treatment H. was more effective in reducing orolingual and rotation LID.

Conclusion: Hemantane could be used as adjunctive therapy for levodopa-induced dyskinesia.

P-10-042 Pre-analysis storage conditions influence measured peripheral blood BDNF levels

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Objective: Brain-derived neurotrophic factor (BDNF) is a neurotrophin with a pivotal role in the regulation of neuronal function throughout life and is regarded as a potential biomarker of mental disorders. Previous studies suggest that plasma BDNF levels are more variable than serum BDNF levels.

Methods: We determined the influence of time and temperature on the measured peripheral blood BDNF levels. Blood samples were aliquoted into 4 types of tubes: heparin, EDTA and citrate tubes for plasma and anticoagulant-free tubes for serum. The samples were stored at 4 °C or 25 °C for 0, 1, 2, 4, 6, 24 or 48 hours.

Results: The plasma and serum BDNF levels were measured by ELISA. The measured plasma BDNF levels increased over time, whereas the serum BDNF levels were unchanged. The BDNF levels detected in heparin-plasma and EDTA-plasma samples stored at 4 °C were much higher than those in samples stored at 25 °C.

Conclusion: This study indicates that the measured plasma BDNF levels are dependent on the time and the temperature of storage after blood sampling.

P-11. Dementia

P-11-001 Psychopathology in alzheime's disease

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Objective: In this review we analyze the psychopathological variants found in this stereotype of patient and diagnostic difficulties.

Methods: It carries out a review about the data currently available on this topic.

Results: Semiology psychic: depressive syndrome (20 to 40%), psychotic symptoms (30 to 50%) are not correlated with the severity of dementia, aggression and psychomotor agitation (20%)and sleep disturbance (40 to 70%). They also appear frequently delirium, progressive deterioration in recent memory, disinhibited or socially inappropriate behavior, personality changes and emotional lability. Somatic semiology: Table afas-apraxic-agnostic. It should also be noted that the prognosis may overshadow the association with extrapyramidal signs, psychotic disorders and myoclonus.

Conclusion: We note that Alzheimer's disease and psychopathology are correlated. It hath in mind the existing diagnostic difivulatdes have to go deeper into these issues.

P-11-002 Depressive disorders and medical conditions among patients with alzheimer's disease: A case-control study of a national managed care database

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Objective: To compare the prevalence of depression and comorbid medical conditions between patients with a diagnosis of Alzheimer's Disease (AD) (cases) in comparison with a matched control group of patients without AD, in the National Managed Care Benchmark Database (IHCIS).

Methods: The prevalence of depression and comorbid medical conditions was compared between patients with AD (defined by ICD-9 codes) and controls using data from the IHCIS, a fully de-identified, HIPAA compliant database made up of more than 35 Managed Care health plans within the US and covering seven census regions. Matched case-control method was used to compare depression and medical comorbidity. Controls were matched to cases by type of health plan and pharmacy benefit on a 3:1 ratio.

Results: Among the 488,091 patients with full year of eligibility during 2001, 2,947 were identified with a diagnosis of AD and 63.6% were women. The prevalence of depressive disorders was much higher in the AD group compared to a random selection of matched non AD patients 12,880 (32.48% vs. 3.45%, $p < 0.001$). AD patients had

more comorbid medical conditions than patients without dementia. In general, AD patients had more convulsions [odds ratio (OR) = 6.16, 95% CI = 3.3–11.5]; hypotension (OR = 2.90, 95% CI = 2.0–4.2); anemia (OR = 2.31, 95% CI = 1.4–3.8); heart failure (OR = 2.21, 95% CI = 2.0–2.5); urinary system disorders (OR = 1.73, 95% CI = 1.4–2.7); COPD (OR = 1.53, 95% CI = 1.2–1.8); gastrointestinal hemorraghe (OR = 1.46, 95% CI = 1.2–1.9); and circulatory disease (OR = 1.39, 95% CI = 1.0–1.9); compared with the controls.

Conclusion: The present study confirms that depressive disorders and medical comorbidities are complications of AD and physicians should be alert to the presence of this clinically important diseases in patients wit AD.

Policy of full disclosure: Dr. Castilla-Puentes is currently working as Global Medical Safety Physician with Johnson & Johnson, Pharmaceutical Research and Development.

P-11-003 Comparison of cognition measured by MMSE between alzheimer's disease and depression

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Objective: The Mini-Mental State Examination (MMSE) is the most widely used screening measure for cognitive impairment. The aims of this study are to compare the psychometric properties of the Mini-Mental State Examination – Korean Version (MMSE-KC) between Alzheimer's disease and depression and to detect differential item function (DIF).

Methods: Data were analyzed from a nationwide sample of Korean elders, a total of 485 participants age 65 or older from cross-sectional community-based study. All participants were assessed using Mini-Mental State Examination by door-to-door home visit. Diagnostic assessments of depression and dementia were administered using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) Clinical Assessment Battery.

Results: All items of MMSE-KC fit the model and together spanned a range of threshold parameter (difficulty) from −3.86 (easier) to 1.15 (more difficult) logits, and slope parameter (discrimination) from 0.55 to 8.6 logits. Depression group were more likely to have errors like items about 'recall of three words' and 'attention' were the most difficult items. In contrast, dementia group had errors in most of items. Detecting DIF using IRTLRDIF, people with dementia showed DIF such items as orientation to place, the last two items of 'recall of three words (car and cap)', and The last two items of' attention', 'three stage command'. People with depression showed DIF such items as 'time orientation (week)', 'repetition', 'recall of three words (car)'.

Conclusion: The MMSE-KC can provide a reliable and valid quantitative estimate of cognitive ability. However, some items have DIF in case of people with depression or dementia.. Therefore, more attention should be paid to items showing DIF.

P-11-004 The outcome of mild cognitive impairment after administering treatment

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Objective: Mild cognitive impairment(MCI) is a frequent clinical entity, considered today to be a prodromal stage of Alzheimer's dementia. The aim of this study is to determine the outcome of the patients diagnosed with MCI treated with different therapies and the patients diagnosed with MCI and non-treated.

Methods: The study comprises a number of 157 patients (over 60 years) diagnosed with MCI. The patients were evaluated with MMSE (Mini Mental State Evaluation) at the inclusion into the study, after 6 months, after 1year and after 2years. The patients were divided in: group A −43 patients with MCI treated with Galantamine (16 mg/day) group B −44 patients with MCI treated with Rhodiola-rosea, 2capsules/day group C −41 patients with MCI treated with Vitamin E, 800UI/day group D −29 patients with MCI, which did not received treatment.

Results: The average of MMSE scores at the inclusion into the study was 23.62 points for group A, 24.36 for group B, 24,82 for group C and 25.0 for group D. After 1year, cognitive performance improves with 2.07 points for group A, with 2,04 for group B, 2,69 in group C; in group D we did not observed any improvement. After 2 years of treatment cognitive performance improves with 3,14 points for group A, 2,48 points for group B, 2,25 points for group C and in group D we have observed an impairment of cognitive performance with 2,49 points.

Conclusion: Comparing the outcome of patients long time treatment show a better improvement in group treated with cholinesterase inhibitor (galantamine). The study prove the importance of early treatment of MCI to improve the cognitive function and to delay the progression to dementia.

P-11-005 Clozapine as mono-therapy in the management of huntington's chorea

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Objective: Huntington's Chorea, an autosomal dominant neurodegenerative disorder comprising movement disorder, cognitive deficits and distressing psychiatric symptoms, often poses a significant therapeutic and management challenge to clinicians and caregivers alike. While a number of medication strategies, including amantadine, tetrabenazine (the first drug to receive specific US FDA approval for the managing the choreiform component of the disorder), clonazepam and antipsychotics like haloperidol and risperidone, have been tried, none seems to produce sustained symptomatic relief or significantly reduced care-giving burden. Psychotic symptoms, irritability, aggression, depression, apathy and suicidality are major contributors to the care-giver burden and, despite considerable research, often remain unaddressed or inadequately managed. Clozapine, with its demonstrated superior efficacy and extremely low risk of extra-pyramidal side-effects (EPS) and tardive dyskinasia (TD), would appear to be the ideal antipsychotic for the purpose and its usefulness in this regard is supported by findings from several studies. Unfortunately, however, it remains under-used in patients with Huntington' Chorea.

Methods: This naturalistic observational study describes an illustrative case. The patient, a 57 year old (European) male with the diagnosis of Huntington's Chorea and persisting paranoid delusions, aggressive/disruptive/violent behaviour, aggravated movement disorder despite multiple medications (including risperidone 6 mg/day) was referred for review as he had become unmanageable in the rest-home where he had been assigned to live. He was transitioned uneventfully to clozapine 100 mg/day, with amelioration of psychotic symptoms, as well as improvement in the movement disorder.

Results: Complete remission of psychotic symptoms, aggression, disruptive and violent behaviour, along with significant improvement in the movement component.

Conclusion: Clozapine monotherapy is an effective and safe therapeutic option in patients with Huntington' Chorea. Further research is required to generate robust evidence in this area.

P-11-006 Effects of intestinal endotoxemia (IETM) on learning memory ability and brain levels of Aβ, Tau protein in rats with alzheimer's disease

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Objective: To investigate the relationgship between intestinal endotoxemia (IETM) and learning memory ability, brain levels of β-amyloid protein (Aβ), Tau protein in rats with Alzheimer's disease (AD).

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), interleukin-1β(IL-1β) and Tau protein were determined by ELISA; the apoptotic neuron was detected by Flow cytometry; the expression levels of Aβwas tested by Immunohistochemical.

Results: Compared with the normal control group, the model group had longger latency ($P < 0.01$) and more error times ($P < 0.05$) in Morris water maze test; LPS, TNF-α, IL-1β and PD in AD rats were increased ($P < 0.05$); the expression levels of Aβand Tau protein in brain were increased ($P < 0.05$).

Conclusion: The rat model of Alzheimer's disease is accompanied IETM and that may plays an important role in the development of AD.

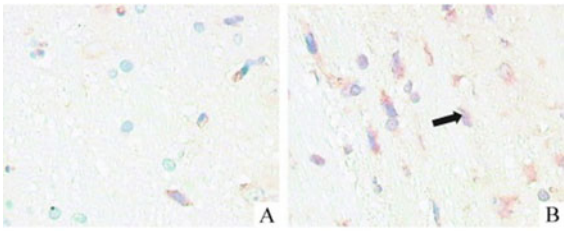

Figure4 The levels of $A\beta_{1-40}$ in rats brain

P-11-007 Effects of intestinal endotoxemia (IETM) on learning memory ability and cell apoptosis in rats with alzheimer's disease

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Objective: To investigate the relationship between intestinal endotoxemia (IETM) and learning memory ability, cell apoptosis in rats with Alzheimer's disease (AD).

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α) and interleukin-1β(IL-1β) were determined by ELISA; the apoptotic neuron was detected by TUNEL.

Results: Compared with the normal control group, the model group had longger latency ($P < 0.01$) and more error times ($P < 0.05$) in Morris water maze test; LPS, TNF-α, IL-1βand PD in AD rats were increased ($P < 0.05$).

Conclusion: The model of Alzheimer disease's rats which were established by D-galactose and AlCl3 is accompanied IETM and that may plays an important role in the cell apoptotic of AD. [Key words] Alzheimer's disease (AD); Intestinal endotoxemia (IETM); Lipopolysaccharide (LPS); Tumor necrosis factor-α (TNF-α); Interleukin-1β(IL-1β); Apoptotic.

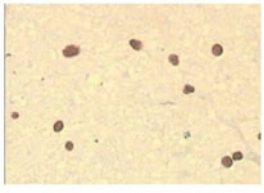

Figure3 Control group×400

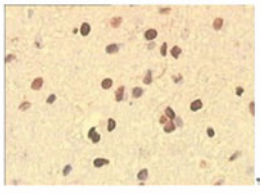

Figure4 Model group×400

P-11-008 Effects of intestinal endotoxemia (IETM) on learning memory ability and hippocampal gene expression of APP and PS1 in rats with alzheimer's disease

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Objective: Alzheimer's disease (AD) brains are characterized by accumulation of amyloid β protein (Aβ) and neuroin_ammation. Deposition of Aβ is the main component of the plaques, and the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition. To investigate the effect of intestinal endotoxemia (IETM) on learning and memory ability in rats with Alzheimer's disease (AD) and its possible mechanisms.

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS) and tumor necrosis factor-α (TNF-α) were determined by ELISA; the apoptotic neuron was detected by (TUNEL); hippocampal gene expression of amyloid precursor protein (APP) and presenilin1 (PS1) was tested by RT-PCR.

Results: Compared with the normal control group, the model group had longger latency ($P < 0.01$) and more error times ($P < 0.05$) in Morris water maze test; LPS, TNF-α and PD in AD rats were increased ($P < 0.05$); the expression of APP and PS1mRNA in hippocampus were increased ($P < 0.05$).

Conclusion: The rat model of Alzheimer's disease is accompanied IETM and that may plays an important role in the development of AD. [Key words] Alzheimer's disease (AD); Intestinal endotoxemia (IETM); Lipopolysaccharide (LPS); Tumor necrosis factor-α (TNF-α); Amyloid beta-protein precursor (APP); Presenilin1 (PS1).

P-11-009 The study on the level of intestinal endotoxemia (IETM) in alzheimer disease rats

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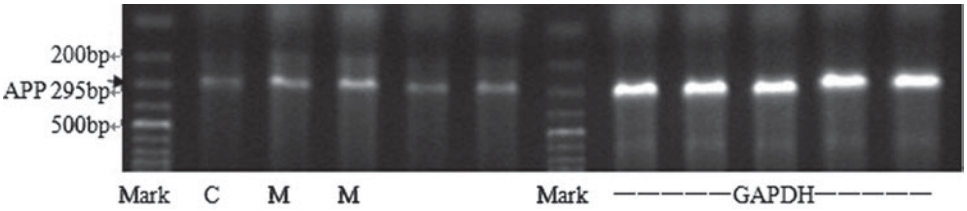
Objective: The objective of the present study was to explore the level of intestinal endotoxemia (IETM) in the model of Alzheimer disease's rats which were established by D-galactose and aluminum trichloride (AlCl3).

Methods: Adult Wistar rats were subjected to 90 days of intraperitoneal injection with D-galactose and AlCl3 to establish the Alzheimer disease's model. After the administration, the study and memory ability of the Alzheimer disease's rats were observed by Morris water maze; The level of Lipopolysaccharide (LPS) in the sera of Alzheimer disease's rats was determined by tachypleus amebocyte lysate method; The level of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in the sera of Alzheimer disease's rats were determined by radioimmunity method.

Results: Compared with the normal control, the level of LPS, TNF-α and IL-1 in the sera of Alzheimer disease's rats were markedly increased ($P < 0.01$).

Conclusion: The model of Alzheimer disease's rats which were established by D-galactose and AlCl3 is accompanied IETM. Key words: intestinal endotoxemia; lipopolysaccharide; Alzheimer disease; D-galactose; aluminum trichloride; model.



P-11-010 The evaluation of anti-androgen therapy to dementia patient with hyper sexuality using SPECT: A case study

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Objective: To investigate the changes in cerebral blood flow in dementia patient with hyper sexuality after anti-androgen therapy.

Methods: We performed 99mTc-ECD SPECT studies before and after anti androgen therapy in a senile dementia patient with hyper sexuality using statistical parametric mapping analysis.

Results: Statistical parametric mapping analysis showed that increased cerebral blood flow occurred in bilateral frontal gyri after anti-androgen therapy. Furthermore, temporal gyri showed marked increased cerebral blood flow compared with baseline study. Patient improved the sexual problem after the therapy, but cognitive function did not change throughout the study.

Conclusion: Our findings indicate that the change of blood flow in frontal and temporal cortices may reflect the effect of anti-androgen therapy in patient with hyper sexuality. The patient with fronto-temporal dementia sometimes shows abnormal behavior like hyper sexuality. Our results might contribute to solving the problem.

P-11-011 Neuropharmacological evidences of biochanin-A in cognitive deficit mice for the management of alzheimer's disease

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Objective: To evaluate the behavioural and neurochemical evidence of Biochanin-A in cognitive deficit mice for the management of Alzheimer's disease in scopolamine induced and naturally induced amnesic models in young and aged mice.

Methods: Elevated Plus Maze, Passive Avoidance Shock were used. Brain AchE, GSH and TBARS were analysed. Neurochemical evidence was obtained by assay of brain Dopamine and Nor-Adrenaline assay, brain tissue damage was analysed.

Results: BCA decreased in the Transfer Latency, increased Step Through latency significantly in Scopolamine treated and natural aged mice in Elevated Plus Maze and Passive Shock Avoidance Paradigm. A dose dependent (BCA 40, 20 & 10 mg/kg) significant ($P < 0.01$) antioxidant (TBARS & GSH) and inhibition of acetylcholinestease activity was observed as compared to Standard Piracetam (400 mg/kg). BCA insignificantly ($P < 0.05$) reduced Dopamine and Nor-adrenalin content of young mice, where as in scopolamine treated mice showed significant ($P < 0.01$) increase in the content of Nor-adrenaline and insignificant ($P < 0.05$) increase in Dopamine, which is sign of dementia.

Conclusion: Further in histopathology of hippocampus of BCA treated mice protected the formation of pyknotic black neurons compare to Scopolamine. In the light of above, it may be worthwhile to explore the potential of this Biochanin-A in the management of Alzheimer's disease.

P-11-012 A comparison of clinical and neuropsychological features in patients with alzheimer's disease and mixed dementia

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Objective: We designed this study to diagnose Mixed dementia (MD) using brain imaging data as well as clinical criteria, and compare the clinical features and neuropsychological characteristics of AD (Alzheimer's disease) and MD.

Methods: A total of 1757 AD patients and 987 MD patients were included from the Clinical Research Center for Dementia of South Korea (CREDOS). All patients underwent comprehensive neuropsychological tests as follows: the Korean version of the Mini-Mental State Examination (K-MMSE), the Clinical Dementia Rating (CDR) scale, the Barthel Index for Daily Living Activities (Barthel-ADL), the Seoul-Instrumental Activities of Daily Living (S-IADL), the Korean-Neuropsychiatric Inventory (K-NPI), the 15-item Geriatric Depression Scale (GDS), and the Dementia version of Seoul Neuropsychological Screening Battery (SNSB-D).

Results: The results of a clinical features comparison revealed that depressed mood and vascular factors such as hypertension, heart disease, focal neurological symptoms and signs, and stroke were present in MD patients more than in those with AD. With respect to cognitive function, no significant difference was found between AD and MD patients in terms of SNSB-D scores except frontal/executive function. Also, AD patients showed better performance than MD patients with respect to activities of daily living.

Conclusion: This study reports that MD patients showed significantly different clinical and neuropsychological features than AD patients. These findings will be helpful in the development of prevention and treatment strategies for MD.

Policy of full disclosure: This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health, Welfare, and Family Affairs, Republic of Korea (A050079) and of the Samsung Biomedical Research Institute, #SBRI C-A9–205.

P-11-013 Comparative assessment of attention and clinical efficacy after treating galantamine between the patients with pure alzheimer's disease and mixed dementia

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Objective: The purpose of this study was to compare the efficacy of galantamine treatment, especially attention ability between patients with pure Alzheimer's disease (AD) and Mixed dementia (MD) during a 24-week trial.

Methods: A total of 40 patients were recruited for this 24-week study. The effect of galantamine on attention was measured using Seoul Computerized NeuroCognitive Function Test (SCNT) and frontal functions test of Seoul Neuropsychological Screening Battery (SNSB). Patients' activities of daily living using the Seoul-Activities of Daily Living (S-ADL) and the Seoul-Instrumental Activities of Daily Living (S-IADL); behavioral symptoms using the Korean version Neuropsychiatric Inventory (K-NPI) were measured at baseline and 24-week.

Results: 17 pure AD patients and 23 MD patients were analyzed in this study. Attention as measured by SCNT was not significantly different from baseline after 24 weeks of treatment in both groups. There was no significant difference between two groups in mean change from baseline in the SCNT, S-ADL, S-IADL and K-NPI scores at 24-week.

Conclusion: Galantamine showed a therapeutic effect on cognition, activities of daily living, neuropsychiatric symptoms in pure AD and MD. Furthermore, Galantamine may specifically help to maintain attention and it may have positive effects on other cognitive and functional abilities.

Policy of full disclosure: This study was supported by Janssen Korea Ltd.

P-11-015 Investigation of donepezil effect to the prevention of hippocamal volume loss in alzheimer's disease

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Objective: Alzheimer disease (AD) is the most common disease in the cognitive impairment diseases, and the AD patients have been increasing in recent years. AD shows memory impairment, disturbance of orientation and higher brain dysfunction such as visuospatial disorder and executive dysfunction with disease progression. In AD, the hippocampal atrophy is progressively seen in disease course. Meanwhile, it is suggested that donepezil has neuroprotective effect and prevents the disease progression. However, there are patients of AD for whom donepezil is effective or not. In this study, we followed the AD patients who were medicated with donepezil and investigated hippocampal volume change with each of the donepzil respeonder and non-responder.

Methods: Voxel-based morphometry analysis was perfomed in 13 AD patients who are prevented in cognitive decline with donepezil treatment and 14 who are not. All participants were medicated with donepezil. In the analysis. Voxel-based Specific Regional Analysis System for Alzheimer's disease (VSRAD: developed by Eisai Co., Ltd. & Pfizer Japan) was used, and calculated hippocampal region atrophy index defined as Z score. The subjects were performed magnetic resonance imaging scan at the baseline and the follow point, and calculated the difference between the Z score at baseline and follow point. Group analysis was performed using Mann-whitney U test.

Results: There was a significant difference between donepezil effective and donepezil non-effective patients in AD regarding the severity of hippocampal region atrophy ($p = 0.038$).

Conclusion: In this study, we found that the progression of the hippocampal atrophy was more suppressed in AD patients who were effective with donepezil treatment than those who were non-effective. It is suggested that donepezil may play an important role in the suppression of the neurodegeneration and help the neuronal protection, and consequently delay the cognitive decline in AD patients.

P-11-016 Effects of high-frequence transcranial magnetic stimulation on cognition of elderly with cognitive impairment no-dementia (CIND)

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Objective: To verify the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) on global cognition of functionally independent elderly with subjective complaints of memory decline.

Methods: Clinical trial. Nineteen (8 male and 11 female) elderly, aged between 60 and 74 years old (mean age $= 64.5 \pm 3.8$), independent for instrumental activities of daily living (IADL) with subjective memory complaints and evidence of some impairment in neuropsychological assessment, characterizing cognitive impairment no-dementia (CIND). The MoCA test was used for screening. For each patient, a brain magnetic resonance image excluded major causes of cerebrovascular disease and white matter lesions, evidence of focal atrophy or lacunes. Subjects were randomized into two groups: (I) active rTMS ($n = 9$) and (II) sham rTMS ($n = 10$). A rapid magnetic stimulator and a figure-of-eight cooled coil was used. We delivered 10 sessions of high-frequence rTMS (10 Hz) for 5 seconds to the left DLPFC, with the parameters: 50 stimuli/train, 40 trains, 25 seconds of intertrain interval, 2.000 pulses/session and intensity of 110% of motor threshold. The placebo group used a sham coil. Follow-up ('off-line'' paradigm) was obtained by detailed neuropsychological assessment encompassing all cognitive domains including the Rivermead Memory Behavioural Test (RMBT) and Stroop. Testing was applied at baseline, after rTMS and one month later. All participants gave written informed consent.

Results: These preliminary results showed improvement higher than 10% in the performance of RMBT and Stroop tests (ANOVA, $p = 0.028$ and $p = 0.038$, respectively) after rTMS sessions. The improvement was sustained after one month on RMBT scores, but not on STROOP test. (Updated results will be showed on the poster presentation).

Conclusion: Although sample size is still statistically limiting, the results suggest cognitive response in memory and attention to high-frequency rTMS, and a sustained effect in memory after one month.

P-11-017 Vascular risk factors and cognition in persons with moderate cognitive impairment

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Objective: To investigate the impact of vascular diseases (assessed by the number of vascular risk factors) on the cognition of persons with amnestic moderate impairment. Persons with moderate cognitive impairment are characteriyed by marked memory deficits and show brain atrophy in the mediotemporal areas of the brain.

Methods: This study included a total of 110 participants, including 52 persons with CI (cognitive impairment) and 58 healthy elderly controls. Vascular risk factors (hypertension, hypotension, diabetes mellitus) and vascular diseases (transient cerebral ischemia, carotid stenosis, coronary artery disease) are clinically reported or recorded in the individual charts of patients by their treating physican. All participants were tested on a range of cognitive tests.

Results: A larger vascular burden among patients with cognitive impairment is associated with lower performance in the executive domain.There was no other significant correlation in patients with CI.There was no significant correlationin the control group.

Conclusion: Our results show that vascular load is related to executive dysfunctions in patients with CI similar to what has been repeatedly reported in healthy older adults.In this study vascular load was not associated with processing speed,episodic memory or overall cognitive functioning.

P-11-018 Comparing frontotemporal dementia and schizophrenia using EEG microstate analysis

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Objective: Recent study reveals electroencephalogram (EEG) microstate map D is correlated with frontal-parietal associated network: linked to frontoparietal network or executive-control network, and map C is correlated with salience network: hub of attention and controls the other networks. To determine the relationship of resting stage networks from EEG and mental disorders, microstate analysis was performed in mild frontotemporal dementia (FTD) patients, which has typical frontal lobe degeneration and hypoactivity in the salience network, and compared with schizophrenia (SZ) patients whose microstate abnormalities are well established.

Methods: We performed EEG Microstate analysis in mild FTD, and in SZ. Moreover, we collected a sample of age-matched normal controls (NC) for each of the two study groups. Firstly, we compared the duration of each Microstate map (A, B, C, and D) of the FTD and the SZ group separately to the NC using a t-test. Next, we were interested in the comparison of the standardized values of the durations of map C and D between FTD and SZ.

Results: In FTD patients, the duration of the map C was significantly decreased compared to NC. However, in SZ patients, the duration of the maps A, B and D were significantly decreasing in comparison to NC. No group difference in the Map C was detected between FTD and SZ, while the duration of the map D showed a tendency towards a shorter duration in SZ than in FTD patients.

Conclusion: Previous results support the view that the duration of various microstates (map A, B, D) in SZ were affected, on the contrary, mild FTD demonstrates showed more limited pathological changes (only Map C). We speculate that the decreasing duration in the map C is specific for the FTD, while the difference in the duration in schizophrenia may represent the wide range dysfunction in total brain.

P-11-019 The effect of 12-week open-label memantine treatment on cognitive function and on alcohol consumption in patients with alcohol dementia

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Objective: Alcohol dementia (AD) usually follows long-term alcohol dependence. AD can occur in around 25% of alcohol dependent patients. Despite its clinical relevance, few studies have been published up to now on neuropsychiatric treatment of AD. The central nervous glutamatergic system, with its N-methyl-D-aspartate (NMDA) receptors, is suggested to be involved in toxic neuronal loss due to alcohol withdrawal and may subsequently contribute to the development of AD. Also, it was hypothesized that the low-affinity NMDA receptor antagonist memantine would improve the cognitive function of patients with AD. The aim of this study was to evaluate the effect of memantine on the cognitive improvement and on alcohol consumption of patients with AD.

Methods: The study was designed as a 12-wk open-label study investigating the efficacy of 20 mg memantine, a low-affinity NMDA receptor antagonist, as a treatment for cognitive and behavioural

problems in 15 patients with probable AD according to the criteria for ARD proposed by Oslin and colleagues. All participants were selected from patients attended at the Alcoholism Programa in our hospital (''12 de octubre'' University Hospital, Madrid, Spain). The CERAD-K (Consortium to Establish a Registry for Alzheimer's Disease – Spanish version) and several clinical assessment scales were completed before and after the 12-week memantine treatment period.

Results: Significant improvements in the mean scores from baseline to final assessment were observed in the Global Deterioration Scale ($p < 0.05$), Brief Psychiatric Rating Scale ($p < 0.01$) and Alcohol consumption ($p < 0.05$).

Conclusion: In this open-label study, patients with AD treated with 20 mg/d memantine for 12 weeks showed improvement on global cognition, behavioural symptoms and alcohol consumption. The result of this study suggests the possible usefulness of memantine for the treatment of AD.

P-11-020 Response to galantamine administration in patients with alzheimer's disease: Exploring subdomains of cognitive function

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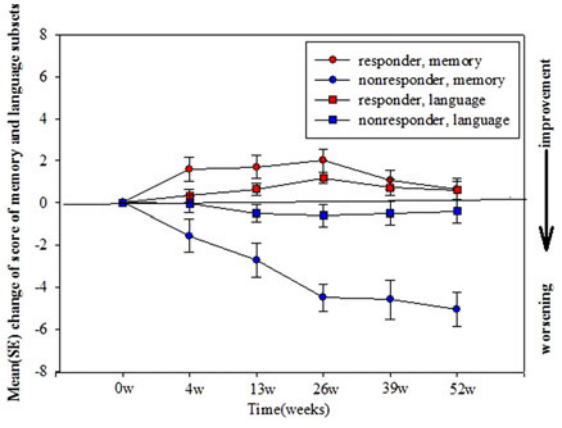
Objective: To investigate galantamine's effect on cognitive subdomains, we examined the clinical response to galantamine in patients with Alzheimer's disease (AD) during a 12-month trial.

Methods: Sixty-six patients with mild to moderate AD were recruited for this 52-week study. The effect of galantamine on cognitive function was measured using the Korean version of Alzheimer's Disease Assessment Scale-cognitive subscale (K-ADAS-cog). To assess frontal/executive dysfunction, K-ADAS-cog included trail making test-part A and B, digit span, and category fluency. Patients' activities of daily living using the Seoul-Instrumental Activities of Daily Living (S-IADL) and Seoul-Activities of Daily Living (S-ADL); and behavioral symptoms using the Neuropsychiatric Inventory (NPI) were measured at a given point of time. We defined patients responsive to galantamine as either those who have shown a cognitive improvement or no change during the first six-month clinical trial.

Results: Overall, patients administered with galantamine showed less cognitive decline through a 52-week period than those with a placebo, as predicted by the Stern equation. Based on the operational criteria, 66.7% of patients were ascribed to treatment responders. The responders showed effects in the cognitive subdomains of memory and language through a 26-week period. The responder group had an average 2-point drop in the memory subdomain and a 1.18-point drop in the language subdomain, while the non-responder group had rose by 4.5 points on average in the memory subdomain and rose by 0.59 points on average in the language subdomain.

Conclusion: Approximately two-thirds of the patients responded to galantamine, and they have shown maintenance or improvement of cognitive functions through 6 months of the clinical trial. The responders gained a cognitive improvement in memory and language functions.



P-11-021 Comparative efficacy of cholinesterase inhibitors in dementia associated with Parkinson's disease

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Objective: All the cholinesterase inhibitors were investigated in PDD, but there is a lack of head-to-head drug comparisons in this field. There are important reasons, both pharmaco-economic and clinical, to investigate if cholinesterase inhibitors are equally efficient in the treatment of PDD.

Methods: In order to assess the comparative efficacy of these drugs we selected a group of 45 patients diagnosed with PDD, who presented a documented history of PD for at least 3 years, and we randomized them on single-blinded flexible doses of galantamine (mean daily dose 16 mg, dose range 8–24 mg/day, n = 16), donepezil (mean daily dose 7.5 mg, dose range 5–10 mg/day, n = 15) or rivastigmine (mean daily dose 9 mg, dose range 6–12 mg/day, n = 14). Patients were evaluated every 4 weeks for 6 months using Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale- Cognitive subscale (ADAS-Cog), Global Assessment of Functioning (GAF) and Unified Parkinson Disease Rating Scale (UPDRS).

Results: Patients diagnosed with dementia had a better evolution under treatment with rivastigmine and galantamine, without significantly intergroup differences ($+0.9 \pm 0.7$ points on MMSE, $+0.5 \pm 0.3$ points on ADAS-Cog and $+4.1 \pm 2.2$ on GAF, $p < 0.05$). Donepezil had a positive impact over the mental clinical status, but lesser than the other two cholinesterase inhibitors ($+0.8 \pm 1.0$ MMSE and $+2.1 \pm 1.9$ ADAS-Cog), although the intergroup difference didn't reach a level of significance of 0.05. There was recorded no drop out due to adverse events during the study. The UPDRS scores didn't vary significantly, reported to baseline, in none of the three groups.

Conclusion: Patients with PDD associated dementia responded better to galantamine and rivastigmine, in the absence of significant impact over the basic neurologic disease symptoms. Donepezil was also efficient in PDD, with no clinical significant negative interference with Parkinson's disease evolution.

P-11-022 An internet based instrument for cognitive function assessment

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Objective: Many large scale registry trials in normal and pathological aging are being planned or conducted. In Alzheimer's disease, interest is turning to prevention studies which may be conducted in healthy populations identified to be at risk of developing Alzheimer's disease.

Methods: Four tests from a computer based cognitive methodology, the CDR System, were internet enabled. Participants logged on to a website, entered their age and gender, and performed the tests online. Their data were compared to normative data from the standard administration of these CDR tests.

Results: A total of 52,237 individuals aged 18 or over performed at least one of the tests. There were highly significant declines with increasing age on the measures of speed on all tasks, as well as for the ability to correctly identify the pictures. Further, variability in reaction times increased with age, as did cognitive reaction time (the difference between choice and simple reaction time). The declines from 18 to 25 years to successive five year age bandings (eg 26 to 30, 31 to 36 etc) were generally comparable between the internet based testing and the standard administration. Also performance on a number of measures was directly comparable between the two forms of administration.

Conclusion: This study has shown that large cohorts can be assessed using internet based cognitive tests, and that the general performance on these tests is directly comparable to that from the same tasks administered in the standard fashion. Notably, rates of decline with aging were directly comparable, as were the patterns of declines on various measures. These findings suggest that internet based cognitive testing is a viable technique in large patient trials, and should prove a useful and convenient means of longitudinally assessing cognition in patient registry studies or large long-term clinical trials.

Policy of full disclosure: The CDR System is owned by Bracket Global and is offered as a sertvice in clinical trials. Keith Wesnes is employed by Bracket and owns stock in the company.

P-11-023 Cognitive declines year by year in non-demented elderly aged 70 to 90 years

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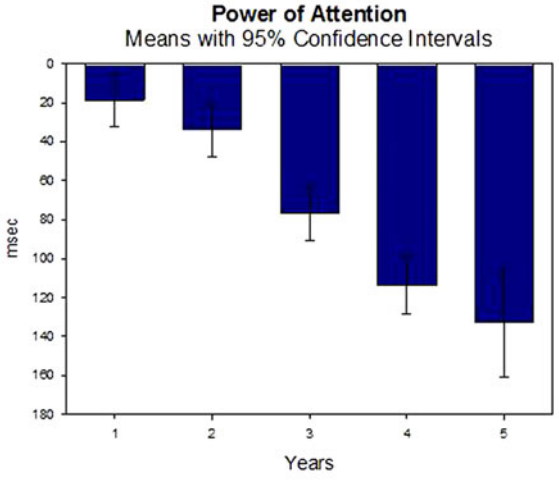
Objective: The deficits to cognitive function which occur in normal ageing can potentially be treated with pharmaceutical and other products. Further, as criteria have now been proposed for pre-clinical dementia, trials are now being planned with compounds designed to prevent or reduce cognitive decline in groups of 'healthy volunteers' identified to be at risk of developing Alzheimer's disease. However, in order to conduct such trials, cognitive tests need to be employed which can reliably assess such change.

Methods: The CDR System is a computerised set of 9 tests of attention, working and episodic memory which has been widely used in trials of potential cognition enhancers in healthy volunteers, age-related cognitive decline, MCI and the dementias. 256 normotensive volunteers (113 females), mean age 76 years (range 70 to 90), mean MMSE 28.8 (range 23 to 30), were trained on the CDR System before a baseline was established, and then retested yearly for up to 5 years.

Results: Composite factor scores were derived from the various test measures. Performance was found to decline significantly over the study period on four of the five scores: power of attention ($p < 0.0001$), quality of episodic recognition memory ($p < 0.0002$), quality of working memory ($p < 0.015$) and speed of retrieval of information held in memory ($p < 0.0001$). Power of attention showed significant deficits from year one onwards, two other measures showed deficits by year one, and all showed significant deficits from year three onwards.

Conclusion: This study has demonstrated that the use of validated and sensitive tests of cognitive function can detect decline over a 5-year period in healthy elderly volunteers. Such testing is therefore fit for purpose for the evaluation of treatments aimed at preventing or even reversing age-related declines in cognitive function, as well as treatments which may delay the onset of Alzheimer's disease in high risk but otherwise healthy populations.

Policy of full disclosure: The CDR System is owned by Bracket Global which offer the use of this in clinical trials as a scientific service. Keith Wesnes is an employee of Bracket Global and owns stock in the company.



P-11-024 Differential involvement of cathepsin B and NLRP3 inflammasome in chromogranin A- and amyloid β-induced pathways for microglial production of IL-1β

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Objective: It is well known that neuroninflammation is exacerbating pathology in Alzheimer's disease (AD). Chromogranin A (CGA), a secretory 49 kDa glycoprotein, is localized in senile plaque dystrophic neurites of AD brain. Besides amyloid β (Aβ), CGA is also considered to serve as a pro-inflammatory inducer of neuroinflammation in AD, whereas little is known about differences between CGA and Aβ in microglial activation. In the current study, we have compared the CGA- and Aβ-induced microglial production pathway of IL-1β, a key pro-inflammatory cytokine.

Methods: Electrophoresis and immunoblotting, immunohistohemical stainings, NLRP3 konck-down with siRNA were conducted in MG5 microglial cell line and AD brain sections.

Results: CGA alone could induce production and secretion of mature IL-1β by cultured microglia. Furthermore, CGA alone activated both nuclear factor (NF)-κB and pro-caspase-1 through proteolytic processing by cathepsin B (CB), a lysosomal cysteine protease. However, NLRP3 was not involved in CGA-induced IL-1β production pathway by microglia. On the other hand, fibrillar Aβ alone failed to produce mature IL-1β, because fibrillar Aβ induced activation of pro-caspase-1, but not NF-κB. It was noted that fibrillar Aβ-induced activation of pro-caspase-1 depended on both CB and NLRP3 inflammasome. Cytosolic leakage of CB in cultured microglia was observed after treatment with Aβ. Furthermore, in the frontal cortex and the hippocampus of AD brain, CR3/43-positive microglia surrounded and their processes infiltrated more frequently in CGA-positive than Aβ-positive plaques. Microglia surrounded CGA-positive plaques were intensely expressed both CB and IL-1β.

Conclusion: These observations strongly suggest that CGA is more potent microglial activator than Aβ to produce mature IL-1β through CB-dependent activation of pro-caspase-1. Therefore, it is considered that CB inhibitors can be pharmacological interventions against AD.

P-11-025 Serum brain-derived neurotrophic factor levels are decreased in different dementias

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Objective: There is a great need for a reliable early diagnosis of the neurodegenerative diseases. New biochemical markers, obtained with non invasive procedures, together with existing clinical, biological and neuroimaging markers may add accuracy to differential diagnosis and prognosis of dementias and movement disorders. The neurotrophin brain-derived neurotrophic factor (BDNF) plays a critical role in neuronal survival, synaptic plasticity, and memory in the adult brain. Altered functionality of BDNF in post mortem brains and abnormalities in the serum concentrations have been observed in different neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's Disease (PD). Despite the numerous evidences about involvement of BDNF in the neurological diseases, to date no study has investigated the possible role of this neurotrophin as biochemical marker for differential diagnosis of this neurological diseases. Starting from these considerations, we compared serum BDNF in different dementias and movement disorders and in a group of healthy subjects in order to evidence alterations across different diagnoses.

Methods: The sample is composed by 631 subjects: 169 healthy controls, 263 AD, 40 Lewy Body (LBD), 91 Vascular Dementia (VaD), 28 Fronto-Temporal Dementia (FTD) and 40 PD patients. Serum BDNF levels were analyzed by the enzyme-linked immunosorbent assay (ELISA) method.

Results: Decreased serum BDNF levels were observed for AD, LBD, VSD and FTD patients when compared with the control group ($p = 0.005$, $p = 0.006$, $p = 0.017$ and $p = 0.003$ respectively). No significant differences were observed for PD patients. Moreover, lower BDNF levels were evidenced in patients taking benzodiazepines ($p = 0.024$) while increased concentrations were detected in PD patients treated with L-DOPA ($p = 0.008$).

Conclusion: In conclusion our results support the hypothesis that BDNF alterations are involved in the neurodegenerative mechanisms and suggest the potential usefulness of the serum dosage as a marker for differential diagnosis in dementias and movement disorders.

P-12. Childhood & Adolescent Disorders

P-12-001 Neuroeducation: Neurocognitive enhancement of the developing brain

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Objective: I report clinical evidence in children from 4 to 9 years old that have been treated through neurocognitive enhancement techniques. The objective of these studies has been to improve specific cognitive functions targeted through diagnoses of cognitive and emotional disturbances and assessed through neurocognitive analyses and testing.

Methods: In response to specific disorders, for instance dyslexia, dysgraphia or dyscalculia, specific neurocognitive training tasks have been proposed and used on an individual basis to specifically remediate the assessed condition-disorder. More specifically, the treatment of a purely dysgraphic child, a severely disabling learning condition resulting from difficulty in expressing thoughts in writing, including litteracy and deduction impairments, requested selective use of auditory tone discrimination tasks, auditory noise-background discrimination, vowel or consonant word completion, visual scanning ability and kinesthetic working memory tasks.

Results: Sessions of intensive and frequent neurocognitive training resulted in massive reduction of the disability manifestations in clinical assessment and school performance. In experimental post-treatment measures, highly improved general processing speed abilities and word visual and auditory recognition scores have been obtained.

Conclusion: Our clinical results of neurocognitive enhancement in children highly support straightforward improvement of specific cognitive disturbances through selective training of their cognitive sub-components. The effects of this type of improvement seem exhibiting a structural or long-lasting character, conserving however the specificity of the cognitive abilities that have been endorsed.

P-12-002 Teen depression prevention – an issue of great social impact

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Objective: The number of depressive episodes in teenagers has increased dramatically for the past two decades. Depression is a common condition among teenagers, with prevalence between 3% and 8%, becoming acknowledged as a public health problem. More than 25% of teenagers of about 18 have had at least one depressive episode.

Methods: This is a retrospective study, assessing suicide attempts of adolescents registered for a period of three years (2006–2008) and was carried out at the Iasi Children Hospital. The study group consisted of 19 teenagers aged between 14 and 18 years. Only one of these cases was diagnosed as depression and medication associated with psychotherapy was prescribed. The other 18 cases are under the observation of family and family physicians.

Results: The conclusions state that males resorted more easily to suicide methods, even compared to the girls-boys' ratio of 1,5:1 for the entire population. The teenagers living in rural areas represented only 13% of the attempted suicide cases, because they are less frequently subjected to the risk factors of depression and suicidal ideation comparing to the teenagers living in the urban areas. An accelerated increase in number from the groups of younger age to the older ones is also to be noted.

Conclusion: The study is the first published research comparing the risks of suicide attempts before and after treatment. It shows that suicide attempts are twice as common in teenagers than in adults patients. Still, a time model is contained in both age groups: an attempted suicide most likely occurs before treatment, the chances decrease by 50% after starting the treatment, to almost disappear after treatment.

P-12-003 Asperger syndrome with recurrent psychosis in adulthood

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Objective: Asperger syndrome (AS) is a pervasive developmental disorder characterized by autistic social dysfunction and idiosyncratic interests in the presence of normal intelligence. We try to analyze the aspects of psychosis in two cases of Asperger syndrome and the response at treatment.

Methods: Two male patients (18–20 years) diagnosis with AS were hospitalized for psychotic symptoms. One of them was born prematurely and the other has family history of psychotic syndrome. Both patients finished with difficulty the high school and presented aggressivity and hostility; the psychotic syndrome included ideas of revenge about the colleagues. Behavioral and emotional disturbance was characteristics. After hospitalization one patient was included in cognitive- behavioral therapy (CBT). For measurement the psychotic symptoms we used Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity (CGI-S). Functioning was evidenced on Quality of Life Scale (QLS). Period of study 4 month with visits.

Results: The patients presented resistance at many antipsychotics and the remission of symptoms was difficult with long period of hospitalization. In first case the psychotic syndrome was resolved with Quetiapine 600 mg/day and in the second case we use Venlafaxine 225 mg/day and Risperidone 4 mg/day. Venlafazine was necessary because one of the patients had a depressive symptoms with suicidal ideation.

Conclusion: AS has comorbid psychiatric conditions with resistance at therapy. CBT is important in a second period of recover. The family involvement has a positive role in remission psychotic episode.

P-12-004 Clinical experience in Chile with clozapine in child and adolescents under 18 years

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Objective: Increase in severe psychopathology in adolescents who are resistant to common treatment creates a need to search new alternatives in pharmacological treatment. Background: to describe a sample 47 child and adolescent patients treated with clozapine between 1985 and 2010, indicating: age, gender, diagnoses, hospitalization, electroconvulsive therapy, dosing, adverse effects specially hematological ones.

Methods: 47 patients between the ages of 10 and 18 were treated with clozapine. Review of clinical charts, protocol investigation and Excel statistic analysis.

Results: the sample consisted in: male: 40%, female: 60%, the youngest was 10 and the oldest 17 years and 11 month old; the most frequent age was 15 years. The mean number of hospitalization was 1.5. Diagnosis axis-I, DSM-IV: affective disorders 64%, schizophreniform disorder 23%. Electroconvulsive therapy: 57%.Treatment indications: irreducible psychosis 23%. Suicidability: 33%. Average dosing 200 mg. Adverse effects: sedation: 76%, hypersalivation: 68%, increase in weight: 66%. Neutropenia: not severe (more than 2000/mm^3): 17%; severe I: 15%, severe II: 2%, severe III: 2%.

Conclusion: Clozapine appears as an effective drug, with moderate but frequent adverse effects. Hematologic adverse effects where transient; only one in 47 patients presented a severe neutropenia and require cancellation of treatment, which was reinstalled after three month without mayor side effects. There is a need for control studies with larger population and a longer period of time.

P-12-005 The factors associated with metabolic syndrome in Japanese patients with mental retardation

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Objective: Mental retardation sometimes co-occur with psychiatric and/or behavioral disorders, and those patients are usually treated by psychotropic agents. Adverse effects of antipsychotics are believed to cause Metabolic Syndrome (MetS), significantly contributing to the

risk of death due to coronary artery diseases. As is the case in patients with psychiatric disorders, patients with mental retardation may have an increased risk of MetS. We conducted a study of the MetS in patients with mental retardation to clarify the factors associated with its prevalence and incidence.

Methods: A total of 199 patients with mental retardation were eligible to participate in this study. All patients were engaged in ongoing outpatient visits or were inpatients admitted to support facilities for people with intellectual disabilities in Japan. We reviewed the patients' medications and prevalence of MetS at the two periods: from October 2006 to March 2007 (term A), and from July 2011 to August 2011 (term B). The MetS diagnostic criteria were based on the consensus guidelines created by Japanese Society of Internal Medicine.

Results: We divided the patients without a diagnosis of MetS at term A into 2 groups: those diagnosed with MetS at term B (''A-B+ group'') and those without a diagnosis of MetS at term B (''A-B- group''), and examined the clinical characteristics of both groups. At term A, the ''A-B+ group'' showed a significantly larger diameter of waist circumference and a higher triglyceride compared to the ''A-B- group.'' These significant differences were also observed in logistic regression analyses. On the other hand, a significant difference between the two groups was not found in terms of the use of psychotropic medications.

Conclusion: In the items of MetS diagnostic criteria, diameters of waist circumference and triglyceride may be important predictive factors for the future onset of MetS in patients with mental retardation.

P-12-006 Agreement and disagreement between parent and teacher regarding child psychopathology: Comparing SDQ with CBCL

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Objective: The assessment of childhood psychopathology requires data from multiple informants. Because children have a limited ability to describe themselves and are often affected by situations. And confusions in the diagnosis in outpatient department are often caused by the difference between parent's and teacher's perspectives about a child's behavior. In Korea, no systematic review of the inter-rater disagreement has yet taken place. Considering SDQ is a brief screening questionnaire, this study was designed to evaluate the usefulness of SDQ in clinical setting using information regarding the level of parent-teacher agreement and symptoms with discordance.

Methods: K-CBCL and SDQ-Kr were completed by parents and teachers in charge of 105 children (28 girls, 77 boys) aged 6–12 years and the clinical diagnosis were made by a child and adolescent psychiatrist. Spearman's correlations were computed to assess associations between parent's and teacher's ratings in subscale level. And we used Mann-Whitney U test to analyse the influence of child's age and sex on parent-teacher report. Finally, AUC values were calculated to measure the diagnostic capacity of parent-teacher ratings, and the difference between two AUCs was tested with the z test.

Results: Correlations between parent- and teacher- reported SDQ were high (range 0.362–0.545, $p < 0.01$) in every scale except emotional problems. Parents were more sensitive to emotional symptoms of girls ($p < 0.01$), while teachers seemed to be more sensitive to conduct problems and inattention-hyperactivity of boys ($p < 0.05$). Parents were more sensitive to conduct problems of seniors, whereas teachers seemed to be more sensitive to Inattention-hyperactivity of young children ($p < 0.05$). Teacher's CBCL was shown to be most discriminating of conduct disorder/oppositional disorder and teacher's SDQ demonstrated the highest prediction of ADHD and Emotional disorder ($p < 0.05$).

Conclusion: In situations where parents are unavailable or when their reliability is low, teacher's SDQ can be used instead of parent's report in identifying child psychopathology early.

P-12-007 Prenatal lead and cadmium coexposure and infant neurodevelopment at 6 months of age

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Objective: Little is known about the potential interactive effect of prenatal coexposure of lead (Pb) and cadmium (Cd) and cognitive development of infants. The aims of this study were to investigate the association of maternal blood concentration of Pb and Cd during pregnancy with infant development at six months; and also to explore the potential interaction between prenatal Pb and Cd coexposure.

Methods: Between 2006 and 2010, Pb and Cd levels were measured in blood samples of 889 mothers during first and third trimester pregnancy as part of Mothers' and Children's Environmental Health Study. We examined the interaction between prenatal exposure to Pb and Cd and the mental (MDI) and psychomotor (PDI) developmental indices of the Bayley Scales of Infant Development at six months.

Results: The interaction between Pb and Cd status for the maternal blood at first trimester was significant for MDI and PDI at 6 months. In stratified linear model, the MDI at six months correlated significantly with the third trimester maternal blood Pb concentrations, for the children with high Cd exposure. When maternal blood Pb and Cd concentration were entered in a stepwise fashion to the linear model for all subjects, the Cd concentration at first trimester showed inverse association with PDI at 6 months. In the third trimester, the Pb concentration showed inverse association with MDI at 6 months.

Conclusion: The results of this study shows that prenatal exposure to Pb and Cd may be inversely associated with MDI and PDI of the infant at 6 months. The present study also shows that there may be an interaction between exposure to Pb and Cd during first trimester on the infant development at 6 months.

P-12-008 Prevalence of mental disorders in Thailand: Results from the epidemiology of mental disorders national survey

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Objective: To estimate the prevalence rates of mood, anxiety, alcohol and psychotic disorders in Thailand.

Methods: Nationally representative face-to-face household survey based on a multistage area probability sample of non-institutionalized people aged 15 to 59 years (n = 17,100) and selected each stage by means of random sampling. The data were conducted between June and August 2008 using Mini International Neuropsychiatric Interview (M.I.N.I.) by trained psychiatric professional. The data analyses were calculated by means of adjust weighted with prevalence rate for generalized to Thai population.

Results: The participants of this survey were 17,140 people in 4 regions and the Bangkok accounted for 93% of response rate. The results of weighted analysis for estimate the prevalence rate in Thais population have shown any mental disorders about 7,348,902 people (15.2%) which indicated approximately 14.3% of any current mental disorders and 0.9% of any lifetime mental disorders. An alcohol dependence current was the highest prevalence of mental disorders accounted for 6.6% (SE = 0.30) and the prevalence rate of an alcohol abuse current was about 4.2% (SE = 0.24). Furthermore, the prevalence rates of a major depressive episode current accounted for 2.2% (SE = 0.2) and recurrent represented about 0.7% (SE = 0.1), while a dysthymic disorder episode found 0.7% (SE = 0.1).

Conclusion: The alcohol use disorders have shown the commonest of mental disorders in Thais especially in male and the major depressive episode has frequently found in female of Thailand. These findings have significantly been evidences for the establishment of mental health care and prevention programs.

P-12-009 Comorbidity in children and adolescents with behavioral disorders

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Objective: Behavioral disorders are frequents in children and adolescents. This is a common symptom, often associated with other psychiatric disorders. This comorbidity is a predictor of early onset of other disruptive behavior, with a more rapid evolution and a bad prognosis and many social problems. The interest of this study is to assess psychiatric comorbidity between the behavioral disorders and the other psychiatric disorders.

Methods: We conducted a retrospective study over a period of two years with 120 children and teenagers showed in consultation for behavioral disorder. The diagnosis of behavioral disorders and associated diseases was made according to the diagnostic criteria for DSM IV-TR. Analysis of the results was made by epi-nfo10.

Results: The average age of patients is 7.34 years. 90% of our patients are boys. The diagnosis of ADHD was found in 68% of cases, conduct disorder in 17% of cases, the oppositional defiant disorder in 25% of cases.The comorbidity of behavioral disorders is noted in 70%. 68, 7% of patients have at least 2 concomitants disorders. The comorbidity with learning disorders is noted in 28.3%, with anxiety disorders in 23% of cases, with mood disorders in 13.3% of cases, with substance abuse in 15% of cases and with other medical disorders in 10.8% of cases.

Conclusion: behavioral disorders is frequent in child psychiatry. the comorbidity is multiple, the management is multidisciplinary and depends on the type of behavioral disorder and associated disorders.

P-12-010 Suicidality in autism: A review

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Objective: This review focuses on suicide in patients with pervasive developmental disorders as well as risk factors and comorbities seen in patients who have attempted suicide.

Methods: Research in PubMed for articles dating from 1999 to 2011 on this subject. 25 articles were found.

Results: Suicide in autism is largely understudied. A higher mortality in autistic patients is related to medical disorders like epilepsy and accidents. Suicide occurs more frequently in high functioning autism. Patients with PDD present with most of the risk factors leading to suicide. Furthermore, a history of mood disorders is frequently associated with suicide attempts as well as personal vulnerabilities and other psychiatric comorbidities.

Conclusion: Patients with PDD present risk factors inherent to their diagnosis, along with risk factors pertaining to the general population. The inability of persons with PDD to express emotions and thoughts makes the diagnosis of suicidal ideation difficult. Therefore, more studies are needed on the issue.

P-12-011 Functional restoration as an adjunct to pharmacotherapy in treatment of postural orthostatic tachycardia syndrome (POTS)

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Objective: Introduction: POTS is a clinical syndrome that has been estimated to effect up to 500,000 adults in the US and is being increasingly recognized and identified in adolescents. POTS is defined by the presence of excessive tachycardia, (>30 beats per minute) on the assumption of an upright posture. Associated symptoms can include lightheadedness, dizziness, palpitations, and sweating. The functional disability observed in these patients can be severe and can include incapacitation such as being bed or wheelchair bound. The treatment of POTS to date has focused upon pharmacological treatment and has included the use of beta blockers, midodrine, and fludrocortisones. No studies have examined the effectiveness of a functional restoration program in adolescents with POTS. The current study examines the efficacy of such a program as an adjunct to pharmacotherapy for adolescents with POTS.

Methods: Patients, who were severely impaired despite adequate pharmacotherapy, were referred to participate in a program designed to restore their function.. In a group setting, patients and their parents learn how to adaptively self-manage their chronic physical symptoms through a structured, multidisciplinary intervention that utilized medical, psychological, PT, and OT services. Functional status was assessed with the Functional Disability Index.

Results: Thirty-three patients, ages 12–18, diagnosed with POTS, were participants in this study. Seventy-four percent of patients with a diagnosis of POTS were on one or more POTS medications upon admission including beta blockers, Midodrine and fludrocortisone Pharmacotherapy initiated for the treatment of POTS was continued during the program. After participation in the program, adolescents with POTS demonstrated a significant increase in overall functional abilities ($t = 6.166$, $p < 0.001$).

Conclusion: A functional restoration program appears to be successful as an adjunct to the pharmacotherapy currently used for the treatment of POTS in adolescents.

P-12-012 Development of new diagnostic measure based on integrated correlation analysis of behavior and physiological parameters for socio-emotional difficulties in Asperger's disorders (AD)

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Objective: Early diagnosis and intervention is crucial to improve the quality of child life suffering developmental disorder like AD. Brain imaging and genetics/epigenetic analyses which are two major diagnostic tools are not fully applicable for developing child. Here we developed another diagnostic measure based on non-contact or least contact way of behavioral and physiological measurement, which can be applicable at every-day clinic and non-clinical situations. This algorithm that freely bridges over objective and subjective information was named as BOUQUET (Senoo et al., Koshiba et al., 2011).

Methods: The study population comprised two groups, one diagnosed as asperger's disorders (AD) (male 5, female 2, 6–13 years old) according to DSM-IV and ADI-R and another, their healthy siblings (Typically developed, TD) (male 1, female 4, 7–15 years old). They were interviewed alternatively by unfamiliar lady, unfamiliar gentleman, their doctor in charge, and finally their mother for 2–5 min each. As the default condition, they played TV game. We recorded them by video-camera and infrared camera during the interview. We also recorded EEG (Fp1, Fp2, T3, T4, Cz, O1, 2) and ECG (Intercross 410). Serum cortisol and prolactin were measured a month before the interview and just after the interview. All the protocol was approved by Sawa hospital, Osaka and internationally registered (NIH). The correlation of behavioral and physiological parameters was analyzed by BOUQUET based on principal component analysis.

Results: The difference between two groups was visualized in the feature space reconstituted by two major principal components. The parameters which contributed to the discrimination was high variations of EEG and head surface temperature in AD, head movement velocity and gaze-frequency toward interviewer during self or family episode consolidation in AD.

Conclusion: These results suggest the usefulness of the integrated correlation analysis of behavior and physiological parameters by BOUQUET to extract the feature of socio-emotional adaptability in AD compared with TD child.

P-12-013 Violence in adolescents: Gender differences

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Objective: Violence phenomenon in urban centres is undestood as a social process including wide spectrum of forms of aggression having an expansive and multiplying effect not only on the victims but also on the whole society; I for this reason its increase is a source of concern. Objetive: To determine some feature of violent adolescents and their association with some personal, familial and environmental characteristics in youngsters taken care by the National Council for the Youngsters and the Family.

Methods: Material and Methods: Violent adolescent was defined when having participating in fghts (physical aggression) during the prceeding year. Population: 522 adolescents, both sexes, ages 10 to 21 years, assisted in the National Coucil for the Youngsters and the Family. Survey Instrument: Two epidemiologic questionnaires (including the Present State Examination) to register current pshychic state as well as personal, familial and environmental history.

Results: With violent behaviour 21.3%. Males showed significant association with diagnosis of disocial behaviour and consume of tobacco, marijuana, cocaine and sedatives. In women significant association was found with diagnoses of mild depression, defian behaviour, history of sexual harassment, and consume of alcohol.

Conclusion: The psychopharmacological treatment covers the etiologic diagnosis insofar as it has been studied that the selective serotonin reuptake inhibitors (SSRIs) not only have a therapeutic effect but also exert equilibrium on the serotonergic function. At adequate doses, both neuroleptics as well as antireccurence agents decrease the violent behavior.

P-13. Psychoneuroimmunology

P-13-001 Antidepressant effects of macrophage migration inhibitory factor gene deletion

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Objective: Depression is a global health problem with high mortality. Current treatment strategies only give sufficient symptom relief to approximately half of the patients. It has been established that depressed patients display immune alterations. Recently it was reported that the cytokine macrophage migration inhibitory factor (MIF) correlate positively with depression scores. It has also been shown that depressed individuals show exaggerated MIF levels following antigen challenges. In the current study we wished to examine the causality between MIF and depression. We therefore examined whether MIF knockout (KO) mice would show altered depressive-like behaviour compared to wildtype (WT) animals.

Methods: Male and female MIF KO mice and WT littermates were tested for locomotor behaviour in the open field, anhedonia in the sucrose preference test (SPT), and despair in the forced swim test (FST) and tail suspension test (TST). Brain mRNA expression of the cytokines IL-1B and IL-6 was subsequently examined using RT qPCR.

Results: Results showed that MIF KO mice had a slight decrease in locomotor activity compared to WTs. In SPT a genotype/sex interaction was found, with male KO animals showing increased sucrose preference compared to control males. A similar interaction was found for FST, where male KO mice showed decreased immobility. In TST both male and female KO mice showed decreased immobility. No genotype/gender effects were found on IL-1B or IL-6 expression, but a significant positive correlation was found between IL-6 and stillness in the TST.

Conclusion: Our results suggest that MIF gene deletion has clear antidepressant effects, possibly most pronounced in male animals. Furthermore, a positive relationship between depressive-like behaviour in the TST and IL-6 was found, suggesting that IL-6 is involved in this behaviour. These data supports the growing line of evidence for an involvement of inflammatory factors in depression and further suggests that MIF ligands have potential as antidepressant drugs.

P-13-002 Plasma interleukin-6 as a biomarker in the treatment of major depressive disorder

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Objective: 1. Confirm that plasma IL-6 is higher in patients with MDD than healthy controls 2. Examine the relationship between IL-6 and the severity of depression, anxiety, and perceived stress 3. Evaluate whether IL-6 values normalized after monotherapy with either escitalopram, or quetiapine. 4. Assess whether abnormal IL-6 specifically correlated with treatment resistant depression.

Methods: A cohort of 48 patients with MDD and 23 healthy subjects were analyzed from two consecutively run studies of identical design. Subjects met DSM-IV criteria for primary MDD, with an index episode of at least one month duration. Screening included structured psychiatric interviews, physical exam, and laboratory studies. Subjects with medical illness or co-morbid Axis-I diagnoses were excluded from the study.

Results: Patients with MDD had significantly higher baseline plasma IL-6 than healthy controls ($n = 20$) ($p = 0.05$). IL-6 failed to normalize with either escitalopram or quetiapine after treatment. Treatment response ($\geqslant 50\%$ reduction or $\leqslant 7$ in HAM-D17 score) did not correlate with the baseline level of IL-6. There was a significant correlation between baseline IL-6 level and depression severity as measured by HAMD-7 ($p = 0.05$). Additionally, there appeared to be a trend for IL-6 to correlate with acute suicidality.

Conclusion: MDD patients had elevated IL-6 and this elevation did not correlate with depression severity as measured by HAM-D7. This scale emphasizes the core features of depression such as depressed mood, guilt, and anhedonia. Patients in both studies experienced high rates of treatment response, but neither escitalopram nor quetiapine normalized IL-6 levels. Thus, inflammation persisted despite the improvement in mood symptoms possibly because the length of treatment may have been inadequate to reverse inflammation. Antidepressants have been shown to inhibit the production and/or release of pro-inflammatory cytokines and to stimulate production of anti-inflammatory cytokines. Although current therapies may attenuate inflammation, they may not sufficiently resolve it.

P-13-003 IL-1β induces TDO and provokes the release of kynurenic acid from human astrocytes in vitro

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Objective: Kynurenic acid (KYNA) and interleukin-1β (IL-1β) are elevated in the cerebrospinal fluid (CSF) of patients with schizophrenia. KYNA is an antagonist of the nicotinic α7* acetylcholine receptor and the glycine site of the N-methyl D-aspartate (NMDA) receptor and has been shown to modulate dopaminergic neurotransmission, implicating a role for KYNA in schizophrenia pathology. Indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) are the rate limiting enzymes of the kynurenine pathway, and it is known that other cytokines, in particular interferon-γ (IFN-γ) induce IDO. This study was designed to investigate if IL-1β induces the kynurenine pathway in human astrocytes, the main KYNA producing cells of the brain.

Methods: Human astrocytes were cultured in AM medium supplemented with 2% fetal bovine serum and a mix of growth factors. Following 24 hours serum starvation cells were stimulated with IL-1β (10 ng/ml) or vehicle. Cell culture supernatants were collected and RNA and protein was extracted. RNA was reverse transcribed to cDNA and real time quantitative PCR was performed. Protein levels of IDO and TDO were analyzed using Western Blots. Levels of KYNA in supernatants were analyzed using a high performance liquid chromatography system.

Results: IL-1β increased levels of KYNA in the cell culture medium. Stimulation with IL-1β also induced the expression of TDO mRNA and protein. IDO was however only induced on the transcriptional level.

Conclusion: This study shows that KYNA production increases following IL-1β-induced upregulation of TDO. Interestingly, increased TDO expression and activity have previously been reported in patients with schizophrenia. Present results thus highlight the notion that increased TDO expression and CSF KYNA levels observed in patients with schizophrenia may result from activation of brain IL-1β signaling pathways.

P-13-004 CSF biomarkers in suicide attempters – inflammation biomarkers and monoamine metabolites

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Objective: The objective of the present study was to identify biological patterns (factors) among 20 cerebrospinal fluid (CSF) biomarkers in suicide attempters and subsequently analyse their association with suicidal behaviour.

Methods: We measured kynurenic acid, orexin, homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4- hydroxyphenylglycol, chemokines, matrix metalloproteases and cytokines in the CSF of 124 drug-free suicide attempters. Patients were evaluated for suicidality and psychiatric symptoms using well-defined psychiatric rating scales and followed-up regarding future suicide. We used principal component analysis to identify factors among the biological substances.

Results: Four factors were extracted from the 20 biomarkers, explaining 52.4% of the total variance. Factors 1 and 2 were characterized by high loadings of chemokines and cytokines respectively. They were both associated with severe depressive symptoms. Factor 2 was also associated with a high suicidal intent. Factor 4 was characterized by strong loadings of the monoamine metabolites 5-HIAA andHVA, as well as orexin and interleukin-6. High scores on this factor were found in patients who performed a violent suicide attempt and in patients who subsequently completed suicide.

Conclusion: Our results suggest that specific combinations of CSF biomarkers may discriminate between types of suicidal behaviour and indicate increased risk for future suicide.

P-13-005 Psychoneuroimmunomodulation in treatment of patients with schizophrenia

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Objective: To study dynamic of parameters of the immunity in group of schizophrenic patients with different efficacy of treatment.

Methods: Dynamic of psychopathological symptoms in 388 schizophrenics was registered with ''Clinical Global Impression'' (CGI) in two points – at baseline and after 6 weeks of appropriate for mental state treatment. According to results of clinical dynamic patients were divided into 3 groups: group 1 (n = 54) – with significant improvement of mental state; group 2 (n = 143) – with essential improvement; group 3 (n = 191 s) – with insignificant improvement and without changes of mental state. Immunological examination included identification of phenotypes of surface receptors of immunocompetent cells, immunoglobulins IgM, IgG, IgA, level of circulating immune complexes (CIC); spontaneous and mitogen-induced production of IFN-γ, IL-4, TNFα by mononuclear leukocytes of patients, serum concentration of cortisol and aminotransferases.

Results: It has been shown that in the first two groups as compared with group 3 reliably higher values of T-helpers-inducers CD4+ ($p = 0.0001$), cytotoxic T-lymphocytes CD8+ ($p = 0.0001$), mitogen-induced production of IFN-γ ($p = 0.0001$) and reliably low values of production of TNF-α ($p = 0.0001$), CD95±lymphocytes, levels of CIC, cortisol and amisnotransferases were high in all three groups ($p = 0.0001$ regarding to control in all groups). Study of psychoneuroimmunomodulation under influence of psychotropic therapy has shown that in the first two groups high clinical efficacy was accompanied by normalization of most parameters of homeostasis: T-lymphocytes CD3+, CD4+, CD95±lymphocytes, levels of CIC, cortisol and aminotransferases, mitogeninduced production of IFN-γ and TNF-α. In group of absence of the effect to the therapy positive dynamic of immunobiological indices has not been revealed.

Conclusion: Thus, it has been shown that favorable clinical dynamic in process of 6 weeks therapy of schizophrenic patients was accompanied by positive dynamic of some indices of the immunity what probably reflects optimization of mechanisms of psychoneuroimmune interaction.

P-13-006 Human CD8+ T cells and NK cells express and secrete S100B upon stimulation

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Objective: Previous studies have demonstrated the utility of S100B as a surrogate marker of brain-related pathologies, e.g. neuropsychiatric disorders, and melanoma progression, which have an inflammatory component.

Methods: This study addresses the relevance of S100B+ lymphocytes in mediating such responses. S100B expression was determined in human peripheral blood leukocytes isolated from healthy volunteers using flow cytometry. S100B+ lymphocytes were characterised for phenotype, cytokine production and S100B secretion. In addition, we investigated whether S100B activates monocytes and neutrophils.

Results: S100B+ cells comprised 2–4% of all lymphocytes and the majority displayed a CD3+ CD8+ phenotype; fewer cells were CD3+ CD56+ NK lymphocytes. Comparison of S100B+ and S100B+ CD3+ CD8+ cells revealed no differences in production of interferon gamma (IFN-gamma) and interleukin-2 (IL-2). Stimulation of S100B+ CD3+ CD8+ lymphocytes with anti-CD3 or phytohaemagglutinin resulted in release of S100B. High concentrations of recombinant human S100B triggered upregulation of CD11b and membrane shedding of CD62L in granulocytes and monocytes.

Conclusion: These findings set the stage for a new field of research addressing a S100B-mediated crosstalk between the innate and adaptive immune systems if close proximity of effector and responder cells accomplishes sufficient local S100B levels. In various physiological and pathological conditions S100B might function as an interface to immunological processes, distinct from known cytokine- and chemokine-mediated pathways.

P-13-007 Decreased expression of S100B in a genetic rat model of depression

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Objective: The glial-specific protein S100B has both neurotrophic and apoptotic effects, depending on its concentration. Elevated serum levels of S100B have been shown in patients diagnosed with psychiatric disorders. Genetic variability in the S100B gene has been associated with schizophrenia and the personality trait self-directedness, which is strongly correlated to general mental health. The aim was to study S100B expression in brain and behaviour in a genetic model of depression, the Flinders Sensitive line (FSL) and its control, the Flinders Resistant line (FRL) both before and after lipopolysaccharid (LPS)-induced peripheral immune activation.

Methods: Changes in behaviour were assessed using the forced swim test (FST), an animal model to test for depressive-like behaviour. S100B mRNA levels in amygdala, hippocampus, prefrontal cortex, hypothalamus and striatum were measured using quantitative real time PCR.

Results: S100B expression was significantly lower in FSL compared to controls in all investigated brain areas, both at baseline and after peripheral immune stimulation. Immobility was larger in FSL compared to FRL rats. Reduced S100B expression correlated significantly with increased immobility. Furthermore, LPS increased both the time spent immobile and climbing in both lines.

Conclusion: The results in this study indicate the involvement of S100B in behavioural differences of the FSL depression rat model. This model may be useful in further studies regarding the influence of S100B on mental functions.

P-13-008 Mind-Body Interface: Polyunsaturated fatty acids and somatic symptoms in major depressive disorder

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Objective: Lower n-3 polyunsaturated fatty acids (n-3 or omega-3 PUFAs) levels and genetic variations on their metabolic enzymes of PUFA metabolic enzymes, phospholipase A2 (PLA2) and cyclo-oxygenase-2 (COX2), have been found to be associated with the risk of depression (1–4). In this study, we aimed to examine specific roles of n-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and the polymorphisms on PLA2 and COX2 in different clusters of depressive symptoms.

Methods: Patients with major depressive disorders (n = 122) and their healthy controlled subjects (n = 122) were assessed to examine the effects of PUFA levels and single nucleotide polymorphisms (SNPs) of PLA2 BanI and COX2 rs4648308 genes on the development of major depression and on specific clusters of depressive symptoms.

Results: Patients with major depressive disorders had a significant lower level of EPA ($p = 0.03$) and a trend of lower level of DHA ($p = 0.08$). The COX2 rs4648308 AG genotype was associated with a higher risk of major depression ($p = 0.006$; odds ratio = 2.36, 95% CI = 1.27–4.40), while the PLA2 BanI GG genotype had a borderline effect ($p = 0.06$; odds ratio = 1.81, 95% CI = 0.87–3.79). The ''at risk'' COX2 polymorphism was associated with more somatic symptoms ($p = 0.003$) and lower DHA ($p = 0.002$), and the ''at risk'' PLA2 polymorphism was associated with more somatic symptoms ($p = 0.025$). In addition, lower EPA and DHA levels were both significantly correlated with more somatic symptoms in patients with depression.

Conclusion: Genetic variations in the COX2 and PLA2 genes have effects on depression and somatic features, possibly by affecting the levels of EPA and DHA. N-3 PUFAs may be a potential biomarker to understand clinical subtypes of depression (1).

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P-14. Depression

P-14-001 Relation between unintended pregnancy among teenagers and post-partum blues

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Objective: Unintended pregnancy continue to many countries in the world especially among teenagers. The aim of this study was to assess the prevalence of post-partum blues in teenage mothers with unintended pregnancy, compared with teenage mothers with planned pregnancy.

Methods: 100 normal primiparous women with age less than 19 were studied and divided two groups who had unintended pregnancy and planned pregnancy. Maternity blues assessed in two groups.

Results: There was postpartum blues in women with unwanted pregnancies more than women with planned pregnancies in 3 and 10 days after delivery and this deferences are statistically significant.

Conclusion: unintended pregnancy may be a potential causal factor for maternity postpartum blues in teenagers.

P-14-002 Persistent effect of lead chronic toxicity on depression and anxiety in male wistar rat

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Objective: The objective of this study was to investigate the persistent effect of lead on depression and anxiety of adult male Wistar rats.

Methods: Male adult Wistar rats are submitted to chronic intoxication by lead nitrate (50 mg/L) diluted in tap water during six months. After that, the intoxication was stopped for 4 months, and the neurobehavioral tests were assessed. Depression was evaluated using the Forced Swim Test (FST) by calculating the immobility time (IT). Anxiety was measured by calculating the number of Entries in Open Arm (EOA) and the time spent in the Open Arm (TOA), in the Elevated Plus Maze Test (EPM).

Results: The results have shown that the IT was significantly low in intoxicated rats even the administration of toxic was stopped ($p < 0.05$), compared to control ones. However, no significant difference was registered in the intoxicated rats compared to the control in the EOA and TOA.

Conclusion: Chronic lead toxicity had an antidepressant-like effect but had no effect on anxiety in rats even after stopping the intoxication.

P-14-003 The galanin system in the human brain with focus on locus coeruleus and the dorsal raphe nucleus

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Objective: Major depressive disorder is a serious disease that affects about 10% of all men and 20% of women in their lifetime. The noradrenaline (NA) neurons in the locus coeruleus (LC) and the 5-hydroxytryptamine (5-HT) neurons in the dorsal raphe nucleus (DRN) are a central focus in research on depression. The neuropeptide galanin, for which three receptors (GalR1–3) have been cloned is of interest in relation to major depression (Branchek et al., 2000). Galanin coexists with 5-HT in the DRN as well as with NA in LC and has inhibitory actions on both NA and 5-HT neurons (Xu et al., 2005).

Methods: In this study, we have used in situ hybridization to visualize galanin and its receptors in LC and DRN of postmortem human brains, and in addition, tryptophan hydroxylase (TH), nitric oxide synthase (NOS) and vesicular glutamate transporters.

Results: Our results, when compared to rodent brains, show that galanin is found in LC of all three species, but only in rat DRN. GalR1 was detected in rat LC, but in sharp contrast, GalR3 seems to be the major galanin receptor in human LC and DRN. Thus in human, GalR3 is expressed in two nuclei of key importance for depression, that is LC and DRN. In addition, VGLUT1 and −2 were strongly expressed in the pontine nuclei, but could not be detected either in LC neurons or 5-HT neurons. Neither was NOS found in these regíons. Thus, considerable species differences occur with regard to brain messenger molecules, especially neuropeptides.

Conclusion: The present results, taken together with electrophysiological experiments in rats, suggest that a small, blood-brain barrier-penetrating GalR3 antagonist could have anxiolytic and/or antidepressive activity. Such an antagonist has been developed and shown to have anxiolytic/antidepressive-like effects in animal models of depression (Swanson et al., 2005).

P-14-004 Levomilnacipran in the treatment of major depressive disorder: Functional health and well-being efficacy results from a phase III clinical trial

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Objective: Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Data from a positive Phase III trial (NCT00969709) were used to evaluate the functional health and well being of patients with major

depressive disorder (MDD) treated with sustained release (SR) levomilnacipran.

Methods: A double-blind, multicenter, parallel group, placebo-controlled, fixed-dose study was conducted in patients aged 18–65 years who met DSM-IV-TR criteria for MDD and Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR) score ⩾30. The study comprised a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients were randomized to placebo (n = 175) or once-daily levomilnacipran (n = 529) 40 mg, 80 mg, or 120 mg (titrated-up from an initial dose of 20 mg). Functional health and well being were measured using change from baseline to Week 8 on the SF-36v2 acute (1-week recall) health survey. Individual health dimensions, and physical (PCS) and mental (MCS) component summary scores were compared for levomilnacipran and placebo (ITT population) using an ANCOVA model.

Results: Patients in both groups had deficits in mental-health at baseline (MCS scores: placebo, 17.2 ± 9.2; levomilnacipran, 18.2 ± 8.5); in contrast, baseline PCS scores (PBO: 52.6 ± 11.1; LVM: 51.1 ± 11.1) were slightly higher than the population norm. Following 8 weeks of treatment, levomilnacipran patients versus placebo demonstrated significantly greater MCS improvement (LSMD = 4.4 ± 1.36; P = .0013) and on several individual dimensions (General Health [2.3 ± 0.69; P = .0007], Vitality [2.4 ± 1.05, P = .0228], Social Functioning [3.1 ± 1.17; P = .0086], Role Emotional [3.1 ± 1.20; P = .0097], and Mental Health [4.3 ± 1.16; P = .0003]). Nonsignificant PCS [−0.2 ± 0.74; P = .8386] and other dimension score changes were noted.

Conclusion: Levomilnacipran patients experienced statistically significant and clinically meaningful improvements in functional health and well being as measured by SF-36 MCS and associated individual dimensions. Changes in PCS and associated individual dimensions were nonsignificant potentially due to limited physical impairment at baseline.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc.

P-14-005 The efficacy and safety of levomilnacipran in the treatment of major depressive disorder: Results from a phase III clinical trial

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Objective: Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Efficacy and safety were evaluated in a fixed-dose Phase III trial (NCT00969709).

Methods: A double-blind, multicenter, parallel-group, placebo-controlled, fixed-dose study with 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients (18–65 years) who met DSM-IV-TR criteria for MDD, with current major depressive episode ⩾8 weeks and ⩾30 on the Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR) were randomized to placebo or once-daily levomilnacipran sustained release 40 mg, 80 mg, or 120 mg (20-mg initiation; 7-day titration to target dose). Primary efficacy: MADRS-CR score change from baseline to Week 8 (mixed-effects model for repeated measures [MMRM]; intent-to-treat [ITT] population); secondary efficacy: Sheehan Disability Scale (SDS); safety: adverse events (AEs), clinical laboratory measurements, vital signs, ECGs.

Results: Least squares mean difference for MADRS-CR total score change from baseline was significantly superior for all levomilnacipran doses versus placebo: 40 mg (−3.23, P = .0186), 80 mg (−3.99, P = .0038), and 120 mg (−4.86, P = .0005); results remained significant after Hochberg adjustment for multiple comparisons. Significantly greater improvement (P < 0.05) was seen for levomilnacipran 80 mg and 120 mg versus placebo on the SDS, HAMD17, SF-36, CGI-S, and CGI-I assessments. AEs led to significantly higher discontinuation of levomilnacipran 40-mg (7%; P = .0185), 80-mg (15%; P < 0.0001), and 120-mg patients (7%; P = .0316) compared with placebo (2%). Treatment-emergent AEs (TEAEs) occurred in 64%, 76%, 83%, and 77% of placebo and levomilnacipran 40-, 80-, and 120-mg patients, respectively. Common TEAEs (⩾10% of any treatment group) were headache, nausea, constipation, dry mouth, increased heart rate, and hyperhidrosis.

Conclusion: Levomilnacipran SR 40 mg, 80 mg, and 120 mg demonstrated significant improvement in depressive symptoms versus placebo. Levomilnacipran SR was generally well tolerated; however, significantly more levomilnacipran SR patients discontinued due to AEs.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc.

P-14-006 Side effects and treatment discontinuance of reboxetine; treatment of depression in parkinson's disease: Three cases reports

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The efficacy and tolerability of reboxetine, a norepinephrine reuptake inhibitor, have been shown in patients with depression in Parkinson's patients (1,2). Depression in Parkinson's disease occurs frequently %25–40 (3), associated with greater involvement of dopaminergic and non- dopaminergic system. Treatment options in depression of Parkinson's disease vary, including SSRI's (commonly first choice), TCA, MAO inhibitors and new generation antidepressants (4). Main criteria treating depression of Parkinson's disease; side effect profile and efficacy, because of antiparkinson treatment may cause many side effects including nausea, vomiting, orthostatic hypotension, headache and also deterioration of cognitive and motor symptoms. Antidepressant treatment in depression of Parkinson's disease may deteriorate the side effects of antiparkinson treatment causing discontinuance of treatment. We report three cases that used reboxetine treatment in depression at Parkinson's disease. Three cases of our group could not have tolerated the drug and stopped treatment due to side effects reboxetine. Contrary to our experiences and studies on positive effects and well tolerability of drug, we could say that if reboxetin is chosen for depression at Parkinson patients, giving information to patients about side effects and close follow up is necessary.

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P-14-007 Desvenlafaxine naturalistic trial in outpatients

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Objective: This trial evaluated the efficacy and tolerability of desvenlafaxine in the treatment of mayor depressive disorder.

Methods: We worked during 6 months, in an open, naturalistic trial with adult outpatients (24–70 years) with a primary diagnosis of mayor depressive disorder (DSM IV criteria) rating outcome with Clinical Global Impression, Hamilton Scale for Depression, and Sheehan Disability Scale at baseline, 30, 90 and 180 days.

Results: All patients included could complete the trial, with side effects that did not require removal. The results were statistically significant for all variables studied, with a special point that just at first month them were observed.

Conclusion: Desvenlafaxine seems to be a useful therapeutic tool and well tolerated in outpatients with major depression, considering of course; the limited study population and its characteristics.

P-14-008 Suicidal thoughts and reasons for living in hospitalized patients with severe depression: Post hoc analyses of a double-blind randomized trial of duloxetine

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Objective: To evaluate suicidal thoughts in relationship to depressive symptom severity and to Reasons For Living (RFL) in patients hospitalized for severe major depressive disorder (MDD).

Methods: Post-hoc analyses of a duloxetine trial in adult inpatients with MDD who met criteria of DSM-IV, showing a Montgomery-Åsberg Depression Rating Scale [MADRS] score $\geqslant 30$ and a Clinical Global Impression of Severity [CGI-S], $\geqslant 4$. Suicidal thoughts were assessed with MADRS item-10 (suicidal thoughts), depression severity with the MADRS 6-item subscale and protective factors with the patient-rated RFL questionnaire assessing 'survival and coping beliefs', 'responsibility to family', 'child-related concerns', 'fear of suicide', 'fear of social disapproval' and 'moral objectives'. Descriptive statistics and correlation analyses were performed.

Results: At baseline, patients (N = 336) had varying severity of suicidal thoughts on MADRS item-10: 18% had a score of $\geqslant 4$ (4:''Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention''). The proportion of patients with a score $\geqslant 4$ decreased to 7% at Week-1 and 1% at Week-8 of treatment. RFL scores at baseline were lower in patients with higher baseline suicidal thoughts; all RFL domain scores improved significantly during treatment (all $P < 0.01$). Correlations between RFL domains and single depressive symptoms were low and only negatively significant for suicidal thoughts (all $P < 0.05$) and pessimistic thoughts (5 of 7 $P < 0.05$). Suicidal thoughts were significantly, although poorly, positively correlated with depression severity (per MADRS 6-item core symptoms). RFL scores were not significantly correlated with the MADRS 6-item core symptoms.

Conclusion: 18% of inpatients with severe depression had explicit baseline suicidal thoughts scores, which decreased rapidly with treatment. Protective RFL scores increased with decreasing depression severity, suggesting that their protective power depends on the affective status. Depression severity, suicidal thoughts and RFL are mainly independent dimensions since most correlations were low.

P-14-009 Cerebrospinal fluid biomarkers for major depression confirm relevance of associated pathophysiology

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Objective: Individual characteristics of pathophysiology and course of depressive episodes are at present not considered in diagnostics. There are no biological markers available that can assist in categorizing subtypes of depression and detecting molecular variances related to disease causing mechanisms between depressed patients. Identification of such differences is important in order to create patient subgroups which will benefit from medications that specifically target the pathophysiology underlying their clinical condition.

Methods: In order to find characteristic biological markers for major depression we analyzed the cerebrospinal fluid proteome of twelve depressed versus twelve control persons using twodimensional polyacrylamide gel electrophoresis and time-of-flight mass spectrometry peptide profiling. Proteins of interest were identified by matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF/TOF). Validation of a subset of protein markers was performed by immuno-blotting.

Results: We found 11 cerebrospinal fluid proteins and 144 peptide features that differed significantly between depressed patients and controls. In addition, we detected differences in the phosphorylation pattern of several CSF proteins. A subset of the differentially expressed proteins implicated in brain metabolism or central nervous system disease was validated by immunoblotting. The identified proteins are involved in neuroprotection and neuronal development, sleep regulation and amyloid plaque deposition in the aging brain.

Conclusion: This is one of the first hypothesis-free studies that identifies characteristic protein expression differences in CSF of depressed patients. Proteomic approaches represent a powerful tool for the identification of disease markers for subgroups of patients with major depression.

P-14-010 Electrophysiological effects of long-term administration of paroxetine and bupropion on serotonin transmission in olfactory bulbectomized rats

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Objective: Olfactory bulbectomized (OB) rats generally manifest many of the neurochemical, physiological, and behavioural features of a depressive disorder in humans. Another interesting feature of this model is that it responds to chronic but not acute antidepressant treatments, including SSRIs. The purpose of the present study was first to characterize the firing activity of dorsal raphe serotonin (5-HT) neurons in OB rats and then examine the effects of two antidepressants namely bupropion and paroxetine.

Methods: Olfactory bulbectomy was performed by aspirating olfactory bulbs in anesthetized rats. Vehicle and drugs were delivered for 2 and 14 days via subcutaneously implanted minipumps. In vivo electrophysiological recordings were carried out in male anesthetized Sprague-Dawley rats.

Results: Following ablation of olfactory bulbs, the firing rate of 5-HT neurons was decreased by 33%. In OB rats, bupropion (30 mg/kg/day) reversed firing rate of 5-HT neurons to control level following 2- and 14-day administration and also induced a disinhibition of CA3 pyramidal neurons following i.v. injection of WAY100635; paroxetine administration (10 mg/kg/day) did not result in normalizing the decrease observed in OB rats. In the hippocampus, although to a lesser extent than bupropion, paroxetine administration also resulted in disinhibition of pyramidal neurons.

Conclusion: The decrease in firing of 5-HT neurons in OB rats is consistent with the hypothesis of a decreased 5-HT neurotransmission in depression. This supports the use of this model to test the action of antidepressants on firing activity of monoaminergic systems. The present results also indicate that unlike paroxetine, bupropion administration promptly normalized 5-HT neuronal activity and increased tonic activation of the 5-HT1A receptors in hippocampus.

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P-14-011 Electrophysiological effects of the multimodal antidepressant LU AA21004 on serotonin transmission in the rat hippocampus

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Objective: Newer classes of antidepressants with more than one mode of action have the potential to increase remission rates. LuAA21004 is a novel multimodal antidepressant that is a 5-HT3 and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the 5-HT transporter in vitro.

Methods: In vivo electrophysiological recordings and stimulations of the ascending 5-HT bundle originating from the raphe nuclei were used to determine the effects of LuAA21004 on CA3 hippocampal pyramidal neurons in anesthetized male rats. LuAA21004 was injected intravenously (2–6 mg/kg) or administered subcutaneously for 14 days, at a dose of 5 mg/kg/day via an osmotic minipump.

Results: The recovery time from complete inhibition of pyramidal neurons after micro-iontophoretically applied 5-HT, an index of 5-HT transporter activity, was increased after 14-day administration of LuAA21004. In contrast, the inhibition of CA3 pyramidal neurons

after micro-iontophoretically applied 5-HT was unchanged. Injection of the 5-HT1A receptor antagonist WAY100635 increased CA3 pyramidal neuron firing, indicating an enhanced tonic activation of post-synaptic 5-HT1A receptors. Stimulation of the 5-HT bundle produced a decreased inhibition of the firing of CA3 pyramidal neurons at 5 Hz compared to 1 Hz.

Conclusion: LuAA21004 blocks 5-HT transporters, but does not dampen the sensitivity of postsynaptic 5-HT1A receptors. In addition, LuAA21004 decreased the function of the terminal 5-HT1B autoreceptor, thus showing that its partial agonism led to increased 5-HT release. Long-term LuAA21004 administration increased the tonic activation of the postsynaptic 5-HT1A receptor in the hippocampus, an effect common to all antidepressants.

Policy of full disclosure: Mostafa El Mansari and Maurice Lecours have no disclosures. Pierre Blier has received grants and/or honoraria from Astra Zeneca, Biovail, Bristol Myers Squibb, Valeant, Eli Lilly, Janssen, Labopharm, Lundbeck/Takeda, Schering-Plough/Merck, Sepracor, Servier, and Wyeth.

P-14-012 Chronic low-grade inflammation induces depression-like behavior in rats

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Objective: Depression has been associated with a low-grade inflammation, as revealed by clinical studies showing elevated levels of pro-inflammatory cytokines in depressed patients. These patients are often treatment-resistant, and some studies show that elevated markers of inflammation predict a poor response to treatment. Furthermore, increasing evidences show that metabolic abnormalities such as obesity and diabetes mellitus type 2 are associated with a low-grade inflammation. The aim of this study is to investigate the effects of a systemic low-grade inflammation induced by lipopolysaccharide (LPS) on Sprague-Dawley rats on depression-like and metabolic parameters.

Methods: Chronic infusion of LPS (at a high, medium and low dose) for 28 days was performed by using subcutaneously implanted osmotic minipumps, administering LPS through a catheter into the abdomen. Depression-like behavior was assessed in the forced swim test (FST). Peripheral and central levels of pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6) together with the expression of enzymes involved in the tryptophan-kynurenine pathway, will be analyzed in specific brain regions using real-time qPCR. Body weight and food intake was measured once a week, while fasting glucose and insulin sensitivity was assessed after four weeks of LPS administration.

Results: Our results showed that a low dose of LPS increased immobility in the FST relative to vehicle treatment, indicative of depression-like behavior. We did not find any difference in body weight, fasting glucose and insulin values. However, a high dose of LPS caused an increase in liver weight. Analysis of cytokine and mRNA expression levels is currently being carried out and these results are pending.

Conclusion: Our results indicate that a low dose of LPS can produce depression-like behavior, without inducing metabolic disturbances or sickness behavior. Thus, this model might help elucidating some of the mechanisms underlying inflammation-associated depression, in order to assist in developing more effective treatment strategies for this group of patients.

P-14-013 Lower frequency of early discontinuation of mirtazapine in elderly Japanese patients with depression

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Objective: Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), and has been approved in many counties for the treatment of major depression. In Japan, it has been available since 2009 and has been safely used for elderly patients. Treatment continuation is an important measure of effectiveness in patients with depression, reflecting the efficacy, safety, and tolerability. This retrospective study examined whether there was association between age of patients and the rate of early discontinuation of mirtazapine.

Methods: A total of 89 patients with major depression, who were on mirtazapine monotherapy, were surveyed. The rate of the patients who discontinued mirtazapine within eight weeks from the initiation was compared between elderly patients (65 years or older, $n=33$) and non-elderly patients ($n=56$). In the patients who continued mirtazapine, the final dose, and its efficacy assessed by Clinical Global Impression – Improvement (CGI-I), were compared between the two groups.

Results: The discontinuation rate of elderly patients within eight weeks was significantly lower than that of non-elderly patients (18% vs. 63%, respectively, $p<0.001$). In the patients continuing mirtazapine, there was no significant difference in the final dose between two groups (26 ± 11 mg/day vs. 26 ± 11 mg/day). In addition, there was no significant difference in the efficacy between two groups; the ratio of very much improved and much improved was 62% and 56%, respectively. The most common reasons of discontinuation in non-elderly patients were sedation ($n=16$) and increased appetite ($n=4$), while there were only two patients who developed sedation in elderly patients.

Conclusion: This study shows that the rate of early discontinuation of mirtazapine is lower in elderly patients than non-elderly patients, possibly due to lower incidence of side effects. Therefore, mirtazapine might be effective, safe and tolerable agent especially for elderly patients with depression.

P-14-014 Levomilnacipran in the treatment of major depressive disorder: An analysis of efficacy and safety data from two phase III studies

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Objective: Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Data from Phase III trials (Study 1: NCT00969709; Study 2: NCT00969150) were used to evaluate the efficacy and safety of levomilnacipran sustained release in major depressive disorder (MDD).

Methods: Studies were double-blind, multicenter, randomized, placebo-controlled with a 1week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients with Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR) scores $\geqslant 30$ with current major depressive episode $\geqslant 8$ weeks (Study 1) or $\geqslant 4$ weeks (Study 2) were randomized to once-daily levomilnacipran 40, 80, or 120 mg (Study 1; fixed-dose) or levomilnacipran 40–120 mg/day (Study 2; flex-dose) or placebo. Primary and secondary efficacy: MADRS-CR and SDS total score change from baseline to end of Week 8, respectively; safety: adverse events (AEs), laboratory measures/vital signs. Data were pooled and analyzed using a mixed-effects model for repeated measures (MMRM); statistical difference in primary efficacy was seen in Study 1 only.

Results: Pooled baseline characteristics were similar for placebo ($n=358$) and levomilnacipran ($n=712$); 80.2% of placebo and 70.6% of levomilnacipran patients completed the studies. Significant improvement was seen for levomilnacipran versus placebo on MADRS-CR (LSMD $=-2.73$; $P=.0009$) and SDS (LSMD $=-1.44$; $P=.0190$). Discontinuation due to AEs occurred in 2.0% of placebo and 9.1% of levomilnacipran patients; 63.1% of placebo and 78.8% of levomilnacipran patients reported treatment-emergent AEs (TEAEs); the majority were transient and mild/moderate in intensity. The most common ($\geqslant 10\%$) TEAEs (placebo vs. levomilnacipran) were headache (12% vs. 17%), nausea (3% vs. 16%), and dry mouth (8% vs. 10%).

Conclusion: Pooled analyses showed that levomilnacipran-treated patients achieved statistically significant and clinically meaningful improvement in depressive symptoms and functional impairment. Higher placebo response in Study 2 may explain different individual study outcomes. Levomilnacipran was generally well tolerated.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc.

P-14-015 Tolerability of polypharmacotherapy in psychiatry

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Objective: In this study we analyzed data from psychiatric inpatients treated under naturalistic conditions and supervised by therapeutic drug monitoring (TDM) to compare the occurrence of side effects under monotherapy and polypharmacy. Combination therapies were screened for potential risks to reveal if combinations considered as critical are associated with an increased risk of side effects.

Methods: Data were collected from the request and reporting forms of psychiatric inpatients for whom TDM of antipsychotic or antidepressant drugs was requested during a period of 6 months. All drug combinations were checked by a drug-drug interaction program (www.psiac.de) for potential risks.

Results: The study included data from 488 inpatients, most of them with the diagnosis of either schizophrenia (46%) or major depression (40%). The prefered antipsychotic drugs were olanzapine (n=139), quetiapine (n=101), clozapine (n=90) and risperidone (n=85). Antidepressant drugs included venlafaxine (n=145), mirtazapine (n=96), sertraline (n=72), escitalopram (n=37) and citalopram (n=32). Only 21% of the patients receiving antipsychotic drugs were under monotherapy and under antidepressant medication, we identified 23% of monotherapies. Side effects were reported for 16% of the patients under monotherapy and for 39% under polypharmacy with antipsychotic drugs. Most frequent were sleepiness and extrapyramidal symptoms. Treatment with antidepressant drugs was associated in 12% with side effects under monotherapy and in 29% under polypharmacy. Under combinations with antipsychotic drugs for which a potential risk was identified by the computer program side effects were reported for 51% of the cases. For antidepressant drugs, side effects were reported in only 29% of the combinations considered as critical.

Conclusion: Combination therapies with antipsychotic or antidepressant drugs is associated with reduced drug-tolerance. Polypharmacy must therefore be considered as a risk for more side effects. Computerized analysis of drug combinations could be useful to detect potential risks due to drug-drug interactions and thus improve tolerability.

P-14-016 Adjunctive acetaminophen therapy for major depression: A preliminary report

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Objective: To investigate the efficacy of adjunctive acetaminophen in the treatment of major depressive disorder.

Methods: In this preliminary open-label study, patients with major depressive disorder (DSM-IV), who were aged between 20 and 80 and failed to show a 20% reduction in the total score of Montgomery-Asberg Depression Rating Scale (MADRS) from screening to baseline were included. Exclusion criteria included presence of any psychotic feature and/or suicidal thought and any past history of, or current gastrointestinal ulceration, liver dysfunction, or allergic reactions to acetaminophen. Acetaminophen was given at fixed dose of 1500 mg/day for 4 weeks while other psychotropic medications, including antidepressants, were kept constant during the study. Assessment scales included the MADRS, the Quick Inventory of Depressive Symptomatology self–report (QIDS-SR), and Visual Analogue Scale (VAS) for pain at baseline and 1, 2, and 4 weeks. Adverse effects were monitored at every visit. Data were reported, using a last-observation-carried-forward method.

Results: Seven patients entered this study. These patients had been treated with their antidepressants for X+Y weeks at the time of baseline assessments. One patient showed an improvement during the screening phase and was therefore excluded. Thus, six patients proceeded to the augmentation stage and provided the data for analyses. One patient prematurely withdrew from this study due to abdominal discomfort and another due to deviation from the protocol. As a result of 4-week acetaminophen augmentation, mean total MADRS score was reduced from 21.7 to 12.2. Likewise, the mean total QIDS-SR score improved from 15.2 to 9.8, and the VAS score from 4.7 to 3.2.

Conclusion: Although the data are still preliminary, the results point to some possibility of acetaminophen as an augmentation strategy for patients with treatment-refractory major depressive disorder.

P-14-017 Personality dimensions in major depressive disorder predict cortisol reactivity to the combined dexamethasone/CRH test

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Objective: It is generally acknowledged that depression is associated with altered hypothalamic-pituitary-adrenal (HPA) axis function, most notably hypercortisolism. However, findings on HPA axis function in depression are not entirely unequivocal, such that hypercortisolism has not been observed in some studies. Another line of research has demonstrated that various psychiatric conditions, including atypical depression, are associated with hypocortisolism. Moreover, personality is shown to be associated with HPA axis alteration. Taken together, different personality pathology in depression may play a role in the distinct HPA axis alteration.

Methods: Eighty outpatients with DSM-IV major depressive disorder were recruited. Personality was assessed by the Temperament and Character Inventory (TCI). Depressive symptoms were assessed by the Hamilton Rating Scale for Depression. HPA axis reactivity was measured by the combined dexamethasone/corticotropin-releasing hormone (CRH) test. According to previous studies, two subgroups were considered based on their cortisol responses to the dexamethasone/CRH test: incomplete-suppressors whose cortisol response was exaggerated and enhanced-suppressors whose cortisol response was blunted.

Results: Of the seven TCI dimensions, cooperativeness was significantly positively correlated with cortisol levels after combined dexamethasone/CRH challenge ($p<0.001$). Incomplete-suppressors scored significantly higher in cooperativeness than enhanced-suppressors ($p=0.003$). A logistic regression analysis, controlling for age, gender and symptom severity, was performed to predict the cortisol suppression pattern (i.e., incomplete- vs. enhanced-suppression) from TCI scores, which revealed that reward dependence ($p=0.04$) and cooperativeness ($p=0.003$) were significant predictors for enhanced- and incomplete-suppression, respectively.

Conclusion: These findings can be viewed in light of the known association of atypical depression with personality pathology and hypocortisolism. Given the evidence that atypical depression and melancholic depression could benefit from different treatment approaches, our findings would be of clinical importance as they suggest the possibility of distinguishing these different types of depression based on the distinct directions of HPA axis alteration.

P-14-018 Dopamine transporter gene (DAT1) possible affects personality traits in early-onset patients with major depressive disorder

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Objective: Comorbid personality pathologies may affect the outcomes of patients with major depression (MD). The dopamine transporter gene DAT1 (SLC6A3) has been suggested to play a role in both depression and specific personality traits. The aim of this study selected five polymorphisms of DAT1 to explore whether this gene influences personality traits in patients with MD or its subgroups.

Methods: The DAT1 polymorphisms were analyzed in 463 unrelated Han Chinese MD patients. All patients were screened using the same assessment tool and the diagnosis of MD was made based on a consensus opinion. The personality traits novelty seeking (NS) and harm avoidance (HA) were examined using the Tridimensional Personality Questionnaire. The patients were also divided into four clinical subgroups based on differences in their sex (male or female) and age at disease onset (early or late).

Results: There was no association between DAT1 and either NS or HA in the total MD patient sample. However, in a subgroup analysis, male MD patients with the T/T genotype of rs2975226 had lower HA scores than patients with the other genotypes (Pcorrected = 0.015). Furthermore, early-onset MD patients with the G/G genotype of rs2550948 and the T/T genotype of rs2975226 had lower NS scores than patients with other genotypes (Pcorrected = 0.005 for rs2550948 and Pcorrected = 0.0005 for rs2550948).

Conclusion: Our study suggests that DAT1 promoter variants influence specific personality traits in male and early-onset subgroup of depressed patients among Han Chinese population. Further prospective cohort studies are required to verify our preliminary finding and to confirm the effects of personality susceptibility on long-term disease outcomes.

P-14-019 Depressed patients with a mild inflammatory phenotype display robust tryptophan depletion in the absence of kynurenine pathway activation

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Objective: The kynurenine pathway (KP) and its rate-limiting tryptophan degrading enzyme indolamine 2,3 dioxygenase (IDO), have been implicated in the pathogenesis of major depression. IDO expression is driven by the inflammatory cytokines IFN-γ, IL-6 and TNF-α, and it has been suggested that IDO induction and resultant KP activation may be the link between inflammation and a decrease in tryptophan availability, which could lead to a serotonergic deficit in depression.

Methods: Here we examined circulating concentrations of the acute phase protein CRP, the inflammatory cytokines IFN-γ, TNF-α and IL-6, alongside plasma tryptophan and kynurenine concentrations and whole blood IDO mRNA expression in a group of depressed patients (average HAM-D score > 25) (n = 39) compared with healthy age and sex-matched control subjects (n = 39).

Results: Whilst no significant change was observed in plasma TNF-α, plasma concentrations of IFN-γ, IL-6 and CRP were increased in the depressed cohort relative to controls. Despite this inflammatory phenotype, IDO mRNA expression or plasma kynurenine concentrations were not significantly different between depressives and controls, indicating that the KP was not activated. Nonetheless, a robust depletion in tryptophan was evident in the depressed cohort relative to controls.

Conclusion: These data support the idea that a mild inflammatory signature is evident in depressed patients, and that this is accompanied by a depletion of tryptophan. However, we found no indication of KP activation in the depressed cohort suggesting that an alternative mechanism/pathway mediates the depletion of tryptophan observed in depressed patients.

P-14-020 Quality of living, depression and psychosomatic diseases in medical doctors

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Objective: Material achieved from my four research works is used for composing of this paper. This paper is related to one target group – the medical doctors.

Methods: Thinking about doctor's quality of living, from the aspect of free-time, without free-of-charge professional engagement, we have asked our colleagues specific questions (trought the anonymous questionnaire). The questionnaire analysis of 50 polled doctors aged 30–55 y. gave the following results. Thirty polled doctors (60%) used its own free-time for extra professional engagement. Seventeen polled doctors (34%), partially managed to evade those activities, but only three of them (6%) did not practice extra professional activities.

Results: As a research instrument, the scale for self-estimation of depression (ZUNG) is used. Fifty two doctors of both sexes filled the questionnaire out, 30–55 years aged. According to the scale recognition key, the following results appeared. Depression – free were 8 of polled (15.38%), and 10 of them (19.23%) suffered depressivity in remission. In category of depression with other disorders, belong 30 polled doctors (57.69%) and four (7.69%) of them need depression treatment. Aim of the fourth examination is to show psychosomatic diseases and related depres-sivity occurrence with general practice medical doctors. We have used anonymous questionnaire on catching psychosomatic diseases, and the self-estimating scale of depressivity (ZUNG), as research instruments. Thirty six doctors and general medicine specialists of both sexes, 30–55 year aged, were completed those lists. In the polled group there is one third suffering from psychosomatic diseases with doubled level of depressivity that needs medical treatment, in relation with complete group (30.76% to 16.66%).

Conclusion: Depression is occurred considerably also in total number of polled doctors. As the most important factors for depression and psychosomatic diseases occurrence there are: stress and overload at work, status in wide social environment and bad economic situation.

P-14-021 Recurrence of winter amenorrhea in affective illness

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Objective: Affective illness and endocrine dysfunction can worsen perimenopausally. We described the phenomenon of winter amenorrhea in affective illness (Jacobsen and Comas-Diaz, 2004). Our longitudinal study now reveals that women suffering depressive illness may experience recurrent amenorrhea during successive winters, sometimes years before perimenopause.

Methods: Subjects were mood-stabilized female bipolar spectrum or unipolar outpatients without previous amenorrhea (skipping three consecutive periods) or recent steroid use. Naturalistic monitoring included bimonthly evaluation of menstrual cycling, sleep, appetite/weight, energy/activity, sexual function, cognition, and mood. Other data analysed included menarche, parity, laterality, diurnality, headache, neuroendocrinology, family genetic and treatment history.

Results: 26 women (17 bipolar, 9 unipolar) treated for 15.7 ± 5.9 years experienced 4.6 ± 1.9 months of fall/winter amenorrhea beginning age 48.8 ± 3.3 years. 17 (65%) had past fall/winter depressions. – 7 of 26 (19%) had amenorrhea in 2+ successive winters – depression ratings remained unchanged during amenorrheic episodes. – 85% of winter amenorrheics (N = 22) suffered migraine (usually perimenstrual), which lessened in only 3 while amenorrheic. – 18 (69%) reported feeling menstrual cycle manifestations while amenorrheic – two long-stabilized amenorrheic bipolars abruptly menstruated and switched into mixed-mania following 7+ days mid-winter exposure to greatly increased environmental sunlight + temperature – two unipolars experienced 7+ days of insomnia + racing thoughts coincident with abrupt resumption of menstruation in spring.

Conclusion: Winter amenorrhea can be a recurrent phenomenon in affective illness. During winter amenorrhea mood appears stable while physical feelings of menstrual cycling may recur, suggesting a complex relationship between seasonally decreased serotonergic function and perimenopausal estrogen decline. Sudden intense light + heat exposure during winter may dramatically alter endocrine and affective symptomatology in perimenopausal women.

P-14-022 Efficacy and clinical relevance of vilazodone in the treatment of major depressive disorder: A pooled analysis of phase III clinical trials

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Objective: Vilazodone, a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, is FDA approved for treatment of major depressive disorder (MDD) in adults. Data from Phase III trials, both of which were positive, were analyzed to evaluate efficacy across depression symptoms (MADRS total and single items) and clinical relevance of results (number needed to treat [NNT] and harm [NNH]).

Methods: Data from 2 double-blind, 8-week, randomized, placebo-controlled trials (NCT00285376, NCT00683592) were pooled. Patients

(18–70 years) with DSM-IV-TR-defined MDD and HAMD17 score ⩾22 received vilazodone (n = 436) or placebo (n = 433); trials comprised a 1-week screening and 8-week double-blind treatment. Vilazodone was titrated to 40-mg (taken once daily with food) over a 2-week fixed-dose titration period. Primary efficacy outcome: MADRS total score change from baseline to Week 8. Post hoc analyses estimated treatment effects of vilazodone versus placebo on MADRS total and single items (using analysis of covariance and last observation carried forward approach), NNT for response (MADRS ⩾50% improvement) and remission (MADRS ⩽10), NNH for adverse events (AEs) and AE discontinuations.

Results: Vilazodone significantly improved MADRS total scores relative to placebo: least squares mean difference (LSMD), −2.79 (P < 0.0001). Significant improvement for vilazodone versus placebo occurred on every MADRS single item (LSMD): apparent sadness, −0.24; reported sadness, −0.29; inner tension, −0.31; reduced sleep, −0.30; reduced appetite, −0.20; concentration difficulties, −0.24; lassitude, −0.27; inability to feel, −0.25; pessimistic thoughts, −0.35; suicidal thoughts, −0.29 (P < 0.01 for all). NNT (95% CI) for response and remission: 8 (5, 17) and 12 (7, 37), respectively; NNH (95% CI) for AE discontinuations: 26 (15, 106).

Conclusion: Vilazodone showed broad efficacy across depression symptoms. An NNT ⩽10 for response is generally regarded as evidence for clinical relevance in depression treatment; the NNT and NNH analyses suggested a lower risk of AE discontinuation relative to clinically meaningful improvement for vilazodone.

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P-14-023 Hormones, cytokines, and adipokines in the course of depression – potential biomarkers for treatment response?

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Objective: A plethora of alterations in different biological systems such as hormonal axes, immune system, and metabolic pathways have been described in major depression and gave rise to several theories regarding pathophysiological mechanisms of depressive disorders. This led us to investigate whether serum parameters indicating status and changes of these biological systems are altered among patients with major depression or could serve as potential biomarkers for treatment response in depressed patients.

Methods: We analyzed hormones, cytokines, and adipokines (cortisol, leptin, ghrelin, insulin, insulin like growth factor 1 (IGF-1), sexual hormone binding globulin (SHBG), testosterone, C-reactive protein (CRP), and interleukin 6 (IL6)) in healthy subjects and patients with major depression from the Munich Antidepressant Response Signature Project (MARS) at admission and after 6 weeks of antidepressant treatment.

Results: We observed significantly elevated IGF-1 in depressed patients compared to healthy controls. Additionally, IGF-1 was significantly decreased in patients responding to antidepressant treatment at baseline and after 6 weeks in comparison with non-responders. Furthermore, non-responders showed elevated inflammation parameters (IL6 at baseline and CRP after 6 weeks) and testosterone increased during antidepressant treatment in responders compared to non-responders.

Conclusion: We conclude that easily accessible serum parameters like IGF-1, CRP, IL6 or testosterone, could possibly serve as biomarkers in antidepressant treatment. In particular, differences in IGF-1 and IL6 levels between responders and non-responders were already present at baseline. Further validations in prospective studies as well as investigations particularly with regard to biological mechanisms in major depression are necessary to substantiate these findings.

P-14-024 Thai women with depressive disorder: Explanatory model

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Objective: This qualitative study aims to describe an explanatory model of illness in Thai women with Major Depressive episode.

Methods: The study was conducted in a semi-rural area with 25 Thai women who were diagnosed with major depressive disorder. These women were under a two-year project of the Thai Depression Surveillance System. Semi-structure interviews based on Kleinman's explanatory framework were used. Data were collected by in-depth interviews and focus groups. Content analysis was used to disclose the relevant themes.

Results: Most participants called their illness as ''stress''. Only seven participants perceived it as depressive disorder. All expressed that ''thinking a lot'', especially around family related issues was the cause of their illness. The other common cause of their depression was the inability to let go (Thum- jai) of the unwanted situation. Almost all participants benefited from the use of antidepressants. However, they were not taken as prescribed. Some participants reported that listening to community broadcasting radio's Dhrama was helpful. The other method was self-agency. All women felt stigmatized from getting treatment from a psychiatric hospital. They preferred to get treatment from a community hospital instead. Almost all revealed that they were more comfortable to receive treatment from a female therapist.

Conclusion: The findings suggest that effective psycho-education program on depressive disorder is needed. Therapists have to listen to and take patients' perspectives into account. Mental illness treatment should be integrated in a primary care setting and Buddhist teaching should be employed.

P-14-025 The prevalence of major depressive disorders in Thailand: National survey

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Objective: To present nationally representative data on prevalence of major depressive disorder (MDD) and dysthymia in Thailand.

Methods: Nationally representative face-to-face household survey based on a stratified three-stage cluster sampling of non-institutionalized people aged 15 years and over (n = 19.000) and selected each stage by means of random sampling. The data were conducted between June and August 2008 using Mini International Neuropsychiatric Interview (M.I.N.I.) by trained psychiatric professionals. The data analysis were calculated by means adjust weight of prevalence for generalized to Thai population.

Results: The number of participants of this the national survey was 20,579 people of 15 and over years. The overall of prevalence rates in major depressive episode current accounted for 2.40% (SE = 0.19) that could estimated the number of population about 1,311,797 in Thailand with 1.7% (SE = 0.16) in male and 2.9% (SE = 0.32) in female, while all of major depressive episode recurrent found approximately 386,712 in Thais with 0.7% (SE = 0.13) of prevalence and 0.4% (SE = 0.08) of male and 0.9% (SE = 0.22) of female. Also, the prevalence of dysthymia current found approximately 0.3% (SE = 0.06) that could estimate the number of Thai about 181,809 with 0.2% (SE = 0.04) in male and 0.5% (SE = 0.09) in female. Moreover, the age group among 80 years and older indicated the prevalence rates of major depressive disorder about 5.0% (SE = 2.32), found in women rather than men with 1.71 : 1 sex ratio and shown the highest in the region of capital of Thailand, Bangkok, account for 4.1% (SE = 0.51).

Conclusion: Major depressive disorder is a common disorder in the general population of Thailand. These findings will establish the programs for preventing and planning mental health services for people who suffer from major depressive disorder or dysthymia especially in female and older person.

P-14-027 Psychopharmacological studies on atrovastatin and its solvatomorphs in experimental paradigm of depression

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Objective: A complex relationship exists among stressful situations, body's reaction to stress, and the onset of clinical depression. Chronic unpredictable stressors can produce a situation similar to clinical depression and such animal models can be used for the pre-clinical evaluation of antidepressants. There is a complex relationship between lipid-lowering drug therapy and psychological well-being and it remains an issue of debate for long. Atorvastatin's poor bioavailability and brain penetration limits its neuroprotective efficacy. Polymorphism could enhance the stability, solubility and bioavailability of existing drugs. The present study was designed to investigate possible antidepressant potential of atorvastatin and its solvatomorph in unpredictable chronic stress-induced depressive like behavior.

Methods: Animals were subjected to different stress paradigms daily for a period of 21 days to induce depressive-like behavior. The sucrose preference, immobility period, locomotor activity, memory acquisition and retention were evaluated.

Results: Chronic treatment with atorvastatin and its solvatomorph significantly reversed the unpredictable chronic stress-induced behavioral (increased immobility period, reduced sucrose preference), biochemical (increased lipid peroxidation & nitrite levels; decreased glutathione levels, superoxide dismutase, catalase & MAO activities) and inflammation surge (serum TNF-α) in stressed mice.

Conclusion: The study revealed that atorvastatin and its solvatomorph exerted antidepressant-like effects in behavioral despair paradigm in chronically stressed mice, specifically by modulating central oxidative-nitrosative stress, MAO activity and inflammation independent of its lipid lowering effect. However, solvatomorph showed better antidepressant efficacy as compared to atorvastatin.

P-14-028 The concentration of brain glucagon-like peptides (GLP-1 and GLP-2) in an animal model of depression

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Objective: Recent findings have shown that insulin resistance and, in consequence, disturbed glucose metabolism in the brain might play a role in the pathogenesis of depressive disorder. Insulin action and metabolic processes are regulated by various hormones and proteins, interactions of which have been thoroughly examined in peripheral tissue, however, their role in brain tissues, especially in depression, is weakly recognized, yet. Among compounds crucially involved in insulin action, incretin hormones – glucagon-like peptides (GLP) play an important role. The aim of the present study was to find out whether there are any changes in the amount of GLP-1 and GLP-2 in an animal model of depression.

Methods: Pregnant Sprague-Dawley rats were subjected to stress from 14 to 21 days of pregnancy. After weaning, male rats were housed for 3 months and next the forced swim test (Porsolt test) was performed. Two days after the Porsolt test, the animals were killed by rapid decapitation and the brain structures were dissected. The concentrations of GLP-1 and GLP-2 were determined by ELISA methods and glucose level was measured by fluorometric assay.

Results: It has been found that prenatally stressed rats had statistically significantly higher levels of immobility behavior in the forced swimming test than control animals, i.e. they showed depression-like behavior. A biochemical study demonstrated that prenatally stressed rats had about a 30% higher glucose concentration in the frontal cortex, but the amount of GLP-1 and GLP-2 in frontal cortex and hippocampus did not differ from those observed in control animals, however, a decreasing tendency was observed.

Conclusion: The obtained results indicated that prenatal stress significantly prolonged the immobility time in the Porsolt's test, i.e. evoked depression-like behavior, and enhanced glucose level in the frontal cortex. However, these changes were not accompanied by a significant difference in the concentration of incretin hormones.

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P-14-029 Contribution of socioeconomic conditions to association studies of serotonin transporter gene-linked promoter polymorphism and depressiveness

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Objective: Environmental varieties affect association between serotonin transporter gene-linked promoter polymorphism (5-HTTLPR) and depression [Karg et al., 2011, Arch Gen Psychiatry 68: 444–454]. In addition to the nature of stressful life events (SLE), other factors such as ethnicity should be considered as modifiers because ethnic minorities often experience socioeconomic disadvantages [Black et al., 2006, Rev Econ Stud 88: 300–313] and are therefore possibly more exposed to stress compared to ethnic majorities.

Methods: The data of the first and second follow-up of the older cohort of the Estonian Children Personality, Behaviour and Health Study [Harro et al., 2009, Biol Psychol 81: 9–13] were used. Data were collected in 2001 and 2008 when participants were 18 (n = 454, 194 male and 260 female; 356 Estonians, 98 Russians) and 25 years old (n = 540; 229 male and 311 female; 423 Estonians, 117 Russians), respectively. Symptoms of depression were measured with the self-report version of the Montgomery-Åsberg Depression Rating Scale [Montgomery and Asberg 1979, Brit J Psychiat 134: 382–389]. The history of noninterpersonal SLE in the preceding year was self-reported at age 25.

Results: The score of depressiveness, education level and income were similar in Estonians and Russians. By age 25, Russians had experienced more stressful life events. Eighteen years old Estonians reported higher monthly income of both parents and better economic conditions compared to Russians. Estonian males with the l′/l′ genotype of the 5-HTTLPR and more SLE had higher depressiveness. On the contrary, in Russians, the s′-allele carriers who had experienced higher level of SLE reported higher depressiveness. In females, the 5-HTTLPR x environment interaction effect on depressiveness did not differ between Estonians and Russians.

Conclusion: In conclusion, association between the 5-HTTLPR genotype and depressiveness qualitatively depends on demographic variables and the impact of the latter can be gender-dependent.

P-14-030 Neonatal tryptophan depletion and corticosterone supplementation result in depressive-like abnormalities in adult male mice

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Objective: Current rodent models of human depression suffer from limited construct and external validity whereby they disregard the nature-nurture interactive origin of the disease and are normally suited to inflexible conditions (e.g. single background strain). We developed a animal model reproducing several depressive-like features (symptoms) through the combination of reduced serotonin and environmental stress during the early stages of postnatal life (aetiology). We tested whether the adult mice thereon obtained exhibited behavioral and neurochemical alterations isomorphic to symptoms of human depression.

Methods: We administered, to outbred CD1 mouse dams, during their first week of lactation, a Ltryptophan deficient diet (T) and corticosterone (C) via drinking water (80 μg/ml). Four groups of dams (animal facility rearing, AFR; T treated, T; C treated, C; T and C treated, TC) and their offspring were used in the study. Maternal care was scored throughout treatment and adult male offspring were tested for: anhedonia (progressive ratio schedule); anxiety-related behavior (approach-avoidance conflict paradigm); BDNF, dopamine and serotonin concentrations in selected brain areas.

Results: Compared to AFR, T, C and TC treatments reduced maternal care. Adult TC offspring showed significantly increased anxiety- and anhedonia- related behaviors, reduced striatal and

increased hypothalamic BDNF and reduced dopamine and serotonin in the prefrontal cortex and their turnover in the hippocampus.

Conclusion: The present mouse model recapitulates both the independent (aetiology) and the dependent (symptoms) variables involved in human depression. Furthermore, the independent variables used in this study are plausible to be translated to different mammalian species and ultimately allow externally valid test strategies.

P-14-031 Inflammation, cytokines and brain in psychiatric disorders

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Objective: There is evidence that in many psychiatric disorders, like stress, depression, schizophrenia, and Alzheimer disease there are involved inflammatory and immune processes. The objective is to modulate them and reduce the symptoms. Psychoneuroimmunendocrinology PNIE is concerned with the interaction between the nervous, immune and endocrine system. The immune system influences the brain and endocrine system by releasing cytokines which also activate the central nervous and endocrine system, the hypothalamus and the hypothalamic-pituitary-adrenal (HPA axis) Cytokines can be synthetized and liberated in the brain by astrocytes and microglia. In depression proinflammatory cytokines are increased, IL1,IL6 TNF soluble receptors IL2 and IL6, there is a shift to Th1 cytokines. Antiinflammatory cytokines IL4,IL10,IL13, inhibit syntesis of cytokines. In schizophrenia there is a shift to the Th2 antiinflammatory cytokines and a reduction of IL2 and increment of IL6. In Alzheimer disease there is an elevation of IL1,IL6, cytokines and a reduction of IL2. and they favor synthesis of amyloid precursors that produce senile plaques. Some cytokines like Interferon, TNF, IL2 can alter neurotransmission, produce fatigue, depression, anxiety, suicidal ideation cognitive, psychotic and somatic symptoms.

Methods: Omega 3 fatty acids are the precursors of antiinflammatory prostaglandins, eicosanoids. In patients with moderate depression, we administered polyunsaturated fatty acids omega 3, of Chia capsules, 600 mg, 4 times a day, during 6 months. We evaluated the ratio of TGL/HDL, that are an indirect marker for inflammation, and with Beck depression scale.

Results: We obtained a lowering of the ratio TGL/HDL and an improvement in Beck scale with stabilization of mood.

Conclusion: We suggest omega 3 fatty acids as an adjuvant to modulate inflammatory and antiinflammatory eicosanoids and cytokines. A disbalance could affect the brain and modify the endocrine, immunological, neurological, behavioural responses and the functioning of the PNIE systems.

P-14-032 Efficacy and safety of lisdexamfetamine dimesylate in adults with executive dysfunction and partial or full remission of major depressive disorder

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Objective: Evaluate lisdexamfetamine dimesylate (LDX) augmentation of antidepressant monotherapy for executive dysfunction in participants with major depressive disorder (MDD).

Methods: This randomized, placebo-controlled study enrolled participants (18–55 y) with mild MDD (Montgomery-Asberg Depression Rating Scale [MADRS] total score $\leqslant$18) and executive dysfunction (Behavior Rating Inventory of Executive Function–Adult Version [BRIEF-A] Global Executive Composite [GEC] T-score $\geqslant$60) on stable antidepressant monotherapy for $\geqslant$8 weeks. After 2 weeks of screening, participants were randomized to 9 weeks of double-blind LDX or placebo augmentation, followed by 2 weeks of single-blind placebo. Double-blind treatment was initiated at 20 mg/day and optimized over 6 weeks in 10-mg weekly increments (maximum dose, 70 mg/day); the optimized dose was maintained through week 9. Efficacy (change from baseline to endpoint in BRIEF-A GEC T-score [primary outcome] and MADRS total score [secondary outcome]) was analyzed using analysis of covariance with last observation carried forward. Treatment-emergent adverse events (TEAEs) were recorded.

Results: Of 143 randomized participants (placebo, n=72; LDX, n=71), 119 completed double-blind treatment (placebo, n=59; LDX, n=60). Mean$\pm$SD BRIEF-A GEC T-scores decreased from baseline (placebo, 74.2$\pm$8.88; LDX, 76.8$\pm$9.66) to endpoint (placebo, 61.4$\pm$14.61; LDX, 55.2$\pm$16.15); the least squares (LS) mean (95% CI) treatment difference significantly favored LDX ($-$8.0 [$-$12.7, $-$3.3]; P=0.0009). Mean$\pm$SD MADRS total scores decreased from baseline (placebo, 11.8$\pm$3.77; LDX, 12.7$\pm$3.23) to endpoint (placebo, 8.9$\pm$5.67; LDX, 7.6$\pm$6.28); the LS mean (95% CI) treatment difference significantly favored LDX ($-$1.9 [$-$3.7, 0.0]; P=0.0465). Double-blind TEAE rates were 73.6% with placebo and 78.9% with LDX and included 5 serious TEAEs (placebo, 3; LDX, 2).

Conclusion: LDX augmentation significantly improved executive dysfunction and depressive symptoms in participants with fully or partially remitted MDD. The safety profile was generally consistent with published data.

Policy of full disclosure: Dr. Madhoo is an employee of Shire Development, LLC and holds stock and/or stock options in Shire. This study was funded by Shire Development, LLC.

P-14-033 Agomelatine vs. venlafaxine in major depression: Focus on anhedonia and tolerability

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Objective: In this study we compared the effects of agomelatine and venlafaxine XR on anhedonia in patients with Major Depressive Disorder. Secondary endpoints were to test the overall clinical condition as to the evaluator (CGI) and the safety profile.

Methods: Sixty patients were enrolled and randomly assigned to two different treatments: agomelatine (25–50 mg/day; N=30 subjects) or venlafaxine XR (75–150 mg/day, N=30 subjects). Psychopathological assessment was performed at baseline and after eight weeks of treatment with the Snaith Hamilton Rating Scale (SHAPS), the Hamilton Depression Rating Scale (HAM-D), and the Clinical Global Impression (CGI). Safety parameters were monitored with ECG, urinalysis, haematological and clinical chemical analyses of blood samples at the start and end of the study. Self-reported adverse events provided a measure of safety and tolerability.

Results: Both groups showed a significant reduction in time for SHAPS and HAM-D scores, with higer reduction in the agomelatine group for anhedonia scores. Only patients treated with agomelatine showed a statistically significant improvement in CGI scores. Common adverse events occurred in 1 (3.2%) patient of the AGO group and in 11 (39.2%) patients of the VLX group. Nausea and vomiting (n=6), dizziness (n=2) and hypotension (n=3) were the most common effects across the VLX group. Confusion (n=1) was the adverse event that led to patient withdrawal from the study in the AGO group.

Conclusion: In this study, agomelatine showed significantly greater efficacy on anhedonia and similar antidepressant efficacy to the SNRI venlafaxine XR in patients with Major Depressive Disorder. The subjective evaluation of the treatment efficacy was in favor of agomelatine as to CGI. Agomelatine's safety profile compared favourably with that of venlafaxine XR. Fewer patients withdrew and there were fewer withdrawals due to adverse events in the agomelatine group. In particular, agomelatine treatment was associated with lower incidence of nausea, vomiting and dizziness.

P-14-034 Painful syndromes as signs of masked depression

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Objective: Purpose of this paper is to show how primary painful syndromes, among them mostly cervical and lumbar, are often being unrecognized as depression symptoms.

Methods: 50 patients, diagnosed with cervical and lumbar syndromes have been followed. Age of these patients was between 35–55 years. Appropriate RTG diagnostics have been performed on these patients, in order to find the source to their pain. These

diagnostics excluded existence of serious diseases, which could explain intensity of pain at these patients. Patients have been treated for several months with analgesics and have undergone rehab treatment. After that, patients have been appointed to psychiatric examination. After appropriate psychiatric tests have been conducted (MADRS, HAM-D scales), scores confirmed diagnosis of depression at 34 patients.

Results: All 34 patients received drug therapy (antidepressants) and psychotherapy. 23 patients showed after three months significant improvement that was visible through decreasing of depressive symptoms and minimized score on MADRS and HAM-D scales.

Conclusion: Patients with symptoms of lumbar and cervical syndrome achieved significant improvement after receiving antidepressive treatment. When patient complains of pain in the cervical and lumbar area, it should be taken into consideration that this can be a symptom of depression.

P-14-035 A possible involvement of pro-BDNF processing enzymes in antidepressive effects of electroconvulsive seizure

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Objective: Electroconvulsive therapy (ECT) is the most effective treatment for antidepressant-resistant depression, though the molecular mechanisms remain to be fully elucidated. It was previously shown that electroconvulsive seizure (ECS) strongly increased mRNA levels of brain-derived neurotrophic factor (BDNF) in the rat hippocampus (Nibuya et al., 1995). Although mature BDNF (mBDNF), that is produced through intracellular processing of biosynthetic precursor BDNF (pro-BDNF) in central nervous system neurons (Matsumoto et al., 2008), is antidepressive, recent studies demonstrate that pro-BDNF has negative effects on neurons if secreted. Here, we hypothesized that 1) robust transcription of BDNF induced by ECS led to excess production of pro-BDNF, 2) certain levels of pro-BDNF might be secreted without undergoing intracellular processing, and therefore 3) expression of prohormone convertase 1 (PC1) and tissue-plasminogen activator (t-PA), those are involved in intra- or extracellular processing of pro-BDNF respectively, might be regulated by ECS.

Methods: Male Sprague-Dawley rats (250–300 g) received ECS treatment as reported (Nibuya et al., 1995). Hippocampal levels of pro-BDNF and mBDNF were determined by immunoprecipitation/Western Blotting. PC1 and t-PA levels were determined by Western Blotting or zymography respectively.

Results: Hippocampal pro-BDNF increased within 2 hours after single administration of ECS. More rapidly, single ECS increased the levels of not only PC1 but also t-PA. Interestingly, both pro-BDNF and t-PA were transported to synaptic terminals within 4 hours after ECS, suggesting that t-PA is secreted together with pro-BDNF. Repeated ECS for 10 days increased mBDNF strongly. Finally, chronic treatment with tricyclic antidepressant imipramine slightly increased mBDNF, however, without changes in the levels of pro-BDNF, PC1 and t-PA.

Conclusion: These results suggest that ECS-induced increase in hippocampal mBDNF levels is supported by the robust induction of BDNF transcription and efficient pro-BDNF processing. Such strong increase in mBDNF levels may be important for antidepressive effects of ECT.

P-14-036 Dysregulated HPA-axis in major depression due to FKBP5 polymorphism

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Objective: The FK 506 binding protein 51 or FKBP5 has been implicated in the regulation of the glucocorticoid receptor (GR) sensitivity, especially in major depression and posttraumatic stress disorder. Since the dysregulation of the hypothalamic-pituitary-adrenal (HPA-) axis is one of the most robust biological findings in major depression, we wanted to characterize GR sensitivity in healthy volunteers and depressed patients in dependence of previously identified functional FKBP5 SNPs.

Methods: FKBP5 mRNA expression (baseline and following in vivo GR-stimulation with 1.5 mg dexamethasone p.o.) was analyzed together with plasma cortisol, ACTH, dexamethasone levels and FKBP5 polymorphism rs1360780 in 72 depressed patients and 88 healthy controls. To further evaluate the function of the HPA-axis, we employed the combined dexamethasone/corticotropin-releasing hormone (dex/CRH) test in a subgroup ($n = 64/45$).

Results: While there were no baseline differences in FKBP5 mRNA expression, patients showed less induction of FKBP5 mRNA expression following dexamethasone stimulation ($p = 0.04$). We also observe a significant interaction between disease status and FKBP5 risk allele carriers status (minor allele T), $p = 0.007$. Patients carrying the risk T allele, but not patients carring the CC genotype showed a reduced induction of FKBP5 mRNA. Cortisol and ACTH suppression following dexamethasone was also differentially regulated between T allele and the CC carriers with a reduced suppression only in depressed patients carrying the T allele. These results remained significant when correction for differences in blood dexamethasone concentrations.

Conclusion: Only depressed patients carrying the FKBP5 rs1360780 risk allele show significant GR resistance compared to healthy controls, as measured by dexamethasone-induced FKBP5 mRNA induction and suppression of cortisol and ACTH. This finding might explain why endocrine alterations are not observed in all depressed patients.

P-14-037 Delivery of electroconvulsive therapy in Canada

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Objective: Electroconvulsive Therapy (ECT) continues to be used widely in Canada, but no account of current practices exists. The need for nationwide data about current practices was one of the motivating factors for the Canadian ECT Survey.

Methods: An association of clinicians for Canadian ECT Survey (CANECTS/ECANEC) was created. After first identifying all sites in Canada where ECT was delivered, we subsequently developed a detailed questionnaire (13 pages; 76 questions in 11 sections), translated it into French, piloted it at fourteen sites and then sent a final version to all 175 ECT centres.

Results: Thus we were able to gather wide ranging information pertaining to the practice of ECT in Canada, including the ECT apparatus used, the parameters of the electrical stimuli used to induce seizures, and stimulating electrode placements.

Conclusion: Our findings confirm that the practice of ECT in Canada is generally consistent with contemporary guidelines. Sine wave stimulation is rarely employed, and three placements of the stimulating electrodes are commonly used: bitemporal, bifrontal and right unilateral. Some practical suggestions are recommended to address a few specific concerns.

P-14-038 Vascular endothelial growth factor (VEGF) serum: Putative predictive biomarkers for the electroconvulsive therapy (ECT) in depressed patients

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Objective: Despite controversial issues, electroconvulsive therapy (ECT) remains one of the most eligible therapies among patients with treatment resistant depression (TRD). The Vascular endothelial growth factor (VEGF) is an angiogenic cytokine able to induce vasopermeability in many types of tissues, including the Blood Brain Barrier. Our group have demonstrated that serum VEGF levels in major depressive disorder (MDD) patients were unaffected by escitalopram and that TRD patients have higher serum levels of VEGF following ECT. In addition, a correlation between the increase in VEGF expression and the amelioration of symptoms after ECT was observed. On these bases, the aim of the study was to investigate if VEGF serum levels before treatment might be predictive of ECT response in TRD patients.

Methods: Sixty-four DSM-IV TRD patients were enrolled in the study. Patients were maintained on the same pharmacological treatment for at least 3 weeks before ECT and during the entire study period. Illness severity and the outcome of ECT treatment were assessed using the Montgomery and Asberg Depression Rating Scale (MADRS), before the treatment (T0), and one month later the end of ECT (T1). The Pearson coefficient was used to evaluate bivariate correlations. T-test was used to evaluate differences of means.

Results: The ECT treatment reduced symptomatology as measured with MADRS ($p < 0.0001$), and 73.4% of the patients were considered responders (non responder if percentage MADRS reduction at T1 was <50%). VEGF serum levels at baseline correlate significantly with the percentage reduction of symptomatology after ECT ($p = 0.004$) and were significantly lower in patients non responder at follow-up ($p = 0.002$).

Conclusion: Our results suggested that VEGF serum levels might play a role in the mechanism of response to ECT in TRD patients. The dosage of serum VEGF may be helpful to identify patients who might have a significant benefit from ECT supporting physicians in choosing the better approach to treat TRD.

P-14-039 Investigation to effectiveness of neurofeedback on treatment major depressive disorder in patients' client of Qods hospital

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Objective: 20 patients that have received MDD diagnosis by psychiatrists of Qods hospital contributed in research. patients were divided to experimental and control group. 10 patients in experimental group and 10 patients in control group. Hamilton rating scale for depression scale (HDRS) was filled as pre test (before neurofeedback sessions) and post test (after neurofeedback sessions). In follow up session after 3 month HDSR was filled for both experimental and control group.

Methods: Technician of neurofeedback done neurofeedback sessions. Per patient in experimental group had received 12 sessions of neurofeedback therapy. Both groups have received psychiatric drugs. Cut off point for depression diagnosis was 13. Because of ethical aspects of research control group after research process have received 1 session nurofeedback.

Results: Results show that experimental group has more significant improvement than control group ($p > 0/01$). Results show 53% of differences relate to group membership.

Conclusion: Neurofeedback treatments for depression appear very promising not only in bringing relief from depression, but in modifying the underlying biological predisposition for becoming depressed. Neurofeedback focuses on retraining the brain, for example, reversing the frontal brainwave asymmetry, with the goal of producing an enduring change that does not require people to remain on medication indefinitely.

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P-14-040 Prognostic implications of somatic symptoms in patients with depression. Results from a three-month, prospective, observational study from Asia

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Objective: Patients with major depressive disorder (MDD) frequently suffer from concomitant somatic symptoms. This study aims to investigate the existence of a group of patients depending on the presence of somatic symptoms and to understand the impact of these symptoms on the course of depression.

Methods: Nine hundred and nine patients from Asia presenting with a new or first episode of MDD (DSM-IV/ICD-10) were enrolled in this 3-month prospective observational study. Depressive symptoms (Hamilton Depression Scale-HAMD-17 and Clinical Global Severity score – CGI-S) and somatic symptoms (Somatic Symptom Inventory) were assessed. A cluster analysis was used to define patient groups based on the presence of somatic symptoms. Confirmatory factor analysis was used to classify somatic symptoms in different groups. Regression models were employed to assess the relevance of somatic symptoms on outcomes.

Results: A three cluster solution was chosen based on the variance explained. Cluster 1 patients (39%) had a low level of somatic symptoms. Cluster 2 patients (53%) had a significant level of somatic symptoms. Cluster 3 patients (8%) had severe somatic symptoms. Patients with more somatic symptoms at baseline had more severe depression (HAMD17 and CGI-S) and lower response and remission rates. Response rates were 82% in cluster 1, 72% in cluster 2 and 55% in cluster 3. Remission rates were 68%, 55% and 29% respectively. Four groups of symptoms were validated with the confirmatory factor analysis: as Pain, Autonomic Symptoms, Energy and CNS symptoms. A regression model showed patients with pain symptoms had a lower response (OR = 0.65; 95% CI 0.53–0.80) and remission rates (OR = 0.61; 95% CI 0.49–0.74).

Conclusion: Somatic symptoms are frequent in Asian patients with MDD. Patients with more somatic symptoms have higher depression severity and lower response and remission rates. Pain symptoms are most associated with poorer outcomes.

Policy of full disclosure: Diego Novick, William Montgomery, Alan Brnabic, Zbigniew Kadziola and Xiaomei Peng are full time Eli Lilly & Co. employess Jordan Bertsch was a statistical consultant for the SOHO and EMBLEM studies. He was working with the Fundacio Sant Joan de Deu under a contract with Eli Lilly & Co. Josep Maria Haro has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: Astra-Zeneca, Eli Lilly, Glaxo-Smith-Kline, and Lundbeck Roberto Brugnoli has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: BMS, Eli Lilly, Innovapharma and Sigma-Tau.

P-14-041 DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in psychiatric disorders

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Objective: Psychiatric disorders, for example major depression or schizophrenia, are diagnosed on the basis of clinical symptoms in patients. The search for specific biological markers is of great importance to advance the method of diagnosis for psychiatric disorders. We examined the methylation profiles of the CpG islands at the promoter of exon I of the brain-derived neurotrophic factor (BDNF) gene, which is well known to be involved in the pathophysiology of depression.

Methods: We analyzed genomic DNA from peripheral blood of 38 Japanese patients with major depression and 40 patients with schizophrenia and 18 healthy subjects to identify an appropriate epigenetic biomarker to aid in the establishment of an objective system for the diagnosis of psychiatric disorders. Methylation rates at each CpG unit was measured using a MassArray® system (SEQUENOM), and 2-dimensional hierarchical clustering analyses were undertaken to determine the validity of these methylation profiles as a diagnostic biomarker.

Results: Analyses of the dendrogram from methylation profiles of the CpG islands at the promoter of exon I of BDNF, demonstrated that the classification of healthy subjects and patients at the first branch completely matched the clinical diagnosis. At the next branch, classification of depression and schizophrenia by methylation profiles of CpG islands of exon I was also completely matched the clinical diagnosis.

Conclusion: Despite the small number of subjects, our results indicate that the classification based on the DNA methylation profiles of the CpG islands of the BDNF gene may be a valuable diagnostic biomarker for psychiatric disorders.

P-14-042 Prediction of antidepressant drug response of patients with major depression by citalopram serum concentrations on day 7 and clinical improvement on day 14

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Objective: Clinical trials have shown that early improvement on the Hamilton depression rating (HAMD) scale and citalopram serum concentrations on day 7 are required to attain appropriate clinical response. The aim of this study was to calculate cut off levels for serum concentrations of citalopram and clinical improvement during the early phase of treatment to predict later response and to analyse the predictive power of the combined marker.

Methods: Data of 55 inpatients with a major depressive disorder (MDD) according to ICD-10 who received citalopram were submitted to the analyses. Psychopathology was assessed by the 17-item HAMD rating scale and in parallel serum concentrations of citalopram were measured in weekly intervals for five weeks.

Results: Receiver Operating Characteristics (ROC) analysis revealed for citalopram a serum concentration of 53 ng/ml on day 7 and clinical improvement on the HAMD scale by at least 24% on day 14 to predict response on day 35. The serum concentration of citalopram on day 7 and early improvement on day 14 taken together, predicted response on week 5 with 73% sensitivity and 85% specificity.

Conclusion: Our results show that treatment with citalopram should be guided by symptom rating on day 14 and serum concentration measurement on day 7 to guide antidepressant drug treatment and minimize the risk of treatment failure in patients suffering from major depression.

P-14-043 Dopamine and adenosine antagonism have opposite effects on the activational and the directional components of sucrose-motivated behavior: Studies in rats and mice

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Objective: Functional interactions between adenosine and dopamine (DA) receptors play an integral part in the regulation of striatal areas, including nucleus accumbens (Nacb). Mesolimbic DA is a key component of the brain circuitry regulating motivated behaviors, and Nacb DA regulates behavioral activation and effort-related processes. Caffeine and theophylline are minor psychostimulants that act as nonselective adenosine receptor antagonists. While adenosine antagonists increase motor activities, DA antagonists reduce them. However, because studies in the literature argued for a reduction in the hedonic value of sucrose after DA antagonism, the present experiments were undertaken to study the impact of adenosine and DA antagonism on the activational and directional components of motivated behaviors using sucrose as the reinforcer.

Results: Male CD-1 mice with one-hour access per day to a solution containing 10% sucrose in the home cage consumed significant amounts of sucrose. A low dose of the DA D2 antagonist haloperidol did not block sucrose consumption. A2A KO mice however, consumed less sucrose than WT animals. A stimulus associated with sucrose presentation in the home cage stimulated exploratory activity in a novel environment. A low dose of haloperidol blocked this conditioned behavioral activation. On a FR7/free access choice procedure, Sprague-Dawley rats press the lever to obtain 5% sucrose and drink low quantities of free 0.3% sucrose. Haloperidol decreased lever pressing for 5% sucrose but increased free 0.3% sucrose intake, thus inducing a shift in the choice towards a less effortful behavior. Caffeine reduced lever pressing but also free access sucrose consumption. These pharmacological manipulations in rats drinking in the home cage under free access conditions do not change preference for the high concentration and do not reduce total sucrose intake.

Conclusion: These results may have implications for understanding phenomena related to motivation and energy-related disorders such as psychomotor slowing or anergia in depression.

P-14-044 Meta-analysis on cognitive function of depressive patients compared with healthy controls

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Objective: Depression is a neurodegenerative disorder related with chronic elevated corticosteroid level and decreased hippocampal size. Functional decline in the cognitive functions including memory, attention, and concentration often related with easy forgetfulness, mild cognitive impairment, and dementia. However, the results about the relationship of cognitive function and depression are often controversial. Authors performed meta-analysis about the difference of cognitive function between depressive patients and control.

Methods: Reports of Randomized controlled trials (RCTs) of antidepressants from 2000, in which they measure cognitive domains were searched from PubMed and Cochrane library. Search terms were; ('depression' OR 'major depression', OR 'depressive illness', OR 'major depressive disorder', OR 'depressed') AND ('cognitive function' OR 'cognition' OR 'cognitive' OR 'neuropsychological' OR 'neuropsychology'). Values of cognitive functions (mean, standard deviation, and number of subjects) were recorded and the effect sizes, 95% confidence intervals of each study were calculated using Comprehensive Meta-Analysis Version 2.0 (Biostat Inc., Englewood, NJ, USA).

Results: Among 4,140 papers, 27 RCT papers were finally analyzed.

Conclusion: Depressive patients showed significant lowered performance in the subsets of Digit Span, CPT, TMT A, Digit Symbol, Stroop test, WCST, verbal fluency, verbal memory immediate. We might use these subsets to compare the cognitive change of depressive patients during their course of illness.

P-14-045 Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant

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Objective: Evaluate the efficacy and safety of lisdexamfetamine dimesylate (LDX) augmentation of antidepressant monotherapy in participants with major depressive disorder (MDD).

Methods: This randomized, double-blind, placebo-controlled trial enrolled participants (18–55 y) with nonpsychotic MDD. After 8 weeks of open-label escitalopram (week 1: 10 mg/d; 20 mg/d thereafter), participants with residual symptoms (Hamilton Rating Scale for Depression 17-item score ≥ 4) were randomized to 6 weeks of double-blind LDX (20, 30, or 50 mg/d) or placebo augmentation. The primary endpoint, mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from augmentation baseline to study endpoint, was analyzed by analysis of covariance (prespecified $\alpha = 0.10$) in nonremitters (i.e., participants with augmentation baseline MADRS total scor >10) who had ≥ 1 randomized study drug dose and ≥ 1 postrandomization MADRS assessment. Safety assessments included treatment-emergent adverse events (TEAEs).

Results: Of 246 enrolled participants, 173 (placebo, 85; LDX, 88) received double-blind treatment and 157 (placebo, 79; LDX, 78) completed the study. For the 129 nonremitters (placebo, 64; LDX, 65) receiving randomized treatment, mean $\pm$SD MADRS total scores decreased from augmentation baseline (placebo, 20.8 ± 6.42; LDX, 20.3 ± 7.16) to study endpoint (placebo, 15.9 ± 9.17; LDX, 13.3 ± 8.77) the LS mean (90% CI) treatment difference significantly favored LDX (-2.3 [-4.5, -0.1]; $P = 0.0902$]). During double-blind treatment,

49.4% of participants receiving placebo and 60.2% receiving LDX had a TEAE; 1 serious TEAE occurred in a participant receiving placebo. TEAEs occurring in ⩾5% of participants with placebo and LDX were dry mouth (0%, 11.4%, respectively), headache (4.7%, 11.4%), decreased appetite (2.4%, 6.8%), nasopharyngitis (3.5%, 5.7%), and insomnia (7.1%, 4.5%).

Conclusion: LDX augmentation of escitalopram monotherapy in participants with residual MDD symptoms met prespecified signal detection parameters. Further studies are needed. The safety profile of LDX was consistent with prior literature.

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P-14-046 Memory deficits produced by serotonin depletion in rats are reversed by the multimodal antidepressant Lu AA21004, but not escitalopram

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Objective: To compare the ability of escitalopram and the multimodal antidepressant LuAA21004 to reverse serotonin (5HT) depletion-induced memory deficits in rats.

Methods: General design: 5HT was depleted in female rats by administering the irreversible tryptophan hydroxylase inhibitor 4-chloro-DL-phenylalanine methyl ester HCl (PCPA; 100 mg/kg/day, sc, 4 days). Memory performance was assessed in novel object recognition (NOR) and spontaneous alternation (SA) tasks after acute vehicle or drug administration. Experiment 1: PCPA-treated females were administered vehicle or 1 mg/kg carbidopa + 50 mg/kg of the 5-HT precursor 5-hydroxytryptophan (5HTP). Experiment 2: PCPA-treated females were administered vehicle, 10 mg/kg LuAA21004 or 0.5 mg/kg escitalopram (s.c.) and compared to PCPA-naïve rats. Experiment 3: A dose-response curve was generated by administering vehicle, 0.1, 3, or 10 mg/kg LuAA21004 to PCPA-treated animals.

Results: Experiment 1: PCPA impaired memory performance in NOR ($F(2,22) = 9.6$, $p < 0.01$) and SA tasks ($F(2,19) = 10.8$, $p < 0.001$). Restoring central 5HT levels with acute 5HTP normalized memory performance. Experiment 2: PCPA-treated females were impaired in NOR ($F(3,28) = 13.7$, $p < 0.0001$) and SA performance ($F(3,27) = 19.2$, $p < 0.0001$). Treatment with LuAA21004 improved PCPA-induced memory deficits, while escitalopram had no effect despite similar 5HT transporter occupancies. Experiment 3: LuAA21004 dose-dependently improved memory compared to vehicle in PCPA-treated rats in NOR ($F(4,45) = 6.5$, $p < 0.001$) and SA ($F(4,47) = 4.8$, $p < 0.01$).

Conclusion: The current study demonstrates that PCPA-induced 5HT depletion leads to robust memory deficits as assessed by NOR and SA. Treatment with the 5HT precursor 5HTP or LuAA21004, but not escitalopram, normalized memory deficits. These data imply that targets other than the 5HT transporter mediate the effects of Lu AA21004. The clinical implications of these findings remain to be investigated.

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P-14-047 Platelet serotonin re-uptake velocity predicts anterior cingulate activity

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Objective: Anterior cingulate cortex (ACC) activity has been related to emotion and social stress processing and alterations of ACC function have been implicated in depression. Although the serotonin transporter (5-HTT) rich subgenual portion of the ACC (sACC) has been demonstrated to be under significant genetic control of the serotonin transporter gene (SLC6A4), it remains unknown today whether transmembrane 5-HTT function mediates sACC activity under physiological conditions in adult humans.

Methods: Eight healthy male subjects were included in our [11C]DASB PET study, 48 healthy subjects were enrolled in our MRI study. During a block design fMRI task subjects underwent an emotion-inducing paradigm. Platelet solution (50 µl) was incubated using a dilution technique with unlabeled 5-HT to reveal Vmax and Km values.

Results: Here we show a linkage between maximal serotonin uptake velocity (Vmax) using a in vitro model system of neural 5-HTT function in blood platelets and neural activity of the sACC assessed by functional magnetic resonance imaging, a region also showing maximal 5-HTT availability within the cingulate cortex with positron emission tomography. We further report that genetic variation within SLC6A4 cannot sufficiently explain this linkage, which contributes to the understanding of the complex gene-protein-function relationship of 5-HTT.

Conclusion: Our findings expand the knowledge of neuronal consequences of altered 5-HTT protein function by relating in vitro measures of 5-HTT function to in vivo human brain activity for the first time. While genetic studies investigating the 5-HTT gene have provided insights about developmental effects on brain wiring and consecutive functional changes, this study among others underscores the importance to investigate protein function in order to untangle the complex gene-protein-function relationship in the context of mental illness.

P-14-048 Metabolic syndrom and C-reactive protein in patients with depression disorder on antidepressive medication

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Objective: The aim of this study was to investigate is there any difference in CRP levels in patients with Recurrent depressive disorder, treated with antidepressants medication, compared to health control group of subjects and if there is an association between increased CRP levels and the presence of MetS in these two groups.

Methods: Sixty subjects entered the study, the experimental group of patients (diagnosis of recurrent depressive disorder) included 35 subjects (18 male, 17 female), average age 47.85 ± 7.35 years. Healthy control group of subjects ($n = 25$), age 42.08 ± 4.93 years. The Metabolic syndrome was defined according to NCEP ATP III criteria. The cut-off point for elevated CRP was set at 5 mg/L.

Results: There was no statistically significant difference in the prevalence of MetS and CRP values between the studied groups. As an independent variables, Age, Waist circumpherence and Total cholesterol levels were significantly different in favor of the experimental group. In addition, patients that fulfilled the NCEP ATP III criteria for MetS showed significant difference for its constituting variables Central obesity and Arterial hypertension, in a favor of experimental group, too. Elevated CRP levels were associated with increased risk for the development of MetS in depressed patients, while both CRP values and BMI were significant predictors of MetS for the control group. Smoking habit was a considerable predictor for high CRP values (<5 mg/L) for depressed patients. Depression symptom severity (measured by HAMD score), length of illness, such as lenght of the antidepressant drug treatment didn't show signifficant impact on both the MetS and CRP values.

Conclusion: Both the CRP levels and Metabolic risk profile screening may be beneficial in order to obtain better assessment for depressive long term medicated patients, preventing the risk for future cardiovascular events.

P-14-049 White matter integrity in major depressive disorder: A comparison between distinct stages of the illness

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Objective: To study the white matter (WM) integrity in patients with major depressive disorder (MDD) recruited in different illness stages as compared to healthy subjects, by means of diffusion tensor imaging (DTI). We hypothesized that WM disruptions of the neuronal circuits underlying the pathophysiology of MDD can be even worsened in those patients with higher past illness burden.

Methods: Magnetic resonance imaging protocol (3T scanner) and diffusion tensor images were acquired from a sample of forty-seven right-handed adult patients with MDD (DSM-IV criteria): 14 patients suffering a first episode (score >14 on the Hamilton Rating Scale for Depression; HRSD); 15 patients with more than two previous episodes and currently remitted in the last six months (HRSD<8); and 18 patients with a chronic depressive episode (HRS>17); and from 17 healthy subjects, comparable for age and years of schooling. DTI analyses were performed with the FMRIB Software Library, FSL v4.1.4 to obtain maps of fractional anisotropy (FA, WM integrity measure) by means of Tract-based Spatial Statistics Package (TBSS) using a general linear model (family wise error correction).

Results: Voxel-wise whole brain results revealed a generalized significant reduction of FA in chronic patients compared to healthy controls (FWE $p<0.05$) affecting bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus, forceps major and forceps minor, body of corpus callosum and bilateral cingulum (Fig. 1). Differences (FWE $p<0.05$) also appeared between treatment-resistant chronic and first episode patients, affecting body of corpus callosum, right inferior fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, forceps minor, forceps major, bilateral cingulum, and bilateral inferior longitudinal fasciculus.

Conclusion: The results revealed that decrements of FA are observable in the most severe illness stages of MDD as compared to healthy controls, but also as compared to the earlier stages of the illness. Therefore, higher past illness burden entails greater white matter disruptions in patients suffering MDD.

P-14-050 Prevalence of depression among type II diabetes mellitus in primary family health care centers

A. Rady[1], A. Khairy[1], O. Akl[1], G. Orfali[1]. *[1]Alexandria, Egypt*

Objective: Diabetes is one of the major world health problems. Recent estimates from the World Health Organization (WHO) predict that if current trends continue, the number of people with diabetes will be more than double from 176 to 370 million people by 2030. In Egypt, the total number of persons with diagnosed and undiagnosed

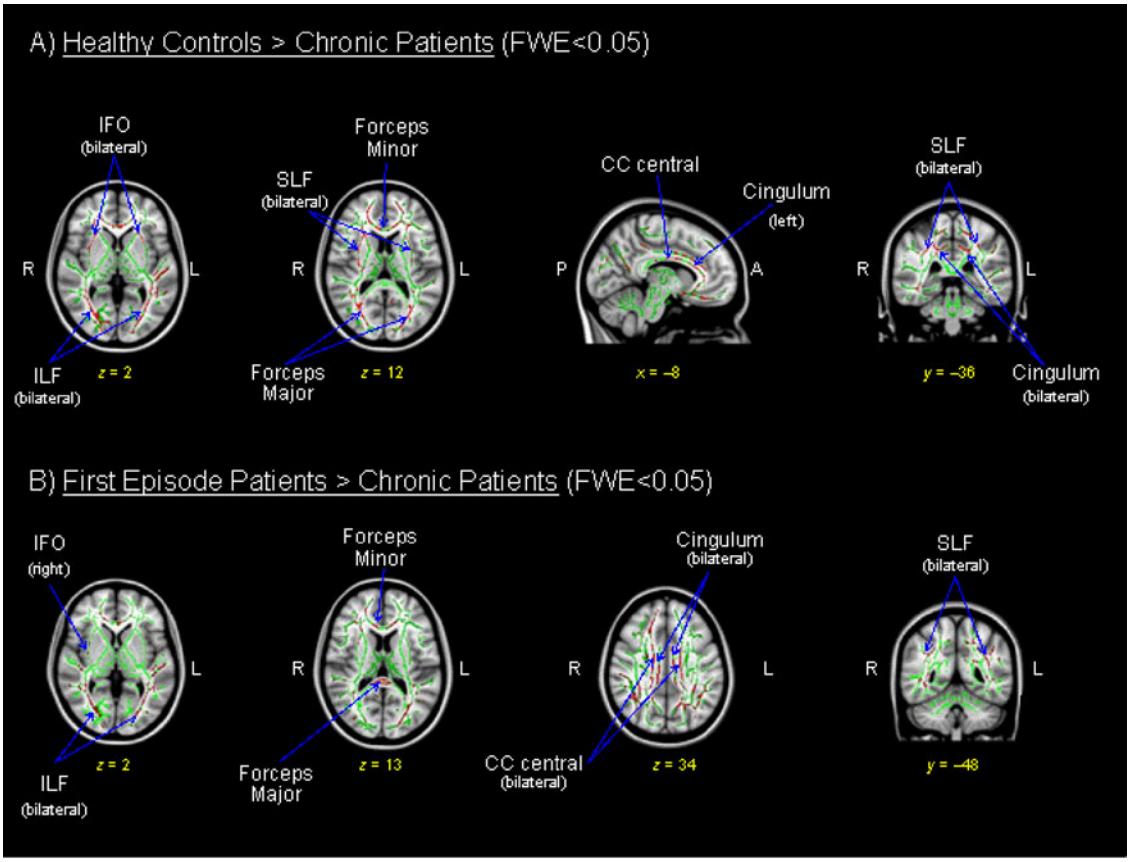

Figure 1. Rows show selected axial, sagital and coronal slices in which tracts with a significant FA decrease is observed for healthy controls vs. chronic patients (A) and for first-episode patients vs. chronic patients (B). The background image is the standard MNI152 1x 1x 1 mm brain template (MNI coordinates). Green voxels represent the FA white matter skeleton. Red voxels represent regions in which FA was significantly decreased. ifo=inferior frontal-occipital; ilf=inferior longitudinal fasciculus; cc=corpus callosum; slf=superior longitunal fasciculus.

Diabetes is expected to increase more than double from 3.80 million to 8.80 million by the year 2025. compared with the prevalence of depression among normal subjects.) These reports indicate tha >25% of patients with diabetes reach clinical criteria for depression, a rate far higher than in the general population. The comorbidity of diabetes and depression is associated with adverse diabetic outcomes, compared with nondepressed diabetic patients. This work aim at determining the prevalence of depression among type II diabetic patients attending family health centers in Alexandria.

Methods: A sample size of approximately 303 adult diabetic cases of type II in the age category of (20–60) years old based on a prevalence of 27% of depression in diabetics, degree of precision of 5% and confidence level of 95%, will be randomly selected from the attendees of the studied family health facilities. Two days of the week will be selected randomly to visit the studied primary health care facilities till the allocated sample size is reached. An interview questionnaire will be designed for depression assessment by using the Hamilton Depression Rating Scale (HAM-D) among type II diabetic patients.

Results: 40.18% (n=135) of diabetic patients in our study showed moderate to severe depression, 12.2% (n=41) showed mild depression while 47.62% (n=160) showed normal values on HAM-D scale. Moderate to severe depression was present in 39.1% and 40.7% in males and females respectively.

Conclusion: Awareness campaigns against depression for primary health physician is a major public halth issue.

P-14-051 WCST Performance in schizophrenia and psychotic depression

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Objective: Differentiating between schizophrenia and major depression with psychotic features often reveals diagnostic dilemma. Both share psychotic features and severe impairment in occupational functions. Severe psychomotor retardation, not uncommon in psychotic depression, may simulate negative symptoms of schizophrenia. Our work aims at utilizing Wisconsin Card Sorting Test (WCST) performance as a potential differentiating neurocognitive tool.

Methods: 60 patients were recruited randomly from the outpatient service at Alexandria University Hospital: 30 patients with schizophrenia and 30 patients with chronic psychotic depression. They were subjected to Clinical Global Impression for Severity (CGI-S) scale and Wisconsin Card Sorting Test (WCST) 128 card computerized version.

Results: Both groups were balanced in terms of gender distribution, severity and duration of illness. The study compared all parameters of WCST. Only perseverative errors showed mild significant difference ($P<0.05$) that disappeared when applying Bonferroni adaptation, setting significance level at 0.01 instead of 0.05.

Conclusion: Performance on WCST is similar in schizophrenia and severe depression with psychotic features in most of the measured parameters, hence WCST could not serve as a supplementary tool differentiating between both diagnoses in our study.

P-14-052 Efficacy and tolerability of vilazodone in patients with moderate, moderately severe, and severe depression-pooled analyses from 2 phase III trials

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Objective: Vilazodone, a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, is approved for treatment of major depressive disorder (MDD) in adults. Post hoc analyses of the Phase III trials (NCT00285376, NCT00683592), both of which were positive, evaluated efficacy and tolerability across baseline depression severity.

Methods: Data from 2, double-blind, 8-week, randomized, placebo-controlled trials were pooled. Patients (18–70 years) with DSM-IV-TR-defined MDD and HAMD17 ⩾22 were included; trials comprised a 1-week screening and 8-week double-blind treatment. Vilazodone was titrated to 40-mg (taken once daily with food) over a 2-week fixed-dose titration period. Primary efficacy outcome: MADRS total score change from baseline to Week 8 using an analysis of covariance model based on the Intent-to-Treat [ITT] Population and last observation carried forward approach. Severity of baseline depression for subgroup analyses was defined by MADRS threshold scores: moderate (MADR<30), moderately severe (30⩽MADR<35), and severe (MADRS⩾35).

Results: Baseline depression severity was moderate in 31% (placebo=143; vilazodone=130), moderately severe in 49% (placebo=205; vilazodone=220), and severe in 20% (placebo=85; vilazodone=86) of patients (Safety Population). Least squares mean difference (LSMD) in MADRS total score change from baseline to week 8 was significantly greater for vilazodone versus placebo in each depression subgroup: moderate (LSMD=−2.9; P=0.0056), moderately severe (LSMD=−2.3; P=0.0314), and severe (LSMD=−4.1; P=0.017) (ITT Population). Response rates (⩾50% MADRS improvement) for vilazodone and placebo were 41% versus 31% in the moderate (P=0.0810), 41% versus 29% in the moderately severe (P=0.0130) and 44% versus 26% in the severe depression (P=0.0124) subgroups. Adverse event profiles were similar across severity subgroups.

Conclusion: Vilazodone treatment versus placebo significantly improved MADRS scores in patients with moderate, moderately severe, and severe depression with no obvious trend across severity of illness; treatment effects (>2 point MADRS change from baseline) were clinically significant, with efficacy and tolerability similar among depression severity subgroups.

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P-14-053 Electroconvulsive stimulation alters levels of BDNF-related microRNAs

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Objective: Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depression but its mechanism of action is not yet fully understood. Electroconvulsive stimulation (ECS), an animal model of ECT, is known to increase levels of the neurotrophin brain derived neurotrophic factor (BDNF) within the brain, though the precise means by which this occurs and how it contributes to the antidepressant effects of ECS are unknown. One possibility is that such effects involve a recently identified class of endogenous, small RNA species termed microRNAs (miRNAs) since evidence suggests that BDNF can both regulate and be regulated by miRNAs. We therefore investigated the effects the expression of BDNF-related miRNA species in rat brain and blood following treatment with ECS.

Methods: Male Sprague-Dawley rats were randomised into groups to receive either ''sham'' or ''real'' ECS. ECS was administered either acutely (×1) or chronically (×10) following a protocol which mimics that of clinical ECT (100 pulses/s; 0.5 ms; 0.7 s; 75 mA; thrice weekly). Total RNA was extracted from dentate gyrus, hippocampus, frontal cortex, cerebellum and whole blood samples and TaqMan® RT-PCR was performed using stem-loop primers for BDNF-related miRNAs.

Results: Of the miRNAs examined, miR-212 levels were found to be significantly increased in dentate gyrus following both acute ($p<0.01$) and chronic ($p<0.05$) ECS. miR-212 levels were also increased in blood following chronic ECS. Notably, a positive correlation was observed between miR-212 levels in dentate gyrus and in blood (Pearson's $r=0.61$, $p<0.001$).

Conclusion: Alterations in miRNA expression may be informative about the mechanism of action of ECS/ECT and in turn may give insight into the neurobiology of depression. Furthermore, examination of miRNAs in blood from severely depressed patients undergoing treatment with ECT will ascertain their potential to act as clinical biomarkers for the treatment of depression.

P-14-054 Impact of family history on drug placebo separation in RCTS: Site rater and computer outcomes

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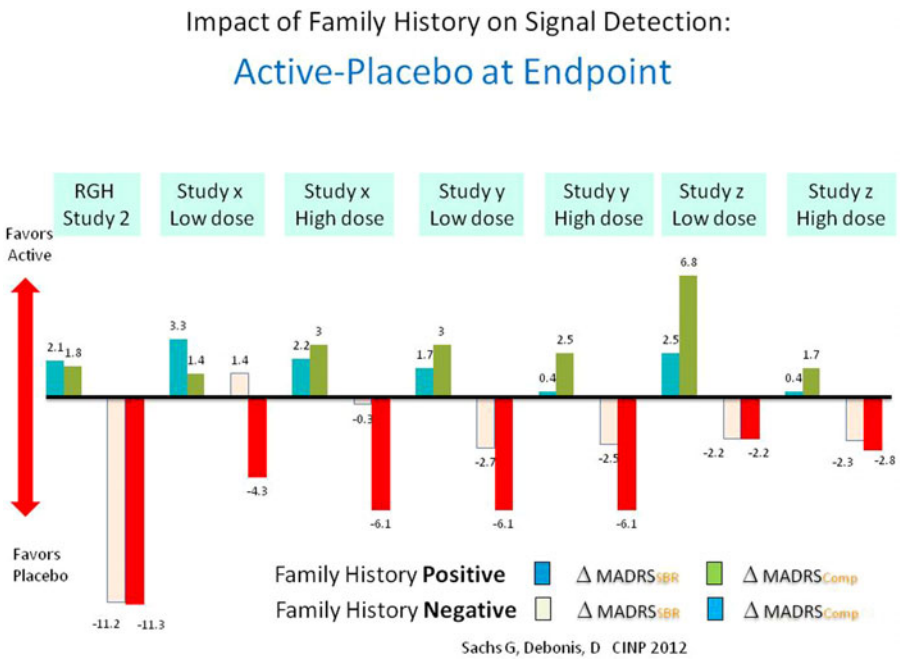
Objective: High placebo response often hampers signal detection in randomised clinical trials. We used data from 4 recent failed studies to explore the impact of family history of mood disorder (FamHx) on signal detection.



Methods: We examined outcomes from 4 failed double blind studies with 4 placebo groups and 7 active treatment groups that collected outcomes independently from site-based raters (SBR) and computer (Comp). Comparison groups were constructed based on subject report of family history of mood disorder (FamHx) collected by the computer. The studies were all powered to detect a drug-placebo difference (Signal) of 3–4 points on the primary outcome measure (change from baseline MADRS or HAMD). A priori, for these exploratory analyses FamHx was defined as Impactful if the difference in signal for FamHx(−) vs. FamHx(+) was ⩾1 (⩾25% of the estimated effect size).

Results: FamHx was impactful in all trials for all 7 comparisons based on both SBR and Comp outcomes. A trend favouring active treatment over placebo was found in all FamHx(+) subgroups. The difference in signal detection for FamHx(+) vs. FamHx(−) subgroups was large ranging in magnitude from 1.9–13.4 for SBR and 5.7–13.1 for the Comp ratings. A contrary trend favouring placebo over active treatment was found in 6 of the 7 FamHx(−) subgroups. In three of the four trials examined the drug-placebo difference for FamHx(+) reached statistical significance based on MADRS-COMP or HAMD-COMP. but not MADRS-SBR or HAMD-SBR.

Conclusion: The high rates of placebo response observed in subjects reporting no family history of mood disorder likely contributed to the failure of the clinical trials in this report. If this finding is replicated further study is needed to clarify the correlates of the FHx(−) subject status associated with high placebo response (e.g. diagnostic validity or enrolment rate).

Policy of full disclosure: Dr. Sachs and Mr. DeBonis are employees of Bracket Global.

P-14-055 Neural correlates of remission in major depressive disorder

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Objective: While overwhelming evidence points to alterations within emotional brain circuitries including the amgydala and the subgenual anterior cingulate cortex (sACC) in patients with concurrent major depressive episodes and under antidepressant treatment, neural mechanisms underlying stable remission are largely unknown. Hence, we aimed to investigate the neural dynamics between the amygdala and sACC in remitted and untreated Major Depressive Disorder (MDD) patients and healthy controls.

Methods: Within a multi-center, cross-sectional magnetic resonance imaging study functional and structural local as well as brain systems level measures of the amygdala-sACC circuitry have been compared between thirty-eight adult, drug-free remitted MDD (rMDD) patients and 38 healthy controls without any psychiatric life-time diagnosis. Subjects underwent a functional block-design matching paradigm comprising emotional stimuli, angry/fearful faces or fearful/threatening scenes derived from the International Affective Picture System (IAPS). Based on our straight-forward a priori hypothesis, functional and structural local (BOLD, gray matter volume) as well as brain systems level measures (functional connectivity, structural covariance) have been analyzed restricted to the amygdalae and the cingulate cortex using AFNI, SPM8 and the DARTEL extension of SPM8.

Results: Decreased amygdala (right: $t = -3.83$; left: $t = -3.13$) and sACC (bilateral: $t = -2.02$) activation during conscious perception of unpleasant visual stimuli was found in rMDD patients in comparison to healthy controls. No structural differences could be found in both structures between groups. On a brain systems level, rMDD patients exhibited increased functional ($t = 3.03$) and structural connectivity ($t = 3.84$) between the amygdala and sACC compared to controls. In rMDD patients, functional coupling between amygdala and sACC was related to means of illness duration ($P = 0.021$).

Conclusion: This study demonstrates functional and morphometric differences within the amygdala-sACC circuitry between drug-free rMDD patients and healthy controls. Our findings suggest that remission of MDD cannot simply be interpreted as a disease-free condition from a neurobiological perspective.

P-14-056 Characteristics of the single event related [Oxy-Hb] changes in patients with depressive disorder

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Objective: The aim of this study was to examine characteristic of single event related Oxy-hemoglobin (Oxy-Hb) changes in patients with depressive disorder measured by multi-channel near-infrared spectroscopy (NIRS) during word generation task, Japanese 'Shiritori'.

Methods: 26 patients with depression and 32 age and gender matched healthy subjects participated in the study. All the patients were

right-handed and native Japanese speakers. Diagnosis of depression was made for ICD-10 by two experienced psychiatrist. In all patients psychiatric symptoms were evaluated using HAM-D (15.9 ± 5.3). The ethical committee of the Kurume University approved this study. All subjects gave written informed consent after a complete explanation of the study. The 44-multi-channel NIRS machine (ETG-4000, Hitachi) measures relative changes of [Oxy-Hb] and [deoxy-Hb]. The present study has segregated specific regions (ROI) in the prefrontal cortex associated with executive function (left 11Ch and right 12Ch). As word generation tasks, standard shiritori, vertebrae shirotori and word fluency were used in this study. The cognitive activation task induced a 12-s pre-task baseline and a single generation task of letter or word projected by TV monitor. The pre-tasks and tasks were performed repeatedly 20 times and the data was analyzed using average wave form.

Results: The changes of [Oxy-Hb] in patients with depressive disorder were significantly smaller than that of healthy subject during all word generation task. In both left 11Ch and right 12Ch (ROI), the changes of Oxy-Hb concentration in patients with depressive disorder were smaller than that of healthy subjects during vertebrae shiritori task, but there was not significantly difference between two groups during word fluency task.

Conclusion: These data suggested that the examination using word generation task measured by multi-channel NIRS were useful for a psycho-physiological index of patient with major depressive disorder.

P-14-057 Medication taking behavior and its correlates in patients with comorbidity of depression and type 2 diabetes

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Objective: The objective of this study was to examine the differences between depressed and non-depressed patients with diagnosis of type 2 diabetes (T2DM) in sociodemographic, clinical characteristics, metabolic control and medication taking behavior as well as correlation between medication taking behavior and other examined variables.

Methods: A group of depressed diabetic patients comprising those with major depressive episode, first or repeated (ICD-10) and endocrinologist-diagnosed T2DM, duration ⩾5 years on oral, insulin therapy or both (N = 35) and non-depressed ones (N = 32) (67 in total) of both genders (<65 years) were included in this cross-sectional study. The Mini international neuropsychiatric interview (MINI) were used to establish diagnosis. The Beck Depression Inventory (BDI; cut off ⩾16) for self-assessment of depression severity, The Medical Adherence Questionnaire (MAQ) for self-assessment of medication taking behavior and The Problem Areas in Diabetes (PAID) for self-assessment of diabetes distress were also used. We performed laboratory and non-laboratory measures to assess metabolic control and the presence of metabolic syndrome. The exclusion criteria were determined.

Results: Significantly higher frequency of psychiatric heredity and neuropathy in depressed diabetic patients in comparison to non-depressed ones were found. Depressed diabetic patients had significantly higher MAQ (Mann-Whitney U test) and PAID score (Student's t test) in relation to non-depressed ones. MAQ score significantly positively correlated with PAID score and number of metabolic components in depressed diabetic patients. In non-depressed diabetic patients significantly positive correlation between MAQ score and frequency of patients on oral hypoglycemic therapy and coronary artery diseases were found (Pearson's Correlation).

Conclusion: Depressed diabetic patients had significantly higher frequency of diabetic neurological complications, significantly more problematic medication taking behavior and significantly higher level of diabetes distress in comparison with non-depressed ones. Suboptimal medication adherence was significantly associated with elevated diabetes distress and metabolic risk in depressed diabetic patients.

P-14-058 Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: Evidence for an immune-modulated glutamatergic neurotransmission?

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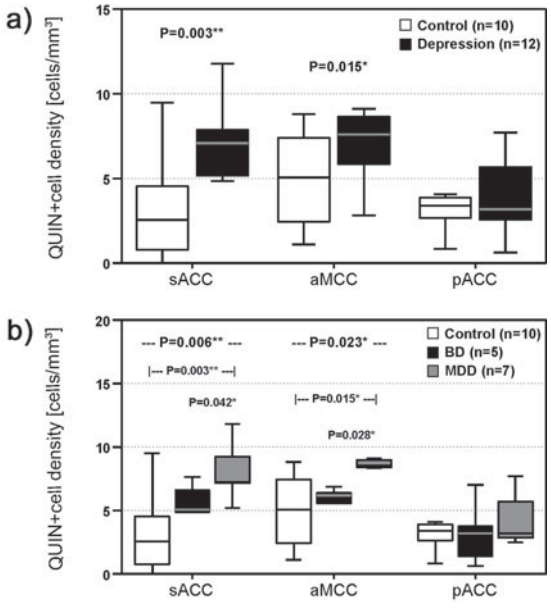
Objective: Immune dysfunction, including monocytosis and increased blood levels of interleukin-1, interleukin-6 and tumour necrosis factor a has been observed during acute episodes of major depression. These peripheral immune processes may be accompanied by microglial activation in subregions of the anterior cingulate cortex where depression-associated alterations of glutamatergic neurotransmission have been described.

Methods: Microglial immunoreactivity of the N-methyl-D-aspartate (NMDA) glutamate receptor agonist quinolinic acid (QUIN) in the subgenual anterior cingulate cortex (sACC), anterior midcingulate cortex (aMCC) and pregenual anterior cingulate cortex (pACC) of 12 acutely depressed suicidal patients (major depressive disorder/MDD, n = 7; bipolar disorder/BD, n = 5) was analyzed using immunohistochemistry and compared with its expression in 10 healthy control subjects.

Results: Depressed patients had a significantly increased density of QUIN-positive cells in the sACC (P = 0.003) and the aMCC (P = 0.015) compared to controls. In contrast, counts of QUIN-positive cells in the pACC did not differ between the groups (P = 0.558). Post-hoc tests showed that significant findings were attributed to MDD and were absent in BD.

Conclusion: These results add a novel link to the immune hypothesis of depression by providing evidence for an upregulation of microglial QUIN in brain regions known to be responsive to infusion of NMDA antagonists such as ketamine. Further work in this area could lead to a greater understanding of the pathophysiology of depressive disorders and pave the way for novel NMDA receptor therapies or immune-modulating strategies.



P-14-059 The association between sunshine duration and paroxetine response time in patients with major depressive disorder

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Objective: A recent study indicates that the serotonin transporter function varies with the duration of monthly sunshine. This finding may suggest that the efficacy of serotonin selective reuptake inhibitors

(SSRIs) is associated with the duration of monthly sunshine, but information on this possible association is lacking.

Methods: Ninety-one Japanese subjects with depression completed a 6-week treatment with paroxetine. Clinical evaluation was performed using the Montgomery and Asberg Depression Rating Scale (MADRS) before treatment and after 1, 2, 4 and 6 weeks of treatment. Data on the duration of monthly sunshine were obtained from the meteorological agency website. We divided the patients into four groups: nonresponders (NRs), later responders (LRs), early responders (ERs) and ultra-early responders (UERs).

Results: The responses to paroxetine treatment of the group that began treatment in fall and winter and of the group that began treatment in spring and summer did not differ significantly. The effect of the duration of monthly sunshine on paroxetine response time did not differ significantly among the four groups, whereas the change in the duration of monthly sunshine had a significant effect on paroxetine response time.

Conclusion: The change in the duration of monthly sunshine is associated with paroxetine response time.

P-14-060 Resistant depression in elderly

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Objective: Knowing the most effective therapeutic strategy used in Brief Hospitalization Unit (UHB) for elderly patients with depression who just entering after several treatments in the period between 2005 and 2010.

Methods: We performed a descriptive study using data based on medical records of patients over 65 years with a diagnosis of depression for those who have used therapeutic alternatives are not effective should be finally hospitalized in University Hospital Prince UHB de Asturias de Alcalá de Henares (Madrid). We use the variables: gender, age, socio-demographic data, previous antidepressant treatments, comorbidities, length of stay, type of therapeutic strategy used.

Results: We have found that treatment strategies are used ECT and augmentation with atypical antipsychotics.

Conclusion: We have found that treatment strategies are used ECT and augmentation with atypical antipsychotics.

P-14-061 BDNF, NTF3, NTF4 and GDNF neurotrophic factors serum levels in drug-naïve first episode depression during 8-weeks of treatment with sertraline or venlafaxine

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Objective: Neurotrophic factors signalling disturbances have been implicated in the etiopathogenesis of mood disorders. Antidepressant treatment has been shown to influence neurotrophic factor expression in different brain areas. The aim of this study was to analyze Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin 3 (NTF3), Neurotrophin 4 (NTF4) and Glial-Derived Neurotrohpic Factor (GDNF) serum protein levels in first-episode drug-naïve depressed women during 8-weeks treatment with sertraline or venlafaxine. Correlations with clinical variables have been performed.

Methods: 30 drug-naïve first-episode women (mean age 38 years, SD 10.5) with depression episode were recruited. Diagnosis was made according to DSM IV criteria using Structured Clinical Interview for DSM-IV SCID. Severity of depression was evaluated using 17-item Hamilton Depression Rating Scale (HDRS) at the beginning of antidepressant therapy and after 8 weeks of treatment. Patients were administered with sertraline (n = 16) or venlafaxine (n = 14). Control group consisted of 30 healthy, age-matched women. BDNF, NTF3, NTF4 and GDNF serum levels were measured using ELISA method.

Results: We have found lack of differences between BDNF, NTF3, NTF4 and GDNF serum levels in first-episode drug-naïve women compared to the control group. There were no changes in BDNF, NTF3, NTF4 and GDNF serum levels during 8-week treatment with sertraline or venlafaxine. No correlation have been found between BDNF, NTF3, NTF4 and GDNF serum levels and depression severity measured with Hamilton Depression Rating Scale as well as, age, BMI, smoking status, family history of mental illness, psychosocial stressor prior to onset and suicidal ideations. We have observed strong positive correlation in NTF3, NTF4 and GDNF serum protein levels in the studied group.

Conclusion: In our study we did not find differences in serum BDNF, NTF3, NTF4 and GDNF levels in first-episode drug-naïve depressed women during treatment nor correlations with clinical variables. Limitation of the study was relatively small sample size.

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P-14-062 Pharmacological management of affective symptoms after primary hepatic tumor surgery

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Objective: Patients diagnosed with primary hepatic tumors could develop affective pathology, either during the evolution of the oncologic disease, or as a result of therapeutic interventions (radiotherapy, surgery, chemotherapy). There are several factors involved in the pathophysiology of affective disorders in patients diagnosed with hepatic tumors: psychological factors- due to the acknowledge of the diagnosis and prognosis, somatic factors- the side events of chemotherapy and radiotherapy, the effects of the tumor per se.

Methods: We selected a group of 18 patients who had surgery for various stages of primary hepatic malignancies, diagnosed with depressive episodes through DSM IV TR criteria in the first month post-intervention. These patients were evaluated using Hamilton Depression Rating Scale (HAMD), Global Assessment of Functioning (GAF) and Clinical Global Impressions – Severity and Improvement (CGI-S/I) at baseline and every 4 weeks for 3 months. Patients received psychopharmacological treatment with escitalopram (flexible daily dose 10–20 mg, n = 10) or tianeptine (flexible daily dose 25–37.5 mg, n = 8). Intent-to-treat analysis and last observation carried forward method were applied in this study.

Results: Patients responded well to the therapy, as the final HAMD (-16.2, $p < 0.01$) and GAF ($+22.3$, $p < 0.01$) scores reflected, with no significant inter-group difference ($p = 0.23$). The CGI score improved with 2.4 points at week 12 ($p < 0.01$). Patients tolerated well both drugs, with a similar rate of mild and moderate adverse events (6 reports in the escitalopram group and 4 in the tianeptine group). No drop out due to adverse events was recorded.

Conclusion: The treatment of post-surgery depression in oncologic patients with primary hepatic tumors with escitalopram or tianeptine eis associated with a high rate of response, while the tolerability of both drugs was satisfactory.

P-14-063 Magnesium deficiency induces anxiety- and depression-like behavior and metabolic dysfunction in C57Bl/6J mice

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Objective: There are indications that balance of magnesium (Mg) ions may regulate mood. Magnesium deficiency is also linked with altered glucose metabolism and an inflammatory response in the gut. In addition, mood disorders have been linked to a dysfunctional metabolism. In this study we investigated the involvement of Mg in regulating depression- and anxiety-like behaviour and metabolism, by using mice that have been deprived of dietary Mg and studying several behavioral and metabolic markers.

Methods: We examined the behavioral effects of Mg deficiency (deprival of dietary Mg for 6 weeks) in mice through depression- and anxiety phenotyping experiments, namely the forced swim test and light-dark box respectively. We determined the behavioural effects 30 minutes after treatment with imipramine ($20\ mg \cdot kg^{-1}$), diazepam ($2\ mg \cdot kg^{-1}$) and ketamine ($3\ mg \cdot kg^{-1}$). The glucose tolerance test was used to assess metabolic function in Mg deficient mice.

Results: We found that, compared to control (n = 10), mice receiving Mg deficient diet (n = 10) (10% RDA), were more immobile in the forced swim test ($p < 0.01$), which suggested depression-like behavior

which was significantly attenuated by imipramine and ketamine ($p < 0.0001$ and $p < 0.001$ respectively). Mg deficient mice also displayed anxiety-like behavior in the light-dark box ($p < 0.01$) compared to control, although diazepam did not significantly reverse this behaviour. The glucose tolerance test showed an elevation in glucose response after 30 minutes in Mg-deficient mice compared to the controls ($p < 0.05$).

Conclusion: Insufficient dietary Mg may contribute to depressive and/or anxiety symptoms, as well as metabolic dysfunction. This data warrant further investigation into whether supplementation with Mg may relieve these disorders.

P-14-064 Effects of subanesthetic doses ketamine on the serotonergic neuronal system in conscious monkey brain

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Objective: The antidepressant effects of subanesthetic doses of ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, are well known. The serotonin transporter is a target protein for many antidepressants. Hence, the aim of present study was to determine the effects of subanesthetic doses of ketamine on serotonergic activity in the conscious monkey brain.

Methods: The brains of three young adult monkeys were scanned using [11C]DASB for the serotonin transporter (SERT) and [18F]MPPF for the serotonin 1A receptor (5-HT1AR). Ketamine hydrochloride in doses of 0.5 and 1.5 mg/kg or vehicle was infused intravenously over 40 min. PET scans were taken after the end of ketamine infusion. Heart rate and blood pressure were monitored throughout the study. Arterial blood sampling was conducted during the PET scan. Time-activity curves (TAC) of metabolite-corrected arterial plasma were used as the arterial input function. Logan plot analysis for each TAC and each brain region was used for calculation of [11C]DASB and [18F]MPPF binding to SERT and 5-HT1AR, respectively.

Results: No significant changes in heart rate and blood pressure were observed with either dose of ketamine. Furthermore, ketamine infusion did not induce any substantial change in the plasma levels and metabolism of each radioligand. With ketamine infusion, the binding of [11C]DASB to SERT was reduced in a dose dependent manner. The binding of [18F]MPPF to 5-HT1AR tended to reduce compared with the control vehicle.

Conclusion: The present results from this conscious monkey PET study suggest that one of the mechanisms for the antidepressant efficacy of subanesthetic doses of ketamine is via modulation of the brain serotonergic neuronal system.

P-14-065 Comparison the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depressive disorder

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Objective: Only two-thirds of depressive patients respond to antidepressant treatment. Recently, addition of an atypical antipsychotic drug to ongoing treatment with an antidepressant has been considered effective and well-tolerated. We have previously reported that the augmentation of SSRI or SNRI therapy with an atypical antipsychotic drug was effective and well tolerated refractory depressed patients, and its response is 42% (Yoshimura et al., 2010). In the present study, we compared the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depression.

Methods: Twenty-four patients who met the DSM-IV criteria for major depressive disorder who did not at least two different classes of antidepressants were enrolled in the study. Nine were male and 13 were female, and their ages ranged from 26 to 64 (mean $\pm$ SD $=39 \pm 17$) years. Patients were randomly prescribed paroxetine ($n=11$) or sertraline ($n=13$) for 4 weeks. The doses [mean $\pm$ SD] of paroxetine and sertraline were 33 ± 8 mg/day and 88 ± 16 mg/day, respectively. The dose of aripiprazole [mean $\pm$ SD] was 11 ± 7 mg/day. Paired t-test and simple regression analysis were used for statistical analysis. The study was approved by the Ethical Committee of the UOEH.

Results: Two patients with paroxetine group were dropped out because of its side effects. Those who their scores of 17-item of Hamilton Rating Scale for Depression (HAMD17) decreased below 50% were added aripiprazole for 4 weeks after aripiprazole augmentation. Reduction rates in paroxetine or sertraline at week 4 were 36.7% and 37.3%, respectively. No difference however was found in HAMD17 scores between paroxetine plus aripiprazole group and sertraline plus aripiprazole group.

Conclusion: Aripiprazole addition to paroxetine or sertraline is both effective and well tolerated in refractory depressed patients.

P-14-066 Enhanced perception of negative emotion in depression: A preliminary study

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Objective: It has been hypothesized that biases in the processing of emotional stimuli may play an important role in interpersonal difficulties in patients with depression. A good interpersonal relationship requires capacity of context-based emotional processing. However, previous studies investigating emotion perception in patients with depression were mostly focused on perceiving facial or bodily expressions without social context. In the present study, we used movie scenes to examine context-based emotional processing of patients with depression.

Methods: A set of movie clips lasting 10 to 20 seconds with various emotional situations was presented to a total of 33 participants, grouped by depression ($N=7$) or healthy non-psychiatric individuals ($N=16$). The participants were asked to rate 5-point Likert scale, ranging from 0 (never expressed) to 5 (very highly expressed), on 11 kinds of emotions including happy, love, humor, sympathy, sorrow, fear, embarrassment, anxiety, anger, hatred, and greed. The symptom severity of depression was measured by PHQ-9. The degree of perception in each kind of emotion was compared between two groups using independent samples t-test.

Results: While there was no group difference for positive emotions, the patients with depression showed enhanced perception extensively for negative emotions including fear ($p < 0.01$), anxiety ($p < 0.05$), anger ($p < 0.05$) and hatred ($p = 0.07$) to the negative emotional scene.

Conclusion: The findings suggest that negatively biased emotional processing is a salient feature, which can explain interpersonal difficulties in depression.

P-15. Animal Models

P-15-001 Morphological studies on the distribution and expression of neuropeptide S and its receptor after REM sleep deprivation in rat

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Objective: The recently described 20 amino acid neuropeptide S (NPS) is involved in the modulation of arousal. Here we describe a detailed anatomical mapping of NPS expressing neurons in the rat brainstem, examining the expression of NPS and NPSR1 after a 72-hour REM-sleep deprivation and a subsequent 3-hour rebound sleep.

Methods: We applied the single platform-on-water (flower pot) method. NPS and NPSR1 expression was detected by quantitative in situ hybridization. The NPS immunoreactivity (IR) was visualized by immunohistochemistry and quantified by densitometry.

Results: The highest expression of NPS was found in the peri-coerulear region and in a cell cluster close to the Kölliker-Fuse nucleus (KF cluster). A moderate expression level was detected in the lateral parabrachial nucleus (LPN) and in occasional neurons in the medial parabrachial nucleus and around the fourth ventricle. The NPS expression was significantly increased in the peri-coerulear cluster but not in the LPN or KF clusters after the deprivation. There was no such significant increase in the large pot (stress control) animals. The

expression level in the peri-coerulear cluster returned close to control levels after the 3-hour rebound sleep. The NPS IR fiber density was significantly decreased after the sleep deprivation in the preoptic region of the hypothalamus. The expression of NPSR1 did not alter significantly in the preoptic region or in the rhomboid thalamic nucleus.

Conclusion: Our results suggest a differential response of NPS expressing neuron clusters after sleep deprivation and emphasize the role of the peri-coerulear cluster in the modulation of arousal. This modulation is, however, not associated with changes of NPSR1 expression. The decreased NPS fiber density suggests extensive release of NPS in the preoptic region after sleep deprivation. As this is a sleep promoting region, the release of NPS during the forced wakefulness raises the possibility that NPS facilitates the arousal by an inhibitory action here.

P-15-002 Modulation of biogenic amines, substance p and neurotrophic factor produces chronic muscular pain and tactile allodynia accompanied by depression-a putative animal model of pain-depression dyad

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Objective: The present study was designed to investigate the effect of para-chlorophenylalanine (PCPA) on modulation of biogenic amines, Substance P and nerve growth factor on the pain-depression dyad to establish a new rodent model and support the possibility of a relationship and specifically address the neurogenic mechanism that might be involved in this syndrome.

Methods: Pain and depression was induced by the intrperitoneal administration of PCPA (350 mg/kg). The effects of different doses of duloxetine (3–30 mg/kg; p.o.), pregabalin (3–30 mg/kg; p.o.) and diclofenac (1–10 mg/kg; p.o.) treatment was evaluated for behavioural (pain and depression), neurochemical (dopamine, norepinephrine, and 5-hydroxytryptamine) and molecular alterations (Substance P and nerve growth factor) induced by PCPA.

Results: Administration of PCPA (350 mg/kg) led to a significant decrease in nociceptive threshold as evident from reduced paw withdrawal threshold in Randall Sellitto and von-Frey hair test as well as marked increase in immobility time in forced swim test. This behavioural deficit was integrated with decrease in biogenic amines (dopamine, norepinephrine, and 5-hydroxytryptamine) along with increased Substance P and nerve growth factor levels in both brain and serum of the PCPA administered rats. Pregabalin and duloxetine ameliorated the behavioural deficits associated with pain and depression by restoring behavioural, neurochemical and molecular alterations against PCPA-induced pain—depression dyad in rats.

Conclusion: The validity of the use of this PCPA model is demonstrated from three different aspects, i.e., face validity (manifestation of chronic pain and depression), construct validity (dysfunction of biogenic amine Substance P and nerve growth factor-mediated CNS pain control is involved), and predictive validity (similar responses to treatments used in pain and depression).

P-15-003 Substance P1–7-amide – a peptide-derived molecule with potential effects on chronic pain and opioid withdrawal

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Objective: The neuroactive peptide substance P (SP) is well recognized for its critical role in the regulation of many processes in the central nervous system. SP has received particular interest for its involvement in pain processing and the development of opioid tolerance and dependence. Following neurokinin NK-1 receptor activation SP is degraded into several fragments, some of which retain biological activity. One of its major bioactive metabolites, the N-terminal fragment SP1–7, is known to counteract several effects of SP. For instance, the heptapaptide opposes the SP-induced enhancement of pain transmission and expression of opioid withdrawal. In order to find suitable drugs capable of relieving pain and attenuate opioid withdrawal we have synthesized several analogues of SP1–7. One of these, the SP1–7 amide, that exhibits higher affinity for the SP1–7 specific binding sites compared to the native heptapeptide, was investigated for its effects on chronic pain and opioid withdrawal using experimental animal models.

Methods: Hypersensitivity to thermal stimuli was investigated in streptozotocin (STZ)-induced diabetic mice. The expression of naloxone-induced opioid withdrawal was evaluated using morphine-tolerant rats.

Results: The results showed that the SP1–7 amide profoundly alleviates signs of thermal hyperalgesia when injected intrathecally in mice with STZ-induced diabetes. In addition, intracerebroventicular administration of the amidated heptapeptide prior to naloxone administration in rats reduced withdrawal signs in a dose-dependent manner. In both cases the effects surpassed those seen for native SP1–7.

Conclusion: To conclude, we have synthesized an analogue to the bioactive N-terminal SP fragment SP1–7 that significantly and more potently than the native compound attenuates the expression of opioid withdrawal and hyperalgesia in rodents through a mechanism that does not involve any neurokinin or opioid receptor. This finding opens for new possibilities to design and develop non-opioid and perhaps also non-peptide mimetics as potential drugs for the treatment of chronic pain and opioid dependence.

P-15-004 Stressful experience during peri-adolescent period induces depression-like phenotype in adult mouse

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Objective: Psychologists have long supposed that early life trauma can increase risk for psychiatric disorders. The observation that during early development individuals are susceptible to adverse environmental influences is confirmed by mouse studies. During mouse postnatal development, the third week (peri-adolescent age) represents a critical stage for the maturation of several brain functions. Moreover during this week it is possible to observe high levels of forebrain synaptogenesis. In terms of behavioral development the first rudimentary elements of social play are observable during this week. In spite of the relevance of this developmental period, there are no studies investigating if exposure to stressful experience during this week can induce long term changes on mouse behavior and brain functionality.

Methods: We exposed mouse pups to an adverse experience, consisting in social isolation in novel environment for 25 minutes per day from postnatal day 14 to 21. These mice were tested in the Social Interaction Test (SIT), Forced Swimming Test (FST), and Sucrose Preference Test (SPT) in adulthood.

Results: Stressed mice showed a depression-like phenotype characterized by increased social avoidance in SIT, behavioral despair in FST, and absence of sucrose preference in SPT. Moreover inspired by the hypothesis that environment has long term consequences on behavior, acting through changes at level of epigenetic mechanisms in the brain, we tried to protect the mouse pups from developing the pathological phenotype injecting them with drugs acting on these mechanisms. This pharmacological treatment was partially able to rescue the depression-like phenotype observed.

Conclusion: Our findings confirm that the peri-adolescent age is a critical period for the development of adult mouse behavior and exposure to stressful experiences during this period promotes depression-like phenotype in adulthood through modification of the epigenetic machinery in the brain.

P-15-005 Mitochondria plasticity of the hippocampus in a genetic rat depression model after antidepressant treatment

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Objective: A large body of data suggests that mitochondria may play an important role in the pathophysiology of depressive disorders and

effects of antidepressant therapy. Here, we investigated whether chronic antidepressant treatment of rats induced changes of the mitochondrial number in hippocampus.

Methods: For this report, the effects of the tricyclic antidepressant imipramine were tested in two strains of rats; the Sprague – Dawley and the other strain from the Flinders sensitive line, which has been bred to a phenotype with certain ''depressive-like'' phenotype. Design-based stereological methods were used to estimate the number and the volume of mitochondria of mitochondria in CA1 stratum radiatum (CA1SR) of the hippocampus.

Results: The results showed that the number of mitochondria in CA1SR was significantly smaller in the FSL saline group compared to the FRL saline group. However, the mean volume of mitochondria was significantly larger in the FSL saline group compared to the FRL saline group. Following treatment, the FSL imipramine group showed a significant increase in the number of mitochondria compared to the FSL saline group. But treatment with imipramine did not induce significant differences in the number of CA1 mitochondria between the SD saline group and SD imipramine group.

Conclusion: In conclusion, our results support the mitochondria plasticity hypothesis that depressive disorders and the pharmacological treatment thereof may be related to impairments of mitochondria plasticity in the hippocampus and that antidepressant treatment may counteract the structural impairments.

P-15-006 βCCT as well as flumazenil prevent the diazepam withdrawal-induced anxiety in the elevated plus maze in rats

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Objective: Despite a half century of clinical use and the recognized potential of benzodiazepine dependence, the mechanisms underlying benzodiazepine withdrawal remain insufficiently understood. The aim of the present study was to assess the influence of the non-selective antagonist (flumazenil) and the preferential α1-subunit selective antagonist (βCCt) on the anxiety level after diazepam withdrawal.

Methods: The male Wistar rats were protractedly treated during 21 days with diazepam (2 mg/kg) or solvent. On the testing day, 24 hours after the last injection, animals from the diazepam-treated groups received either antagonist (flumazenil or βCCt) or solvent, and animals from the solvent-treated groups received solvent or diazepam. Twenty minutes after administration of treatment on the testing day, single animals were placed in the elevated plus maze in order to assess the level of anxiety.

Results: Two-way ANOVA revealed that animals withdrawn from diazepam spent significantly less time on the open arms than control animals ($p = 0.023$). One-way ANOVA, followed by post hoc test, revealed that administration of flumazenil (10 mg/kg) or βCCt (1.25, 5 or 20 mg/kg) reversed the diazepam withdrawal-induced anxiety (percentage of open arm time: $p = 0.003$, $p = 0.032$, $p = 0.031$ and $p = 0.014$ compared to the diazepam-withdrawn group, respectively). Concomitant administration of antagonists (10 mg/kg flumazenil, or 1.25, 5 or 20 mg/kg βCCt) induced an anxiolytic effect comparable to that observed after acutely administrated diazepam (percentage of open arm time: $p = 0.142$, $p = 0.187$, $p = 0.243$ and $p = 0.290$, respectively).

Conclusion: The present study demonstrated that administration of the α1-selective antagonist βCCt or non-selective antagonist flumazenil could prevent the withdrawal-induced anxiety and also induce an anxiolytic-like effect. Moreover, presented results have suggested that mechanism of preventing the withdrawal-induced anxiety involves the antagonism at α1-containing GABAA receptors.

P-15-007 Effects of novel dopaminergic derivates on depression-like behavior: A pilot study

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Objective: Recent evidences suggest that the dysfunction of the central dopaminergic pathways may be a critical component of the neurobiological basis of depression. The effects of novel dopaminergic substances, 3,4-dimethoxyphenylethylamine derivates, on experimental model of depression were studied in male rats after acute or chronic administration in comparison to those of the classical antidepressant, clomipramine.

Methods: The novel DA derivates, PK-2111, PK-2122, PK-2123, PK-2126 (0,1, 1,0, 10,0 mg/kg, i.p.) and clomipramine (50.0 mg/kg) were injected acutely (1 h prior to behavioral testing) or chronically (for 21 days, the last injection being made 1 h prior to behavioral testing) in animals subjected to the forced swimming test (FST) and the locomotor activity test.

Results: In dose of 0.1 mg/kg PK-2122 exerted depressant-like effect, while in doses of 1.0 or 10.0 mg/kg PK-2122 exerted antidepressant-like effect as compared with the control group. Chronic treatment with PK-2123 or PK-2122 (0.1, 1.0 or 10.0 mg/kg) produced antidepressant-like effect which was significant as compared with control group and group treated with clomipramine. Also, chronic treatment of PK-2122 in high dose of 10.0 mg/kg induces antidepressant-like effect as compared with the control group, and this effect was less effective than it in a doses of 0.1 and 1.0 mg/kg.

Conclusion: These results suggest that PK-2126 independently from dose and PK-2122 in the middle and high doses may be effective in experimental model of depression in rats when administered acutely, PK-2111, PK-2122 or PK-2123 may be effective in experimental model of depression in rats when administered repeatedly.

P-15-008 The role of the 5-HT1A receptor in the murine 5-HT-syndrome

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Objective: In humans the incidence of the serotonin (5-HT)-syndrome has increased over the last decade, likely due to a higher prescription rate of serotonergic drugs. The 5-HT-syndrome can be evoked by serotonergic drugs in high doses. It is characterized by severe autonomic, neuromuscular and mental symptoms. It is also possible to elicit a 5-HT-syndrome in mice, which has been linked to the occurrence of the Straub tail response. We revealed in male NMRI mice five core responses that reliably occur and dose-dependently increase in frequency and intensity after the treatment with fluoxetine, 5-HTP, and tranylcypromine as well as their combinations. Here, we investigated which signs of the 5-HT-syndrome are mediated by the 5-HT1A-receptor.

Methods: We administered a full 5-HT1A-receptor agonist, 8-OH-DPAT, and a partial 5-HT1A-receptor agonist, buspirone, in increasing doses to male NMRI mice and assessed the occurrence and intensity of 15 behavioral and physiological responses including body temperature.

Results: Both agonists produced all five core responses (hindlimb abduction, low body posture, tremor, piloerection, decrease of rearing). Exclusively the 8-OH-DPAT induced the Straub tail, which was not evoked by buspirone and any other tested serotonergic agonist.

Conclusion: 5-HT1A-receptor activation elicits the core responses of the murine 5-HT-syndrome. However, the Straub tail response was only provoked by the full agonist. Based on the presynaptic 5-HT1A-receptor reserve and the higher intrinsic activity of the full agonist, the Straub tail response seems to be associated to postsynaptic 5-HT1A-receptor activation. Therefore, the Straub tail response is not a parameter for describing the 5-HT-syndrome in mice.

P-15-009 Different contributions of nucleus accumbens subregions to probabilistic reversal learning

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Objective: Impairments in positive reinforcement mechanisms and behavioural flexibility are core features of clinical depression. Cognitive deficits associated with depression have been demonstrated using a probabilistic decision-making task. Disruption in nucleus accumbens (NAc) functioning has been linked to motivational and cognitive abnormalities associated with the disorder. Studies in animals have revealed dissociable roles for NAc subregions in different aspects of behavioural flexibility. Interestingly, lesions in these brain regions do not impair flexible responding on simpler (ie: non-probabilistic) reversals. However, contribution to more complex

forms of cognitive flexibility remains unexplored. Here, we investigated the contribution of the NAc core and shell to probabilistic reversal learning, using an operant task developed for rats.

Methods: Over daily sessions of 200 discrete-choice trials, rats were required to press one of two levers for food reward. One lever initially designated 'correct', delivered reward 80% of the time, and the other 'incorrect' lever delivered reinforcement on only 20% of trials. After 8 consecutive 'correct' responses, reinforcement contingencies were reversed, and this pattern continued throughout the daily session. After ~10 days of training, rats received counterbalanced microinfusions of saline or GABA A/B agonists muscimol/baclofen into the NAc core or shell on separate test days.

Results: Inactivation of the shell markedly impaired probabilistic reversal performance, reducing the number of reversals completed and increasing errors. These effects were accompanied by a selective decrease in win-stay strategy, indicating a reduced sensitivity to positive reinforcement. In contrast, inactivation of NAc core did not impair reversal learning, but did increase the number of incomplete trials.

Conclusion: These results indicate that the NAc shell, but not core, plays a key role in facilitating reward sensitivity and cognitive flexibility in situations of reward uncertainty. Furthermore, they raise the possibility that impaired cognitive flexibility associated with depression may be due in part to abnormal function in the ventral striatum.

P-15-010 Growth hormone treatment improves spatial memory in rats

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Objective: Growth hormone (GH) is a polypeptide with a wide range of functions in the periphery and also in the brain. Replacement therapy with recombinant human GH (rhGH) has been demonstrated to alleviate cognitive deficiencies and improve memory in patients with growth hormone deficiency. Furthermore, GH has been suggested to be involved in neuroprotection and neuroregeneration and has recently been shown to counteract opioid-induced apoptosis in hippocampal cells. Anabolic androgenic steroids (AAS) have been demonstrated to affect several peripheral organs and also several CNS-related behaviors such as aggression, anxiety, depression and cognitive functions. In the present study, we investigated the effects of GH on rats treated with nandrolone decanoate.

Methods: Male Wistar rats received the steroid (15 mg/kg) or peanut oil every third day for three weeks and were subsequently treated with rhGH (1.0 IU/kg) or saline for ten consecutive days. During the GH/saline treatment spatial learning and memory were tested in the Morris water maze (MWM), where the rats had five training days with four swims each day. Two days after the last training session a probe trial was performed.

Results: The results demonstrated a significant impact of GH on spatial memory. In general, the behavior of the AAS animals was unaffected by GH treatment suggesting that the underlying mechanisms does not seem to be directly coupled to the GH signaling system. Both GH and AAS demonstrated important effects on body weight gain and GH was able to counteract the reduction of weight gain induced by AAS.

Conclusion: To conclude, GH improved performance in the MWM, suggesting an important impact of GH on memory functions.

P-15-011 Effects of gastrodia elata blume on spatial memory and choline acetyltransferase and acetylcholinesterase levels in a rat model of alzheimer's disease

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Objective: Gastrodia elata Blume (GEB) is a herb used in traditional Chinese medicine to treat dizziness, paralysis, and epilepsy. Here, we investigated the effects of GEB on spatial memory in a rat model of Alzheimer's disease (AD) and on choline acetyltransferase (ChAT) expression and acetylcholinesterase (AChE) activity in several regions of the model rat brain.

Methods: A rat AD model was established by bilateral injection of amyloid-beta peptide (Aβ25 35) into the hippocampus. The AD model rats were subsequently treated daily either with 0.5% cellulose (Aβ25 35/cellulose group), with 500 mg/kg GEB (Aβ25 35/GEB500 group), or with 1000 mg/kg GEB (Aβ25 35/GEB1000 group). Vehicle rats received vehicle injections followed by daily treatment with 0.5% cellulose. After 6 weeks, spatial memory was assessed using the Morris water maze test, and ChAT expression and AChE activity in the prefrontal cortex, medial septum, and hippocampus were measured using Western blotting and a commercial AChE assay kit, respectively.

Results: In the probe trial, significant differences between the Aβ25 35/cellulose group and the vehicle, Aβ25 35/GEB500, and Aβ25 35/GEB1000 groups were observed in terms of both time spent and distance traveled in the target quadrant. The Aβ25 35/cellulose rats also had significantly lower ChAT protein levels in the hippocampus and higher AChE activity levels in the prefrontal cortex, medial septum, and hippocampus than the other rats.

Conclusion: Intrahippocampal injection of Aβ25 35 peptide impairs spatial reference memory and has detrimental effects on ChAT expression and AChE activity in the brain. The long-term administration of GEB acts to reverse these effects, suggesting that it has potential as a treatment for AD.

P-15-012 The impact of acute administration of escitalopram on freezing behaviour in two different strains of rats

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Objective: Acute administration of selective serotonin reuptake inhibitors (SSRIs) may cause anxiety in susceptible subjects. Freezing behaviour is a well-established measure of fear/anxiety in animal research. In the current study, freezing was used in two different rat strains to assess the effect of acute administration of an SSRI, escitalopram, in a contextual conditioning model.

Methods: Wistar and Sprague-Dawley rats were investigated under similar conditions. In both experiments, half of the rats received a series of electric foot-shocks (''foot-shock'') in the experimental chamber the day before freezing was scored, whereas half of them only habituated to the chamber (''non foot-shock''). These groups were subsequently divided to receive escitalopram (10 mg/kg) or vehicle. All animals received s.c. injections one hour before testing in the experimental chamber. Freezing was scored during habituation (first 5 minutes in chamber) and in the presence of an aversive stimulus (25 ms noise bursts, 30 sec interval).

Results: Non foot-shock group: In rats never exposed to foot-shock, a significant increase in freezing behaviour during habituation (first 5 minutes) was observed for the animals injected with escitalopram compared to those treated with vehicle regardless of strain. This effect was however more pronounced in Sprague-Dawley rats. No significant effect of the drug was obtained during the presence of the aversive stimulus. Foot-shock group: Among rats exposed to foot-shock the previous day, escitalopram did not enhance freezing during the first 5 min of habituation in any of the two strains. However, a significant increase in freezing behaviour was observed during the presence of noise bursts (5–20 minutes) in Wistar rats only.

Conclusion: The results imply that acute administration of escitalopram causes an increase in freezing behaviour that tentatively may correspond to the anxiogenic effect of this substance in humans. The effect appears to be both context- and strain-dependent.

P-15-013 Pituitary adenylate cyclase-activating polypeptide (PACAP) plays significant roles in mental function and neuronal development

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Objective: PACAP is a multifunctional neuropeptide acting as a neurotransmitter and neuromodulator. Previously, we demonstrated that PACAP-deficient (PACAP-/-) mice display notable psychomotor

abnormalities, most of which were reversed by atypical antipsychotic drugs, and that PACAP gene SNPs were associated with schizophrenia. These results suggest that PACAP might be a risk factor for psychiatric disorders including schizophrenia, however, a pathogenic pathway involving PACAP signaling remains unknown. Recent evidence implicates abnormal spine morphology in the pathogenesis of psychiatric disorders. In this study, we therefore examined if PACAP-/- mice have such an abnormality. In addition, since serotonin (5-HT)7 receptors have been implicated in psychiatric disorders and as a promising novel target of antipsychotic drugs, we also examined if a similar feature of 5-HT7 antagonism is observed in PACAP-/- mice to address predictive validity of the mutants as a model for psychiatric disorders.

Methods: After Golgi staining, dendritic spine morphology was analyzed in hippocampal CA1 neurons in PACAP-/- and wild-type littermate mice. The number of postsynaptic density protein (PSD)-95-immunolabeled synaptic puncta was determined in primary cultured hippocampal neurons from both genotypes. For behavioral analyses, mice were subjected to an open field test, the Porsolt forced swimming test, and a Y-maze working memory task.

Results: Golgi staining of hippocampal CA1 neurons revealed dendritic spines are morphologically immature in PACAP-/- mice. In primary cultured neurons from the mutant mice, the volume of PSD-95-labeled synaptic puncta was decreased. SB-269970, a selective 5-HT7 antagonist, significantly ameliorated the abnormal psychomotor behavior and impaired working memory performance in PACAP-/- mice.

Conclusion: The present results implicate PACAP signaling in synaptic pathology and provide predictive validity of PACAP-/- mice in modeling psychiatric disorders. Taken together, it is suggested that the PACAP signaling pathway may emerge as a potential therapeutic target for psychiatric disorders.

P-15-014 Toxicity effect of cisplatin-treatment on cerebellar purkinje cells at during lactivorous in neonate mice

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Objective: Cisplatine is a Vina Alkaloid which is a cell-cycle-specific agent and blocks. Cisplatin is a drug to treat certain types of cancer. Although genital neoplasia can be supposed soon after cisplatin treatment, its side effects, although uncommon, may prevent the drug from becoming a standard of therapy. At lactation period, it is not known whether this drug is excreted in breast milk. In this research we studied the effect of cisplatin on Cerebellar Purkinje cells at During Lactivorous in Neonate Mice.

Methods: 50 Female Mice at lactation period divided randomly to control & experimental groups. Mices of experimental group were injected by cisplatin (10 mg/kg IV for one dose on days 1th, 8th, 15th of lactation period. One week after the inject, neonate brains (21days old) fixed with perfusion procedure & removed from skull. Then cerebellum embedded in 10% formalin solution. The 5-micromiter sections taken from cerebellum of neonate were stained by H&E & Gold chloride. Density & volume of purkinje cells & distance of cells from each other studied with light microscopy & digital camera. One other way, T-test were used for analysis ($P < 0.05$).

Results: The body weight in experimental group reduced in contrast to control group. The volume of purkinje cells in experimental group were increased than the control group. The number of cells were a few decreased and the distance of cells in experimental group a few increased.

Conclusion: Cisplatin effect on neonate purkinje cells is excreted in breast milk with histopalothogic channges and decrease of number of the purkinje cells.

P-15-015 Toxicity effect of cisplatin-treatment on mice cerebellum formation

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Objective: Cisplatin is an alkaloid that is administered to inhibit the division of malignant tumor cells. Occurrence of malformation in embryos has been proved in treated pregnant mothers. However, there was no adequate information about its toxic effect on cerebellar structures of newborns. Considering the passage through the Blood Brain Barrier and its cytotoxic effect, the destructive effects of cisplatine on the formation of cerebellum in newborns was demonstrated.

Methods: In this study 30 pregnant female mice were randomly divided in two groups (control and experimental). The treated group received 10 mg/kg at days 8 and 13 of pregnancy (I.P). At the end of pregnancy, 60 newborns (control and experimental groups) were selected for examination by H&E staining. T-test and SPSS software were used to analyze data obtained from quantifying parameters.

Results: Morphologic observations showed significant decrease in weight, skull size and newborn growth ($P < 0.05$) On microscopic observation, cerebellar white matter of cerebellum showed decreased compaction of glial cells accompanied by deficiency in myelination of nervous fibers. Occurrence of apoptosis was seen in epithelial cells of choroid plexus and in white matter glial cells.

Conclusion: Based on these results, we can conclude that the effects of anti-mitosis drugs can include inhibitory activity on the proliferation of cerebellar cortical cells. The results also show induction of apoptosis in choroid plexus cells and cerebellum.

P-15-016 Protective effects of betaine on lipopolysaccharide-induced memory impairment in mice and the involvement of GABA transporter 2

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Objective: Betaine (glycine betaine or trimethylglycine) plays important roles as an osmolyte and a methyl donor in animals. While betaine is reported to suppress expression of proinflammatory molecules and reduce oxidative stress in aged rat kidney, the effects of betaine on the central nervous system are not well known. In this study, we investigated the effects of betaine on lipopolysaccharide (LPS)-induced memory impairment and on mRNA expression levels of proinflammatory molecules, glial markers, and GABA transporter 2 (GAT2), a betaine/GABA transporter.

Methods: Mice were continuously treated with betaine for 13 days starting 1 day before they were injected with LPS, or received subacute or acute administration of betaine shortly before or after LPS injection. Then, their memory function was evaluated using Y-maze and novel object recognition tests 7 and 10–12 days after LPS injection (3 μg/mouse, i.c.v.), respectively. In addition, mRNA expression levels in hippocampus were measured by real-time RT-PCR at different time points.

Results: Repeated administration of betaine (0.163 mmol/kg, s.c.) prevented LPS-induced memory impairment. GAT2 mRNA levels were significantly increased in hippocampus 24 hr after LPS injection, and administration of betaine blocked this increase. However, betaine did not affect LPS-induced increases in levels of mRNA related to inflammatory responses. Both subacute administration (1 hr before, and 1 and 24 hr after LPS injection) and acute administration (1 hr after LPS injection) of betaine also prevented LPS-induced memory impairment in the Y-maze test.

Conclusion: These data suggest that betaine has protective effects against LPS-induced memory impairment and that prevention of LPS-induced changes in GAT2 mRNA expression is crucial to this ameliorating effect.

P-15-017 Behavioral profiling for voluntary ethanol intake and ethanol seeking in male outbreed rats

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Objective: The development of alcohol use disorder (AUD) is dependent on the interaction between genetics and environment, mirrored by the individual variation in voluntary ethanol intake and seeking between, and within, outbreed rat strains. We used the Novel Cage Test (NCT) to evaluate the emotional reactivity and stress coping styles in relation to ethanol consumption in Rcc Wistar, Lister Hooded and Long Evans rats.

Methods: The latency time, frequency and duration of locomotor, explorative, risk assessment and anxiety-like behaviors were calculated from 5 min of spontaneous behavior in a box. The rats were

thereafter subjected to intermittent-access 20% ethanol two-bottle-choice paradigm and operant self-administration of 20% ethanol. The NCT results were correlated with voluntary ethanol intake and ethanol seeking behavior through a pattern recognition analysis – the prinicipal component analysis (PCA).

Results: The Wistar rats had the highest voluntary ethanol consumption of the three strains and were cautious, proactive stress copers, with high emotionality. However, nearly half of the Wistar rats did not perform any ethanol seeking behavior. In contrast, Lister Hooded that were very explorative with low emotionality, had the lowest voluntary ethanol intake, but the highest level of ethanol seeking behavior. The Long Evans rats were anxious, reactive stress copers with high emotionality and had a low degree of both voluntary ethanol consumption and seeking behavior.

Conclusion: In conclusion, the rats that had the highest ethanol intake in a two-bottle-choice setting had a proactive stress coping style and a higher level of emotionality compared to rats with a high level of ethanol seeking behavior, which were more explorative. Being too emotional or anxious in combination with a reactive stress coping style decreased the initiative to voluntary ethanol consumatory behavior significantly. Behavioral profiling has potential to be a valuable tool in the prediction of high or low individual responders in preferred AUD models.

P-15-018 Effect of hemantane on depressive-like behavior and memory in rat model of parkinson's disease

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Objective: Non-motor symptoms precede motor disturbances in Parkinson's disease. The aim of the study was to evaluate the effects of the novel antiparkinsonian drug Hemantane (N-2(adamantyl)hexamethylenimine hydrochloride) and Amantadine sulfate in methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned rats, a model of the pre-motor stage of Parkinson's disease.

Methods: Male white outbred rats were distributed into 4 groups: 1st – sham operated, 2nd – MPTP-lesioned, animals of the 3rd and 4th groups were injected intraperitoneally with Hemantane (10 mg/kg) or Amantadine (20 mg/kg) daily starting 5 days before the MPTP infusion and throughout the study. MPTP (100 μg/1 μl) was infused bilaterally into substantia nigra pars compacta (SNc). Three weeks after surgery, rotarod, modified forced swimming and passive avoidance tests were performed.

Results: No motor alterations were determined in the rotarod test in animals of all groups. In the swimming test, animals of group 2 presented depressive-like behavior; swimming activity was significantly reduced (38%), and immobility increased 10-fold compared to group 1. Hemantane completely normalized immobility and swimming duration. Amantadine significantly decreased immobility. But its effect was 3 times less than that of Hemantane. In passive avoidance test, impairment of the hole reflex was determined in 50% of MPTP-lesioned rats, which did not enter the dark compartment at the training session. The other group 2 animals demonstrated impaired acquisition in retention trial. Hemantane and Amantadine prevented these alterations.

Conclusion: Bilateral injection of MPTP into the SNc induced depressive-like behavior and impaired learning and memory in rats. Hemantane and Amantadine are able to prevent or reduce these disturbances. The effect of Hemantane was more pronounced than that of Amantadine.

P-15-019 Perinatal NMDA receptor blockade causes lasting impairments to the synaptic and intrinsic physiology of fast-spiking interneurons in a developmental model of schizophrenia

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Objective: NMDA antagonists induce psychotic states that closely resemble schizophrenic symptoms and are therefore widely used to model schizophrenia (SZ). Neonatal mice sub-chronically treated with NMDA antagonists incur long-lasting behavioral deficits, and repeated exposure decreases staining of biochemical markers of inhibition. However, the impact on inhibitory physiology is less clear. Thus, the aim of this study is to determine the impact of perinatal NMDA receptor blockade on cortical inhibitory neurotransmission.

Methods: Whole-cell patch clamp electrophysiology was performed on fast-spiking/parvalbumin-positive interneurons (FS cells) from cortical brain slices of adult animals treated with the MK-801 as neonates. Immunohistochemical analyses was also performed.

Results: Neonatal MK-801 treatment caused a four-fold reduction in near-threshold spike latency of FS cells; a 61% increase in membrane resistance; and a 23% increase in AP 1/2 width. The AP threshold of FS cells from MK-801 treated animals was strongly dependent on the amplitude of the depolarizing current, which did not occur in vehicle treated animals. Consistent with these findings, immunohistochemical analysis revealed dramatic reductions in the somatic expression of the potassium channel, KV1.1. MK-801 treatment also disrupted excitatory synaptic input to FS cells. We found that thalmo-cortical synapses on FS cells were twice as likely to express functional NMDA current in MK-801 treated animals (80% MK-treated vs. 40% vehicle-treated), and immunohistochemical analyses revealed a substantial increase in the expression of the NR2B subunit in the soma of FS cells. Electrically evoked responses from the thalamocortical synapses of MK-801-treated animals contained 300% more NR2B-mediated current than vehicle-treated controls.

Conclusion: Together these data demonstrate that transient NMDA receptor blockade during early development elicits changes in the physiology of cortical FS cells that persist into adulthood, and may provide a physiological basis for the behavioral deficits observed in this model.

P-15-020 Cognition improving and antioxidant effects of asparagus racemosus willd in mice

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Objective: In the present study, nootropic activity of aqueous extract of roots of A. racemosus (AR) was studied in mice.

Methods: Elevated plus maze and passive avoidance paradigm were employed to evaluate learning and memory. Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) were used to induce amnesia in mice. AR (50 and 100 mg/kg, p.o.) significantly attenuated amnesic deficits induced by scopolamine, diazepam and natural aging. To delineate the possible mechanism through which A. racemosus elicits anti-amnesic activity, effects on whole brain acetylcholinesterase activity, brain lipid peroxide levels and antioxidant enzymes activity were estimated.

Results: AR significantly decreased acetylcholinesterase activity and increased brain levels of thiobarbituric acid reactive substances and gluthione peroxidase activity. These findings suggest that the roots of A. racemosus exert a preventive effect against cognitive deficits induced by scopolamine, diazepam and natural ageing.

Conclusion: The memory improving activity of A. racemosus may be attributed to its antioxidant, neuroprotective, pro-cholinergic and anti-acetylcholinesterase properties and can be of enormous use in delaying the onset and reducing the severity of Alzheimer's disease.

P-15-021 Behavioral and neurochemical effects of calcium salt of N-(5-hydroxy-nicotinoyl)-L-glutamate in accelerated aging male mice SAMP10

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Objective: Senescence-accelerated mouse prone 10 (SAMP10) strain is one of the models for study of neurodegeneration associated with aging. It is known that SAMP10 mouse over 6 mo exhibits behavioral disorders (memory deficiency, increased anxiety, depressive-like responses) and shifts of neurotransmitter contents in brain structures. Novel neuroprotective substance calcium salt of N-(5-hydroxy-nicotinoyl)-L-glutamate (Ampassae® (AMPS)) modulates an activity of the glutamate receptors AMPA-subtype and possesses anti-hypoxic, anti-ischemic and anti-amnestic activities in standard rodent's tests.

Methods: The aim of the study was to investigate AMPS (5–20 mg/kg) effects on behavior and neurotransmitter amino acids contents in male SAMP10 of 9–16 mo. In behavioral experiments memantine (2 mg/kg), a low-affinity noncompetitive antagonist of glutamate receptors NMDA-subtype, used as reference drug. The substances were injected intraperitoneally once per day 30 min before testing. Memory was studied in one-trail passive avoidance step-through paradigm, anxiety – in elevated plus maze, depression-like response – in the Porsolt's forced swimming test. In the neurochemical assay AMPS (5 mg/kg) was administered intraperitoneally for 5 days, the last injection −30 min before the animals were decapitated. The neurotransmitter amino acids glutamate, aspartate, taurine, glycine and gamma-aminobutyric acid contents were determined in frontal cortex, hypothalamus, striatum, hippocampus by HPLC/PD.

Results: AMPS (20 mg/kg) completely eliminated the memory deficiency and anxiety and had no effect on the animal's depression-like behavior. Memantine provided a greater corrective action on emotion than on the memory in the mice. AMPS increased the level of all recorded amino acids in striatum and glutamic acid and glycine levels in hypothalamus.

Conclusion: Thus, AMPS decreases neurochemical shifts in the animal brain, especially in striatum, one of the structures most prone to atrophy in mice SAMP10, and the mechanism may at least partly underlie its neuroprotective effects in SAMP10.

P-15-022 Local GluN2B antagonism in responses to stress and anxiety- and depression-related behavior

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Objective: Increasing evidence points to a role for N-methyl-D-aspartate receptors (NMDARs) in the treatment of mood and anxiety disorders. Systemic administration of drugs acting as antagonists at the GluN2B subunit of the NMDAR has fast-acting clinical efficacy in depression, and reduces anxiety- and depression-related behaviors in rodent preclinical assays. However, the specific brain regions mediating these effects remain to be determined. Prior studies have shown that acute antidepressant-related effects of systemically-delivered GluN2B antagonists parallel synaptic changes in the medial prefrontal cortex (mPFC) (Li et al., 2010), while gene deletion of GluN2B in corticohippocampal principal neurons attenuates depression-related responses to repeated swim stress (Kiselycznyk et al., 2011). Here we examined the role of GluN2B localized in the mPFC and basolateral amygdala (BLA) in mediating depression- and anxiety-like behaviors.

Methods: Male C57BL/6J mice were cannulated to bilaterally infuse the GluN2B-selective antagonist, Ro 25–6981, into either mPFC or BLA prior to testing in the light/dark exploration test for anxiety-like behavior or the forced swim test for depression-related behavior. To compliment these pharmacological studies, mPFC GluN2B expression was reduced via lentiviral-mediated knockdown and mice were tested for depression-related responses to repeated swim stress.

Results: Results showed that Ro 25–6981 infused into mPFC, but not BLA, reduced depression-related behavior. By contrast, there were minimal effects of Ro 25–6981 infused into mPFC or BLA on anxiety-like behavior.

Conclusion: Collectively, these data are consistent with the mPFC as a major effect-locus for the antidepressant-like effects of GluN2B antagonists. This has implications for understanding the mechanisms underlying the fact-acting antidepressant effects of these drugs in human patients.

P-15-023 The influence of selective serotonin reuptake inhibitors (SSRI) and 3,4-methylendioxymethamphetamine (MDMA) on neurogenesis in the adult rat hippocampus

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Objective: There are two regions of high density cell division in the adult mammalian brain that produce new neurons throughout adulthood: the subventricular zone of the lateral ventricle (SVZ) and the subgranular zone of the dentate gyrus in the hippocampus (SGZ). We examined the influence of two serotonin reuptake inhibitors (SSRI – fluoxetine, citalopram) and a serotonin releaser 3,4-methylendioxymethamphetamine (MDMA) on proliferation and maturation of neuronal cells in the hippocampus of adult rats.

Methods: Adult male Wistar rats were administered with the tested substances (citalopram 10 mg/kg i.p., fluoxetine 5 mg/kg i.p., MDMA 5 mg/kg i.p., saline) for 3 (proliferation) or 21 (maturation) days. Newly generated cells were labeled with 5-bromo-2-deoxyuridine (BrdU; 3 × 50 mg/kg s.c.) one day before (maturation) or after (proliferation) drug treatment. Rat brains were perfused (4% paraformaldehyde), sliced (40 μm) and every 6th section was immunohistochemically stained (rat anti-BrdU, Serotec OBT0030). The number of BrdU positive cells was counted under a light microscope (Zeiss Axio Imager Z1).

Results: Acute administration of SSRI and MDMA nonsignificantly increased the number of BrdU positive cells in the dentate gyrus compared to the controls. We detect no statistically significant difference in the number of BrdU positive cells after chronic drug administration among the tested groups.

Conclusion: According to our result, proliferation of new hippocampal cells is not dependent on the way the serotonin system is stimulated. However, it seems that maturation of neurons is not influenced by the serotonin system, which is in conflict with various studies. These data have an implication for neurogenesis in depression as an underlying factor of antidepressant effect. This study was supported by the grants IGA MHCR NS 10374-3, NS 10375-3, MEYSCR 1M0517, MHCR MZ0PCP2005, VG2VS/200 and VG2VS/271.

P-15-025 Modulation of ketamine-induced oxygen amperometry signals in awake rats – a translational imaging biomarker for novel antipsychotics?

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Objective: Human functional imaging has had a major impact on cognitive neuroscience, linking brain structure to function. The technique is translatable but rodent fMRI is limited to anaesthetised or restrained animals. In-vivo oxygen amperometry is an alternative approach that can measure oxygen changes related to behaviour since it allows real time monitoring of extracellular tissue oxygen in freely-moving animals. Neuroimaging techniques have previously been used to determine the effects of NMDA antagonists on brain activation in humans and animals; these compounds have been shown to be psychotropic and to induce cognitive disturbances. Pharmacological reversal of the NMDA antagonist-induced imaging response may represent antipsychotic activity, as previously seen with mGlu2/3 agonists. Here, we compared the effect of i.v. ketamine challenge on neuroimaging signals in healthy volunteers and anaesthetised rats to the oxygen response in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC) of freely-moving rats using in vivo oxygen amperometry. The modulation of the oxygen amperometric ketamine response by the mGlu2/3 agonist LY379268 was also assessed.

Methods: For the oxygen amperometry, rats were implanted with oxygen sensors in the mPFC and dHPC and were given a 1 mg/kg i.v. infusion of ketamine over 2 minutes. For the mGlu2/3 agonist modulation studies, LY379268 (1, 3, and 10 mg/kg) was dosed i.p. 30 minutes before ketamine was administered.

Results: Our results show a translational response to i.v. ketamine challenge, with the human fMRI, anaesthetised rat CBV imaging, and freely-moving rat oxygen amperometry showing similar increases in activation in the cingulate/mPFC. Pretreatment with LY379268 caused a dose-dependent reversal of the ketamine response in the oxygen signal in freely moving rats.

Conclusion: We show that oxygen amperometry may be a good translational surrogate for imaging studies in freely-moving animals, and modulation of the oxygen ketamine response may provide a translational neuropharmacological biomarker of antipsychotic activity.

P-15-026 Hypothalamic expression of Kiss1/Gpr54 and GnIH/Gpr147 systems in adult male and female rats exposed to early life stress and/or to juvenile olanzapine administration

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Objective: Hypothalamic circuitries responsible for the homeostatic control of essential body functions can be permanently affected by the early-life environment. A single episode of maternal deprivation (MD, 24 h on postnatal day, pnd, 9) compromises metabolic and endocrine homeostasis, and provokes behavioral outcomes that resemble symptoms frequently observed in neuropsychiatric disorders. In humans, the pharmacological management of such disorders includes administration of atypical antipsychotics, i.e. olanzapine (Olan), often prescribed to children and adolescents despite adverse side-effects. We aimed to investigate the long-lasting effects of these manipulations on hypothalamic key hormonal systems controlling reproduction and energy balance, namely Kiss1/Gpr54 and GnIH/Gpr147.

Methods: Male and female Wistar rats exposed to MD or left undisturbed were orally administered with Olan (7.5 mg/kg/day) or vehicle (1 mM acetic acid) from pnd 28 to 49 and hypothalamic mRNA expression of Kiss1/Gpr54 and GnIH/Gpr147 was analyzed in adult animals.

Results: MD resulted in a persistent decrease in body weight that extended to adolescence in males and to adulthood in females. MD induced sex-dependent alterations in the kisspeptin system; decreased Kiss1 levels in males and Gpr54 expression in females. Olan only induced a subtle reduction in body weight gain among females together with a reduction in Kiss1 levels in males that was exacerbated by prior exposure to MD. Male animals exposed to both MD and Olan exhibited the lowest levels of Gpr54 and GnIH/Gpr147. In females, Olan reduced Gpr147 expression whereas Kiss1/Gpr54 seemed not to be affected. The combination of both manipulations also diminished hypothalamic GnIH level among females.

Conclusion: Present data indicate that MD critically interferes with hypothalamic developmental programming in a sex-dependant manner, mainly through modulation of the Kiss1/Gpr54 system. Adolescence is also suggested as a sensitive period for pharmacological hypothalamic modulation. Further research on the long lasting effects of antipsychotic drugs and their interaction with early life events is urgently needed.

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P-15-027 The neuroprotective role of rivastigmine in the treatment with haloperidol (animal model)

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Objective: Evaluation of the neuroprotective role rivastigmine in the treatment with haloperidol, noting the need to maintain balance between neuron and glia.

Methods: Animal model study, on two lots consisting of 5 Winstar rats each, male adults, weight 200–250 g, held during the study in temperature, humidity, food and ambient stressless conditions. On N1 lot, from day 1 to 14 has been administered saline solution through stomach tube, and from day 15 to 28 has been administered haloperidol intraperioneally (equivalent to 0.20 mg/kg/day) and saline solution. On N2 lot, from day 1 to 14 has been administered rivastigmine through stomach tube (equivalent to 0.5 mg/kg/day), and from day 15 to 28 has been administered haloperidol intraperioneally (equivalent to 0.20 mg/kg/day) and rivastigmine (equivalent to 0.5 mg/kg/day). In the day 29 the rats were sacrificed. The sample brain (frontal cortex, hippocampus, striatum, Meynert nucleus, white matter) was histopathologically processed: formalin (10%) and ethyl alcohol (96%) fixation and paraffin embeded. Microtome slices were stained in hematoxyline-eosine, trichromicGS, PAS-hematoxyline, toluidine blue, methylen blue for Nissle corpuscles and argentic impregnation for neurofibriles. The obtained slices were studied with optical microscope.

Results: Haloperidol significantly alter the neural structures and white substance (neural apoptosis and vacuolisations). Rivastigmine exercise neuroprotection on N2 lot by reducing neuronal loss in the frontal cortex and hippocampus and reduction in neural changes of striatum and Meynert nucleus. Rivastigmine ensures high protection for the white substance, with minimum number of vacuolisations.

Conclusion: Rivastigmine presents neuroprotective qualities, both for the gray substance and white substance on brain structures involved in the cognitive process (hippocampus, frontal cortex, striatum, Meynert nucleus) under the treatment with haloperidol.

P-15-028 Effects of BACE1 ablation on a phencyclidine-induced model of schizophrenia

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Objective: Genetic association studies have linked the neuregulin1 (NRG1) and its ErbB4 receptor to schizophrenia. Altered NRG1/ErbB4 signaling has also been shown to result in hypofunction of glutamatergic system. We hypothesized that NRG1/ErbB4 pathway interacts with glutamatergic receptors pathways by homeostatic mechanisms in a way that the deficits in one of the pathways could result in adaptive changes in others.

Methods: To analyze primary changes in NRG1/ErbB4 pathway we used knockout mice that lack beta-site APP cleavage enzyme 1 (BACE1). BACE1 participates in the proteolytic processing of NRG1 and its deletion results in multiple endophenotypes related to schizophrenia as observed in BACE1ko mice. For analysis of secondary changes in NRG1/ErbB4 signaling we used sub-chronic phencyclidine treatment (PCP), a non-competitive antagonist of the NMDA receptors, on postnatal days (PND) 7, 9, and 11 (10 mg/kg, i.p). Wild type (WT) and BACE1ko mice were behaviorally tested at PND 28–30.

Results: As expected, WT-PCP mice developed numerous schizophrenia-like behavioral traits such as deficits in prepulse inhibition, spatial recognition memory, and increased sensitivity to MK-801. BACE1ko mice demonstrated similar deficits on the vehicle treatment. Interestingly, PCP administration in BACE1ko mice resulted in the amelioration of some of the deficits. Western blot analyses showed decreased levels of BACE1 protein in WT mice after PCP treatment. The levels of two major substrates of BACE1, APP and NRG1, as well as phosphorylation of NRG1 receptor, ErbB4, were modified. In addition, PCP treatment in WT mice resulted in reduced levels of myelin basic protein (MBP), one of the down stream markers of NRG1/ErbB4 pathway activity. In contrast, PCP-treated BACE1ko mice showed some recovery of low levels of MBP, a marker of central hypomyelination in these mice.

Conclusion: Results of this study indicate that the perinatal PCP treatment modify activity of the BACE1/NRG1 pathway implicating the interactions of these pathways during development.

P-15-029 Functional studies of altered Eaat3 expression in obsessive-compulsive disorder

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Objective: SLC1A1 gene (Eaat3) is an attractive candidate gene implicated in Obsessive-Compulsive Disorder (OCD): Eaat3 regulates extracellular levels of glutamate in cortico-striato-thalamo-cortical (CSTC) circuits consistently implicated in OCD. SLC1A1 is the most evident 'brain-related' gene of interest located in the chromosomal region 9p24. 3) In the first case-control study of this gene in OCD we found that SLC1A1 was associated with OCD. The strongest evidence from this study indicated that a certain haplotype was almost two times more frequent in OCD patients than controls (OR = 1.89); two of three SNPs of this haplotype were found to be expression Quantitative-Trait Loci (eQTLs). These findings, plus earlier family

studies point to to SLC1A1 as being the most solidly established gene identified in OCD. This work aims to generate transgenic mouse models for conditional Cre-recombinase-dependent Slc1a1 overexpression and knockout.

Methods: We developed and fully characterized in vitro a construct to achieve conditional, Cre-recombinase dependent Eaat3 ovexerpression. We performed transient expression of our construct in N2A cells and evaluated the cre-mediated Eaat3 expression levels by Western Blot. We also measured (3H)-glutamate uptake in N2A cells, as well as glutamate-induced currents in HEK293 carrying the construct.

Results: We show here that our construct allows for conditional, Cre-mediated Eaat overexpression. We recenlty obtained the first generation of Eaat Tg mice mated with CamKII-Cre mice to achieve Eaat3 overexpression restricted to forebrain.

Conclusion: Our animal model is expected to provide seminal information regarding the mechanism of SLC1A1 dysfunction at the gene regulatory, neurochemical, and anatomical levels during various stages of development. In addition, mice with conditional Slc1a1 expression alterations may offer exciting possibilities for generating new animal models of psychiatric and/or neurodegenerative disorders and also help in the development of drugs that target glutamate neurotransmitter system for effective OCD treatment.

P-15-030 Expression of serotonergic genes in the raphe nuclei is associated with anxiety-related behaviour in rats

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Objective: Numerous genetic studies imply variation in brain serotonergic neurotransmission as a determinant of differences in temperament in humans. Since the biochemical underpinnings of such associations are difficult to study in man, it is of interest to explore if similar associations are at hand also in experimental animals. To this end, this study aimed at investigating (in rat) the possible association between inter-individual differences in anxiety-like behaviour on the one hand, and the expression of a number of genes important for serotonergic transmission on the other.

Methods: 30 male Wistar rats were used. Inter-individual differences in anxiety-like behaviour were assessed using the elevated plus-maze. Three weeks later, the animals were sacrificed and the brains extracted. Expression of serotonergic genes in the raphe nuclei was determined using TLDA cards.

Results: Animals exhibiting high levels of anxiety-like behaviour had significantly higher mRNA levels for several of the genes normally expressed by serotonergic neurons, such as those encoding tryptophan hydroxylase 2, amino acid decarboxylase and the serotonin transporter.

Conclusion: The results suggest that the expression of serotonergic genes in the raphe nuclei is associated with anxiety-like behaviour in the rat, with animals exhibiting stronger such behaviour displaying higher expression of a number of genetic markers of brain serotonergic transmission.

P-15-031 Memantine attenuates and reverses hyperthermia induced by 3,4-methylenedioxymethamphetamine (MDMA) in rats

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Objective: Life-threatening hyperthermia occurs in some individuals consuming 3,4-methylenedioxymethamphetamine (MDMA). No effective pharmacological treatment for MDMA-induced hyperthermia has yet been established. In the present study, we evaluated the effectiveness of memantine, a non-competitive NMDA receptor antagonist and α-7 nicotinic Ach receptor antagonist, in treating MDMA-induced hyperthermia. We also examined the pharmacological effects of MDMA using in vivo microdialysis.

Methods: MDMA (10 mg/kg) was injected and the dopamine and serotonin levels in rat hypothalamus were measured by the microdialysis method. In the prior-administration experiment, saline, memantine (10 mg/kg or 20 mg/kg), MK 801 (0.5 mg/kg), CGS 19755 (5 mg/kg), or methyllycaconitine (6 mg/kg) was injected intraperitoneally. MDMA (10 mg/kg) was then injected subcutaneously 30 minutes later. Rectal temperature was measured every 30 minutes. In the post-administration experiment, MDMA was injected and then memantine (10 mg/kg and 20 mg/kg) was injected intraperitoneally 30 minutes later.

Results: The extracellular concentrations of serotonin (5-HT) and dopamine (DA) in rat anterior hypothalamus were increased 50- and 15-fold, respectively, compared with their respective pretreatment levels after administration of MDMA. Pretreatment and post-treatment with memantine each inhibited the peak increase in body temperature. Although pretreatment with the NMDA receptor antagonists MK-801 and CGS 19755 suppressed the increase in body temperature induced by MDMA, pretreatment with methyllcaconitine did not suppress the hyperthermia induced by MDMA. These findings suggest that MDMA increases the concentrations of 5-HT and DA in the hypothalamus, and that memantine suppresses MDMA-induced hyperthermia via its NMDA receptor-antagonistic effect.

Conclusion: Our findings suggest that memantine may be an off-label effective drug for the treatment of MDMA-induced hyperthermia in humans.

P-15-032 Prolonged activation of microglia induced by systemic lipopolysaccharide administration in mice

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Objective: Peripheral lipopolysaccharide (LPS) administration induces sickness behavior in experimental animals, and higher dose of LPS may cause prolonged behavioral suppression. In the present study, we assessed the systemic LPS-induced behavioral change and time-course of microglial activation in mice brain.

Methods: BALB/c mice (male, 8–9 weeks old) were injected with LPS (0.8 mg/kg, i.p.). Sickness behavior was measured at 23–24 h post injection. Brain sections were obtained 2, 8, 24 and 48 h after LPS injection, and distribution of microglia was visualized by immunohistochemical method with antibody against ionized calcium-binding adaptor molecule 1 (Iba-1). Activation of microglia was estimated by measuring the Iba-1-immunoreactive areas in digital images with Image J software.

Results: Food and water consumption, body weight and locomotor activity in a new cage were decreased after LPS injection. Iba-1 positive cells (microglia) showed time-dependent and region-specific distribution. Activation of microglia was observed even 48 h after LPS injection in some regions, including ventral hypothalamus and dorsal medulla.

Conclusion: Our data suggested that prolonged microglial activation in specific brain regions may contribute to the lingering behavioral suppression induced by considerable dose of LPS.

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P-15-033 Effect of L-carnosine on repeated social defeat stress-induced behavioral and neurochemical changes in mice

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Objective: Mood and anxiety disorders are two major mental illness, and more than one-third people reported the symptoms of these disorders in their life. Since current treatments are poorly effective, new curatives are greatly needed. Mice experiencing repeated social defeat stress (SDS) develop a persisted aversion to social contact. This aversion can be normalized by chronic treatment with antidepressants, which resemble depression in human. Previous studies indicated that dipeptide L-carnosine produced many effects in nervous systems, such as antinociceptive and hypnotic actions. The present study was, then, designed to investigate the antidepressive-like activity of L-carnosine on repeated SDS model in mice.

Methods: Mice were subjected to daily social defeat, and then separated from the aggressor behind a protective wire mesh barrier, which allowed for sensory contact, for the remainder of the day.

Mice were exposed to a different aggressor each day for 10 days, and were then examined for social behavior. Mice showed aversion to social contact at 1 day after SDS was used. Imipramine or L-carnosine treatment was started from 1 day after SDS for 10 days.

Results: Repeated social defeat stress-induced aversion to social contact was attenuated by the repeated, but not acute, treatment with imipramine or L-carnosine. We also examined the changes of the glutamate receptors in anterior cingulate cortex (ACC) where modulates emotions responses. The expressions of NR2B NMDA receptor subunit and GluA1 and GluA2 AMPA receptor subunits were increased in the ACC of SDS mice. This increases were attenuated by imipramine or L-carnosine treatment.

Conclusion: Our present results suggest that L-carnosine might be effective for long-lasting behavioral plasticity in response to aversive social experience. We also hypothesized that enhanced glutamatergic functions in ACC might be involved in the avoidance of social contact after repeated SDS.

P-15-034 The effects of mGlu2/3 agonist on neurochemical and electrophysiological changes induced by hallucinogen 4-bromo-2,5-dimethoxyphenetyhlamine (2C-B)

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Objective: Increases in the release of glutamate in the prefrontal cortex (PFC) and disrupted functional connectivity induced by hallucinogenic drugs have been proposed to be linked to hallucinogenesis and psychotic symptoms. Therefore we examined whether inhibition of this release by the metabotropic glutamate 2/3 (mGlu2/3) receptor agonist (LY379268), will normalize the neurochemical and electrophysiological effects of the hallucinogen 4-bromo-2,5-dimethoxyphenetyhlamine (2C-B). We concentrated on neurotransmission in the prefrontal cortex (PFC) and cortical functional connectivity (EEG spectra and coherence).

Methods: Male Wistar rats were used in all experiments. Microdialysis of PFC was performed to measure levels of dopamine, serotonin and their metabolites, and of glutamate and GABA. Cortical EEG was recorded from 6 pairs of electrodes on each hemisphere above the frontal, parietal and temporal cortex in freely moving rats. EEG power spectra and coherence in EEG traces that correspond to behavioral inactivity were subsequently analyzed in Neuroguide Deluxe v.2.6 software.

Results: 2C-B increased the levels of dopamine, serotonin and glutamate and decreased the levels of GABA in PFC. LY379268 normalized the effects of 2C-B on glutamatergic neurotransmission, slightly potentiated the release of dopamine and serotonin and had no effect on GABA. 2C-B induced EEG power decreases except in theta and alpha bands and globally decreased coherence. LY379268 normalized 2C-B induced a power decrease in delta, potentiated the decrease in all other bands and completely reversed decreased coherence in the gamma band.

Conclusion: mGLU2/3 agonism selectively reversed changes in the glutamate release in PFC and gamma coherence. However, the lack of effectiveness on most other parameters revealed that the glutamate release induced by 2C-B only partially contributes to its psychedelic potential. Our data have implications for serotonin-glutamate interactions in psychoses and hallucinogenesis. This study was supported by the grants IGAMHCR NS10374-3, NS 10375-3, MEYSCR1M0517, MHCRMZ0PCP2005, MICR VG2VS/200 and VG2VS/271.

P-15-035 Long-lasting memory abnormalities following exposure to the mouse defense test battery

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Objective: Memory dysfunctions are thought to play a crucial role in development and maintenance of post-traumatic stress disorder (PTSD). Patients persistently re-experience the traumatic event particularly when exposed to trauma-related cues and display memory alterations (Morey et al., 2009; Chemtob et al., 1999). The objective of the present study was to investigate potential long-term effects of predatory stress exposure on short-term episodic memory in mice by evaluating their cognitive performance following or not trauma context exposure.

Methods: Mice were exposed to the mouse defense test battery (MDTB), a test designed to investigate defensive responses of mice confronted with a rat (Griebel et al., 1995). Two weeks later, stressed and control mice were placed in the MDTB apparatus. Locomotion and escape attempts from the cage were measured. Two hours later, their cognitive performances were evaluated using the object recognition task.

Results: Mice exposed to the MDTB procedure displayed flight, avoidance, defensive and attack reactions, risk assessment behaviors and increased escape attempts. When mice were exposed again to the MDTB apparatus two weeks later, they displayed significantly more escape attempts than naive animals. Moreover, stressed mice not exposed to the MDTB prior to memory testing displayed impaired cognitive performance in the object recognition task. In contrast, stressed mice exposed to the MDTB apparatus two hours prior to the memory test, had similar cognitive performance than control animals.

Conclusion: These findings demonstrate that MDTB exposure causes long-lasting behavioral alterations. Interestingly, the stress-induced cognitive deficit can be alleviated by exposure to the traumatic environment in the absence of stressor. It can be hypothesized that re-exposure to the context resulted in an increase of arousal or vigilance, which subsequently led to an improvement in cognitive performance. In conclusion, this procedure reproduces some of the symptoms observed in patients suffering from PTSD and may thus be of interest for studies on the complex interaction between emotion and memory in PTSD.

P-15-036 Sexually dimorphic dopaminergic dysfunction in a mouse model of Huntington's disease and depression

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Objective: Depression is the most common psychiatric disorder in Huntington's disease (HD) patients. There is yet to be a study of sexual dimorphism in the development and presentation of depression in HD patients. Interestingly, we have previously reported a female-specific depression-like phenotype in the R6/1 transgenic mouse model of HD associated with serotonergic system alterations. We now extend these findings to include sex-dimorphic dopaminergic (DA) dysfunction at an early pre-motor symptomatic disease stage.

Methods: In order to investigate whether transgenic HD mice display depressive-like endophenotypes associated with dopaminergic impairments, we assessed the effect of several dopaminergic ligands (including the DA transporter inhibitor bupropion, as well as SKF-81297 and ropinirole, respectively D1 and D2/D3 receptor agonists) on the forced-swim test (FST) and on locomotor activity in 8–12-week-old male and female HD mice.

Results: Overall we found that compared to female animals, males were more sensitive to the locomotor stimulating effects of bupropion at both 8 and 12 weeks of age, which were successfully attenuated with the selective D1 antagonist SCH-23390. In addition, 8-week-old HD females but not males showed an impaired locomotor response to bupropion. The HD mutation also resulted in a decrease of locomotor response to the D1 agonist SKF-81297. In contrast, the selective D2/D3 agonist ropinirole significantly reduced locomotor activity in all animals. However, this effect seemed dose–dependently reduced in HD compared to WT mice. Finally, the depressive-like behavior exhibited by female HD mice in the FST was rescued by acute bupropion, possibly through a mechanism involving D2/D3 receptor signaling.

Conclusion: Our data suggest a crucial role for disrupted dopaminergic signaling in mediating the sexually dimorphic depression-like phenotype in HD mice and provide evidence suggesting that bupropion could be explored as a potential antidepressant in HD.

P-15-037 Pharmacological characterization of the glycine transporter-1 inhibitors RG1678 and SSR504734 in rodent models for treatment of cognitive and positive symptoms in schizophrenia

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Objective: Evidence from numerous clinical and preclinical studies has led to the hypothesis that hypofunction of N-methyl-D-aspartate (NMDA) receptors play an important role in the pathophysiology of schizophrenia involving positive, negative and cognitive symptoms. One approach to counteract NMDA receptor hypofunction is the extracellular increase of the NMDA receptor co-agonist glycine by glycine transporter-1 (GlyT1) inhibitors. Thus, by strengthening glutamatergic neurotransmission, inhibiting GlyT1 has the potential for treatment of positive and cognitive symptoms of schizophrenia, besides the shown efficacy on negative symptoms in a recent clinical trial (Umbricht et al., 2011). In the present study, the GlyT1-inhibitors RG1678 (Umbricht et al., 2011) and SSR504734 (Depoortere et al., 2005) were evaluated in models of positive and cognitive symptoms in rodents.

Methods: Adult male rats were administered with two different GlyT1-inhibitors, SSR504734 (as racemate) or RG1678, and the increase of glycine in CSF was determined via LC/MS-MS analysis. Regarding antipsychotic and memory enhancing efficacy, both compounds were tested for reversal of ketamine induced hyperlocomotion in rats and for reversal of MK-801 induced memory impairment in the mouse T-maze spontaneous alternation task.

Results: RG1678 and SSR504734 led to a dose-dependent increase of glycine in rat CSF. Both compounds also showed antipsychotic-like and pro-cognitiv efficacy in the hyperlocomotion test and T-maze task, respectively. However, the efficacious dose/exposure range in T-maze was 5–10-fold lower than in hyperlocomotion test.

Conclusion: The results of this study demonstrate preclinical efficacy of GlyT1-inhibitors in rodent models for positive and cognitive symptoms of schizophrenia confirming previous findings (Depoortere et al., 2005). The marked difference of efficacious doses between antipsychotic and pro-cognitive activity might indicate that different levels of NMDA receptor potentiation via glycine increase are needed for the treatment of positive or cognitive symptoms. Depoortere et al., (2005), Neuropsychopharmacology 30, 1963–1985. Umbricht et al., (2011), Schizophrenia Bulletin 37(Suppl.), P324.

P-15-038 Behavioral analysis of LRP1 mediated brain adaptation

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Objective: Several lines of evidence positioned the LDL receptor gene family as one of the key players in homeostasis of neuronal signalling. The Low Density Lipoprotein Receptor-Related Protein 1 (LRP1) is well recognized as a receptor for amyloid β (Aβ) and its modulation a possibility in Alsheimeŕs disease therapy. But recently, a new interaction between LRP1 and the NMDA receptor has been found. It was demonstrated that knock-in mutations in the C-terminus of LRP1 directly influence NMDA receptor function. The in vivo relevance of that mechanism is unknown.

Methods: To analyse the effect of a perturbed LRP1 function on the NMDA receptor due to the knock-in mutation in the LRP1 gene we compared transgenic LRP1 KI mice to wild type littermates for a behavioural phenotype. Animals were tested with respect to activity (open field), anxiety (elevated plus maze, light dark chamber), learning and memory (object recognition, Morris Water maze) as well as locomotion (Rotarod).

Results: The open field paradigm revealed a tendency to hyperactivity of the LRP1 KI mice. No differences between genotypes were seen with respect to anxiety-related behaviours. Learning and memory related behaviours in the MWM test indicated that wild type mice learned the position of the hidden platform faster and more accurately compared to LRP1 KI mice. Similarly in a relearning paradigm and with respect to emotional memory wildtype mice were superior. However LRP1 KI mice outperformed wild type littermates on the Rotarod task for locomotion.

Conclusion: Presently those behavioural alterations in form of hyperactivity and altered spatial learning parallel effects seen in conditional knock out of LRP1 but also after antagonism of the NMDA receptor giving a first in vivo indication of a reduced LRP1 NMDA receptor-related interaction in those transgenic mice. This opens new possibilities for NMDA receptor modulation under pathological conditions.

P-15-039 Risperidone attenuated serotonin syndrome animal model induced extracellular nitric oxide and glutamate

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Objective: As serotonergic agents prescription has increasing, serotonin syndrome has been major and important health issue. Recently, several studies reported that glutamate and nitric oxide (NO) play a role in psychostimulant drugs-induced hyperthermia which related to neurotoxicity. Therefore we hypothesized that serotonin animal model can raise glutamate and NO concentration and those increasing may be attenuated by risperidone (potent 5-HT2A and D1 rreceptor antagonist) treatment. We therefore measured the changes in the levels of glutamate and NO metabolites in the anterior hypothalamus by using microdialysis method.

Methods: Male Wistar rats were used in this study. All the animal procedures employed were approved by the Animal Investigation Committee of our School and were in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals. Two different serotonin syndrome animal models were prepared. In the first model, tranylcypromine (3.5 mg/kg) and fluoxetine (10 mg/kg) were simultaneously intraperitoneally (i.p.) administered to rats. We simultaneously administrated clorgyline (1.2 mg/kg) and 5-HTP (80 mg/kg) i.p. to rats in the second model. The perfusate was collected and injected into a HPLC unit by using an automatic injector and the levels of glutamate and NO metabolites (NOx) were immediately determined.

Results: In the both animal models induced NOx levels increasing and each increasing were attenuated by risperidone (0.5 mg/kg) pretreatment. Extracellular levels of glutamate were increased in the first animal model, but not second animal model, and risperiodne pre-administration attenuated which increasing.

Conclusion: Previous studies have reported that D1 receptor activation induces glutamate levels increasing and D1 and 5-HT2A receptors activation increase the NOx synthesis, therefore risperidone's D1 and 5-HT2A receptors antagonistic effect were assumed to suppress glutamate and NOx increasing.

P-15-040 Blockade of the nmda-no pathway in the ventromedial prefrontal cortex (vmpfc) induces antidepressant-like effects

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Objective: Stress exposition enhances glutamate and nitric oxide (NO) levels into the central nervous system. Depressed individuals show enhanced levels of glutamate and neuronal nitric oxide synthase (nNOS) in limbic structures. Administration of antagonists of glutamate NMDA receptors or inhibitors of NO synthesis induces antidepressant-like effects. The aim of the present study was to evaluate the participation of the glutamatergic and nitrergic systems of the vmPFC over the behavioral consequences induced by forced swimming (FS), an animal model of depression.

Methods: Male Wistar rats (230–260 g) with guide cannulas aimed at the prelimbic (PL) region of vmPFC were submitted to a 15 min session of FS and, 24 h later, they were submitted to a 5 min session of the FS test when the immobility time was measured. Injection of LY235959 (LY; NMDA antagonist at 1, 3 and 10 nmol/0.2μL), NPA (nNOS inhibitor at 0.01 nmol/0.2 μL), c-PTIO (NO scavenger at 1.0 nmol/0.2 μL), ODQ (soluble guanylyl cyclase- sGC – inhibitor at 1.0 nmol/0.2 μL) or vehicle was realized 5 min before the test

session. All data were analyzed by ANOVA followed by Dunnet's post-hoc test.

Results: LY administration into vmPFC-PL reduced the immobility time (Mean ± SEM: vehicle: 116.3 ± 21.17; LY 1 nmol: 164.4 ± 18.92; LY 3 nmol: 28.71 ± 10.21*; LY 10 nmol: 39.43 ± 7.99*; *$p < 0.05$ from control group). NPA, c-PTIO and ODQ induced similar effects (Mean ± SEM: vehicle: 140.1 ± 15.23; NPA: 47.57 ± 10.42*; c-PTIO: 56.86 ± 10.62*; ODQ: 81.20 ± 15.99*; *$p < 0.05$ from control group).

Conclusion: These results show for the first time that the blockade of NMDA receptors, NO synthesis or sGC activity in the vmPFC-PL induces antidepressant-like effects. Therefore, the activation of the NMDA-NO-cGMP pathway in the vmPFC in response to stress may facilitate the development of its behavioral/emotional outcomes.

P-15-041 The role of dopamine signalling in the GABAergic neuron development and motor behavior in zebrafish larvae

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Objective: An imbalance in dopamine-mediated neurotransmission and neurodevelopmental abnormalities are features of schizophrenia. The main target of antipsychotics, the dopamine D2 receptor, modulates the activity of Akt and DARPP-32, which are downregulated in the brain of schizophrenic patients. To investigate if altered D2-dependent signalling leads to abnormal neurodevelopment, we first evaluated if dopamine modulates Akt and DARPP-32 signalling in the developing brain. Later, we investigated the role of dopamine in the development of GABAergic neurons and the effects in the motor behavior.

Methods: Since the zebrafish development is external, we used zebrafish as experimental model. We treated 3 days post fertilization (dpf) and 5 dpf zebrafish larvae with dopaminergic agonists and antagonists to evaluate the dopaminergic intracellular pathways. In order to investigate the role of dopamine in the neurodevelopment, we examined dlx6:gfp transgenic 3 dpf larvae, which express GFP in several forebrain GABAergic neurons, chronically exposed to dopamine. Ultimately, we recorded and analyzed the motor behavior of the larvae.

Results: We observed dephosphorylation of Akt at threonine 308 (T308) and DARPP-32 at threonine 34 (T34) through D2 receptors. Chronic exposure to dopamine resulted in region specific alterations in the number of GABAergic neurons, but not the total number of cells. Furthermore, we observed that dopamine affects motor behaviour in 3–5 dpf larvae.

Conclusion: Together, our data suggest that dopamine signalling represses Akt and DARPP-32 signalling in the developing brain and leads to defects in GABAergic neuronal differentiation in the zebrafish larval brain. Furthermore, the alterations in forebrain GABAergic neurons are correlated with altered context-dependent motor behaviour. Thus, with this model system, we could holistically assay the biochemical, morphological, and behavioural consequences of altered dopamine signalling during development. These results will help shape our understanding of the role of dopamine in brain development and provide new mechanistic insight for further assessing the neurodevelopmental origin model of schizophrenia.

P-15-042 Neonatal exposure to mk-801 impairs working memory in adult rats that can be ameliorated by galantamine

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Objective: The N-methyl-D-aspartate (NMDA) receptor plays a crucial role in developmental plasticity. It has been shown that neonatal exposure to NMDA receptor antagonists impairs cognitive function in adult rats. The aim of this study was to examine the effects of acetylcholinesterase inhibitors on working memory deficits in adult rats induced by neonatal MK-801 treatment.

Methods: Timed-pregnant Sprague-Dawley rats were obtained from the Peking University Health Science Center. The day of birth was considered postnatal day (PND) 0. From PND5-14, male pups were injected subcutaneously with MK-801 or saline twice daily beginning at 9:00 and 17:00, respectively. The animals were tested for spatial working memory performed in Morris water maze task in adulthood (PND 63–69). Rats were randomly assigned to treatment with galantamine (1.0 mg/kg) or saline. Drug or saline was injected each day 30 min before the animals were tested in the Morris water maze. Twelve rats were used in each group: saline-saline, MK-801-saline, saline-galantamine, MK-801-galantamine.

Results: Male MK-801-treated rats exhibited impaired working memory during adulthood. This cognitive deficit was ameliorated by chronic treatment with galantamine.

Conclusion: These results suggest that a brief disruption of NMDA receptors during a sensitive period of cortical development can produce long lasting working memory deficits in male rats that are relevant to schizophrenia. In addition, AChE inhibitor galantamine ameliorated memory deficits produced by MK-801, which may have relevance for the cognitive effects of cholinomimetic drugs in patients with schizophrenia.

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P-15-043 The effects of antipsychotics on amphetamine induced recall impairments in a visuo-spatial paired associates learning task using touchscreen equipped operant boxes

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Objective: The use of operant boxes equipped with touchsensitive computer monitors for the testing of cognition in rodents is becoming increasingly popular. However to date the majority of published work has focused on task validation via lesions or direct administration of compound to areas of interest. Little work has been done demonstrating the pharmacological sensitivity of these assays, leaving there utility for the drug discovery process largely unexplored. Here we attempt to demonstrate that a touchscreen test of visuo-spatial paired associates learning (PAL) can be selectively impaired by a pharmacological model of schizophrenia, and that this impairment can be reversed.

Methods: Rats (male lister-hooded, Harlan) were trained in a PAL task (Talpos et al., 2009, Psychopharmacology) performed in Med Associates operant boxes run by K-Limbic software (Conclusive Solutions). Once the task was acquired 0.5 mg/kg of amphetamine given 60 minutes prior to testing, a dose known to selectively impair accuracy, was used to disrupt recall. We then attempted to reverse this disruption with common antipsychotics including risperidone (0.04–0.16 mg/kg) and haloperidol (0.01–0.04 mg/kg) given 30 min prior to behavioral testing.

Results: Haloperidol and risperidone were both shown to dose dependently lessen the amphetamine induced impairment without substantially altering response latencies.

Conclusion: A ''low'' dose of amphetamine consistently induced a selective impairment in performance of an object-in-place PAL task. This impairment was partially reversed by administration of common antipsychotics risperidone and haloperidol. While additional work will be required to see if this model has utility in exploring mechanisms beyond D2 receptor antagonism, these data demonstrate the potential utility of this assay and challenge model for pharmacological research. These results and additional data will be discussed, along with the translational value of this approach.

Policy of full disclosure: All authors work for Janssen pharmaceutical companies of Johnson and Johnson, makers of risperidone and haloperidol.

P-15-044 Social-cooperation is associated with increased levels of hypothalamic nor-epinephrine and striatal serotonin – evidence from a laboratory rat model

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Objective: Explanations and models of cooperation usually focus on the 'economics' of individual's 'invested efforts' and 'outcomes' while down-playing adjunct social dimensions of naturally occurring cooperation. This study examined whether cooperative and

individual behaviors differ in monoaminergic function in a manner that may explain the reported 'bias for cooperation' even in situations where there is no immediate economic gain.

Methods: Cooperation, represented by pairs of rats reinforced for coordinated shuttles within a shared chamber (COOP), was compared with individual rats shuttling for reinforcements (IND), and behaviorally naïve rats (NAIVE). Following training, the hypothalamus and striata were sampled and the activity pattern of the noradrenergic, serotonergic and dopaminergic systems were assessed using HPLC analyses.

Results: Since rates of shuttling and reinforcements were controlled, COOP and IND rats did not differ at the individual level in either 'invested effort' (shuttles) or 'outcomes' (reinforcements). Nevertheless, differences were evident in monoaminergic functions. COOP rats exhibited significantly higher hypothalamic norepinephrine levels than IND and NAIVE rats. Compared to IND rats, COOP rats exhibited significantly higher striatal serotonin levels. Differences in levels of dopaminergic metabolites were restricted to the right striatum; compared to IND rats COOP rats exhibited significantly higher levels of HVA, whereas NAIVE rats exhibited significantly higher DOPAC levels.

Conclusion: These differences are dissociated from the 'economics' of 'effort' and 'outcomes' and thus highlight the importance of social behaviors in the reported 'bias for cooperation' as they demonstrate a relationship between social cooperation and a distinct activity pattern in brain mechanisms that were related with arousal, goal directed behaviors and motivation.

P-15-045 A comparison of electroencephalographic activity in serotonergic and gultamatergic models of psychosis

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Objective: We focused on the electrophysiological changes in the two most reliable pharmacological models of psychosis, serotonergic (indolamine (psilocin), ergoline (N,N-diethyllysergamid, LSD) and phenylethylamine (mescaline) hallucinogens) and glutamatergic (N-methyl-D-aspartate receptor (NMDA) antagonists ketamine and dizocilpine (MK-801)). The objective of this study was to compare these models from the aspect of functional connectivity using quantitative EEG.

Methods: After stereotactical implantation and recovery, cortical EEG was recorded from 6 pairs of electrodes on each hemisphere above the frontal, parietal and temporal cortex in freely moving rats. EEG power spectra (local synchronization) and coherence (long projections) were subsequently analyzed in Neuroguide Deluxe v.2.6. In order to make a translational approach to human recordings only EEG traces that correspond to behavioral inactivity (model of resting EEG) were processed.

Results: In all serotonergic models a general decrease in EEG spectral power as well as in EEG coherences was observed. Psilocin and LSD caused a significant power decrease in all frequency bands, while the decrease after mescaline was significant only in lower frequencies. The most prominent decrease in EEG coherences was observed in delta and theta bands after all serotonergic drugs. In glutamatergic models ketamine and MK-801 increased power in the gamma band; a discrete decrease in theta and beta band after MK-801 was also observed. Both substances induced a significant reduction of EEG coherence across the whole spectrum with most prominent changes in the delta and theta bands.

Conclusion: In conclusion, there was a clear disconnection of long projections in the brain shared by both models. On the contrary there were group specific effects on local synchronization. Both effects were group-specific, indicating the validity of data. Our results will be discussed in comparison with findings from schizophrenic patients. This study was supported by the grants IGAMHCR NS10374-3, NS 10375-3, MEYSCR1M0517, MHCRMZ0PCP2005, MICR VG2VS/200 and VG2VS/271.

P-15-046 Effect of transient blockade of N-methyl-D-aspartate receptors at neonatal stage on stress-induced lactate metabolism in the medial prefrontal cortex of adult rats: Role of serotonin-1A receptor agonism

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Objective: Decreased activity of the prefrontal cortex (PFC) has been considered to provide a basis for the pathophysiology of schizophrenia, an illness associated with a neurodevelopmental origin. Evidence from preclinical and clinical studies indicates serotonin (5-HT)1A receptors play a crucial role in energy metabolism of the PFC. The present study was undertaken to determine 1) if transient blockade of N-methyl-D-aspartate (NMDA) receptors during the neonatal stage inhibit energy demands in response to stress, as measured by extracellular lactate concentrations, in the medial PFC (mPFC) at the young adult stage, and 2) if tandospirone, a 5-HT1A partial agonist, reverses the effect of the neonatal insult on energy metabolism.

Methods: The procedures complied with the National Institutes of Health Guideline for the care and use of Laboratory animals. All experiments were reviewed and approved by the Committee of Animal Research, University of Toyama. Male pups received MK-801 (0.20 mg/kg) on postnatal day (PD) 7 through 10. On PD 63, footshock stress-induced lactate levels were measured using in vivo microdialysis technique. Tandospirone (0.1, 1.0, 5.0 mg/kg) was administered once daily for 14 days before the measurement of lactate levels.

Results: Neonatal MK-801 treatment suppressed footshock stress-induced lactate production in the mPFC, but not caudate-putamen (CPu), whereas basal lactate levels were not significantly changed in either brain region. The MK-801-induced suppression of footshock stress-induced lactate production in the mPFC was attenuated by tandospirone at 1.0 mg/kg/day, but not 0.1 or 5.0 mg/kg/day, an effect antagonized by co-administration of WAY-100635, a selective 5-HT1A antagonist.

Conclusion: These results suggest a role for impaired lactate metabolism in negative symptoms and cognitive deficits of schizophrenia, and provide a novel insight into the ability of 5-HT1A receptor agonists to treat these symptoms.

P-15-047 Postnatal developmental changes in the gene expression patterns induced by systemic administration of methamphetamine in the rat neocortex

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Objective: The onset of schizophrenia and the schizophrenomimetic effects of dopamine agonists and N-methyl-D-aspartate (NMDA) receptor antagonists rarely occur during infancy and childhood, suggesting that schizophrenia-related neuron circuits and molecules in the brain could exhibit an age-dependent and a critical period-associated response to these schizophrenomimetics.

Methods: To test this hypothesis to get an insight into the molecular basis of the onset of schizophrenia, we have explored in the developing rat brain at postnatal days 8, 18, 25 and 50 the areas and genes whose responses to a schizophrenomimetic dopamine agonist, methamphetamine (MAP), are developmentally regulated by employing an activity mapping using c-fos gene expression, a DNA microarray technique and a quantitative RT-PCR method. The present animal experiments have been approved by the ethics committees of the Tokyo Medical and Dental University.

Results: To test this hypothesis to get an insight into the molecular basis of the onset of schizophrenia, we have explored in the developing rat brain at postnatal days 8, 18, 25 and 50 the areas and genes whose responses to a schizophrenomimetic dopamine agonist, methamphetamine (MAP), are developmentally regulated by employing an activity mapping using c-fos gene expression, a DNA microarray technique and a quantitative RT-PCR method. The present animal experiments have been approved by the ethics committees of the Tokyo Medical and Dental University.

Conclusion: These data suggest that the neocortex and the genes showing the critical period-related expressional changes could

compose the neuron circuits and molecular cascades, respectively, which might be involved in the pathophysiology of schizophrenia.

P-15-048 Effects of chronic social defeat stress on behavior in adult mice and expression on ChAT

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Objective: Because social factors play a key role in human stress precipitated brain disorders, social defeat stress is widely used in biomedical research to model various psychiatric disorders in animals. The purpose of the present studies was to observe the behavior of the adult mice and expression on choline acetyltransferase (ChAT) after social defeat.

Methods: Male C57BL/6J mice were divided into two groups (susceptible and unsusceptible groups) after 10 days of social defeat stress. Next, we measured spontaneous locomotion and social interaction test, dark/light test, Morris water maze test, novel object recognition test (NORT) and forced swimming test (FST). Choline acetyltransferase (ChAT) expression was measured in the mouse prefrontal cortex (PFC), amygdala and hippocampus using Western blotting.

Results: There was no difference in locomotor activity between control, susceptible and unsusceptible groups. In dark/light test, the defeated mice spent much more time in the dark box than control group and took longer to emerge from the dark box than control group. However, between susceptible group and unsusceptible group, there was no significant difference. Susceptible group displayed significant impairment of memory for the novel object recognition and decreased social sniffing compared with control group in NORT and social interaction test, respectively. On the other hand, in Morris water maze, there was no difference of escape latency and spent time in the target quadrant between control and defeated groups. In FST, susceptible group displayed significantly more immobility time compared with control and unsusceptible groups. ChAT expression in the PFC, amygdala and hippocampus was significantly decreased in susceptible group as compared to control.

Conclusion: Our results suggest that chronic social defeat stress in mice produces significant decrease of social interaction, impairment of memory for novel object, increase of immobility and significant decreased expression of ChAT in the PFC and hippocampus. The clinical implications of these findings should be discussed with regard to environmental causes for mental disorders.

P-16. Imaging

P-16-001 Quantitative immunohistochemical mapping of neurochemicals in the human brain

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Objective: We developed a human brain mapping analyzer to determine quantitative immunohistochemical distributions of neurochemicals in a large tissue slice at the cellular or near-cellular level (Sutoo et al., 1998). In this study, the distributions of choline acetyltransferase, tyrosine hydroxylase, dopamine-beta-hydroxylase, glutamate decarboxylase, glutamate dehydrogenase, calmodulin and substance P in the human brain were analyzed using this analyzer.

Methods: The brains of three male adults (age range: 50–70) with no history of neurological or psychiatric disorders were perfused with ice-cold fixative within 8 h following death. After fixation, the right hemisphere was sectioned at a thickness of 20 micron, and consecutive coronal slices were stained fluorescent immunohistochemically. Each stained slice was divided into approximately 3 million microareas at 50 micron intervals, and the fluorescence intensities in the microareas were measured quantitatively.

Results: Autofluorescence in the brain slice was eliminated photometrically, and pure immunohistochemical distribution was obtained (Sutoo et al., 1998, 1999, 2000, 2001). Its quantitative linearity surpasses that of the image analyzers used with TV cameras, and the sensitivity is greater than that of HPLC. Also, the measuring area is far larger than that of laser confocal microscopes.

Conclusion: This method is a powerful technique for quantitative and comparative analysis of the distributions of neurochemicals in the whole brain slices, and we believe that it will facilitate the investigation of the functions of the central nervous system and disorders thereof in various diseases.

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P-16-002 Reduced hippocampal grey matter in depression: Effect of state and short-term antidepressant treatment

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Objective: Loss of grey matter volume in the hippocampus is one of the most replicated structural changes in depression. Antidepressants induce neuroplastic effects in the hippocampus in animal but effects of antidepressants in this region have not been demonstrated in humans. In this study we aimed to determine (1) whether grey matter loss in the hippocampus in depression is a current state or trait abnormality and (2) whether rapid change can be detected following antidepressant treatment and associated clinical improvement.

Methods: We recruited 64 medication free unipolar depressed patients (39 currently depressed and 25 in remission) and 66 healthy controls who underwent structural magnetic resonance imaging. Thirty-two currently depressed participants were treated with the antidepressant citalopram for 8 weeks. Adherence to treatment was evaluated by measuring plasma citalopram concentration. We measured regional variation of grey matter concentration by using voxel-based morphometry (VBM-DARTEL).

Results: In the cross sectional study patients with current depression had reduced grey matter concentration in the hippocampus vs. healthy controls (L: −28, −16, −23; R: 28, −23, −24, both whole-brain FWEc $p < 0.001$) and vs. untreated patients in stable remission (L: −29, −27, −22; FWEc $p = 0.01$ and R: 34, −29, −24, whole brain FWEc $p = 0.013$). In the longitudinal analysis, after treatment, there was bilateral hippocampal grey matter increase in currently depressed participants (L: −24, −4, −25; R: 19, −13, −25, both FWEc $p = 0.050$) but not in healthy controls, although post-treatment grey matter still remained lower than in controls.

Conclusion: Our results confirm grey matter reduction in the hippocampus in currently depressed patient that is not present in those with long-term remission. Short-term, successful antidepressant treatment partially reverses this abnormality suggesting that this may be a state-marker for depression.

P-16-003 Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression

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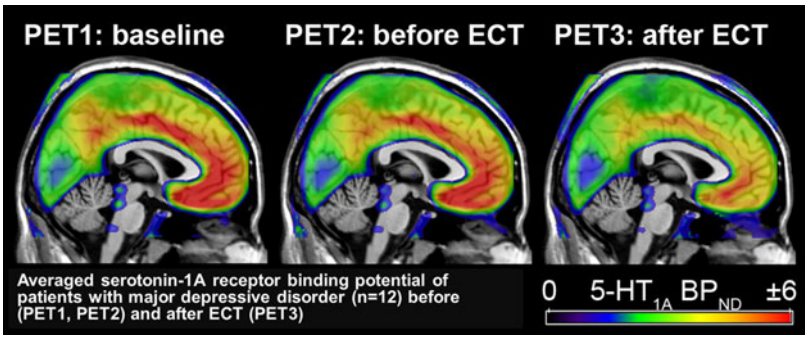
Objective: Electroconvulsive therapy (ECT) has been successfully applied as first-line approach for treatment-resistant depression. However, the neurobiological mechanisms underlying its effectiveness remain unclear, although numerous preclinical studies point towards a significant involvement of the serotonergic system,



particularly the serotonin-1A receptor (5-HT1A). Considering the consistently reported 5-HT1A alterations in depression, this study aims to investigate molecular mechanisms of ECT using positron emission tomography (PET).

Methods: 12 subjects (8 female, mean age ± SD = 47.83 ± 11.12 years) with severe unipolar depression (HAM-D17 score ⩾ 23), participated in this study. Patients underwent 3 PET scans using [carbonyl-11C]WAY-100635, two before (test-retest reliability) and one after completed ECT. ECT was carried out according to international standards, resulting in 10.08 ± 2.35 sessions. Medication remained in steady-state during the investigation, drugs targeting the 5-HT1A receptor were discontinued prior inclusion. PET scans were normalized to MNI-space (SPM8). Quantification of 5-HT1A receptor binding potential (BPND) was carried out in PMOD 3.3 using MRTM2 and the cerebellar grey as reference.

Results: Paired-samples t-test showed a significant decrease ($t = 9.16$, $p < 0.001$; mean = 17.58 ± 6.65) of HAM-D values after ECT. Voxel-wise repeated-measures ANOVA revealed a global decrease of 5-HT1A BPND ($p < 0.05$, FDR-corrected) comparing PET2/PET3, corresponding to one interconnected cluster (436 cm^3) with peak areas in the anterior cingulate cortex (ACC: $t = 4.58$, x/y/z = 2/40/20 mm MNI space), its subgenual part (sgACC: $t = 3.77$, x/y/z = 6/36/-8) and the amygdala ($t = 3.91$, x/y/z = −26/4/-26 mm). There was no significant difference comparing PET1/PET2.

Conclusion: Our results substantiate the effectiveness of ECT in depression. Furthermore, we showed a significant decrease of 5-HT1A BPND in depressed patients after ECT affecting virtually the whole cortex. More precisely, these findings include brain regions, consistently reported to present functional and morphological alterations in subjects suffering from affective disorders.

P-16-004 Functional abnormalities within the working memory network in remitted major depressive disorder

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Objective: Highly variable severity and course as well as a heterogeneous clinical picture comprising emotional, vegetative, psychomotor and cognitive symptoms characterize Major Depressive Disorder (MDD). Previous neuroimaging studies investigated predominantly MDD patients with a concurrent depressive episode compared to healthy controls and repeatedly observed activation increases within emotion as well as cognition brain circuits. While limited evidence is available regarding neural alterations in cognition-related circuits during symptomatic MDD, literally nothing is known concerning the functionality of working memory (WM) networks during stable remission.

Methods: Hence, we conducted a cross-sectional functional magnetic resonance imaging (fMRI) study with the goal to determine if WM function and associated neural activation differ between fully remitted medication-free MDD patients (n = 61) and healthy subjects (N = 84) without any previous psychiatric life-time diagnosis. We employed the so-called n-back WM paradigm.

Results: While no significant differences in task performance were detected between the groups, activation increases in extended frontal, parietal and cingulate areas, with punctum maximum in the frontal gyrus, were identified in both, remitted MDD (rMDD) patients as well as controls, during the 2-back versus 0-back condition. Moreover, relative to controls, rMDD patients showed greater activation in the left frontal cortex, including inferior and middle frontal gyrus as well as adjacent areas such as the medial frontal and insular cortex, with the peak of activation differences between the left inferior frontal and precentral gyrus ($Z = 3.71$, $p < 0.001$, uncorrected; x = −62, y = 12, z = 12).

Conclusion: Our finding of increased WM-related neural activation in rMDD patients in comparison to controls in the absence of any behavioral differences suggest, that rMDD patients have to compensate underlying deficits in cognitive networks by increasing neural processing within the same neural circuits in order to maintain a comparable level of WM performance. Moreover, our results point towards persisting functional alterations in the cognitive networks even after a full recovery of MDD.

P-16-005 Impaired to P-down processing in schizophrenia in the perception of a hollow mask revealed with fMRT and event related potentials

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Objective: Visual illusions can reveal mechanisms of perception that try to make our world around us meaningful. In order to perceive our environment around us as meaningful the interaction between bottom-up and top-down processing has to be intact. In this study we use the principles of the 'hollow-mask illusion' to investigate this interaction. The hollow-mask illusion occurs when a hollow mask is perceived (incorrectly) as a normal face. It is understood to be a process that involves the generation of hypotheses about the three-dimensional shape of faces by interpreting the bottom-up signals received from the eyes using conceptual and perceptual knowledge (top-down processing). Healthy volunteers perceive a hollow mask as a normal face, presumably due to the strength of constraining top-down influences, while patients with schizophrenia do not. However the neural mechanisms underpinning this effect remain poorly understood.

Methods: We used functional magnetic resonance imaging and event related potentials to investigate the hollow-mask illusion in schizophrenic patients and healthy controls. The primary aim of this study was to use measures effective connectivity arising from dynamic causal modelling (DCM).

Results: We identified differences between the two groups in effective connectivity. In particular, there was a strengthening of bottom-up processes, and weakening of top-down ones, during the presentation of 'hollow' faces for the patients. In contrast, the controls exhibited a strengthening of top-down processes when perceiving the same stimuli.

Conclusion: These findings suggest that schizophrenic patients rely on stimulus-driven processing and are less able to employ conceptually-driven top-down strategies during perception, where incoming sensory data are constrained with reference to a generative model that entails stored information from past experience.

P-16-006 Combined in vivo PET-microdialysis studies of NA release in minipig

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Objective: To evaluate the hypothesis that [11C]yohimbine, a selective antagonist tracer of the alpha 2 receptors in tracer dose, may be used to assess in vivo changes in synaptic noradrenaline (NA) during acute pharmacological challenges.

Methods: Isofluorane-anesthetized Gottingen minipigs were positioned in a stereotaxic headholder and a high resolution CT performed in a Siemens PET/CT. Microdialysis probes (CMA70) were placed stereotaxically in thalamus, striatum and cortex and perfused with artificial CSF (2 μL/min). Samples were collected every 10 min throughout the course of the experiment and immediately frozen until assay. After a 2–3 hrs equilibrium period, three 90 min [11C]Yohimbine (200–300 MBq in 10 mL, injected mass: < 1 μg) scans were acquired: the first (baseline) scan was followed by a pharmacological intervention (amphetamine (1–10 mg/kg), a non specific NA/DA releaser or nisoxetine (1 mg/kg), a specific NET inhibitor) and scans at 30 and 150 min after challenge. Vital signs were monitored throughout the course of the study. The animal was humanely euthanized at the end of the experiment to verify probe integrity and location. Samples were analyzed with HPLC for NA and DA and their metabolites. Yohimbine total distribution volume (DVT) were obtained from thalamus, striatum and several cortical regions as previously described.

Results: Both pharmacological challenges induced a significant decrease in yohimbine binding, presumably from competition by the endogenous ligand: cortical and thalamic regions showed the greatest decrease (> 20%) while the striatum had a more moderate decrease (8–15%) consistent with reduced striatal NA innervation. Dialysis samples revealed a significant increase in NA extracellular concentrations after challenge. DA was also significantly increased after amphetamine challenge.

Conclusion: This data suggest that [11C]yohimbine may be a potential tracer to evaluate acute variations in synaptic NA concentrations after pharmacological challenges.

P-16-007 Imaging endophenotypic biomarkers for schizophrenic and affective psychoses in key neural circuits

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Objective: We conducted functional MRI studies in healthy subjects, patients with schizophrenia and affective disorders and in their healthy first-degree relatives. This combination of investigations permits to identify pathophysiological abnormalities in brain circuits of psychiatric patients, to test for their possible role as endophenotypes, and to search the genome for genetic factors that may be involved in the occurrence of these endophenotypic markers.

Methods: We applied a battery of recently established experimental paradigms in order to systematically investigate different core pathophysiological processes and neurocognitive and neurophysiological endophenotypes of schizophrenic and affective psychoses. These paradigms included different versions of circuit-specific working memory tasks (Gruber & von Cramon 2003), a combined task-switching, oddball and incongruency paradigm (Gruber et al., 2009), and the ''desire-reason dilemma'' paradigm (Diekhof & Gruber, 2010), which assesses functional interactions between the reward system and prefrontal control mechanisms. The functional integrity of all of these neural mechanisms was investigated in groups of patients with major psychoses and in their healthy first-degree relatives.

Results: Results from a cohort of more than 300 subjects will be presented. Patients with schizophrenia and patients with bipolar disorder, but not patients with unipolar depression revealed altered brain activation in different prefrontal and parietal brain areas during working memory. In specific decision-making tasks, all patient groups showed (in part diagnosis-specific) alterations in brain regions involved in reward processing and other motivational processes. In part, the same abnormalities in brain activation were also found in the healthy first-degree relatives, i.e. these pathophysiological changes may qualify as endophenotypic biomarkers for the disorder. Genome-wide association studies for these endophenotypic neuroimaging markers are currently underway.

Conclusion: The endophenotypic approach in functional neuroimaging may help to identify genes involved in the pathogenesis of psychiatric disorders and may provide important information for the development of valid animal models for further research.

P-16-008 Reduced hippocampal volumes in bipolar disorders are masked by exposure to lithium – meta-analysis

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Objective: Smaller hippocampal volumes relative to controls are among the most replicated neuroimaging findings in individuals with unipolar but not bipolar depression. Preserved hippocampal volumes in most studies of bipolar patients may reflect putative neuroprotective effects of lithium (Li).

Methods: To investigate hippocampal volumes in bipolar disorders (BD) while controlling for Li exposure, we performed a meta-analysis of neuroimaging studies which subdivided BD patients based on the presence or absence of current Li treatment. Hippocampal volumes were compared by combining standardized differences in means (Cohen's d) from individual studies using random effect models.

Results: Overall, we meta-analyzed data from 101 Li treated BD subjects, 245 BD subjects not treated with Li (non-Li group) and 456 controls from 16 studies. Both the left and right hippocampal volumes were significantly larger in the Li treated BD subjects than in controls (Cohen's d = 0.53, 95% CI = 0.18; 0.88; Cohen's d = 0.51; 95% CI = 0.21; 0.81, respectively) or the non-Li group (Cohen's d = 0.93; 95% CI = 0.56; 1.31; Cohen's d = 1.07, 95% CI = 0.70; 1.45, respectively), which had smaller bilateral hippocampal volumes than the controls (Cohen's d = −0.36, 95% CI = −0.55; −0.17; Cohen's d = −0.38; 95% CI = −0.63; −0.13, for the left and right hippocampal volumes respectively). There was no evidence of publication bias.

Conclusion: Considering the opposite direction of findings in subjects with versus without exposure to Li, the preserved hippocampal volumes among BD subjects in the majority of individual studies and all previous meta-analyses, were most likely related to the inclusion of Li-treated subjects. Our findings provide indirect support for the neuroprotective effects of Li and for the negative effects of bipolar disorders on hippocampal volumes.

P-16-009 Brain network dysfunction as a model for schizophrenia: Preliminary results using ketamine and pharmacological magnetic resonance imaging

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Objective: Alterations of functional brain networks have been frequently demonstrated in schizophrenia, although the exact underlying molecular mechanisms remain unrevealed. Ketamine is known to exert its schizophrenia-like effects through modulation of the glutamatergic system via the NMDA-receptor. Therefore, the aim of the present study was to investigate the impact of this specific transmitter system on resting state functional connectivity of the default-mode network (DMN).

Methods: 10 healthy volunteers (23.2 ± 3.4 years, 6 males) underwent resting state fMRI during esketamine hydrochloride (mean dose 15.12 ± 2.76 mg) intravenous maintenance infusion, lasting for 20 minutes. Functional MRI measurements were performed at 3 Tesla using single-shot gradient-recalled EPI (TE = 38 ms; TR = 1800 ms matrix size 128 × 128 voxel; 23 slices; FoV 190 × 190 mm). Data sets were normalized to MNI-space and analysed in SPM8. To avoid seed selection bias, a recently developed approach for the computation of functional connectivity was applied which allows for the definition of the whole DMN as seed region. A repeated-measures ANOVA was performed to assess differences between baseline connectivity values

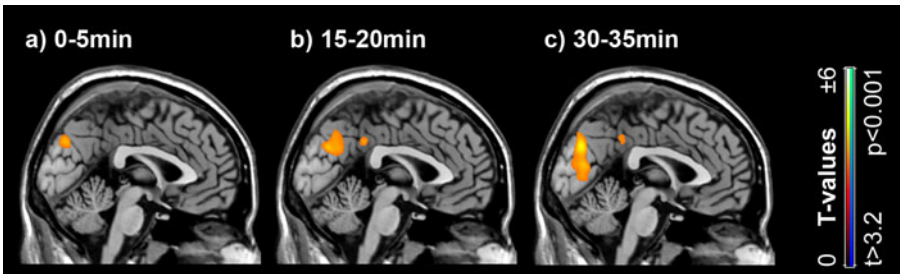

Figure: Sagittal views of differences in the functional connectivity of the default-mode network at different time-periods during (0-20 minutes) and after ketamine infusion (30-35 minutes) compared to baseline. x=0mm MNI-space

and each 5-minutes block beginning at the start of the ketamine infusion ($t = 3.2$; $p < 0.001$ uncorrected voxel level).

Results: Functional connectivity analysis showed a consistent ketamine-induced increase in the precuneus (0–5 min: $t = 3.95$; 15–20 min: $t = 4.38$; 30–35 min: $t = 4.6$) and the posterior cingulate cortex (PCC, 15–20 min: $t = 3.59$; 30–35 min: $t = 3.44$, see figure). For the later time points (15–20 min and 30–35 min) the cluster in the precuneus withstands correction for multiple comparisons ($p < 0.05$ FWE-corrected cluster level).

Conclusion: The application of a subanaesthetic dose of ketamine leads to a significant increase of the functional connectivity of the precuneus and the PCC, which represent key areas of the default-mode network. These results are consistent with findings in schizophrenic patients, which propose a hyperactivity of the DMN, pointing toward a possible implication of the NMDA-receptor on resting-state functional connectivity.

P-16-010 An initial baseline for machine learning classifier performance on resting state FMRI data

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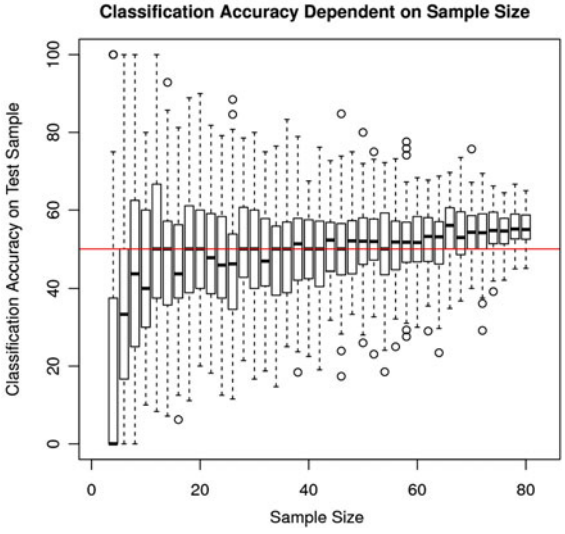
Objective: The classification of disease states has long been an important goal of fMRI research in biological psychiatry. Real world applications on other than severe cases, however, have been hindered by the low signal-to-noise ratio of fMRI data. Multivariate statistical methods can deal with this problem by taking into consideration the covariance structure in addition to the marginal distributions of a multivariate feature space. The goal of this study was to apply various machine learning classifiers to features extracted from resting-state fMRI data in order to classify subjects as male or female and thus establish a baseline for what to expect employing naive features in clinical samples.

Methods: Resting-state fMRI data of 84 healthy subjects (43 male) from the 1000 Functional Connectomes Project database (Biswal et al., 2010) was subjected to standard preprocessing (Weissenbacher et al., 2009), features for subsequent classification were extracted based on the correlation of all pairs of voxel time series. Gaussian Naive Bayes, k-Nearest-Neighbors, Support Vector Machine, and Random Forest classifiers were trained on the raw features and their principal components, classification accuracy was assessed using leave-one-out cross validation.

Results: Classification accuracies for the classifiers were shown to be highly dependent on sample size, with mean accuracies up to 60% (SVM results see figure). Estimation on 20 principal components yielded results comparable to classification on the whole dataset for most estimators.

Conclusion: On an empirical basis, we identified a classification accuracy of about 55 percent as a relatively stable result for our naively selected features, in contrast to published classification accuracies of up to 80 percent using small sample sizes (around 40 subjects). Our results, however, show that those are prone to high variability, warrantin caution when interpreting reliability in the growing field of machine learning in fMRI data analysis (Pereira et al., 2009).

Policy of full disclosure: Siegfried Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, Sepracor, and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, MSD, Pfizer, Organon, Schwabe, Sepracor, Servier, Janssen, and Novartis; and has served on speakers' bureaus for AstraZeneca, BMS, Angelini, Eli Lily, Lundbeck, Schwabe, Sepracor, Servier, Pfizer, Pierre Fabre, and Janssen.



P-16-011 Metabotropic glutamate receptor 5 densities and free glutamate concentrations in occasional and dependent cocaine users

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Objective: The primary focus of previous addiction research was on the dopamine system, by which the rewarding and reinforcing effects of cocaine are mediated. However, over the past decade evidence from preclinical studies emerged showing that cocaine use also leads to long-lasting neuroadaptations in the corticostriatal glutamate system, in which the dopamine axon terminals are embedded (Kalivas, 2009). Disruption of the glutamate homeostasis seems to be particularly relevant for drug-seeking and relapse-related behaviors (McFarland et al., 2003; Reissner and Kalivas, 2010). The metabotropic glutamate receptor 5 (mGluR5) seems an interesting candidate to be

investigated because mGluR5 null mutant mice did not self-administer cocaine and mGluR5 anatagonists attenuated self-administration and reinstatement of cocaine use in rodents (Backstrom and Hyytia, 2006; Chiamulera et al., 2001). Moreover, a human magnetic resonance spectroscopy (MRS) study with chronic cocaine users found lower glutamate levels in the ACC in comparison to controls (Yang et al., 2009). Interestingly, years of cocaine use correlated positively with glutamate levels possibly implying a compensatory neurobiological mechanism over time. Therefore, achieving a more in-depth understanding of cocaine-related glutamatergic alterations in humans may eventually lead to the development of novel drug treatment approaches.

Methods: Sixteen male cocaine users either with an occasional or chronic cocaine use pattern and 16 male controls will undergo [11C]-ABP688 positron emission tomography (PET) and 1H MRS. [11C]-ABP688 is a selective radioligand for the mGluR5, allowing to investigate potential group differences in mGluR5 densities in selected regions of interest such as the DLPFC, OFC, ACC, MPFC, and the striatum. Free in vivo glutamate concentrations of the perigenual ACC and the DLPFC will be acquired in MRS by means of a 2D JPRESS sequence and quantified by using ProFit. In addition, participants will complete a comprehensive neuropsychological test battery to relate putative neurobiological alterations to cognitive impairment.

P-16-012 Relationship between dose, plasma concentration and a4β2 nicotinic receptor occupancy for AZD1446 (TC-6683)

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Objective: Neurodegeneration in Alzheimers disease (AD) involves decreased cholinergic neurotransmission. Restoration of cholinergic neurotransmission presently is limited to the use of inhibitors of the enzyme acetylcholine esterase (AChE) increasing synaptic ACh levels. A strategy, currently in exploratory phase is stimulation of postsynaptic ACh receptors. Neuronal α4β2 nicotinic acetylcholine receptors (NNRs) are expressed in brain regions involved in cognition and may be a target for symptomatic treatment of cognitive impairment in AD. AZD1446 is a novel α4β2 NNR agonist in early clinical development for symptomatic treatment of AD, with minimal desensitization and high selectivity in vitro. AZD1446 has demonstrated efficacy in a broad range of preclinical models of cognition. Initial PET studies in non-human primates showed that AZD1446 occupies α4β2 NNRs, and the plasma concentration at which 50% of receptors are occupied, Kiplasma, was approximately 200 nmol/L. The main aim of this PET study was to determine occupancy of AZD1446 at α4β2 NNRs using 2-[18F]-F-A85380, a radioligand which binds with high affinity and selectivity to α4β2 NNRS. The study serves as a translational step in understanding AZD1446 exposure at target, before clinical studies in patients.

Methods: Nine healthy subjects were examined after administration of 10–200 mg AZD1446. Receptor binding (VT) was calculated for brain regions of interest (ROIs) (frontal and temporal cortex, thalamus, pons, cerebellum, caudate nucleus, putamen, hippocampus). Receptor occupancy was calculated using the population PK/PD model.

Results: Dose-dependent, saturable binding of AZD1446 was demonstrated, radioligand displacement approaching 100%. The AZD1446 Kiplasma was estimated to 128 nmol/L (95% CI 51.8 to 309 nmol/L).

Conclusion: This study confirmed the translatability of AZD1446 binding properties from non-human primate. The study identified a dose range that can be tested in further clinical studies, and suggests that AZD1446 is a suitable compound to explore the clinical benefit of α4β2 NNR agonist action.

Policy of full disclosure: The study is conducted by AstraZeneca.

P-16-013 A volumetric study of hippocampus and amygdala in major depression subtypes: Melancholic versus psychotic depression

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Objective: The aim of the current study was to compare the volumes of the hippocampus and amygdala in depression among patients with melancholic depression, patients with psychotic depression and normal controls.

Methods: Twenty two patients with melancholic major depression, 17 with psychotic major depression and 18 normal controls were included in the study. Hippocampal (HV) and amygdala (AV) volumes were measured on magnetic resonance volumetric images.

Results: There were no volumetric differences between patients with melancholic and psychotic subtypes. We identified larger AVs in both patient groups compared to controls, while there were no differences in HVs across the 3 groups. AV bilaterally differed between early- and late-onset patient groups and between patients with and without sleep disorder. Larger amygdalae bilaterally were significantly associated with smaller tail of the left hippocampus in patients, but not in controls.

Conclusion: Larger AVs were identified in patients with major depressive disorder compared to controls but no structural measures distinguished between melancholic and psychotic subtypes. A possible influence of chronicity on AV is discussed, as well as a possible explanation of amygdala enlargement by its role in sleep and wakefulness control, determined greatly by the hippocampus.

P-16-014 In vivo measurement of fluctuations in glutamate levels: A positron emission tomography study using [11C]ABP688 and N-acetylcysteine

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Objective: An imaging method to probe glutamate levels in vivo would allow the study of glutamate transmission in disease states and in response to therapeutic interventions. Here we demonstrate the feasibility of this approach for the first time using positron emission tomography (PET), and [11C]ABP688, a radiotracer for an allosteric site on the metabotropic glutamate receptor 5.

Methods: We conducted two sets of experiments in anesthetized baboons (n = 3): test and retest without pharmacological challenge, and in combination with N-acetylcysteine (NAC), a promoter of the cystine-glutamate antiporter that increases extrasynaptic glutamate release. NAC 50 mg/kg was administered as constant infusion over 60 minutes. Scan durations were all 90 minutes. Data were acquired on an HR+ scanner. PET data were coregistered to each animal's anatomical magnetic resonance imaging (MRI), regions of interest were transferred from the MRIs to the PET, and time activity curves for each region were generated. Data were analyzed by 2-tissue compartment modeling with metabolite-corrected arterial input. Cerebellum was included as a reference region. Outcome measures were the binding potential relative to the nondisplaceable compartment (BPND). The goal was to assess whether NAC-induced changes in [11C]ABP688 binding potential, ΔBPND, could be detected above the noise in the measurement.

Results: Linear mixed modeling comparing ΔBPND from test-retest to ΔBPND from NAC challenge across all brain regions showed a highly significant effect of treatment [$F(1,40) = 21.2$, $p < 0.001$]. ΔBPND was significantly different from zero following NAC [$F(1,20) = 76.6$, $p < 0.001$] but not after test-retest studies.

Conclusion: NAC induced decrease in [11C]ABP688 ΔBPND may be the result of allosteric modulation, although other mechanisms

may be at play. We outline steps needed to replicate and validate this method as a new tool to measure in vivo glutamate transmission.

Policy of full disclosure: Dr. Girgis has received research support from Janssen and Lilly through APIRE and a travel stipend from Lilly, Forest, and Elsevier Science through the Society of Biological Psychiatry. Dr. Slifstein has received research support from Intracellular Therapies Inc and is a consultant of GlaxoSmitnKline and Amgen, Inc. Dr. Abi-Dargham has received research support from GlaxoSmithKline and is a consultant or a speaker for Bristol-Myers Squibb, Otsuka, Sunovion, Lundbeck and Boehringer Ingelheim. The other authors reported no biomedical financial interests or potential conflict of interest.

P-16-015 AZD5213, a novel histamine H3 antagonist permitting high daytime and low nocturnal H3 occupancy. A PET study in human subjects.

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Objective: The histamine H3 receptor represents an appealing CNS drug target due to its important role in the neurobiology of cognition and sleep-wakefulness regulation. Several H3 specific compounds are currently under development for a range of CNS indications with cognitive impairment. Importantly, the therapeutic benefit of this mechanism may be hampered by disruption of sleep, and adverse events related to sleep has been observed in human subjects at high (>80%) H3 receptor occupancy (H3RO) during treatment with H3 antagonists. AZD5213 is a new highly selective H3 antagonist (in vitro inverse agonist) developed to achieve a pharmacokinetic profile permitting circadian fluctuations of H3RO. Efficacy has been demonstrated in rodent behavioural models of cognition, and in-vivo microdialysis has shown release of histamine, acetylcholine, dopamine and norepinephrine in the rodent brain. In human subjects, AZD5213 was safe and well tolerated following repeated doses (1–14 mg/d) and demonstrated a short (5–6 h) half-life.

Methods: In this PET study H3RO was measured using the radioligand [11C]AZ12807110 ([11C]GSK189254) in 6 young male volunteers following single doses of AZD5213 (0.05 to 30 mg). H3RO was calculated using the Lassen plot method. Population kinetic modeling was used to predict H3RO time course.

Results: AZD5213 showed dose and concentration dependent H3RO ranging from 16 to 90%. Modeling predicted that for most subjects the dose range 0.5–6 mg given in the morning would achiev >90% H3RO at peak while falling clearly below 80% during night.

Conclusion: This study confirms that AZD5213 rapidly equilibrates across the human blood-brain barrier. A dose range permitting high daytime and low nocturnal H3 occupancy has been defined. Such circadian fluctuation may be expected to reduce the risk of sleep disruption while maintaining daytime efficacy. AZD5213 may thus be an optimal compound to evaluate the clinical benefit of selective H3 antagonism in cognitive disorders.

Policy of full disclosure: The study was funded by AstraZeneca R&D.

P-16-016 Diffusion tensor imaging in pathological skin picking

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Objective: Pathological skin picking (PSP) is a common psychiatric condition associated with significant psychosocial distress and functional disability. Studies have identified dysconnectivity of white matter tracts in related conditions such as trichotillomania and obsessive-compulsive disorder (Szeszko et al., 2005), but neuroimaging has yet to be applied in PSP. Further understanding the pathophysiology of PSP may help in advancing treatments for this often disabling disorder.

Methods: Diffusion tensor imaging was conducted in a sample of patients with PSP and compared to a sample of healthy age- and gender-matched controls with no lifetime or current psychiatric history using a 3T system at the University of Minnesota, USA. Diffusion-weighted imaging data were acquired and pre-processed via previously validated methods (Chamberlain et al., 2010). The null hypothesis of there being no significant difference in fractional anisotropy between the 2 groups was tested using two sample t-tests at each voxel within the white matter mask in the SPM5 software package.

Results: A total of 10 individuals with PSP (mean age 30.4 ± 9.8; 100% female) and 12 healthy controls underwent a full psychiatric evaluation and DTI. Compared to controls, patients with PSP had reduced fractional anisotropy within white matter tracts at several locations including those connecting the left IFG (peak MNI coordinates $-42\ 15\ 42$ $t = 4.3$ $p < 0.001$ uncorrected).

Conclusion: These preliminary findings implicate disorganization of white matter tracts involved in top-down cognitive control in PSP and have implications for diagnostic classification systems and future research.

Policy of full disclosure: This research is supported in part by a Center for Excellence in Gambling Research grant by the Institute for Responsible Gaming and an American Recovery and Reinvestment Act (ARRA) Grant from the National Institute on Drug Abuse (1RC1DA028279-01) to Dr. Grant. Disclosures of interest include that Mr. Odlaug has received honoraria from Oxford University Press. Dr. Chamberlain has consulted for Cambridge Cognition, P1Vital, and Shire Pharmaceuticals. Dr. Grant has received research grants from Forest Pharmaceuticals and Psyadon Pharmaceuticals and receives compensation as the Editor-in-Chief of the Journal of Gambling Studies. Dr. Hampshire and Ms. Schreiber report no relevant conflicts of interest.

P-16-017 Residual cognitive impairment in patients affected by bipolar disorder during euthymia: An assessment with functional magnetic resonance imaging (fMRI)

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Objective: Bipolar Disorder (BD) is a chronic mood disorder with a prevalence estimated around 1–2%. Bipolar patients may experience social and working residual impairment even during euthymia. Furthermore, specific cognitive deficits, particularly involving working memory (WM), may persist during eythymia as well. To evaluate the possible presence of cognitive and functional differences between euthymic bipolar subjects vs. healthy controls during euthymia by means of a WM task at fMRI associated with neuropsychological evaluations.

Methods: A sample of 47 subjects aged between 20 and 55 years (12 with BD type I, 12 BD type II and 23 controls) underwent fMRI examination at 3 Tesla with tasks of working memory (n-back). All participants received a neuropsychological evaluation, inlcuding Stroop Color-Word Interference test, Tower of London, Trail Making test, Wisconsin Card Sorting Test and Verbal Fluency Test. Comparison tests were performed using statistical software SPSS and SPM5.

Results: The performance of the control group was significantly higher than both at the n-back task and at the neuropsychological tests. The full-factorial analysis of fMRI data showed a hypoactivation in bipolar patients in particular hippocampus and thalamus, associated with increased involvement of areas not involved in the frontal-parietal networks classically associated with WM.

Conclusion: The results seem to confirm the existence of a residual dysfunction during euthymia phase in BD, suggesting two distinct patterns of activation in the two groups studied, both from a neuropsychological point of view and from a neuroimaging perspective.

P-16-018 Depressive symptoms and apathy are associated with psychomotor slowness and frontal activation

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Objective: Affective symptoms, such as depression and apathy, and cognitive dysfunction, such as psychomotor slowness, are known to have negative impacts on the quality of life (QOL) of patients with mental and physical diseases. However, the relationships among depressive symptoms, apathy, psychomotor slowness, and QOL in a non-clinical population are unclear. The aim of the present study was to assess these relationships and examine the underlying cortical mechanisms in a non-clinical population.

Methods: Fifty-two healthy male volunteers were assessed for depressive symptoms using the Zung Self-rating Depression Scale (SDS), for apathy measured using the Apathy Scale, and QOL using the Short-Form 36 item questionnaire (SF36). The volunteers also performed the Trail Making Test Part A (TMT-A) while undergoing assessment of hemoglobin concentration changes in the frontal cortical surface using 24-channel near-infrared spectroscopy (NIRS).

Results: The scores of the SDS and Apathy Scale showed significant negative correlations with the scores of most of subscales of the SF36. In addition, the SDS score had a significant positive correlation with the time to complete the TMT-A. Further, activation of several frontal cortical areas had a significant positive correlation with the scores of the SDS and Apathy Scale.

Conclusion: These results suggest that the degree of depressive symptoms and apathy are associated with a lower QOL in a non-clinical population, and that cortical hyperactivation during a psychomotor task measured by NIRS may identify objectively individuals with a high degree of depressive symptoms and apathy.

P-16-019 PET imaging of serotoninergic system in monkeys: Effects of maternal separation, and chronic fluoxetine treatment during development

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Objective: Major depressive disorder (MDD) is a serious disorder that often begins following stress during adolescence. Selective serotonin reuptake inhibitors (SSRIs) are a common treatment for both adolescent and adult MDD. While MDD's early onset and available efficacy data support use of SSRIs in adolescents, concerns about safety have arisen, based on associations with suicidal behavior in adolescents, coupled with minimal data on long-term effects on the developing brain. This study used rhesus monkeys as a model to study the long term effects of both early life stress and chronic antidepressant treatment on the central serotoninergic system in young adult rhesus monkeys.

Methods: Thirty-two monkeys were randomly assigned to one of four groups (8 monkeys/group). They were peer-reared (PR) vs. mother-reared (MR), and with or without fluoxetine treatment. For PR, monkeys were separated from mothers at birth and nursery-reared until 6 months of age and thereafter housed with their peers. Chronic fluoxetine treatment began at 2-year of age for one year. One to two years post-washout, monkeys (average age of 5) were scanned with Positron Emission Tomography (PET) using three radioligands: 1) [11C]CUMI, an agonist; 2) [11C]RWAY, an antagonist, both for 5-HT1A receptor; and 3) [11C]DASB for serotonin transporter (SERT).

Results: Preliminary data from 24 monkeys (6 in each group) show 1. A significant global decrease in SERT binding in PR compared to MR monkeys, 2. SERT binding is reversed in PR monkeys that received fluoxetine treatment, and 3. 5-HT1A receptor binding is decreased in PR compared to MR monkeys only in cortex and unlike SERT, the binding was not reversed with fluoxetine treatment.

Conclusion: Our study demonstrates serotoninergic alterations in PR monkeys, and chronic flouxetine treatment may reverse deficits in SERT density that is persistent more than one year after medication discontinuation.

P-16-021 Differential effect of risperidone versus haloperidol on brain activation in firstepisode schizophrenia patients: A multicentre fMRI study

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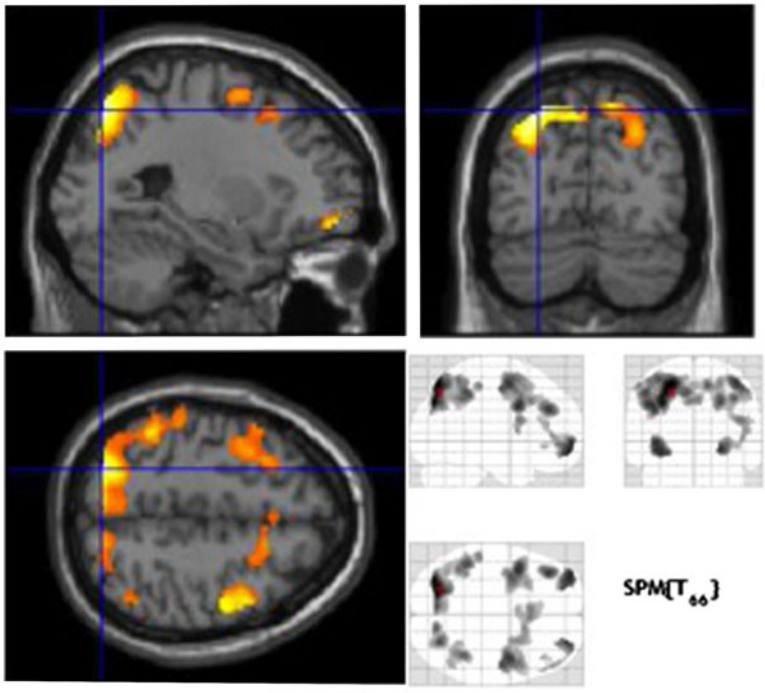
Objective: Neurocognitive impairments in schizophrenia are common and clinically relevant. The majority of people diagnosed with



schizophrenia will experience a significant decline in global, social and occupational function levels in the course of their illness. This disability is largely driven by cognitive impairment. Amongst the different cognitive domains, memory impairments in particular are regarded as possible intermediate phenotypes of schizophrenia. Whether haloperidol and risperidone two neuroleptic drugs with differential receptor binding profiles show distinct impacts on functional networks mediating working memory is subject of the current study.

Methods: 36 first episode schizophrenia patients (DSM IV) were recruited as part of the German Research Network of schizophrenia. Patients received either risperidone (N = 17, mean daily dose: 4.5 ± 1.7) or haloperidol (N = 19, mean daily dose: 2.9 ± 1.5) in a double blind treatment regime. The task during fMRI data acquisition (1.5 Tesla scanner) consisted of an n-back paradigm with a randomized sequence of 0-back and 2-back conditions arranged in a block design. The data was analysed using a flexible factorial design (SPM8) including medication dose (in mg) and gender as a covariate.

Results: Functional analysis revealed greater activations in the risperidone group in a network comprising of superior parietal, orbitofrontal, middle frontal, thalamic, temporal and occipital areas; $p < 0.05$ at voxel level, Monte-Carlo-corrected $p < 0.05$, $\geqslant 147$ continuous voxels.

Conclusion: Risperidone treated patients showed stronger activations in a cortical network that has previously been associated with this kind of working memory task than patients treated with a comparably moderate dose of haloperidol. As the results were controlled for dose, and neither side effects nor co-treatment differed between the groups the results are not likely to be affected by these confounding factors, but rather reflect the drugs different receptor binding profile. Risperidone binds much stronger to 5-HT2A and less strong to D1- and D2-receptors, which might be responsible for the differences in BOLD between the two medication groups.

P-16-022 Spontaneous low-frequency oscillations during resting state and personality traits measured by the temperament and character inventory and NEO Five-Factor inventory in healthy volunteers

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Objective: Default mode network measured by resting state fMRI (R-fMRI) has received a great deal of attention, because of its critical role in ego function, such as attending to environmental stimuli, reviewing the past and planning the future. Using R-fMRI, we examined the relationships between the amplitude of spontaneous low-frequency oscillations (LFO) and the personality traits assessed by two self-rating scales, Temperament and Character Inventory and NEO Five-Factor Inventory in healthy subjects.

Methods: Twenty-four healthy right-handed subjects participated in 5-min R-fMRI and completed the Temperament and Character Inventory and NEO Five-Factor Inventory.

Results: We observed that Neuroticism correlated negatively with regional activity of the middle frontal gyrus (MiFG) and precuneus; Extraversion correlated positively with regional activity of the superior frontal gyrus (SFG), striatum, MiFG, subcallosal and posterior cingulate cortex (PCC); Openness correlated positively with the parahippocampal gyrus, and negatively with the SFG; Conscientiousness correlated positively with regional activity of the MiFG and correlated negatively with the cerebellum. Additionally, we observed that Harm avoidance correlated positively with regional activity of the culmen, and negatively with regional activity of the MiFG and insula; Reward dependence correlated positively with regional activity of the anterior cingulate, medial frontal and superior temporal gyrus; Cooperativeness correlated positively with the PCC; Self-transcendence correlated positively with regional activity of the culmen, inferior frontal gyrus and thalamus, and correlated negatively with the middle temporal and occipital gyrus.

Conclusion: Our results revealed the neural substrates of personality traits in the amplitude of spontaneous LFO.

P-16-023 Effects of ketamine infusion on brain activation during an emotion discrimination task – a double-blind placebo-controlled pharmaco-fMRI study

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Objective: The application of low dose ketamine, a NMDA-receptor antagonist, is used to modify the functional connectivity in brain networks of healthy subjects as a model for schizophrenia associated with altered glutamatergic connectivity. Altered connectivity changes the processing of emotional and cognitive stimuli. Therefore we assessed ketamine-induced changes in brain activation using an emotion discrimination task (EDT).

Methods: 10 healthy volunteers underwent twice fMRI in a double-blind, placebo-controlled study. During a 5 min run, subjects performed EDT, before and after either ketamine (mean dose 15.12 ± 2.76 mg) or placebo (0.9% saline solution) intravenous maintenance infusion. FMRI was carried out at 3T with a single-shot gradient-recalled EPI sequence (TR = 1800 ms, TE = 38 ms, 23 slices, matrix = 128 × 128 voxel). After spatial normalization to MNI-space, individual activations were computed by contrasting EDT vs. ODT (object discrimination task) in SPM8. Effects of ketamine vs. placebo were assessed by paired-samples t-test and random effects analysis.

Results: According to previous fMRI-studies, task-specific activation before infusion was found in several regions, including the amygdalae, fusiforme and dorsolateral prefrontal cortices ($t > 4.3$, $p < 0.001$ uncorr.), when contrasting EDT vs. ODT. Direct comparison between ketamine vs. placebo showed an increased activation in the retrosplenial cortex (RSC) and precuneus ($p < 0.01$ voxel level, $p < 0.05$ FWE corr. cluster level). Subsequent analysis shows that differences of ketamine vs. placebo emerge mainly from a reduced deactivation during EDT in the RSC ($t = 8.22$) and to a lesser extent in the precuneus ($t = 2.6$).

Conclusion: While performing EDT, results revealed a reduced deactivation in the RSC and precuneus, both representing essential regions of the default-mode network (DMN) that is associated with self-related processing. This ketamine-induced activity maintenance in the DMN during goal-oriented tasks might be caused by alterations

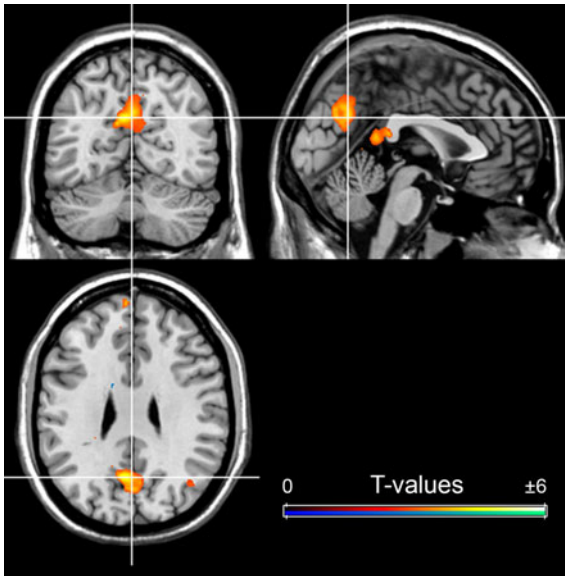

Figure: Triplanar view of fMRI results (3 Tesla) while performing the EDT. Comparing ketamine vs. placebo, differences in activation were found in the RSC and precuneus. p<0.01 voxel level, p<0.05 FWE-corrected cluster level. x/y/z=1/-63/29mm MNI-space.

of NMDA receptor-modulated networks, suggesting an insufficient regulation of DMN in schizophrenia.

P-16-024 The impact of dopamine on behaviour during an aggression provocation paradigm: An 18f FDOPA pet study

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Objective: Aggression is a multifarious type of (re-)action. Whereas impulsivity could be well related to serotonergic deficiency, also dopaminergic mechanisms were postulated in the modulation of aggression. This investigation was performed to enlighten the influence of striatal dopaminergic synthesis capacity on the vulnerability for aggressive, defensive, or resilient behaviour during a standardized aggressive provocation task (PSAP).

Methods: 18 healthy male subjects (24.7 ± 4.0 years)underwent a single [18F]FDOPA-PET scan (124 min.; 10 min. transmission scan; arterial blood sampling; metabolite detection) without any pharmacologic challenge except carbidopa pre-treatment. Directly before the scan, the subjects underwent the Point Subtraction Aggression Paradigm (PSAP). In short, this is an evaluated monetary reward game against a putative adversary which habitually tries to cheat. The proband can react by punishment (money subtraction), by pressing a defensive button, or by continuing his money-making behaviour (resilience). The PET-dynamics were analyzed according to the ''inlet/outlet-model'' of Kumakura et al. (2005) to obtain the net uptake of [18F]FDOPA (K), the total distribution volume (VD) and kloss in the striatum.

Results: The subjects showed mean K values of 0.025 ± 0.006, VD-values of 4.7 ± 1.3, and kloss-values of 0.0059 ± 0.0022 (NC: K = 0.030 ± 0.007, VD: 3.3 ± 0.9, and kloss-values of 0.0078 ± 0.0037). Correlation analyses to the PSAP-parameters revealed that the striatal (especially left putamen) K and kloss parameters were negatively correlated with combined defensive/aggressive behaviour (lePut-K: $r = -0.65$, $p = 0.003$) and positive correlated with the resilient money-making behaviour (bilPut-K: $r = 0.52$, $p = 0.028$).

Conclusion: Apparently, lower presynaptic dopamine synthesis capacity/turnover distract healthy subjects from reward-oriented behaviour during aggressive provocation and let them shift to interactional behaviour. The latter actions were dominated by defensive strategies. This investigation suggests that the influence of dopamine on aggression is not directly linked with harmful-behaviour but with the distractibility from goal/reward-directed behaviour.

P-17. Attention Deficit Disorder

P-17-001 Executive function in adult patients with attention-deficit/hyperactivity disorder during treatment with atomoxetine in a randomized, placebo-controlled withdrawal study

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Objective: To assess executive function in adults with attention-deficit/hyperactivity disorder (ADHD) during longer-term treatment with atomoxetine in a randomized withdrawal trial.

Methods: Responders to an open-label treatment period (12 weeks) with atomoxetine (40–100 mg/day) entered a 37-week double-blind maintenance period. Response criteria: ≥30% reduction from baseline on Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated:Screening Version (adult prompts) and score ≤3 on Clinical Global Impressions Scale-Attention-Deficit/Hyperactivity Disorder-Severity. Patients who maintained response from Weeks 15 to 24 were randomized in 1:1 ratio to treatment with atomoxetine (80 or 100 mg/day; n = 266) or placebo (n = 258) for 25 weeks. Patients and investigators were blinded to response criteria and timing of randomization. Change in executive function was assessed using Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A) Self-Report™ and Informant raw scores from baseline (randomization) to last-observation-carried-forward (LOCF) Week 13 post-randomization and to LOCF (after Week 17) Week 25 post-randomization.

Results: 2017 patients (mean age 33.2 years; male 58.7%) enrolled; 524 patients responded to treatment and were randomized. At Weeks 13 and 25 post-randomization, patients receiving atomoxetine showed significantly ($P \leq 0.05$) greater improvements versus placebo on the following Self-Report™ and Informant subscales: behavioral regulation, global executive composite, and metacognition indices and inhibit, plan/organize, shift, and working memory section scores. Significantly ($P \leq 0.05$) improved for atomoxetine versus placebo at Week 13 were initiate section score on both BRIEF-A scales and task monitor section score on Self-Report™; at Week 25, initiate section score on Self-Report™ and task monitor section score on Informant; and at Weeks 13 and 25, emotional control and organization of materials section scores on Informant.

Conclusion: Treatment with atomoxetine resulted in significantly improved executive function compared with placebo in adults with ADHD; the observed improvement was maintained for at least 25 weeks.

Policy of full disclosure: This work was sponsored by Eli Lilly and Company and/or any of its subsidiaries. Dr. Adler is a consultant for Alcobra Pharmaceuticals, Otsuka Pharmaceuticals, Shire Pharmaceuticals, Theravance, and Major League Baseball; he is on the advisory boards of Alcobra Pharmaceuticals, Otsuka Pharmaceuticals, and Shire Pharmaceuticals; he received research support from Eli Lilly and Company, Bristol Myers Squibb, NIDA, Shire Pharmaceuticals, Chelsea Therapeutics, and Theravance; and he receives royalty payments (as inventor) from NYU for license of adult ADHD scales and training materials since 2004. Drs. Upadhyaya, Goto, Trzepacz, Tanaka, and Allen are full-time employees and minor stockholders of Eli Lilly and Company. Mr Williams and Dr. Heinloth are full-time employees of PharmaNet/i3, an inVentiv Health Company.

P-17-002 Validity of conners' adult attention-deficit/hyperactivity disorder rating scale–investigator rated: Screening version in european patients with attention-deficit/hyperactivity disorder

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Objective: To validate Conners' Adult Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale–Investigator Rated:Screening Version (CAARS-Inv:SV) in European patients.

Methods: We used data from adult patients with ADHD participating in the initial 12-week open-label treatment phase of a long-term clinical trial to examine maintenance of response to atomoxetine 40–100 mg/day. We recruited patients from European countries (E-patients) and from countries outside of Europe (OE-patients). Primary efficacy measures: CAARS-Inv:SV and Clinical Global Impression-ADHD-Severity (CGI-ADHD-S). Internal consistency of CAARS-Inv:SV total and subscales were assessed by Cronbach's alpha (α). Predictive validity of CAARS-Inv:SV total and subscale baseline scores for 12-week scores were tested with an analysis of covariance model. Convergent validity was determined by Pearson's correlation coefficients between the CAARS-Inv:SV total and subscale scores and CGI-ADHD-S scores at baseline and at 12 weeks.

Results: A total of 2017 patients (1217 E-patients [57.7% male; mean age 33.0 years] and 800 OE-patients [60.3% male; mean age 33.4 years]) were included in the analyses. In both patient populations, CAARS-Inv:SV showed good internal consistency (E-patients: Cronbach's $\alpha = 0.930$; OE-patients: Cronbach's $\alpha = 0.938$) and convergent validity (Pearson's correlation coefficients: 0.65 to 0.82, $P < 0.001$) with the CGI-ADHD-S scale over 12-weeks of treatment. Baseline scores on the CAARS-Inv:SV total, inattentive, and hyperactive/impulsive subscales showed significant predictive validity ($P < 0.0001$) for 12-week scores for E-patients and OE-patients.

Conclusion: The CAARS-Inv:SV was validated in adult patients with ADHD in a pan-European population. No substantial differences in scale validity were observed between patients from within and outside of Europe. Based on these results, use of the CAARS-Inv:SV is

appropriate for evaluation of adult ADHD, for clinical or research purposes, in European patient populations.

Policy of full disclosure: This work was sponsored by Eli Lilly and Company and/or any of its subsidiaries. Dr. Kooij has been a speaker for Eli Lilly BV, Janssen-Cilag and Shire, and received unrestricted research grants from Janssen-Cilag and Shire. Dr. Conners is the author of the CAARS scale and receives loyalties from Multi-Health Systems, the publisher of the scale. Drs. Goto, Tanaka, Allen, and Upadhyaya are full-time employees and minor stockholders of Eli Lilly and Company. Mr Williams and Dr. Heinloth are full-time employees of PharmaNet/i3, an inVentiv Health Company.

P-17-003 A microdialysis and behavioural comparison of lisdexamfetamine dimesylate and methylphenidate in freely-moving rats

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Objective: The simultaneous collection of dual-probe microdialysis samples and locomotor activity data in freely moving rats administered lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc), a d-amfetamine (d-AMF) prodrug, or immediate-release methylphenidate (MPH).

Methods: The effects of a range of comparable oral doses of LDX (d-AMF base = 0.5, 1.5, 4.5 mg/kg) and MPH (3, 10, 30 mg/kg) on extracellular levels of norepinephrine (NA), dopamine (DA) and 5-HT in the prefrontal cortex (PFC) and striatum (STR), and locomotor activity, were determined using the Culex Bambino.

Results: In the PFC, LDX dose-dependently and significantly ($p < 0.05$) increased efflux of NA (⩽529% of baseline), DA (⩽296%), and, at the highest dose, 5-HT (⩽284%). MPH increased DA efflux (⩽202%) at the low dose and both DA (⩽217%; ⩽343%) and NA (⩽261%; ⩽289%) at mid and high doses; it had no effect on 5-HT. In the STR, LDX dose-dependently increased extracellular DA (⩽364%) and, at the high dose, 5-HT (⩽359%). MPH (3.0 mg/kg) did not increase DA or 5-HT in STR but DA increases were produced at 10 mg/kg (⩽131%) and 30 mg/kg (⩽243%). MPH (30 mg/kg) only increased 5-HT efflux at one time-point. The actions of LDX and MPH in PFC and STR reached a plateau at 45–60 min, but LDX effects were larger and more sustained. LDX did not significantly enhance locomotor activity at 0.5 mg/kg or 1.5 mg/kg except at two time-points. A small sustained increase (⩽3.6/15 min) was seen at 4.5 mg/kg. All doses of MPH significantly increased locomotor activity (⩽4.7/15 min).

Conclusion: LDX had larger and more sustained enhancing effects on NA and DA neurotransmission in PFC and STR than IR-MPH. That substantial increases in STR DA can be achieved without causing unacceptable locomotor activation predict that LDX will have a greater separation between efficacy and stimulant adverse events than MPH.

Policy of full disclosure: Studies funded by Shire Biosciences, Basingstoke, UK.

P-17-004 Lisdexamfetamine dimesylate and d-amfetamine – important differences for the relationships between extracellular striatal dopamine, locomotor activity and plasma drug concentrations in freely-moving rats revealed by hysteresis analysis

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Objective: Lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc) is a prodrug of d-amfetamine (d-AMF) that is approved for the treatment of ADHD.

Methods: The Culex Bambino automatically collects intracerebral microdialysates, intravenous blood samples and simultaneously measures locomotor behaviour in freely moving rats. The effects of immediate release (IR) d-AMF SO4 (d-AMF base = 1.5 mg/kg ip) and LDX (d-AMF base = 1.5 and 5.0 mg/kg ip) on extracellular dopamine levels ([DA]) in the striatum, locomotor activity and plasma d-AMF concentrations ([d-AMF]) were compared over 8 hr.

Results: LDX dose-dependently increased striatal [DA] ⩽300 min. The effect of LDX (1.5 mg/kg) on [DA] was gradual and sustained with maximum increase of 854% @ 75 min. IR-AMF (1.5 mg/kg) evoked a more rapid and substantial increase of [DA] (1291% @ 30 min). LDX (1.5 mg/kg) produced a small increase in locomotor activity, maximal between 90–120 min returning to pre-drug levels by 195 min. IR-AMF (1.5 mg/kg) evoked much more locomotor activity with an earlier peak (30 min) and shorter duration of effect. Three hysteresis analyses were performed. The most interesting and important difference came from the relationship between the changes in [DA] over time versus locomotor activity. The hysteresis was anticlockwise for LDX, but clockwise for IR-AMF ($P < 0.05$). Thus, with LDX the rats were less prone to activation as extracellular [DA] was rising, but reduced activation was maintained for longer when [DA] declined; the opposite was found for IR-AMF.

Conclusion: The findings are clinically important because subcortical DA is implicated in efficacy and side-effects of ADHD drugs. The sustained increase in [DA] and reduced locomotor activation predict that LDX will have an enlarged ''therapeutic window'' compared with IR-AMF. Moreover, the maintenance of LDX's pharmacodynamic effect when CNS [DA] was declining indicates the unusual PK of LDX optimises the utilisation of its active metabolite, d-AMF.

Policy of full disclosure: Studies funded by Shire Biosciences, Basingstoke, UK.

P-17-005 Efficacy and safety of atomoxetine in Asian adults with ADHD: A multinational 10-week randomized, double-blind placebo-controlled Asian study

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Objective: This study aims to demonstrate efficacy and to assess the safety profile of atomoxetine compared with placebo in Asian adult patients with ADHD.

Methods: This study was conducted in Asian countries including Japan, Korea and Taiwan with approval of the ethical reviews boards. The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was used for Adult ADHD diagnosis. After obtaining informed consent, patients were randomly assigned to treatment with atomoxetine or placebo for 10 weeks. Atomoxetine was initiated at 40 mg once daily and then titrated up to a maximum of 120 mg once daily. The efficacy of atomoxetine versus placebo was evaluated using the mean change from baseline to endpoint in CAARS Inv: SV total score. Safety was assessed by adverse events (AEs), vital-signs, and ECGs.

Results: A total of 388 patients (atomoxetine, n = 193; placebo, n = 195) were included in the efficacy and safety analyses. The mean age (mean ± SD) was 32.3 ± 8.0 years; 52.3% of the patients were female. The study population consisted of patients from Japan (63.7%), South Korea (18.8%), and Taiwan (17.5%). The mean changes of CAARS-Inv: SV total score were −14.3 (atomoxetine) and −8.8 (placebo) ($p < 0.001$; effect size, 0.55). Statistically significant reductions in CAARS Inv:SV total scores following atomoxetine administration versus placebo were observed from week 2 to week 10, with a least-mean difference of 6.18 ($p < 0.001$) at week 10. Treatment-emergent adverse events were reported more frequently in the atomoxetine group (80.8%) than the placebo group (53.8%) ($p < 0.001$). Most AEs were mild or moderate in severity. Ten atomoxetine treated patients and 3 placebo patients discontinued due to AEs.

Conclusion: This is the first placebo-controlled clinical research for adults with ADHD in Asia. Atomoxetine was shown to be superior to placebo in reducing the symptoms of ADHD, and was well tolerated in adult Asian patients with ADHD.

Policy of full disclosure: Yuko Hirata, Yasushi Takita and Michihiro Takahashi are employees of Eli Lilly Japan KK. Taro Goto, Paula T Trzepacz and Albert J Allen are employees of Eli Lilly and Company. Hironobu Ichikawa is an advisor of Eli Lilly Japan and has ever been invited as a speaker of Lilly-sponsored lecture meeting. Dong-Ho Song is an advisor for Eli Lilly Korea and has ever been invited as a chairperson/speaker of Lilly-sponsored lecture meeting.

Susan Shur-Fen Gau is an advisor for Eli Lilly Taiwan and has ever been invited as a chairperson/speaker of Lilly-sponsored lecture meeting.

P-17-006 Improvements of health-related QOL and executive functions of atomoxetine in Asian adults with ADHD: A multinational 10-week randomized, double-blind placebo-controlled Asian study

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Objective: The efficacy and safety of atomoxetine in adult ADHD patients were investigated in a double-blind placebo-controlled Asian study. This study compared Health—related QOL and Executive functions between atomoxetine-treated and placebo-treated patients in Asia.

Methods: This study was conducted in Japan, Korea and Taiwan with approval of the ethical reviews boards. The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was used for Adult ADHD diagnosis. After obtaining informed consent, patients were randomized treatment with atomoxetine or placebo for 10 weeks. Atomoxetine was initiated at 40 mg/day and then titrated up to a maximum of 120 mg/day. Health—related QOL was measured by Adult Attention-Deficit/Hyperactivity Disorder Quality of Life (AAQoL). Executive functions were assessed by Behavior Rating Inventory of Executive Function-Adult Version(BRIEF-A) :Self Report and Informant.

Results: A total of 388 patients (atomoxetine, n = 193; placebo, n = 195) were included in the analyses. The mean age was 32.3 (SD = 8.0) years; 52.3% of the patients were female. The study population consisted of patients from Japan (63.7%), South Korea (18.8%), and Taiwan (17.5%). The mean changes of AAQoL were significantly greater in total score ($p < 0.001$) and its components of life outlook ($p = 0.049$), life productivity ($p < 0.001$) and relationships ($p = 0.007$) in the atomoxetine group than the placebo group. Atomoxetine showed statistically significant reductions in global executive composite ($p < 0.001$), behavioral regulation index ($p = 0.001$) and metacognition index ($p < 0.001$) of the BRIEF-A self report, including all 9 components. Though the group differences in BRIEF-A informant components were not statistically significant, tendency for improvement in atomoxetine group were observed in behavioral regulation index, emotional control and task monitor.

Conclusion: This is the first placebo-control clinical research for adults with ADHD in Asia. Atomoxetine was effective in improving the disease-specific functional impairments measured by AAQoL and executive functions.

Policy of full disclosure: Yuko Hirata, Yasushi Takita and Michihiro Takahashi are employees of Eli Lilly Japan KK. Taro Goto, Paula T Trzepacz and Albert J Allen are employees of Eli Lilly and Company. Hironobu Ichikawa is an advisor of Eli Lilly Japan and has ever been invited as a speaker of Lilly-sponsored lecture meeting. Dong-Ho Song is an advisor for Eli Lilly Korea and has ever been invited as a chairperson/speaker of Lilly-sponsored lecture meeting. Susan Shur-Fen Gau is an advisor for Eli Lilly Taiwan and has ever been invited as a chairperson/speaker of Lilly-sponsored lecture meeting.

P-17-007 A neuropeptide S receptor gene variant and stressful life events are associated with increased hyperactivity and inattention in adolescents

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Objective: Neuropeptide S and its receptor (NPSR) are involved in regulation of activity, anxiety and fear [Reinscheid 2008, Results Probl Cell Differ 46:145–158]. We explored the association of the functional NPSR1 gene A/T polymorphism (rs 324981) and stressful life events (SLE) with inattentive/hyperactive behaviour in a population representative sample of adolescents.

Methods: The data of the younger (n = 593) and older cohort (n = 583) of the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS, Tomson et al., 2011 [Prog Neuro-Psychopharmacol Biol Psychiat 35:1857–1862]) was used. ADHD symptoms were reported by teachers using the Hyperactivity Scale of af Klinteberg (younger cohort at ages 9, 15 and 18; older cohort 15 and 18), and SNAP-IV (younger cohort at ages 15 and 18; older cohort at 18 and ASRS self-report at 25). School grades and the history of SLE were self-reported at ages 15 and 18. Analysis of variance and multilevel modelling were used for statistical analysis with SAS 9.1.

Results: In both cohorts males with T/T genotype of the NPSR1 displayed significantly more ADHD symptoms ($p < 0.05$). No interaction effect of genotype and age on hyperactivity measures was found. In older cohort males with the T-allele were more aggressive than females ($p < 0.001$). In younger cohort the interaction effect of genotype and SLE on ADHD symptoms was found: both males and females with high number of SLE and at least one T-allele exhibited higher inattention ($p < 0.01$) while the increase in motor restlessness was observed only in males ($p < 0.05$). Adolescents of the younger cohort with T/T genotype reported lower school grades ($p < 0.05$).

Conclusion: Our findings suggest that the T/T genotype of the NPSR1 is associated with higher number of ADHD symptoms in males. However, the T-allele in combination with high number of SLE leads to increased hyperactive and inattentive behaviour in both sexes.

P-17-008 Adherence to OROS methylphenidate and symptoms in children with attention deficit hyperactivity disorder

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Objective: The goal of this study was to examine medication adherence to Osmotic-controlled Release Oral delivery System methylphenidate using electronic measurements and other measures of adherence in children with attention-deficit hyperactivity disorder (ADHD). The relationship between adherence and other clinical factors was also analyzed.

Methods: Thirty-nine children diagnosed with ADHD were monitored over the course of eight weeks. Medication adherence was assessed using patient self-report, a clinician rating scale, pill counts, and the Medication Event Monitoring System (MEMS), which is a medication bottle cap with a microprocessor that records the time and date every time the bottle is opened. Agreement among the adherence measures and the relationships between adherence and other factors, including ADHD rating scores of children and their parents, were assessed.

Results: The rate of non-adherence measured by the MEMS was found to be 46.2%, which was considerably higher than the clinician scale (31.7%), patient self-report (17.9%), and pill count (12.8%) rates of non-adherence. The rate of adherence measured by the MEMS was not significantly associated with baseline symptom severity or symptom changes over a short-term period, though non-adherent group experienced more severe symptoms in children with ADHD.

Conclusion: Adherence to OROS methylphenidate varied depending on the method used to measure adherence. There was a discrepancy between adherence measures according to clinician rating and the MEMS. Further studies are needed to evaluate the variables that may impact medication adherence in ADHD.

P-17-009 D1 receptor hyperfunction in the nucleus accumbens of SHR, a rat model of attention deficit/hyperactivity disorder

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Objective: Spontaneously hypertensive rats (SHR) are widely used as a rat model of attention deficit/hyperactivity disorder (ADHD). Here, we conducted behavioral and immunohistochemical studies in SHR

to clarify pathophysiological alterations in neurotransmission and brain regions related to their behavioral abnormalities.

Methods: Juvenile (4–5 weeks old) Male SHR and Wistar Kyoto rats (WKY) were used. Spontaneous activity of animals were evaluated with the open-field test. Fos protein expression in various regions of the brain was immunohistochemically stained using ABC-DAB methods. In addition, the effects of a selective D1 antagonist SCH-23390 on open-field behaviors and brain Fos expression in SHR were also examined.

Results: In the open-field test, juvenile SHR exhibited a significant increase in ambulation and rearing activity as compared with WKY. Brain mapping analysis of Fos-immunoreactivity (IR) revealed that SHR showed a marked increase in Fos expression in the core part (AcC) of the nucleus accumbens (NAc). Small to moderate increases were also observed in the shell part of the NAc and some regions of the cerebral cortex (e.g., parietal association cortex). However, Fos-IR levels in other brain regions including the limbic area, striatum and diencephalon were unaltered. In addition, treatment of SHR with SCH-23390 (0.2 mg/kg, i.p.) significantly reduced behavioral hyperactivity in SHR. Elevation of Fos expression in the AcC and cortices in SHR was also reversed by SCH-23390.

Conclusion: The present study strongly suggests that D1 receptor-mediated transmission in the AcC is region-specifically elevated in SHR, which could be responsible for behavioral hyperactivity.

P-17-010 Identification and management of adult attention deficit disorder: Case discussions and brief literature review

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Objective: Introduction: Not all children with ADHD remit in adolescence and many continue to manifest a host of behavioral and lifestyle problems, and are often treated as 'lazy/disorganized' by family members. Adult ADD needs more clinical and research attention. Objective: To describe the case histories and management of three patients diagnosed as Adult ADHD and present a brief review of relevant literature.

Methods: The case details of three adult male patients (Mr A, 25 yrs; Mr B 30 years and Mr C 34 years) presenting to the out-patient psychiatric clinic of V.I.M.H.A.N.S., New Delhi are being presented. All three patients reported long standing histories of difficulties experienced in organizing work or home affairs, poor time management/inability to keep appointments, at times not even making it on time for examinations/interviews, tendency to delay/procrastinate important things, frequent inattention towards the work at hand affecting the academic/job performance, multiple changes of job, considered to be 'chronically lazy' and 'inattentive' by family members. All three patients had childhood histories of ADHD.

Results: After a careful history and assessments, and ruling out any other psychiatric/medical comorbidity, a diagnosis of Adult ADHD was considered. They were initiated on stimulants and were carefully monitored. Al the three patients responded well to Atomoxetine 15 mg, Methylphenidate 40 mg/day and Atomoxetine 58 mg/day respectively, with a considerable improvement in symptoms of inattention and improved socio-occupational performance. The findings from the cases are being discussed in light of available literature.

Conclusion: The diagnosis of adult ADD should be considered in all patients presenting with chronic histories of inattention. The childhood history of ADHD should be enquired from family members and if positive, these patients can be considered for an adequate trial of stimulant-based pharmacotherapy.

P-17-011 Conversion of lisdexamfetamine dimesylate to d-amfetamine: Low variability in exposure to d-amfetamine after administration of lisdexamfetamine dimesylate to children with ADHD

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Objective: Lisdexamfetamine dimesylate (LDX, Vyvanse®, Shire US Inc) is a long-acting prodrug stimulant that requires hydrolytic cleavage to generate active d-amfetamine. Preclinical studies indicate that LDX is rapidly absorbed via active transport, and is a likely substrate for PepT1 in the small intestine. Here, we describe the formation of d-amfetamine from LDX in human tissues maintained in vitro, and the low variability in d-amfetamine exposure in children with ADHD treated with LDX.

Methods: Studies on LDX hydrolysis were performed in homogenized tissues and fractions of blood obtained from human donors. Tissues were incubated (37 °C) with 1 μg/mL LDX, and samples were collected for <4 hrs. Variability in systemic exposure of d-amfetamine following administration of LDX 30 mg, 50 mg and 70 mg was examined in a single-dose, randomized, crossover study in boys and girls (6–12 years) with ADHD severe enough to require a treatment change.

Results: Half-lives for the disappearance of LDX were 1.6 h, 2.3 h and 9.7 h in whole blood, kidney and liver, respectively; LDX was stable in homogenates of upper and lower intestines, pancreas and plasma. When incubated with red blood cells (RBC), the half-life for the disappearance of LDX was 1.0 h; and there was still substantial conversion at 10–15% of normal haematocrit. In children with ADHD (17 completed the study; mean age 9.6 years), exposure (AUC0–∞) of d-amfetamine increased proportionally with increasing LDX dose (mean [standard deviation] ng.h/mL: 30 mg, 844.6 [116.7]; 50 mg, 1510.0 [241.6]; 70 mg, 2157.0 [383.3]). The variability (percent coefficient of variation) in d-amfetamine AUC0–∞ was below 20% for all three doses of LDX (30 mg, 13.8%; 50 mg, 16.0%; 70 mg, 17.8%).

Conclusion: LDX was converted to d-amfetamine primarily in RBC. In children with ADHD, exposure to d-amfetamine increased in proportion to dose, and variability in exposure was low, within the therapeutic dose range (30–70 mg).

Policy of full disclosure: Studies conducted by Shire Pharmaceuticals Limited.

P-17-012 Does methylphenidate have an impact on ocular motor system? A controlled study on children with attention-deficit/hyperactivity disorder

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Objective: Attention-Deficit/hyperactivity disorder (ADHD) is characterized by behavioral symptoms of inattention and may include hyperactivity and impulsivity. The impulsivity and inattention suggest deficits in the voluntary control of behavior. Eye movements depend on structures implicated in attention and in motor control, both criteria areas of dysfunction in ADHD. In the present study, objective was to evaluate the effect of methylphenidate (MPH) on ocular motor system in ADHD children.

Methods: Subjects were aged 7–12 years, with ADHD on and off MPH (N = 9), and control subjects (N = 9). Saccade latencies, mean velocity, precision, accuracy and percentage of anticipatory errors were determined in visually-guided-saccades (automatic and voluntary attentional tasks) and antisaccades tasks.

Results: Significant differences existed between ADHD on MPH and ADHD off MPH, in latencies ($p < 0.02$), precision ($p < 0.04$), accuracy ($p < 0.05$) and percentage of anticipatory errors ($p < 0.05$). Compared to controls, ADHD on MPH had normalized performances, in automatic task, while they still impaired in voluntary attentional tasks.

Conclusion: MPH modified motor planning and response inhibition in ADHD children. Benefits depend of 1) the type of tasks (automatic and voluntary attention) and 2) the analyzed variables (motor control). These results suggest that eye movements could be a good predictor response to MPH.

P-17-013 Prevalence of adult attention deficit hyperactivity disorder in anxiety disorders sample

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Objective: Adult Attention Deficit Hyperactivity Disorder (ADHD) is a life-long, chronic disorder, affecting 8.1% of the US population.

ADHD is highly comorbid with other psychiatric disorders, however little is known about the prevalence of ADHD in anxiety disorder clinical samples.

Methods: Consecutive adult patients (N = 264) at an anxiety disorders clinic in Hamilton Canada, completed the Adult ADHD self-report scale and were assessed with a Structured Clinical Interview for DSM-IV, and the ADHD module of the Mini International Neuropsychiatric Interview (MINI).

Results: The rate of lifetime ADHD was 37.5 % (48.5 % male, 51.5 % female, $p < 0.05$). Adult ADHD was significantly associated with lifetime comorbid diagnoses of impulse control disorder and bipolar disorder as well as a higher number of comorbid disorders. Symptom severity measure scores on the Padua Inventory, Yale-Brown Obsessive Compulsive Scale, Sheehan Disability Scale (SDS), Anxiety Sensitivity Index (ASI), the QUIDS depression rating scale, the Penn State Worry Questionnaire and the Davidson Trauma Scale were significantly higher in those with ADHD. Individuals with ADHD, plus generalized anxiety disorder, and ADHD plus panic disorder with agoraphobia had higher scores on a variety of symptom severity measures than those without ADHD. Increased ADHD severity was associated with a greater number of lifetime comorbid diagnoses, and higher symptom severity scores. Males were more likely than females to have received ADHD treatment in the past; 76 % with adult ADHD had never received the diagnosis and 17.2 % had received prior ADHD treatment. Of the patients who had received previous ADHD diagnoses, 25 % were diagnosed in childhood.

Conclusion: The prevalence of lifetime ADHD was higher in our anxiety disorders clinic sample than that found in the general population. The presence of comorbid ADHD appears to have a significant impact on the severity and impact of comorbid anxiety disorders.

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P-17-014 Altered tryptophan and alanine transport in cultured fibroblast from boys with attention deficit/hyperactivity disorder (ADHD)

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Objective: The amino acid tyrosine and tryptophan are the precursors for the synthesis of the neurotransmitters dopamine, norepinephrine and serotonin. These neurotransmitters are implicated in the pathophysiology of Attention Deficit/Hyperactivity Disorder (ADHD). A disturbed transport of tyrosine, as well as other amino acids, has been found in a number of other neuropsychiatric disorders, such as autism, schizophrenia and bipolar disorder, when using the fibroblast cell model. Hence, the aim of this study was to explore whether children with ADHD may have disturbed amino acid transport.

Methods: Materials and Methods: The precursor amino acid transport was assessed in cultured fibroblasts derived from biopsies from 14 boys with ADHD diagnosis and 13 matching boys without a diagnosis of a developmental disorder. The kinetic parameters, maximal transport capacity (Vmax) and affinity of the binding sites (Km) for tyrosine, tryptophan and alanine were measured by using the cluster tray method. Student's unpaired t-test or the Mann Whitney U test was used to analyze any difference between the two groups.

Results: The tryptophan transport (Vmax) was significantly decreased in the ADHD group in comparison to controls ($p = 0.039$), while the alanine transport (Vmax) was significantly increased in the ADHD group ($p = 0.031$). There was no significant difference regarding the tyrosine transport between the two groups.

Conclusion: A decreased transport capacity of tryptophan implies that less tryptophan is being transported across the BBB in the ADHD group, since tryptophan uses the same transport systems in both fibroblasts and at the blood brain barrier (BBB). This could lead to deficient serotonin access in the brain that might cause disturbances in both the serotonergic and the catecholaminergic neurotransmitter systems, since these systems are highly interconnected. The physiological importance of an elevated transport capacity of alanine to the brain is not known to date.

P-17-015 Decreased density of muscarinic acetylcholine receptors in fibroblast from boys with attention deficit/hyperactivity disorder (ADHD): An in vitro study

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Objective: Attention Deficit/Hyperactivity Disorder (ADHD) is a neurobehavioral disorder affecting both children and adults worldwide. It is speculated that the neurotransmitters, dopamine and norepinephrine are involved in the pathophysiology of the neurobehavioral disorder ADHD. Moreover, it is known that cholinergic activity can modulate dopaminergic activity in the brain. The aim of this study was to measure the density and affinity of muscarinic acetylcholine receptors (mAChRs) in children with ADHD, by using the fibroblast cell model.

Methods: Fibroblast cell homogenates from 11 boys with ADHD, fulfilling the DSM-IV diagnostic criteria and from 9 matching controls were used in the study. The maximal binding capacity (Bmax) and the equilibrium dissociation constant (KD) of mAChRs were determined by radioligand binding assay, using the mAChR antagonist 3H-QNB. Due to non-normally distribution of the calculated data, three outliers were identified by the MADE method (two in the ADHD group, both with a non-hereditary ADHD and one in the comparison group), and were therefore excluded from the statistical analyses (Students unpaired t-test).

Results: A significantly ($p = 0.01$), lower Bmax for the binding of the muscarinic antagonist 3H-QNB was observed in the fibroblasts from the ADHD children ($n = 9$) with a hereditary family history compared to controls ($n = 8$), while the KD did not differ between the two groups ($p = 0.40$).

Conclusion: The present results indicate a reduced density of mAChR in fibroblasts from children with a hereditary ADHD, which might be a marker of the disorder. However, further studies are needed to confirm these observations.

P-18. Neurophysiology

P-18-001 Simultaneous, but not separate activation of beta-1– and beta-2–adrenoceptors in the nucleus accumbens increases accumbal dopamine efflux in freely moving rats

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Objective: Dopaminergic neurons, which arise in both the ventral tegmental area and the substantia nigra pars compacta, terminate among others in the nucleus accumbens (NAc). The NAc receives a noradrenergic input from the locus coeruleus and the ventral medulla. The NAc contains beta–adrenoceptors. There exists a close beta–adrenoceptor mediated noradrenaline (NA) – dopamine (DA) interaction within the NAc. We have already reported that endogenous NA in the NAc activates accumbal beta–adrenoceptors that, in turn, enhance accumbal DA release (Eur J Pharmacol, 2008, 601, 94–98). In the present study, the effects of selective agonists of the beta–adrenoceptor subtypes on the NA and DA efflux in the NAc of freely moving rats were investigated, using in vivo microdialysis.

Methods: Male Sprague-Dawley rats were used. NA and DA levels in accumbal dialysates taken every 20 min were measured by HPLC-ECD system. Drugs were locally applied through the microdialysis probe.

Results: Neither beta-1– (dobutamine: 60 and 120 fmol) nor beta-2–adrenoceptor agonist (salbutamol: 0.36 and 3.6 pmol) altered the basal NA and DA efflux in the NAc. Co-administration of 60 fmol of dobutamine with salbutamol (3.6 pmol) did not affect the NA levels, but it increased the DA efflux by approximately 120%. Co-administration of 120 fmol of dobutamine with salbutamol (0.36 or 3.6 pmol) also increased DA efflux till approximately 120% without affecting NA levels. The non-selective beta–adrenoceptor antagonist l-propranolol (1.2 nmol) which failed to alter the basal NA and DA levels, suppressed the DA efflux, induced by co-administration of dobutamine (120 fmol) and salbutamol (3.6 pmol).

Conclusion: The present study provides in vivo neurochemical evidence that simultaneous, but not separate activation of accumbal beta-1– and beta-2–adrenoceptors which are suggested to be located on the dopaminergic nerve endings in the NAc, stimulates accumbal DA release.

P-18-002 The role of the arcuate nucleus in the regulation of cytochrome P450 in the liver

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Objective: The neuroendocrine neurons of the arcuate nucleus (ARC) produce and release growth hormone-releasing hormone. Growth hormone released in the anterior pituitary regulates the expression of cytochrome P450 (CYP), in particular of CYP2C11 – one the main male rat isoforms. In our previous study we showed that the intracerebroventricular injection of the noradrenergic neurotoxin DSP-4 led to a decrease in the expression of CYP2C11 and CYP3A in the liver. The aim of present study was to estimate the role of noradrenergic innervation of the ARC in the regulation of cytochrome P450 expression in the liver.

Methods: The experiment was carried out on male Wistar rats. DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine) was injected locally into the ARC. One week after the injection, the brains (and livers) were rapidly removed, dissected into selected structures and stored at −80 °C. The levels of noradrenaline, dopamine and serotonin in the part of the hypothalamus containing ARC were determined (HPLC). Liver microsomes were prepared and the activity of liver cytochrome P450 was measured as a rate of testosterone hydroxylation (HPLC).

Results: A substantial decrease in the noradrenaline level was observed after DSP-4 injection into the ARC. The levels of other neurotransmitters were unchanged. The activity of the CYP2C11 in the liver of the lesioned rats was significantly lower compared to the controls.

Conclusion: In conclusion, our study showed that destruction of the noradrenaline terminals innervating ARC results in the decrease of the activity of CYP2C11 in the liver. The finding seems to be of physiological and pharmacological importance since CYP2C11 constitutes the major part of male liver cytochrome P450 and is responsible for the metabolism of testosterone and some drugs such as lidocaine or antipyrine. (Grant no. N N405 304836 from the Ministry of Science and Higher Education (Warsaw, Poland) and statutory funds of the Institute of Pharmacology PAS).

P-18-003 First and second generation antipsychotic differences in 50 and 100 ms superior temporal gyrus paired-click gating

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Objective: Introduction: Auditory gating deficit continues to be a widely studied schizophrenia endophenotype. Degre of gating is typically measured via a paired-click paradigm that generates two evoked potentials (S1 and S2) at Cz. Individuals with schizophrenia often exhibit a diminished S1 response and higher S2/S1 50 ms (P50) and 100 ms (N100) ratio scores than controls. Previous studies suggest that atypical antipsychotics, particularly clozapine, may be associated with improved 50 ms Cz (P50) ratio scores. Whether such effects are detectable at the primary neuronal generators of the 50 and 100 ms auditory response (superior temporal gyrus, STG) remains unstudied.

Methods: Methods/Hypotheses: Magnetoencephalography (MEG) source localization provided measures of left and right STG paired-click auditory S1 and S2 activity. As previous work demonstrates the importance of prefrontal (PFC) dopamine in enhancing brain signal-to-noise measures such as auditory responses, it was hypothesized that (1) compared to first generation antipsychotics, second generation antipsychotics are associated with smaller ratio scores due to a smaller degree of dopaminergic blockade, and (2) 'normalization' of gating is greater at 100 ms (M100) than 50 ms (M50), due to greater involvement of other cortices such as PFC modulating STG activity.

Results: In a sample of 74 healthy controls and 79 medicated schizophrenia patients (first to second generation ratio of 1:3), second generation antipsychotics were associated with improved gating, with S1 amplitude and ratio scores between healthy controls and patients on first generation Furthermore, these effects were most pronounced at left STG and for M100. No differences were detected among the second generation antipsychotics, although a trend of a more attenuated left S2 M100 response was seen with quetiapine and olanzapine.

Conclusion: Present findings support the hypothesis that auditory gating in schizophrenia is influenced by a left-dominant PFC-driven dopaminergic signaling pathway, a network sensitive to differences across antipsychotics in the degree of dopaminergic blockade.

P-18-004 Prepulse inhibition deficits in unmedicated patients with Parkinson's disease

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Objective: Most patients with degenerative neurological diseases involving the basal ganglia, such as Parkinson's disease (PD), present with functional abnormalities of brainstem reflexes. One method of interest for the assessment of brainstem functions is prepulse inhibition (PPI) of the startle reflex. PPI occurs because processing of the prepulse transiently inhibits brainstem interneurons involved in the generation of reflex blinks. In normal subjects, the response to the second stimulus is smaller than the response to the first stimulus, whereas there is evidence suggesting diminished PPI in PD patients. We aimed to determine whether PPI in PD is impaired at all intervals or whether only some specific PPI levels are impaired.

Methods: We used a sample composed of 49 unmedicated patients with PD and a control group of 37 healthy subjects. We used a commercial human startle response monitoring system (CIBERTEC, S.A.) to generate and deliver the startle stimuli, which were presented to subjects binaurally through headphones. The startle measures used were: prepulse inhibition percentages at 30, 60 and 120 milliseconds (% PPI-30, % PPI-60 and % PPI-120, respectively), and habituation percentage of the startle response. The SPSS statistical package version 15 was used for the statistical analysis.

Results: ANOVA only demonstrated a significant effect of group x intervals interactions at 120 ms ($F(1,84) = 14.35$, $p < 0.001$). Bonferroni post-hoc analysis determined that PD patients exhibited lower PPI at 120 ms ($p < 0.001$), whereas no differences were obtained regarding PPI at 30 and 60 ms and habituation.

Conclusion: Our data suggest that within unmedicated patients with PD, PPI is diminished at some levels compared to controls subjects. Therefore, this examination with PPI can provide relevant information on functional abnormalities in PD. Furthermore, studies with medicated patients with PD will be of interest, in order to determine whether these deficits still persist after being medicated.

P-18-005 Alpha-1–, but not alpha-2–adrenoceptor in the nucleus accumbens exerts an inhibitory control upon the accumbal noradrenaline and dopamine efflux in freely moving rats

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Objective: It is known that there exists a close alpha–adrenoceptor-mediated noradrenaline (NA) – dopamine (DA) interaction within the nucleus accumbens (NAc). We have shown that the alpha–adrenoceptor antagonist phentolamine and the alpha–adrenoceptor agonist phenylephrine increased and decreased accumbal NA efflux, respectively (J Neural Transm, 2007, 114, 1135–1142). Both alpha–adrenergic compounds increased accumbal DA efflux (Neuroscience, 2000, 99, 55–64). However, phentolamine and phenylephrine has a limited selectivity in terms of affecting alpha-1– and alpha-2–adrenoceptors. Therefore, by using selective alpha-1– and alpha-2–adrenoceptor ligands, we studied the role of alpha–adrenoceptor subtypes in the regulation of accumbal NA and DA efflux of freely moving rats.

Methods: Male Sprague-Dawley rats were used. NA and DA levels in the accumbal perfusate samples taken every 20 min were measured by HPLC-ECD system. Drugs were administered intracerebrally through the microdialysis probe.

Results: Alpha-1–adrenoceptor antagonist prazosin (6 nmol) increased the NA efflux by 207% and decreased the DA efflux by 43%, respectively. Alpha-1–adrenoceptor agonist methoxamine (24 pmol) that failed to alter the NA efflux reduced the DA efflux by 85%, and an ineffective dose of prazosin (6 pmol) counteracted these effects on DA efflux. Neither the alpha-2–adrenoceptor antagonist RX821002 (6 nmol) nor the alpha-2–adrenoceptor agonists UK14304 and clonidine (300 pmol) altered NA and DA efflux.

Conclusion: The present study shows that accumbal NA efflux is under tonic inhibitory control of alpha-1–adrenoceptor that are suggested to be presynaptically located on accumbal noradrenergic nerve endings. This study also indicates that the accumbal alpha-1–adrenoceptor that are suggested to be located on dopaminergic terminals, play an inhibitory role on the regulation of DA efflux. The present results imply that accumbal alpha-2–adrenoceptors play no major role in the regulation of NA and DA efflux in the NAc.

P-18-006 Electroconvulsive therapy parameters on parkinson's disease with poor response to levodopa treatment

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Objective: The aim of this study is to determine the use parameters and safety of ECT in patients diagnosed of advanced PD, levodopa resistant and without psychiatric comorbidity.

Methods: 9 patients with PD diagnosis were assessed. The inclusion criteria were: a) PD stage III- IV of Hoehn and Yahr scale, b) age between 45 and 80 years, c) ''on-off'' phenomena pharmacologically resistant, d) pharmacological optimized treatment without changes in the last month and e) signed informed consent. ECT Protocol: 8 sessions of bilateral electrode placement ECT were performed twice a week, using a MECTA brief-pulse device. The anesthetic drugs used in all cases were: atropine (0.5–0.8 mg), succinilcoline (40–50 mg) and sodic tiopenthal (200–300 mg).

Results: 5 men and 4 women were recruited, with a mean age of 75 (SD = 6, range 63–80) years old, with 14 (SD = 9) years of disease, and with 12 (SD = 5) years of treatment with levodopa. Three patients did not end the study. After the ECT treatment, the number of steps to walk seven meters in ''on phase'' and the number of freezings in ''on phase'' showed statistically significant improvement. ECT parameters are showed in a table.

Conclusion: ECT could be a safe and effective therapeutic option in levodopa resistant PD patients with predominantly axial ''on'' phenomena. Related with ECT parameters for PD patients without psychiatric comorbidity found in the literature and with the parameters used by us, we proposed a guide for the safe and effective administration of ECT in this population: current intensity between 0.7 to 0.8 A; frequency between 50 and 90 Hz; bilateral electrode placement with pulse width between 1.6 and 2 mSec (brief stimulus technique), electrical stimulation time between 3 and 9 Sec, and a motor and EEG seizure time target between 20 and 60 Sec.

P-18-007 Neurophysiological hypotheses of electroconvulsive therapy

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Objective: Review the neurophysiological hypotheses associated with the mechanism of action of ECT.

Methods: Bibliographic research: PubMed, EMBASE, ISI Web of Knowledge.

Results: Anticonvulsant hypothesis: this hypothesis proposes that the termination of the ECT-induced seizure is an active inhibitory process essential for the efficacy of the therapy. ECT has potent anticonvulsant properties as demonstrated by 1) the progressive increase of the seizure threshold and decrease of the seizure duration, that we would designate as a tolerance phenomenon during the treatment with ECT; 2) the regional and/or global reductions of the cerebral blood flow and cerebral metabolic index; 3) the induction of a slow wave activity in the EEG and 4) the increase of the functional activity of the neuropeptides and neurotransmitter inhibitors that occurs with the ECT. Seizure generalization hypothesis: a more extensive ECT-induced brain seizure activity produces a better antidepressant clinical response. Prefrontal model: the magnitude of the reductions in the cerebral blood flow (CBF) in the specific prefrontal regions is related with the efficacy of ECT, and the responders to this therapy have more likelihood of post-ictal suppression and of developing slow wave activity on the EEG than the nonresponders. Anatomico-ictal theory: iIs a unification of the neurophysiological hypotheses of ECT. Postulates that the seizure episodes precipitated by ECT will have a better antidepressant clinical effect if they are initiated in the prefrontal regions of the brain and widely extend towards the cortex and subcortex, involving the diencephalic centers.

Conclusion: The different neurobiological series cannot be contemplated independently due to the complexity of the brain function that involves the interaction of biochemical, hormonal and electrophysiological systems. Having better knowledge about these mechanisms can achieve an improvement in the clinical practice and provide a starting point to search for alternative treatments based on the same physical bases.

P-18-008 Early prefrontal theta cordance changes anticipate the antidepressant response to ketamine infusion in patients with unipolar depressive disorder

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Objective: Antidepressant-like properties of glutamatergic agents like ketamine were repetitively studied in animal models and depressive patients (Berman et al., 2000; Zarate et al., 2006). Mechanisms underlying the rapid (hours) and robust (days) antidepressant-like effect are widely studied. Quantitative electroencephalography (QEEG) measure prefrontal theta cordance showed a relationship between changes in prefrontal brain activity in the first week of treatment and later clinical outcome for standard antidepressants (Cook and Leuchter, 2001). Our study fills the gaps of missing evidence about predictive value of prefrontal theta cordance in response to single infusion of NMDA antagonist ketamine in patients with unipolar depressive disorder.

Methods: The study included in-patient with moderate and severe unipolar depressive disorder (n = 29) on stable antidepressant medication. Antidepressant response was defined as 50% decrease of depressive symptoms evaluated by means of Montgomery-Asberg Depression Rating Scale (MADRS). Single infusion of ketamine hydrochloride in subanesthetic dose (0.54 mg/kg) was administrated with simultaneously recorded EEG. Prefrontal QEEG cordance in theta frequency band was calculated according to UCLA algorithm (Leuchter et al., 1994) before, at the end and day after the infusion.

Results: Responders (n = 11) to ketamine in compare to non-responders (n = 18) showed significant difference in cordance at the end of ketamine infusion (Spearman test, $p = 0.039$). The decrease of cordance next day after ketamine infusion positively correlated with antidepressant response fourth day after infusion (two-tailed Fisher's Exact test, $df = 1$, $p \leqslant 0.0076$; NPV 0.91 (95% CI 0.64–0.99); PPV 0.63 (95% CI 0.44–0.68)).

Conclusion: Our study confirmed the capacity of early prefrontal theta cordance changes to anticipate the ketamine induced antidepressant response in patients with unipolar depressive disorder. More evidence is needed for utilizing predictive value of prefrontal theta cordance in clinical practice. The results also support the hypothesis about common antidepressant mechanisms underlying both standard antidepressants and novel glutamatergic agents.

Policy of full disclosure: Supported by Ministry of Health of the Czech Republic (IGA MZCR NS/10379-3). The study was assigned the number 2009-010625-39 in the European Clinical Trials Database (Eudra CT).

P-18-009 Does serotonin depletion augment or counteract the aggression-provoking effect of testosterone in mice?

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Objective: While sex hormones increase aggression in most mammals, the neurotransmitter serotonin has been reported to exert the opposite effect. Since testosterone influences various indices of serotonergic transmission, one possibility would be that it exerts its pro-aggressive influence by reducing a tonic anti-aggressive serotonergic influence. Alternatively, however, the hormone and the transmitter may influence aggression-regulating areas by parallel, independent paths. Here, we sought to shed light on these possibilities by assessing if testosterone is capable of enhancing aggression also in the absence of serotonin, assuming that, in the case testosterone enhances aggression by reducing serotonergic output, serotonin depletion would be at least as effective as testosterone in enhancing aggression, and that no pro-aggressive effect of testosterone above that induced by serotonin depletion would be found.

Methods: Male C57Bl/6 mice were gonadectomised, implanted with slow release testosterone or blank pellets and housed individually after 3 weeks of recovery. Following 9 days of isolation, during which territorial behaviour was established, baseline aggression was assayed using the resident intruder paradigm. After this, mice were treated with the serotonin synthesis inhibitor parachlorophenylalanine (pCPA) or saline for 3 days and re-tested 24 hours after the final dose of pCPA.

Results: While both groups of testosterone-treated animals displayed enhanced aggression as compared to hormone-depleted animals, serotonin depletion did not enhance aggression in mice lacking testosterone, and did hence also not diminish the difference between testosterone-treated and hormone-depleted animals. On the other hand, serotonin depletion did enhance aggression further in testosterone-treated mice (after omission of animals failing to display any aggressive behaviour in spite of hormonal replacement).

Conclusion: Our result do not indicate that testosterone elicits aggression by reducing serotonergic transmission, but suggests i) that serotonin may exert a parallel dampening effect on testosterone-induced aggression, and ii) that presence of testosterone is an indispensable prerequisite for serotonin depletion to enhance aggression.

P-18-010 Event related potentials in occasional and heavy cannabis users while under the influence of cannabis

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Objective: Experienced cannabis users demonstrate tolerance to some of the impairing acute effects of cannabis. The present study investigates whether event related potentials differ between occasional and heavy cannabis users after acute THC administration, as a result of tolerance.

Methods: 12 occasional and 12 heavy cannabis users participated in a double-blind, placebo controlled, cross-over study. On two separate days they smoked a joint containing 0 or 500 μg/kg bodyweight THC. Event related potentials were measured while subjects performed a divided attention (DAT) and stop signal task (SST).

Results: In the DAT, THC significantly decreased P100 amplitude in occasional but not in heavy cannabis users. P300 amplitude in the DAT was significantly decreased by THC in both groups. The N200 peak in the SST was not affected by treatment in neither of the groups. Performance in the SST was impaired in both groups after THC treatment whereas performance in the DAT was impaired by THC only in the occasional group.

Conclusion: The present study confirms that heavy cannabis users develop tolerance to some of the impairing effects of cannabis. This tolerance was also evident in the underlying event related potentials, suggesting that tolerance demonstrated on performance level is not (completely) due to behavioral compensation.

P-18-011 The role of the dorsal noradrenergic pathway of the brain (the locus coeruleus) in the regulation of liver cytochrome P450 expression

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Objective: Cytochrome P450 (CYP) expression is regulated by endogenous hormones and cytokines which remain under control of the central nervous system. Our previous study indicated that intracerebroventricular injection of the noradrenergic neurotoxin DSP-4 decreased noradrenaline concentration in the brain and the activity, level and mRNA of liver CYP2C11 and CYP3A. The aim of the present study was to investigate the role of the brain dorsal noradrenergic pathway (the locus coeruleus) in the expression of liver cytochrome P450.

Methods: The experiment was carried out on male Wistar rats. The anesthetized animals were injected with 6-hydroxydopamine into the locus coeruleus. One week after the neurotoxin injection, selected brain structures (the cerebellum, hypothalamus, nucleus accumbens, striatum, hippocampus, frontal cortex, rest of the cortex, anterior and posterior brain stem) and a liver tissue were isolated. The levels of neurotransmitters (noradrenaline, dopamine, serotonin) in those brain structures and the activities of CYP isoforms in liver microsomes (CYP1A: caffeine 8-hydroxylation and 3-N-demethylation; CYP2A, CYP2B, CYP2C11, CYP3A: testosterone hydroxylation) were determined by HPLC. CYP protein levels in liver microsomes were estimated by the Western blot analysis.

Results: Local injection of 6-hydroxydopamine into the locus coeruleus selectively decreased noradrenaline level in the brain structures tested (except for the hippocampus and cortex). However, in contrast to the intracerebroventricular administration of DSP-4, the expression of isoforms CYP2C11 and CYP3A was enhanced.

Conclusion: Since locus coeruleus fibers innervate the periventricular subnucleus (PeV) of the paraventricular nucleus (PVN) of the hypothalamus, it is concluded that damage to the noradrenergic innervation of the PeV (containing a growth hormone release- inhibiting factor) may be responsible for the enhanced expression of isoforms CYP2C11 and CYP3A, which is positively regulated by the growth hormone. (Grant no. N N405 304836 from the Ministry of Science and Higher Education (Warsaw, Poland) and statutory funds from the Institute of Pharmacology, PAS).

P-18-012 Pharmaceutical choices in involuntarily admitted patients of the psychiatric hospital of Attica

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Objective: Since most mentally ill patients who are involuntary admitted do not accept any kind of pharmaceutical therapies, mostly

because of lack of insight the involuntary admission and hospitalization of mentally ill patients implies the necessity to co-administer medication. Our aim is to show pharmaceutical treatment choices in the involuntarily hospitalized mentally ill patients of the psychiatric hospital of Attica, which accepts the largest number of involuntarily hospitalized patients per year.

Methods: Data were collected by random selection of 532 patients who were involuntarily hospitalized in the psychiatric hospital of Attica from 01/08/08 to 03/09/10. The statistical program SPSS was used for the data analysis.

Results: Our sample consists of 532 patients, mean age 43.64 yrs (SD = 13.7), 64.3% male, 11.1% of which were having first psychotic episode and 61.8% being hospitalized for the first time, 63.3% of which diagnosed with the schizophrenic spectrum disorders, 10.8% with bipolar disorder, 5.1% with depression and 24.1% with other diagnoses. 72.4% of the patients stopped their medication. Typical antipsychotics were administered in 32.7%, atypical antipsychotics were used in 59.4% and combination of typical and atypical antipsychotics in 5.1%. 65.4% received benzodiazepines along with their antipsychotic treatment, while 6.2% received antidepressants. At the discharge 19.7% received typical antipsychotics, 61.8% atypical, 15.8% combination of both typical and atypical, 54.7% benzodiazepines, 10.5% antidepressants and 23.9% long acting and psychotics.

Conclusion: Most of the patients of our sample were patients having psychiatric disorders for more than 10 years and were in an increased need for combination treatment, which was continued during their involuntary hospitalization. The combination treatment could be associated with the high percentage of treatment discontinuation before their involuntary admission.

P-19. Suicide

P-19-001 Depression and history of suicide attempts are risk factors for pregnancy among adolescent girls

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Objective: To examine if depression and history of suicide attempts are risk factors for pregnancy among adolescent girls.

Methods: A matched case-control study with cases and controls identified within a community-based demographic and health survey was conducted in La Paz Bolivia, from January 2010 to November 2011. A questionnaire was applied to 645 adolescent girls (9–19 years of age). Depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CES-D), with score >16 indicative of elevated depressive symptoms. Conditional logistic regression was used to adjust for potential confounders.

Results: Respondents included 99 cases and 546 controls. Through multivariate analysis, depression [odds ratio (OR) 2.16, 95% confidence interval (CI) 1.24–3.77], the history of a prior suicide attempt 12 month and lifetime (OR 2.98, 95% CI 3.70–11.27 and OR 6.23, 95% CI 1.12–64.90 respectively) were factors associated with increased risk of adolescent pregnancies. As expected, another factors statistically associated in the multivariate analysis were: physical and sexual abuse during childhood-adolescence (OR 2.13, 95% CI 1.35–3.38 ;OR 2.07, 95% CI 0.95–4.49 respectively); being use of contraception (OR 5.31, 95% CI 2.92–9.65); history of anxiety disorders (OR 1.69, 95% CI 0.80–3.53); being less than 6 years in school at the time of the interview (OR 2.71, 95% CI 0.82–8.93); and living in a very poor household (OR 7.67, 95% CI 3.81–15.47).

Conclusion: These findings suggest that depression (including suicidality) may be a key mechanism accounting for pregnancy among adolescents. The study found that in addition to depression and lifetime and 12 month suicide attempts, having suffered from physical and sexual abuse during childhood-adolescence, being use of contraception, a reported history of anxiety disorders, lower education and living in a very poor household were associated with adolescent pregnancy in La Paz.

P-19-002 Association between IL-8 and anxiety in suicidal patients

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Objective: IL-8 (CXCL8) is a chemokine that controls migration of neutrophils. Emerging evidence suggests that IL-8 is also involved in diverse physiological functions in the CNS. However, the role of IL-8 in psychiatric disorders remains to be defined. The aim of this study was to assess if IL-8 is altered in patient with suicidal behavior.

Methods: We measured CSF and plasma levels of IL-8, as well as the genotype frequency of a single nucleotide polymorphism (−251A/T, rs4073) in the promoter region of the IL-8 gene, in suicide attempters compared to healthy controls. A total of 250 patients and 579 controls from several cohorts were included in the study. Plasma and CSF levels of IL-8 were quantified using ultra-sensitive electrochemiluminescence-based immunoassay. Psychiatric symptoms were rated with the Comprehensive Psychiatric Rating Scale with subscales for anxiety and depression.

Results: We found negative correlation between plasma IL-8 levels and anxiety scores in suicide attempters. In the CSF, low IL-8 was associated with more severe symptoms of anxiety in females and depression in males. Female suicide attempters had a significantly lower prevalence of the IL-8–251A allele. Moreover, the −251A allele was coupled to higher plasma IL-8 and lower anxiety.

Conclusion: Taken together these findings implicate IL-8 in the pathobiological mechanisms underlying symptoms of anxiety and depression.

P-19-003 The suicidality in Thai population: A national survey

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Objective: To study the rate of suicidality and factors related to the Thai people.

Methods: Nationally representative face to face household survey based on a stratified clustered sampling of people aging 15 to 59 (n = 17.140). The data were conducted between June and August 2008 using Mini International Neuropsychiatric Interview (M.I.N.I.) module C. Suicidality and general information questionnaire by trained psychiatric professionals. The data analysis was determined by means adjusted weight of rate generalized to Thai population and analyzed with descriptive statistical methods by attaining percentage of mean, proportions, standard errors, population estimation and probability inference from the data.

Results: The overall national rate of suicidality accounted for 7.3%, the severity risk of suicide was found mild 6.0%, moderate 0.6% and severe 0.7%. The highest risk of suicide was found in the north (8.8%, severe degree 1.3%) females (8.6%), age of 35 to 44 (8.1%), separated, divorced or widowed (11.8%), being unemployed (13.8%), mood disorders with psychotic features (87.9%), current manic episode (64.3%).

Conclusion: For effective surveillance and prevention of suicide in Thailand's population, the focus should be on the population of Northern provinces, females, those in productive age, being unemployed and those concurrently having mental disorders particulary, mood disorders.

P-19-004 The role of anxiety and its correlates in suicide re-attempters

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Objective: Among the large population of suicide attempters, frequent re-attempters present specific features. They are significant consumers of health care resources. An increasing severity of the attempts could end to be lethal. They have also been associated with

anxiety traits and diagnoses but the relationship of anxiousness and frequent suicide attempts remains unclear.

Methods: We examine a large sample of suicide attempters that were assessed at a specialized unit of the Montpellier University Hospital. Only subjects with one-time lifetime suicide attempt (n = 477; one-time attempters) and subjects with more than two lifetime suicide attempts (n = 411; frequent attempters) were included in the analyses. These two populations were compared with regards to demographic, diagnostic and suicidal features, including characteristics of the first suicide attempt (Suicide Intent Scale, Scale of Suicide Ideation, age at first attempt). Trait anxiety scores of the State-Trait Anxiety Inventory (STAI) were also examined in a subsample of patients.

Results: Frequent attempters were more often females with family history of suicide behavior. Several lifetime diagnoses were associated with frequent attempters: affective disorders, eating disorders, alcohol and substance use disorders. Lifetime diagnoses of anxiety disorders differed significantly between one-time attempters and frequent attempters (p = 0.0008). Frequent attempters were also younger at their first attempt and presented higher suicide ideation scores. However, no difference was found in trait anxiety scores according to the STAI between subjects with and without lifetime anxiety diagnoses or one-time attempters and frequent attempters.

Conclusion: Anxiety diagnoses may be independently associated with frequent attempters when compared to one-time attempters. However, the negative finding of an association between anxiety traits, as measured by the STAI, and frequent suicide attempters limits the possibility of determining a cut-off level of anxiety to distinguish frequent attempters from one-time attempters. The lack of association between anxiety traits and diagnoses in suicide attempters warrants further investigation.

P-19-005 Epidemiological overview on pattern of suicide in the district of Tirana in Albania, over the period 2001–2010

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Objective: Introduction: Suicide is an increasing phenomenon in Albania. Despite recent investments in mental health by authorities there is a widespread culture of shame surrounding mental illness. Aim: To present an epidemiological overview on the pattern of suicide in the district of Tirana over the period 2001–2010.

Methods: A retrospective study with a homogenous cohort. Data were collected from the records of the Prosecution Office of Tirana district. Medical data and the statements of the witnesses were studied.

Results: A total of 254 people have committed suicide in the district of Tirana from 2001 to 2010. The prevalence of suicide was found 0.04% (95%CI 0.035–0.045). Suicide is most frequent among males 163 (64%) and in individuals with a low socio-economical level. The mean age of the victims is 38.5 (16 SD) years old. Suicides are more common during autumn 72 (28%) or during the months of April 35 (13.8%) and September 36 (14.2%). In rural areas is 1.6 times more prevalent than in urban ones. The prevalence among married 132 (52%) is significantly higher compared to single individuals 103 (41%). As regards profession, most affected were workers 64 (25%) followed by housewives 40 (16%) and farmers 26 (10%). The most frequent method was poisoning in 100 (39.4%) cases, followed by hanging in 51 (20%) cases. 165 (65%) cases were previously diagnosed with mental illnesses. 129 (78%) out of them were diagnosed with depression, while only 74 (45%) were treated before the suicide.

Conclusion: For a large number of victims there were no data they suffered from an illness. It means that a relatively large number of the victims have had psychiatric disturbances, but they have not sought medical help. A small number of cases were treated before the suicide.

P-19-006 Pharmaceutical choices in patients with self/hetero aggression

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Objective: The suicide risk in patients with schizophrenia is 20 to 50 times higher than the general population. Recent data show increased association between schizophrenia and self-destruction or/and violence against others. Purpose of this study is to investigate pharmaceutical choice in patients with severe mental illness exhibiting suicidal and violent behaviour issues during their examination at the emergency department of Psychiatric Hospital of Attica.

Methods: The participants (423 patients) were selected randomly from the inpatients of the acute treatment departments of the Psychiatric Hospital of Attica. The statistical program SPSS has been used for the data analysis.

Results: 423 patients participate in the study. The mean age was 45.9% years and 60.8% were men. 63.7% were involuntary hospitalized and the mean age of the first episode was 28.4 years. The main diagnosis were schizophrenic disorders 72.1%, with the rest having bipolar disorders 16.8%, depression 11.1% and drug abuse 18.7%. The main reasons of admission were disease relapse 46.1%, discontinuation of medication 27% and aggression 24.3%. The presenting symptoms at the emergency department were: agression against others 30.8%, self distractive behavior 17.5%, verbal aggression 14.5%, aggression against objects 5.5%. At the admission 25.6% were administered with more than one antipsychotic drug and the second medication used was benzodiazepine at 53.7%, antidepressant at 19.1% and mood stabilizer at 16.8%.

Conclusion: Suicide is the most common cause of premature death among psychiatric patients suffering from both depression or schizophrenia. Several factors have been historically associated with suicidal behaviour such as alcohol or drug abuse. These have been repeatedly indentified as the most important factors for attempted or successful suicide and demand immediate care most efficiently with combination treatment.

P-19-007 Analysis of polymorphism in the gene for alpha-1 subunit of a voltage-dependent calcium channel in suicide victims

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Objective: Suicide is complex, multifactorial phenomenon, and is an outcome of interplay of environmental, genetic, and epigenetic factors. Slovenia belongs to the group of countries with the highest suicide rate in the world; in the year 2011 ranked 7th with suicide rate of 30.9 suicide victims per 100.000. In the present study we investigated association between suicide and gene for alpha-1 subunit of a voltage-dependent calcium channel (CACNA1C). Gene for CACNA1C is localised on chromosome12, and has 55 known exons, whereas 19 follow alternative splicing, consequently leading to numerous different combinations. Efficiencies of alternative splicing, having effects on alternations of neural transmission, have been associated with suicide. In gene for CACNA1C more than 2000 single nucleotide polymorphisms (SNPs) have been identified, but very few have been studied. The most often investigated SNP was rs1006737 in the 3rd intron. In meta-analysis this SNP has been implicated in suicide in depressed, bipolar, and schizophrenic patients.

Methods: We analyzed polymorphism rs1006737 with quantitative real-time PCR using LNA probes in 599 subjects (384 suicide victims, 215 controls) of Slovenian nationality. We determined the impact of polymorphism on suicide, by comparing the distribution of genotypes and alleles between the groups of suicide victims and controls. For detailed analysis additional subgroups were formed (e.g. male, female, violent and non-violent suicide, alcoholics).

Results: Genetic analysis of polymorphism in suicide victims did not show a direct association with suicide in any of the studied groups.

Conclusion: Nevertheless our results are representative and could be important for future studies, because our research was conducted on a population with extremely high suicide rate. Calcium channel gene is still an important candidate gene for further investigation in suicide behaviour.

P-19-009 CNR1 gene polymorphism and psychological functioning in persons who have attempted suicide

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Objective: An analysis of the psychological functioning of patients after their suicide attempts when compared to the comparative group and a description of the link between the occurrence of the polymorphism CNR1 – 1359 G/A (SNP rs1049353) and suicide attempts made by patients of psychiatric units. The work also aims at providing the answer to the question about whether there is a link between genotype 1359 G/A and a higher risk of suicide attempts.

Methods: 78 patients have made psychological tests. 1359G/A CNR1 polimorphism was made in all patients by RFLP method. Allel frequencies were compared between control subjects and patient after suicide attempt. We analysed association between 1359G/A CNR1 polimorphism and suicide attempt.

Results: Allel frequencies did not differed significantly between two groups of subjects. There is signifficant difference between Individuals attempting suicide and the control group in their psychological functioning. There is no evidence for association between SNP rs 1049353 and suicide attempt.

Conclusion: The genetic research and analysis of psychological tests reveal that a 1359 G/A polymorphism does not lead to so drastic a change in the functioning of the endocannabinoid system that this change would have any effect whatsoever on the functioning of other systems of neurotransmitters in the central nervous system and thus on leading to an increased incidence of suicide attempts in persons with this particular polymorphism.

P-20. Anxiolytics

P-20-001 Some psychotropic effects of kolanut (cola nitida) extract on adult wistar rats

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Objective: Kola nut (Cola nitida) is a widely consumed snack in the western part of Africa, and observed effects on consumers indicate it possesses some pharmacological properties. Caffeine is the most active ingredient in the fruit and the potential of its interaction with prescribed medication underscores the necessity for investigations of its pharmacological properties.

Methods: This study investigated the effects of aqueous extract of Kola Nut (C. nitida) on novelty-induced behaviours, weight and food consumption patterns of adult wistar rats. Twenty rats (mean weight of 150.6 g) were divided randomly into two groups (Test and Control) of ten rats each. Each group was subjected to the same environment of experiments. The test group was fed with the aqueous extract of kola nut in addition to normal feeds, while the control group had normal feed plus clean water.

Results: Test rats on kola nuts extract exhibited increased novelty-induced rearing (NIR), (novelty-induced grooming (NIG) and open field locomotion (OFL) at the first two days of oral administration in rats ($P < 0.05$) but prolonged ingestion of the extract caused decreased effects ($P < 0.05$). They also exhibited anxiolytic behaviour as measured by elevated plus maze on the first day ($P < 0.05$) and anxiogenic behaviour after prolonged feeding with the kola nuts extract ($P < 0.05$). The test group compared to the control group had significant weight loss ($P < 0.05$) and progressive decrease in food consumption even when feeding with the kola nut extract was discontinued.

Conclusion: Kola nuts extract possesses anxiogenic, anxiolytic and anorectic properties. These properties could be exploited in designing weight reducing therapies since no toxicity has been associated with human consumption.

P-20-002 Amygdala response to SSRIs in social anxiety disorder

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are commonly accepted as the first line pharmacological therapy for anxiety disorders and depression. However, there is a high percentage of patients that fail to achieve satisfactory response with SSRI treatments. The neural mechanisms underlying effective and ineffective outcome with SSRIs are not well characterized. The amygdala has dense serotonergic innervation, and studies have suggested the amygdala to be a crucial brain target for SSRI treatment. This study aimed at investigating differences in amygdala responsivity between responders and nonresponders to SSRI treatments in patients with social anxiety disorder (SAD).

Methods: Stress-related regional cerebral blood flow (rCBF) was measured in SAD patients ($n = 35$) with [15O]-water positron emission tomography (PET) during public speaking before and after 6–8 weeks of treatment with citalopram or paroxetine. Response rate was determined by the Clinical Global Impression-Improvement scale.

Results: Within-group comparisons revealed reduced rCBF response bilaterally in the amygdala in responders ($n = 20$) as well as in nonresponders ($n = 15$). Between-group contrasts revealed a greater amygdala attenuation in responders (>nonresponders) in the left basolateral/basomedial (x-16, y-6, z-14, $Z = 1.66$, P[uncorr] = 0.024) and right ventrolateral subregions (x26, y-4, z-26, $Z = 2.12$, P[uncorr] = 0.009). However, greater rCBF attenuation in nonresponders (>responders) was observed in the left lateral amygdala (x-28, y-6, z-14, $Z = 2.38$, P[uncorr] = 0.005).

Conclusion: Lowered amygdala responsivity does not seem to be exclusively related to clinical improvement in anxiety patients. In accordance with animal literature, our data suggest that amygdala subregions are functionally heterogeneous with regards to anxiolysis.

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P-20-003 Rapid anti-anxiety effects in women of picogram quantities of a 19-carbon steroid

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Objective: Picogram (pg) quantities of androstadienone (ADO), a naturally occurring non-hormonal steroid in male skin, induces in vitro, robust inward currents in isolated patch recorded human nasal chemosensory neurons (Monti-Bloch, 1995). When administered intranasally to healthy women, ADO rapidly decreases tension, nervousness, and other negative feeling states (Grosser et al., 2000). Similar observations subsequently, have been shown by others (Jacob et al., 2001). Because of these findings, we studied the effects of androstadienol (ADOL), an odorless 19-carbon steroid and analog of ADO, administered intranasally to women with generalized anxiety disorder (GAD).

Methods: Nineteen women with GAD and a Hamilton Anxiety Scale (HAM-A) >18, selected after placebo run-in, were randomized for double blind treatment with 200 pg ADOL ($N = 11$) or placebo ($N = 8$) administered in a one second aerosol pulse directly to nasal chemoreceptors. HAM-A, Covi Anxiety Scale (COVI), and clinical electrophysiological measures (respiratory and cardiac frequency, electromyogram, skin conductance, electroencephalogram, body temperature) were administered at randomization and 30 and 60 min later.

Results: Thirty min after administration of ADOL, there was a significant reduction in the HAM-A ($p < 0.03$) and COVI ($p < 0.02$). Seven of the 11 subjects administered ADOL exhibited decreases in the HAM-A of 50% or more whereas two of the eight controls had similar reductions. After 60 min, all significant improvements had disappeared. Electrophysiological readings were concordant with the reduction in anxiety.

Conclusion: 1. Nasal chemoreceptors appear to be a portal of entry for substances affecting feeling states. 2. The rapid and temporary effect in GAD suggests that ADOL may be useful in rapid-onset and short-lived psychiatric conditions. FDA approved clinical trials of ADOL in social anxiety disorder are currently in progress.

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P-20-004 The influence of an a5GABAA selective agonist XLi356 on rats' performance in morris water maze

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Objective: The impairing effects of diazepam in Morris water maze (MWM) could be partially antagonized with co-administration of an α5 subunit selective antagonist XLi093 (Savić et al., 2009). In order to further assess the role of the α5GABAA receptors population in mediating amnesic effects in rats, the present study examined effects of an α5GABAA selective agonist XLi356 on the MWM performance.

Methods: Male Wistar rats were given vehicle or 5, 10 and 20 mg/kg of XLI356 intraperitoneally 20 minutes before the testing. A single-day water maze task had three swimming blocks, each consisting of 4 trials, lasting a maximum time of 60 s each. Afterwards, a probe trial was given and a number of standard parameters was calculated. Additionally, rats were tested in spontaneous locomotor activity (SLA) and elevated plus maze (EPM) tests, where the sedative and anxiolytic effects were assessed.

Results: Results were analyzed using one-way ANOVA with post hoc Student-Newman-Keuls test where applicable. XLi356 significantly increased latency to platform ($F(3,444) = 3.1287$, $p = 0.026$); post hoc test revealed that the dose of 20 mg/kg was significantly different from vehicle. The same dose of XLi356 significantly increased cumulative distance from the platform zone ($p = 0.028$) and the time spent in the periphery ring ($p = 0.009$), while the path efficiency was on the control level. On the other hand, XLi356 did not show behavioral activity in SLA and EPM tests at either of three doses tested.

Conclusion: The present results suggest that ligands with appreciable agonist activity at GABAA receptors containing α5 subunits may impair memory acquisition in Morris water maze task, without discernible effects on general behavior. Thus the activity of the benzodiazepine type drugs at α5GABAA receptors should be decreased if the amnesic effects are to avoid.

P-20-005 The investigation of 2-mercaptobenzimidazole derivatives interaction with sigma-1 receptors in mice

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Objective: At present sigma-1 (σ1) receptor is considered to be prospective target for neuroprotective and anxiolytic drugs. In ''Zakusov Institute of Pharmacology'' RAMS neuroprotector and anxiolytic afobazole (5-ethoxy-2-[2-(morpholino)-ethylthio] benzimidazole dihydrochloride) was developed. In vitro afobazol revealed ligand properties towards MT1, MT3, σ1 receptors and MAOA with $IC50 = 2.7 \times 10^{-5}$ M, 9.9×10^{-7} M, 7.1×10^{-6} M, 6.2×10^{-6} M correspondingly (Seredenin et al., 2009). The main metabolite of afobazole (2-[2-(3-oxomorpholine-4-yl)-ethylthio]-5-ethoxy benzimidazole hydrochloride) interacted only with MT3 receptors with $Ki = 9.7 \times 10^{-7}$ M. The aim of the research is to study the interaction of afobazole and its main metabolite with σ1 receptors versus prototype σ1 ligands of different pharmacological groups on mice ex vivo.

Methods: Binding experiments were carried out in P2 fraction obtained from brain of male CD-1 mice according Entrena et al. with slight modifications (Entrena et al., 2006).The radioligand used in the assays was [Ring-1,3–3H]-(+)-Pentazocine in final concentration of 1 nM. The cold ligands of different pharmacological groups were used with a concentration range of 10^{-3}–10^{-12} M.

Results: In ex vivo experiments the displacement curves of [Ring-1,3–3H]-(+)-Pentazocine by afobazole versus ligands of different pharmacological groups were obtained. IC50 obtained for afobazole was $2{,}67*10^{-5}$ M. The value is close to compounds, considered as endogenous ligands DHEA and progesterone. IC50 for afobazol main metabolite was in the millimolar range. The results of research on male CD-1 mice confirmed the previously established ligand properties of afobazole and its main metabolite in regard to σ1 receptors in vitro experiments.

Conclusion: Binding experiment with afobazole versus prototype σ1 ligands on CD-1 mice was carried out. Due to the results obtained from the binding experiments afobazol can be regarded as a novel σ1 ligand.

P-20-006 Non-selective and a_5 subunit-selective negative modulators of $GABA_A$ receptors in a single-day morris water maze task in rats

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Objective: It is well known that benzodiazepine binding site ligands influence learning and memory and that the α_5 subunit is significantly involved in cognition enhancement mediated by the negative modulation of $GABA_A$ receptor function. PWZ-029, a moderately selective α_5GABA_A receptor inverse agonist, improved learning in passive but not in active avoidance test, without effects on anxiety or muscle tone. The aim of this study was to investigate effects of PWZ-029 and DMCM, a non-selective inverse agonist, on learning ability and short-term memory in Morris water-maze (MWM) test.

Methods: MWM test was conducted 20 minutes after intraperitoneal administration of treatments (solvent, 5, 15 or 30 mg/kg PWZ-029 or 2 mg/kg DMCM) to male Wistar rats. The single-day MWM task consisted of 3 consecutive blocks of 4 trials lasting maximally 60 s each and a probe trial. During spatial learning the platform was hidden in the middle of the NE quadrant.

Results: Two-way ANOVA with one repeated measure (block) and animals nested in treatment has shown that latency to find the platform, path efficiency and total distance travelled were on the control level for DMCM and all doses of PWZ-029. Factors block and treatment were significant only for latency to first entry to the NE quadrant [block effect: $F(2,386) = 10.50$, $p < 0.001$, treatment effect: $F(4,31) = 3.10$, $p < 0.05$]. Tukey's post-hoc test revealed that animals treated with DMCM and 5 mg/kg of PWZ-029 had longer latency to first entry to the target quadrant than those treated with solvent ($p = 0.001$, $p < 0.001$, respectively). Probe trial performance did not differ significantly between treatments.

Conclusion: These results suggest that neither non-selective nor β_5 subunit-selective negative modulation of $GABA_A$ receptors is sufficient to enhance learning and short-term memory in the single-day MWM spatial task.

P-20-007 Riluzole produces distinct anxiolytic-like effects in rat innate anxiety models

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Objective: Growing evidence suggests that sodium channel blockers, such as riluzole and lamotrigine, are effective as non-benzodiazepine treatments of anxiety disorders. In the present study, we first investigated the anxiolytic-like effect of riluzole using innate anxiety models in rats.

Methods: Male Wistar rats were used for experiments. We used three different innate anxiety models, such as the elevated plus-maze, the light/dark and the open-field tests. A benzodiazepine, diazepam, was used as a positive control anxiolytic drug. To clarify the involvement of sodium channels in the anxiolytic-like effects of riluzole, we examined the effect of co-administration of the sodium channel activator, veratrine.

Results: In the elevated plus-maze test, riluzole (3 mg/kg) significantly increased the time spent in, and entries into, the open arm after 60 min administration. This finding was supported by results obtained from the light/dark and the open-field tests. The magnitude of

the anxiolytic-like effects of riluzole in each of the behavioral models was similar to those produced by diazepam (1 mg/kg). Interestingly, the anxiolytic-like action of riluzole was diminished by the co-administration of veratrine (0.1 mg/kg) in the elevated plus-maze, the light/dark and the open-field tests. In contrast, veratrine had no significant effect on the anxiolytic effects of diazepam in these tests.

Conclusion: In this study, riluzole produced robust anxiolytic-like effects in rats. In addition, it is also suggested that the anxiolytic mechanism of riluzole is clearly distinct from that of diazepam. The voltage-activated sodium channels may play some important roles in these anxiolytic-like effects of riluzole. We propose that riluzole would be considered as a candidate compound for the development of anxiolytics with novel class of actions.

P-21. Pharmacoeconomics

P-21-001 Antidepressant treatment optimization with BrainChip test: Effectiveness and costs

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Objective: BrainChip is a genetic biomarker test that determines CYP450 isoenzyme polymorphisms, making possible response prediction to pharmacological treatment of patients suffering from major depression disorder (MDD). The objective of this study was to assess the efficiency and the budget impact of BrainChip test addition after failure to a first line antidepressant treatment in Spain.

Methods: A Markov model was developed per each treatment after simulating regimen therapy changes derived from BrainChip test addition. Clinical parameters were collected from literature reviews, and health resource use and costs were calculated to the Spanish context. Budget impact results were analyzed during 3 years after BrainChip additionand the efficiency was studied after 1, 3, 5, 7 and 10 years. Both analysis were builtunder the National Health System (NHS) perspective andit wasconsidered a 3% discount for effects and costs (euro 2011).

Results: BrainChip improves patient remission around 9.5%–11.7% and patient response 5.5%–10.2%, reaching after 10 years a total response rate of 72%. Patients with MDD and BrainChip improve their quality of life between 0.04 and 0.25 in terms of quality adjusted life years. BrainChip cost will be compensated after 2 years, being always a cost-effectiveness alternative in a short term and dominant from the third year.24,308 out of 64,713 patients could receive an alternative therapy based on the results of BrainChip information. BrainChip can reach after 3 years cumulative savings of more than 13.6 million euros (6.8% of budget) taking into account direct costs, and 194.4 million euros in terms of total costs (direct and indirect).

Conclusion: BrainChip incorporation allows less risk on pharmacological prescription and health care cost reductions in MDD for the NHS, being a dominant option.

Policy of full disclosure: This study was funded by BRAINcoBiopharma, the manufacturer of BrainChip. Dr. Blanca-Tamayo M receive consulting fees from BRAINcoBiopharma. Crespo C and Villacampa A worked in an independent consultant company and they got funds from BRAINcoBiopharma. Lobo S is an employee of BRAINcoBiopharma.

P-21-002 Is pharmaceutical industry influence distorting psychiatric practice?

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Objective: To examine the impact of pharmaceutical industry on psychiatric practice.

Methods: Interogation of relevant information and data available in the public domain to construct the evidence base for evidence-based evaluation of the ways in which pharmaceutical industry related interests influence psychiatric practice.

Results: Pharmaceutical companies are amongst the most profitable in the corporate world and the margins are rising even as the pill for every ill culture penetrates the emerging economies. The oft-repeated argument that these high profit margins are justified by the high costs of research and development (R & D) of new drugs does not bear scrutiny. These companies spend thrice as much on marketing and advertisements, increasingly supplemented with aggressive direct to patient approaches, as on R & D. This in itself could perhaps be condoned as mildly laissez faire free-market capitalism, but what cannot be glossed over is the lack of transparency in the relationship between the industry and the medical profession. Doctoring research evidence by suppressing negative findings (''failed studies''), subverting the integrity of peer-reviewed medical journals through questionable tactics like ghost writing and passing off hired guns as independent experts are some of the shady tactics which threaten to distort clinical practice at the cost of good patient care. Disease-mongering is an even more worrying phenomenon and the extensive financial linkages of the experts drafting diagnostic systems like the DSM-V with the pharmaceutical industry have resulted in lowered thresholds of caseness and the manufacture of new disorders on an industrial scale. The implications, medical as well as economic, of these pernicious trends are wide and far-reaching.

Conclusion: The proposed presentation aims to examine the evidence in this regard, contextualizing the evidence within practices in the developed and developing world, evaluate possible remedial strategies, and suggest the way forwards.

P-21-003 Healthcare costs before and after diagnosis of depression in patients with unexplained pain: A retrospective cohort study using the United Kingdom general practice research database

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Objective: To assess the impact of pain severity and time to diagnosis of depression on healthcare costs for primary care patients with pre-existing unexplained pain who subsequently received a diagnosis of depression.

Methods: In this retrospective cohort study, 4000 adults (aged $\geqslant$18 years) with unexplained pain (defined as painful physical symptoms [PPS] without any probable organic cause) and a subsequent diagnosis of depression, identified from the UK General Practice Research Database using diagnostic codes, were analysed. Patients were categorised into four groups based on pain severity (milder or more severe based on pain-relief prescriptions with or without opioid use) and time to diagnosis of depression ($\leqslant$1 year or $>$1 year, respectively, from PPS index date). Health care costs were calculated (2009 values) and included GP consultations, secondary care referrals and prescriptions for pain-relief medication for the 12 months before depression diagnosis and in the subsequent two years. Multivariate models were adjusted for age, gender and co-morbid conditions.

Results: Total annual healthcare costs before and after diagnosis of depression for the four groups of patients were higher for the two groups with more severe pain (£819–£988 vs. £565–£628; $p < 0.001$ for all pair-wise comparisons) and highest for the group with more severe pain and longer time to depression diagnosis in the years subsequent to diagnosis ($p < 0.05$). Total GP costs were highest in the group with more severe pain and longer time to depression diagnosis both before and after depression diagnosis ($p < 0.05$). In the second year following depression diagnosis, this group also had the highest secondary referral costs ($p < 0.01$). The highest drug costs were in the two groups with more severe pain ($p < 0.001$), although costs within each group were similar before and after depression diagnosis.

Conclusion: Co-existing pain and late depression diagnosis contribute to higher costs for the UK healthcare system.

Policy of full disclosure: Funded by Eli Lilly and Company. All authors are employees of Lilly and (excluding Jiyhung Hong) minor shareholders.

P-21-004 Factors determining efficacy of specialized psychiatric help under conditions of primary care unit

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Objective: Using clinical diagnostic criteria of course and outcome of mental disorders co-morbid with somatic pathology to distinguish basic treatment programs and to assess their efficacy.

Methods: Clinical-diagnostic, clinical-follow-up ''scale of efficacy of therapy of patients with borderline states'', SF-36, correlation and factor analyses. Material: 680 patients with mental disorders co-morbid with somatic pathology needing systematic therapy and dynamic observation by a psychiatrist.

Results: We have developed six rehabilitative programs with their gradual realization for patients with neurotic and somatoform disorders, organic mental disorders, personality disorders, affective mood disorders, alcohol dependence, for elderly. Basic therapeutic stages: initial, basic therapy and maintenance therapy. Basic and important method of therapy at all stages of treatment was medication. Most effective and used preparations were tranquilizers (sonval, radedorm, nozepam, phenazepam, grandaxin, sibazon, relanium); neuroleptics (sonapax, chlorprotixen, haloperidol, eglonil); antidepressants (amitriptiline, fluoxetin, azafen, pirazidol, anafranil). Conducted by us investigations during 25 years allowed distinguishing basic and obligatory principles of therapy providing its quality and efficacy, gradual character, complexity (treatment of somatic and mental pathology), sufficiency (necessary volume of therapy with minimum side-effects), individual-differentiated approach (along with other factors, account for financial possibilities), accessibility (not only territorial but also psychological), continuity (collaboration of psychiatrist and physicians at all stages of therapy), cooperativeness (possibility of concomitant curing by doctors of various specialties). According to data of follow-up and assessment of efficacy of treatment programs, recovery has been achieved in 46.2% of cases, stable clinical improvement – 44.1%. Temporary disability decreased in patients with somatoform disorders as many as 1.8 times and number of not grounded seeking for help and examinations per 1 patient during the year as many as 2.3 times.

Conclusion: Integrative approach to medical help rendering as well as all-sided differentiated and grounded medication were enough effective according not only on clinical but also economic indices.

P-21-005 Investigations of the accessible drugs used for central nervous system in Bangladesh: An explorative survey among medical-staffs and patients

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Objective: Drugs are usually distinguished from endogenous biochemicals by being introduced from outside the organism. Drugs acting on the central nervous system (CNS) influence the lives of everyone almost every-day. Drugs affecting the CNS are important therapeutically because they may relieve pains, fevers, suppress disorders of movement, induce sleep, reduce the desire to eat, inhibit motion sickness, and schizophrenia etc. Generally CNS patients are not found in the willing for operation. In that cases the CNS drugs play important roles.

Methods: Interviews were conducted of the medical-staffs and patients with the help of a semi-structured questionnaire. Patients' adherence or compliance with the prescribed medication schedule has been a source of concern to the physician, and pharmacist. Specially designed medication containers are useful in assisting to adhere to their medication schedule.

Results: As far as the pharmaceutical market of Bangladesh is concerned it is self dependent. It has a huge collection of the locally produced CNS products at reasonable price. Simply the market of CNS products of Bangladesh is saturated by its own products. It is also an important exporter of CNS products to the 1st and 2nd world countries in addition to the 3rd world countries.

Conclusion: There should be a well coordination of CNS related information to the medical practitioners, pharmacist, and finally the patients for the proper achievement of the great endeavor spent in the field of CNS products in Bangladesh. The CNS products can also be proved as a key factor for the earning of foreign currency through its export.

P-21-006 The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to paroxetine and sertraline in depressed Japanese patients

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Objective: We investigated the relationship between the brain-derived neurotrophic factor (BDNF) polymorphism (Val66Met) and the clinical response of patients with major depressive disorder to selective serotonin reuptake inhibitors (SSRIs; here, paroxetine and sertraline). In addition, serum BDNF levels in these patients were considered together with the clinical response.

Methods: A total of 132 patients who met the DSM-IV criteria for major depressive disorder were enrolled in the study. Of these patients, 54 were male and 78 were female (age range, 20–74 years; mean ± S.D., 51 ± 15). The patients' clinical improvement was evaluated using the 17-item of Hamilton Ra ting Scale for Depression (HAMD-17) at before (T0), and at 8 weeks after, the administration of SSRI treatment (T8). Patients with at least a 50% decrease in the HAMD-17 score were classified as responders.

Results: No correlation was observed between BDNF Val66Met polymorphism and response to SSRIs or between BDNF Val66Met polymorphism and serum BDNF levels at T0. An inverse correlation was found between serum BDNF levels and HAMD-17 scores at T0.

Conclusion: These results suggest that the BDNF Val66Met polymorphism is independent of both the response to SSRI treatment and serum BDNF levels. The finding in the present study reconfirms that serum BDNF level is a stat e biomarker for depression.

P-21-007 A cost-consequence analysis of long-acting injectable risperidone in schizophrenia: A one-year mirror image study with national claim-based database in Taiwan

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Objective: The development of long-acting, injectable, second-generation antipsychotics (SGA) has provided a new treatment paradigm to improve treatment outcome of schizophrenia. Recent studies have demonstrated that risperidone long-acting injection (RLAI) treatment was associated with significant reductions in relapses and hospital service utilization. This study was designed to assess the change of service utilization and costs for schizophrenia before and after treating patients with RLAI in Taiwanese national database.

Methods: This 1-year mirror-image study was conducted with national claimed-data. Comparison was made for service sectors and cost components (outpatient, inpatient, emergency, medication and non-medication costs).

Results: Service uses reduced in the post-RLAI period, with significant reductions of inpatient service costs. However, overall psychiatric service costs went up by 26%, with increases of 190% on total outpatient service costs and 177% on medication costs.

Conclusion: With significant reductions of inpatient service uses, overall psychiatric service costs were compromised by costs incurred from increased outpatient service and RLAI medication costs.

P-21-008 Improving somatic health for outpatients with severe mental illness; the development of an intervention

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Objective: Patients with severe mental illness (SMI) suffer from more somatic illness than the general population. Possible causes are side effects of neuropsychiatric medication, genetic vulnerability,

insufficient health care and lifestyle. This co-morbidity is potentially reversible and augments the costs for health care and diminishes quality of life. Screening on symptoms and risks of somatic diseases and coordination of care are proposed to improve SMI-patients' somatic health status.

Methods: A clinical facility was started to improve the somatic health status of patients in an outpatient centre in southern Netherlands. This outpatient centre was added to the specialized care for severe and enduring SMI. The intervention consisted of the inventarisation of side-effects and the detection of gaps in health care provision for 72 patients. This was based on interviewing the patients, laboratory screening, collecting information from their general practitioner and pharmacy. A list was compiled of possible diagnosis and health risks, and a plan of action was made for the treatment. Healthcare consumption, quality of life and general functioning were assessed to analyze cost-effectiveness. Evaluations were performed with the psychiatric care team on the process.

Results: Mean annual cost of GP's and medical specialist's consultations were €492. There existed a negative relation between EQ5D VAS and the number of self reported chronic diseases.

Conclusion: The authors conclude that the procedure is well feasible, but should be set up in close collaboration with all health care professionals of these patients to make tailor made solutions possible.

P-22. Brain Stimulation/Deep Brain Stimulation

P-22-001 Psychiatric side effects of bilateral monopolar high frequency stimulation or stimulation at the ventro-medial part of the subthalamic nucleus in patients with parkinson's disease

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Objective: To investigated the relationship between contact location within the subthalamic nucleus (STN) or stimulation parameters during programming and the occurrence of psychiatric side effect in patients with parkinson's disease (PD).

Methods: Fifty consecutive patients with PD with bilateral STN DBS were enrolled in a 6-months follow up study. Patients' spontaneous utterances or behaviors were systematically identified during DBS parameter optimization. The location of each of the stimulating electrode contacts within the STN was verified post-operatively. stimulation parameters (polarity, voltage, pulse width, and frequency) were recorded at each follow up visit.

Results: Within 6 months of follow-up period, there were 29 instances (in 15 patients) of emotional or behavioral induction [EBI (+)] at time of adjustment of stimulation parameters to obtain better control of tremors. The majority (86%: 13/15 patients) of experienced EBI occurred during stimulation of ventro-medial contact. The frequency of EBI (+) instances was significantly higher (Fisher's Exact p-value = 0.042) in subjects who received bilateral monopolar stimulation compared to subjects who received non-monopolar stimulation on at least one side. The presence of EBI was associated with lack of improvement in depressive symptoms and quality of life.

Conclusion: We found significant association between bilateral monopolar stimulation or stimulation at the ventro-medial contact and the EBI (+) status. The neurobiological underpinnings of this relationship remain to be investigated.

P-22-002 Regulation of dopaminergic brain functions by exercise or music

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Objective: Our previous studies suggested that the convulsions in epileptic mice rectify the decrease in dopamine synthesis in the brain through the calcium/calmodulin-dependent system and subsequently improve abnormal physiology. These studies led to the hypothesis that neurologic disorders that involve dopamine dysfunction require intense movement to improve the principal disorder. On the other hand, we suggested that music also enhances this pathway. In this study, the effect of daily activities such as exercise and music on brain functions was investigated.

Methods: Spontaneously hypertensive rats (SHR) were used to confirm this hypothesis. A decrease in calcium-dependent dopamine synthesis results in hypertension in SHR.

Results: Exercise or exposure to music increased serum calcium levels, and the calcium was transported to the brain and in turn enhanced dopamine synthesis. The subsequent increase in dopamine rectified hypertension and various other disorders.

Conclusion: Our animal experiments indicate that exercise and music rectify dopaminergic functions and related disorders. We suggest that the activities of daily life such as participating in exercise and listening to music might regulate and/or affect various brain functions through dopaminergic neurotransmission. These daily life experiences therefore might lead to the amelioration of symptoms of various diseases, such as hypertension, Parkinson's disease, dementia with Lewy bodies, epilepsy, and attention-deficit/hyperactivity disorder. Also, it is possible that abnormal movements in neurologic disorders, such as tremor in Parkinson's disease, wandering around and fugue in senile dementia, and movement in attention-deficit/hyperactivity disorder, in addition to convulsions in epilepsy, play a role in improving the principal disorder.

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P-22-003 In vivo alpha2 adrenoceptor binding demonstrates a prolonged effect of electroconvulsive therapy on noradrenergic function in Gottingen minipigs

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Objective: Major depression is one of the leading causes of disability, affecting 121 million individuals worldwide. Approximately one third of depressed patients are unresponsive to antidepressant drugs. Brain stimulation therapies, such as electroconvulsive therapy (ECT) are potential alternatives for drug refractory patients. The noradrenaline (NA) hypothesis of depression posits a deficiency in cortico-limbic NA circuitry. It is supported by the increased presence of NA receptors in the cortex of depressed suicide victims and the effective antidepressant actions of NA reuptake inhibitors. Our objective is to investigate the longitudinal effect of ECT, a highly effective non-pharmacological antidepressant, on NA neurotransmission.

Methods: Here we use positron emission tomography and the alpha 2 adrenoceptor antagonist tracer [11C]yohimbine to study the effect of ECT on NA receptor binding in cortical (frontal, temporal and occipital cortices) and limbic (hippocampus and amygdala) regions in Gottingen minipigs. Seven female adult minipigs were anesthetized with isoflurane and scanned prior to the onset of a clinical course of ECT (baseline), and at 24–48 hours and 8–10 days after the end of ECT (10 ECT sessions in anesthetized animals over a 3.5 week period).

Results: The volume of distribution of yohimbine binding to alpha 2 adrenoceptors was decreased after ECT treatment in all the cortical and limbic regions considered by 15–22% at 24–48 hours after ECT, and by 12–16% 8–10 days post-ECT. Binding data from 3 animals that were scanned at 6–8 weeks after the end of the ECT treatment showed either return to baseline, increased compared to baseline or continued decrease, reminiscent of the wide variability in length of efficacy of the antidepressant effect of ECT observed in the clinic.

Conclusion: The decrease in alpha2 adrenoceptor binding after ECT treatment may suggest increased NA release and/or receptor downregulation. Potential increased NA neurotransmission in the

cortical and limbic regions suggested by our results may contribute to the therapeutic effects of ECT in depression.

P-22-004 The brain stimulation by pulsed low-intensity electromagnetic fields (PLEF) in acute ischemic stroke (AIS) patients with psycho-vegetative disorders, within 24 hours of symptom onset

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Objective: To study the possibility of the usage the PLEF brain stimulation within the first 24 hours of acute ischemic stroke onset. To research the psycho-vegetative and neuro-hemodynamics indices changes, under transcerebral PLEF effect in AIS patients.

Methods: The randomized, double-blind, placebo-controlled study of PLEF brain stimulation had been done in 60 AIS patients. The main group (30 patients) had received the drug therapy and the PLEF treatment, which had begun within the first 24 hours of acute ischemic stroke onset. PLEF (2 mV/cm, 30 Hz) brain stimulation was carried out through optical-vegetative system. It was applied 3 minutes per day, 12 days. The 1-st control (15 patients) applied electric field-placebo (device not included) and drugs. In the 2nd control (15 patients) were used only drugs. In all groups of patients used comparable drug therapy.

Results: In the main group after the treatment course it was showed the positive dynamics of clinical symptoms: reducing of psycho-somatic changes, improved locomotion. The increase percentage slow waves (electroencefalography data) correlated with decrease sadness. It had been estimated the control glycine blood level, reduction of cortizol, what correlated with decrease anxiety. In the main group had been indicated the improve cerebral blood circulation by doppler sonography computed tomography, IMR data. It was indicated a more pronounced dynamics of clinical and laboratory indices effectiveness of the treatment in the main group compared to controls.

Conclusion: It had been stated the improving psycho-somatic, neurohemodynamic indices by the early pulsed low-intensity electromagnetic fields brain stimulation in the examined patients.

P-22-006 The role of transcranial magnetic stimulation in cognitive processes and treatment psychiatrc disorders

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Objective: Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain. This field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation. This has behavioral consequences and therapeutic potential. Due to its easy use and relatively fair side effects, nowadays transcranial magnetic stimulation is widely used in neurosciences and medicine.

Methods: The method of research in this paper is review of literature in that researches that applied TMS for treatment and investigation goals. 104 paper relative to the subject were studied and results gathered here.

Results: TMS through induce the electric field is a useful instrument to visualize regional activities in response to stimulation. the mechanism of effect of TMS is induce depolarization of neurons that in turn activate other neurons and produces behavioral and cognitive outcomes, depends on the stimulated area and its function. for example some of the observable TMS-induced effects are induce phosphene in stimulation occipital cortex or interrupt working memory and speech processes due to stimulate frontal lobe or improving verbal memory in major depressive disorders through modulating effects on dopamine system. TMS has effects on neurochemical and synaptic processes in neurons. depression, mania, schizophrenia, pain disorder, hallucination, catatonia, post traumatic stress disorders, obsessive- compulsive disorder, Parkinson's disease, and epilepsy were improved by TMS procedure.

Conclusion: Current published studies and meta-analyses have evaluated the efficacy of rTMS as given in treatment paradigms that are almost certainly suboptimal (e.g. of two weeks' duration) TMS is a safe and tolerable intervention. These findings raises the possibility of using TMS as a therapeutic device in psychiatric disorders and neuroscience researches.

P-22-007 A double-blind crossover study of subcallosal cingulate gyrus deep brain stimulation in treatment-resistant depression

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Objective: Major depression is one of the leading causes of disability worldwide since it is often accompanied by high rates of resistance to treatment. Poor efficacy of drugs for treatment-resistant depression (TRD) has prompted investigation of alternative treatment strategies. Deep Brain Stimulation (DBS) involves high-frequency electrical stimulation of stereotaxically implanted electrodes. Several studies have evaluated various areas of the brain that may be susceptible to modulation of the cortico-limbic circuits through DBS. Results published to date are encouraging, mainly for the subcallosal cingulate gyrus (SCG) We previously reported findings from the pre-randomisation period for this clinical trial, with response rates of 87.5% (7 of 8 patients) and 62.5% (5 of 8) at 6 months and 1 year respectively.

Methods: Here we report the findings of the double-blind crossover phase of the clinical trial. Five patients (those who responded after one year of chronic DBS) were included, and randomized to 2 trial arms: on-stimulation or off-stimulation for a period of three months. Subsequently, patients were crossed over to the other arm for three additional months for a total of 6 months.

Results: Three patients completed the 6-month trial, without any evidence of clinical changes in that period, regardless of treatment arm. The other two patients relapsed during the off-stimulation arm, as can be observed in Figure 1.

Conclusion: We cannot make any definitive conclusions regarding the effects of turning on or off the stimulator due to the limited number of subjects, but it is important to note that no patient relapsed during the on-stimulation phase, whereas 2 out of 5 (40%) in the off-stimulation arm experienced a relapse.

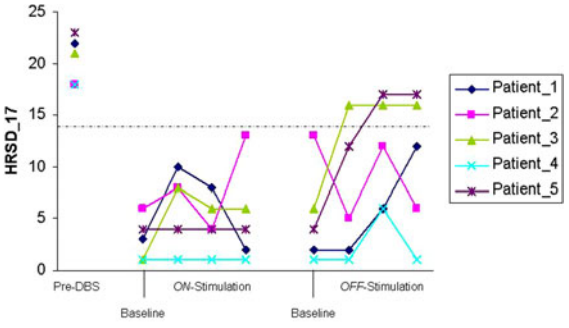

Figure 1. Effect on HRSD_17 scores of the on /off crossover phases in SCG-DBS in TRD patients. Dot line represent the cutoff for relapse criterion

P-22-008 Differential biasing of risk-based decision-making by outcome-contingent stimulation of the lateral habenula

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Objective: Ventral tegmental area (VTA) dopamine (DA) neurons encode reward prediction errors which facilitate making decisions about uncertain outcomes. The lateral habenula (LHb) is a key input to the VTA that provides indirect inhibition to DA neurons. Firing of LHb cells is reduced in response to rewards, and these neurons show phasic increases following reward omission. Likewise, LHb

stimulation inhibits DA neural activity, resembling phasic ''dips'' associated with reward prediction errors. What is unclear is how phasic suppression of DA neural firing may modulate choice in cost/benefit decision scenarios. Accordingly, the present study examined the effects of temporally-discrete stimulation of the LHb on probabilistic decision-making.

Methods: Rats were trained on a discounting task entailing choice between a small/certain (1-pellet) and a large/uncertain reward (4-pellets). The odds of obtaining the larger reward decreased systematically over a session (50–12.5%). Following extended training, electrical stimulation of the LHb (20–80 pulses, 100 Hz, 200 uA) was delivered following or prior to certain outcomes/actions (ie; immediately after a large/risky ''win'', after smaller/certain reward delivery, prior to a choice, during the inter-trial interval).

Results: Phasic manipulation of LHb activity influenced probabilistic choice. Specifically, stimulation of the LHb only after risky ''wins'' decreased choice of the large/uncertain option. Conversely, stimulation only after receipt of the small/certain reward had the opposite effect, increasing risky choice. Similar effects were observed on non-stimulation probe trials, when the large or small reward was never delivered, which decreased/increased risky choice, respectively. Importantly, LHb stimulation did not affect preference for larger vs. smaller reward when both were delivered with 100% certainty. Ongoing experiments are investigating the effects of LHb inactivation on risky choice.

Conclusion: These results suggest that phasic activation of the LHb (and presumably, inhibition of DA neurons) provides an important ''reward omission'' signal that can bias decision making in situations involving reward uncertainty.

P-23. Miscellaneous

P-23-001 The neurosteroid dehydroepiandrosterone sulfate suppresses neurovirulence produced by human and feline immunodeficiency viruses

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Objective: Neurosteroids, cholesterol-derived molecules synthesized within the brain, can exert trophic and protective actions. Infection by human (HIV) and feline (FIV) immunodeficiency viruses causes neuroinflammation and neurodegeneration. The objective of the study reported here was to investigate interactions between neurosteroids and lentivirus infection outcomes.

Methods: Human brain tissue was obtained from a brain bank in the Division of Neurology at the University of Alberta. In the FIV studies, cats were infected with FIV-Ch29 at day 1 postnatal. Behavioural tests included gait analysis, a modified T maze (to test spatial memory, cognitive learning capacity and performance speed) and an object memory test.

Results: Analyses of postmortem brain tissue from HIV-infected and uninfected persons disclosed a reduction in expression of 5α-reductase, P450scc and 3βHSD, enzymes involved in the synthesis of neurosteroids, in neurons of HIV-infected samples. Neurons exposed to supernatants from HIV-infected macrophages exhibited suppressed 5α-reductase and 3β-HSD expression ($p < 0.05$) without reduced cellular viability. We then focused on dehydroepandrosterone sulfate (DHEA-S) and found that HIV-infected macrophages treatead with this neurosteroid showed suppression of inflammatory gene (IL-1β, IL-6, TNFα) expression ($p < 0.05$). Treatment of FIV-infected cats with DHEA-S resulted in a reduction of inflammatory gene transcripts (IL-1β, TNF-α, CD3ε, GFAP) in brain ($p < 0.05$), and blood CD4+ T-cell levels were increased in DHEA-S-treated FIV-infected animals ($p < 0.05$). DHEA-S treatment also markedly reduced neurobehavioral deficits and neuronal loss among FIV-infected animals ($p < 0.05$).

Conclusion: Thus, reduced neuronal neurosteroid-related enzyme expression accompanied lentivirus infections but treatment with DHEA-S limited inflammation and neurobehavioral deficits. Neurosteroid-derived therapies might be effective in the treatment of virus- or inflammation-mediated neurodegeneration. (Funded by CIHR, AHFMR, the Canada Research Chairs program and the University of Alberta).

P-23-002 Cerebral ischemia in mice: Neuroprotection by progesterone and curcumin

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Objective: Ischemic damage to brain leads to morbidities like seizures, motor functional loss, memory impairment and others. The study was designed to evaluate the effects of progesterone and curcumin on sub-acute phase changes induced by partial global cerebral ischemia in male, Swiss strain mice.

Methods: Animals were randomized into four groups (6 animals per group): Sham- operated and Saline-, Progesterone- and Curcumin – treated surgically operated groups. Cerebral ischemia was produced by bilateral common carotid artery occlusion with aneurismal clips for 10 min followed by reperfusion in anaesthetized animals. On post- ischemic day 15, the animals were subjected to: Behavioral studies on elevated plus maze, rota rod, hole- board and kainic acid (20 mg/kg intraperitoneal) – induced seizure susceptibility tests; Biochemical studies for estimation of whole brain tissue malondialdehyde (MDA), catalase, super oxide dismutase (SOD), glutathione peroxidase (GPx) and TNF∞; Histopathological study of brain. The protocol was approved by Institutional Animal Ethics Committee.

Results: Compared to the Sham- operated group, the Saline-treated surgically operated group showed significant decrease in the exploratory behavior in hole- board, retention time on rota rod and entry into the open arm of the plus maze while there was significant increase in the closed-arm entry in plus maze and seizure susceptibility to kainic acid; brain levels for MDA and TNF∞ were increased while that for SOD, catalase and GPx were reduced significantly following ischemia; ischemia caused significant increase in the histopathological score. Intraperitoneal administration of progesterone (15 mg/kg) and curcumin (300 mg/kg), once-a-day, for post-ischemic 14 days, showed significant reversal of the data for all the parameters compared to the Saline- treated surgically operated group of animals.

Conclusion: The study showed the ant oxidative and neuroprotective effects of progesterone, a neurosteroid and curcumin, a phytophenolic compound against cerebral ischemic injury during the sub-acute phase in the mice model.

P-23-003 Alterations in gene expression of FGF2 in HIV and major depressive disorder

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Objective: Altered expression of neurotrophic factors has been implicated in both the pathology of human immunodeficiency virus (HIV) infection and major depressive disorder (MDD) in the brain and may be linked to the higher incidence of MDD in the HIV+ population.

Methods: This current investigation assessed gene expression changes of fibroblast growth factor 2 (FGF2), microtubule-associate protein 2 (MAP2), growth arrest and DNA-damage-inducible protein 45 beta (GADD45β), somatostatin (SST), and serum/glucocorticoid regulated kinase 1 (SGK1), previously implicated in neurodegenerative and mood disorders, in the frontal cortex of a novel brain cohort from patients with documented HIV, MDD, or HIV with MDD (HIV/MDD) by qRT-PCR. We further assessed the contributing effects of HIV and cortisol, known to be elevated in MDD, in primary human neuronal-glial in vitro cultures exposed to 6000 pg/ml HIV (BaL) and/or 500 nM cortisol after 6 and 24 hours.

Results: Post-mortem FGF2 was increased in both HIV and HIV/MDD compared to controls ($p < 0.01$) but was significantly lower in HIV/MDD compared to HIV alone ($p < 0.01$). Additionally, MAP2 was significantly decreased in HIV and HIV/MDD ($p < 0.05$) and was significantly correlated with FGF2 in the post-mortem HIV group ($p = 0.02$). Increased GADD45β and decreased SST were detected in

post-mortem HIV and HIV/MDD groups ($p < 0.05$). With the exception of SST, expression changes corroborated with directional changes in vitro.

Conclusion: Whilst we did not detect significant changes specific to MDD or cortisol alone, upregulated FGF2 in the brains of HIV patients may reflect a neuroprotective mechanism which is diminished in patients with comorbid MDD and associated reduction in MAP2. Our overall findings indicate that HIV is associated with compensatory gene expression changes of several neurotrophic and mood-related genes in the brain.

P-23-004 Protein changes in cholinergic neurons of nucleus basalis in progression of alzheimer's disease

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Objective: The cell cycle protein Rac1 plays a crucial role in the neuronal death during the progression of Alzheimer's disease (AD). Rac1 activates the apoptotic machinery of the low affinity p75NTR and the cytoskeletal abnormalities in nucleus basalis (NB) cholinergic neurons in AD.

Methods: Sections containing cholinergic neurons of the NB were obtained from autopsy cases from people who died with a clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI) or AD. Rac1b was visualized within NB neurons by dual immunostaining using a monoclonal p75NTR and a polyclonal Rac1b-specific antibody visualized by with the chromogens DAB with or without nickel intensification. Additional sections were double or triple immunofluorescence labeled using antibodies directed against Rac1b, choline acetyltransferease (ChAT), the early conformational tau antibody Alz50 and the phosphorylation antibodies AT180 and AT8. Sections were analyzed using light and confocal microscopy.

Results: 1. Dual immunostaining revealed that not all p75NTR NB neurons contain Rac1b and virtually all Rac1b were p75NTR immunoreactive in all clinical groups. 2. The greatest number of p75NTR/Rac1b NB positive neurons occurs in AD compared to MCI and NCI. 3. Many Rac1b positive NB neurons were dual labeled with antibodies for early conformational tau isoform Alz50 and the tau phosphorylational epitopes, AT180 and AT8 in AD. 4. Many more ChAT positive neurons were triple labeled for Alz50 and AT8 in AD compared to NCI or MCI.

Conclusion: 1. Rac1b is co-expressed in a subpopulation of p75NTR NB neurons. 2. Rac1b is found in many more p75NTR NB neurons in AD compared to NCI and MCI. 3. Rac1b is co-expressed in a subpopulation of p75NTR NB neurons, which contain tau conformation (Alz50) and phosphorylation (AT180 and AT8) epitopes to a greater extend in AD compared to NCI and MCI. 4. Rac1b activation induces cytoskeletal reorganization inducing neurofibrillary tangle formation in p75NTR NB neurons. 5. p75NTR activates Rac1b, which induces apoptosis.

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P-23-005 The relationship between cognitive outcome and microinfarctions after coiling of asymptomatic unruptured intracranial aneurysm: A prospective study

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Objective: The aim of this study was to prospectively investigate the possible cognitive impairment in patients undergoing coil embolization for the treatment of asymptomatic unruptured intracranial aneurysm (UAI) under the hypothesis that clinically negligible multiple micorinfarctions would cause higher cortical dysfunction.

Methods: Twenty-nine patients were evaluated preoperatively and postoperatively at 1 and 4 weeks later with a battery of neuropsychometric tests. The results were analyzed by both event-rate and group-rate analyses. For event-rate analysis, a cognitive deficit was defined as a decrease of 1 standard deviation in the postoperative score compared with the preoperative score for each test for individual patients. A patient with deficits in at least one test score was considered to have postoperative cognitive impairment.

Results: Group-rate analysis found that no tests except PAL showed significant impairments from baseline at Week 4. In event-rate analysis, 13(45%) patients had no cognitive deficit or superior performances whereas 16(55%) patients still had cognitive deficits from baseline with 0.68 ± 0.69 of the mean number of cognitive deficit variables at Week 4. Pearson's correlation analysis found no correlations between the number of mircoinfarctions and the cognitive sum z-score at both Week 1 and Week 4 ($r = -.18$, $p = 0.35$; $r = 0.06$, $p = 0.79$). No correlation was also found between the number of microinfarctions and any individual test score.

Conclusion: Neuropsychometric evaluation of patients undergoing coil embolization for UIAs demonstrates recovery or improvements after one month in general. However, we failed to prove any relationships between cognitive changes and microinfarct lesions.

P-23-006 Olig 1-immunoreactive oligodendrocytes are elevated in the white matter of the anterior cingulate gyrus in patients with major depression

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Objective: Alterations in oligodendrocyte cell density, thickness of myelin sheaths and expression of myelin-associated genes have been described in patients with affective disorders and schizophrenia. This may indicate impaired myelinisation, leading to disturbed connectivity of brain regions which are relevant for the pathogenesis of affective disorders and schizophrenia. In this context, the transcription factor Olig 1 is of particular interest, because it is expressed by oligodendrocytes and is involved in myelin-repair.

Methods: In this postmortem study, the cell density of Olig 1-immunoreactive oligodendrocytes was analyzed in the pregenual anterior cingulate (pACC, Brodmann Area 24/32) and dorsolateral prefrontal (DLPFC, Brodmann Area 9) cortices, including a separate analysis of the adjacent white matter in 8 patients with major depression, 8 patients with bipolar depression, 13 patients with schizophrenia and 12 matched control subjects. Statistical analyses were performed with analysis of variance (ANOVA) followed by Post-hoc Tukey-HSD Tests.

Results: A significantly increased density of Olig 1-immunoreactive oligodendrocytes was observed in patients with major depression in the adjacent white matter of the pACC in both hemispheres ($p < 0.001$), as well as in the left DLPFC ($p = 0.029$). Olig 1-immunoreactive cell counts were not correlated with potential confounds like age, gender, duration of disease, autolysis or fixation time, and medication dosage.

Conclusion: This study reveals an increased expression of Olig 1 in patients with major depression compared to healthy controls, particularly in the white matter of the pACC. These findings could indicate a regenerative attempt in order to reestablish connectivity between the pACC and other brain regions, such as the limbic system or the mediodorsal thalamic nucleus in subjects with major depression. Impairment of pACC-connectivity with these brain regions has been shown by various MRI-studies (Liu S. et al., 2011, Anand et al., 2009).

P-23-007 Perceptual disturbance in schizophrenia is related to differential EGFR mRNA expression in cortical layers in post mortem brain

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Objective: There is emerging evidence for dysregulation of the Epidermal Growth Factor (EGF) system in schizophrenia (SCZ). Previously we have shown that the antipsychotic drug clozapine transactivates the EGF receptor (EGFR) which may relate to its effectiveness in treatment resistant SCZ. We hypothesised therefore that EGFR changes in schizophrenia may be related to the clinical characteristics of the disorder and examined EGFR mRNA expression in the DLPFC (Dorso Lateral Pre Frontal Cortex) (BA46) of post mortem tissue from people with SCZ and healthy controls.

Methods: Messenger RNA expression was measured using in-situ hybridization in a cohort of 37 patients with SCZ and 37 controls matched for age, sex, post-mortem interval and pH. All samples were obtained from the NSW Tissue Resource Centre (University of Sydney). Relevant parametric statistical analyses with post hoc tests and correlation coefficients were computed.

Results: In schizophrenia, people without auditory hallucinations (AH) had significantly higher EGFR mRNA expression in layer VIa compared to those with AH (AH negative 0.071 ± 0.008 μCi/g mean ± sem vs. AH positive 0.054 ± 0.002 μCi/g; $p = 0.043$, $t = 2.11$, $df = 35$) and this tended to significance in layer VI (AH negative 0.069 ± 0.01 μCi/g vs. AH positive 0.052 ± 0.002 μCi/g; $p = 0.057$, $t = 1.97$, $df = 35$). In schizophrenia with visual hallucinations (VH) EGFR mRNA expression was significantly higher in layers II (VH positive 0.063 ± 0.008 μCi/g vs. VH negative 0.044 ± 0.002 μCi/g; $p = 0.006$, $t = 2.96$, $df = 35$) and III (VH positive 0.067 ± 0.007 μCi/g vs. VH negative 0.050 ± 0.002 μCi/g; $p = 0.01$, $t = 2.65$, $df = 35$). There were no main effect differences between schizophrenia and control groups and no other differences within the schizophrenia group with regards other symptoms or clinical parameters.

Conclusion: EGFR mRNA dysregulation may be implicated in the pathology of perceptual disturbances within schizophrenia, and this varies between auditory and visual perceptual modalities.

P-23-008 Individual scores on harm avoidance are differentially related to dorsolateral prefrontal cortical and hippocampal serotonin 2A receptor binding indices

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Objective: Although the serotonergic system has been documented to be implicated in healthy as well as in pathological emotional states, knowledge about its involvement in personality is limited. Former research on this topic suggests that post-synaptic 5-HT2A receptors could be involved in particular in fronto-limbic areas.

Methods: In drug-naïve healthy subjects we examined the role of these 5-HT2A receptors with 123I-5-I-R91150 SPECT using the temperament dimension Harm Avoidance (HA), a personality feature closely related to stress and anxiety proneness, thought to be mediated by the serotonergic system. Frequently reported to be implicated in affective disorders, we focused on the dorsolateral prefrontal cortices (DLPFC) and the hippocampus. All analyses were corrected for age and gender.

Results: We found a relationship between DLPFC and hippocampal 5-HT2A receptor binding indices (BI) associated with individual HA scores: HA was positively related with DLPFC and negative related to hippocampal 5-HT2A receptor BI. Further, our results suggest that in particular those individuals with a tendency to worry or to ruminate display significantly higher 5-HT2A receptor BI in the left DLPFC. Participants scoring higher on HA had lower hippocampal 5-HT2A receptor BI with preponderance to the right, possibly reflecting an enhanced sensitivity for stress-related responses.

Conclusion: Our results give support to the hypothesis that 5-HT2A receptors might exert different functions depending as to where they are located in the brain. Although we only examined psychologically healthy individuals, the inverse relationship of 5-HT2A receptor binding indices between the two anatomical regions suggests that a possible serotonergic vulnerability for affective disorders, in line with other studies.

P-23-009 Therapeutic management of borderline personality disorder in emergencies

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Objective: To describe demographic and clinical factors of BPD patients that visit PES and their association with psychotropic drugs and hospitalization indication.

Methods: Socio-demographic, clinical, severity and treatment variables are collected from visits attended at PES during a 4 years period. Logistic regression model is used to analyze which factors are related to pharmacotherapy and hospitalization.

Results: A sample of 11.578 patients was obtained. 1032 (8.9%) received BPD diagnosis and were mostly women (n = 653) with a mean age of 31 ± 9. Psychiatric and substance abuse history were more common in BPD group ($p < 0.001$). They showed more severe symptoms, frequently related to behavior disorders (27%) or anxiety (21.5%). Anxiety was the condition more frequently related to benzodiazepines prescription for BPD patients (OR 3.77, IC 95% 2.52–5.66). Female gender (OR 0.52, IC 95% 0.35–0.76), substance abuse (OR 0.58, IC 95% 0.38–0.88), improper self-care (OR 0.61, IC 95% 0.42–0.88) and lack of family support (OR 0.49, IC 95% 0.27–0.87) decrease likelihood of receiving benzodiazepines. Psychotic symptoms (OR 6.88, IC 95% 1.64–28.90) and danger to others (OR 2.07, IC 95% 1.39–3.06) increase probability to prescribe antipsychotics. BPD patients were less hospitalized ($p < 0.001$). High risk of suicide (OR 10.33, IC 95% 6.38–16.71), opposition to treatment (OR 4.50, IC 95% 1.89–10.69) or danger to others (OR 2.55, IC 95%1.59–4.11) were variables related to hospitalization.

Conclusion: Although clinical presentation was more severe in BPD patients, hospitalization was less indicated. The use of psychotropic drugs was more common in BPD patients with an atypical socio-medical profile.

P-23-010 Personality traits of different professional groups and their impact on coping with stress and job satisfaction

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Objective: Temperament is the most stable dimension of personality. According to the recently validated questionnaire TEMPS-A, there are five distinguishable types of temperament, including depressive temperament, cyclothymic, hiperthymic, irritable, and anxiety temperament. All of the above except for the hiperthymic temperament predispose to psychiatric disorders. With the help of this test one may also predict propensity for addiction. The aim of this study was to evaluate the temperament of different social groups. The study looked at seven different groups. The survey examined ways of coping with stress and the level of job satisfaction.

Methods: The examined group included 77 people, including 30 men and 47 women aged from 21 to 60 years. Mental illness was ruled out in all participants, all of them agreed to participate in the study. We used the TEMPS-A questionnaire to assess temperament, while Minnesotta's questionnaire was used to assess the level of job satisfaction and the COPE questionnaire was used to assess the style of coping. The results were analyzed using Statistica 9.0.

Results: Among the interviewees there was 35 people (45.5%) with no specific temperament, 19 (24.6%) with mixed temperament and 23 (26.9%) people with a determined temperament. Among those of determined temperament, hiperthymics dominated (65%).We observed significant differences in the various study groups and found that there is a correlation between temperament and the level of job satisfaction, but found no clear correlation between the type of temperament and the strategies used to cope with stress.

Conclusion: It may be imprtant to evaluate the personality traits of people working in different professions in oreder to achieve a better job satisfaction. The problem of coping with stress seems to be a more complex phenomenon and needs further ivestigation.

P-23-011 Course and stability of personality disorders in the elderly: A review

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Objective: Personality disorders in the elderly have received little serious attention. They are quite different from younger adult populations in matters of prevalence, symptoms and clinical presentation. The purpose of this article is to provide a comprehensive review about the course and stability of personality disorders across the lifespan.

Methods: 22 cross sectional and longitudinal studies were reviewed.

Results: Older subjects most frequently presented with avoidant and dependent PDs followed by schizoid PDs. Borderline personality disorder become less impulsive but relationship instability persists. Extraversion, Agreeableness, Conscientiousness, and Intellect declined significantly in old age. Neuroticism declined up to the age 70. There was great a variability in stability of PDs diagnostic criteria. 25% of DSM criteria contained poor face validity for use with older adults.

Conclusion: Some personality disorders are being diagnosed more frequently because of the bias created by some DSM criteria for PD diagnosis. It seems that a dimensional approach might eliminate this bias, thus allowing for a better diagnosis and management of personality disorders in the elderly.

P-23-012 Childhood trauma, telomere length and hiv-associated neurocognitive impairments in women

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Objective: The neuropathogenesis of the human immunodeficiency virus (HIV) may manifest as various neurocognitive impairments (NCI). HIV-positive individuals also have significantly shorter telomere length (TL) in peripheral blood mononuclear cells (PBMCs) and CD8+ T cells compared to HIV-negative individuals. Additionally, reduced TL has been found to be associated with chronic psychological stress. This study focused on the effects of chronic stress associated with childhood trauma and HIV status on telomere length and investigated whether leukocyte TL (LTL) in particular represents a risk factor for NCI.

Methods: 83 HIV-positive and 45 HIV-negative women were assessed for childhood trauma and were subjected to detailed neurocognitive testing. Blood from each participant was used to extract DNA. Relative LTL were determined by performing real time quantitative PCR reactions as described by Cawthon et al. (2002).

Results: As expected, relative LTL in the HIV-positive individuals was significantly shorter than that of HIV-negative individuals. Notably, in HIV-positive participants a significant positive correlation was evident between relative LTL and learning performance. Within the HIV-positive group, there also was a significant difference between trauma groups, with a negative correlation between relative LTL and verbal fluency within the trauma group.

Conclusion: Our results suggest that reduced LTL negatively influences the learning process in HIV-positive individuals, indicating that TL could act as a susceptibility factor in increasing neurocognitive decline in HIV-infected individuals.

P-23-013 The dopamine D2 receptor (DRD2) −141C Ins/Del polymorphism affects the personality traits of healthy Japanese participants

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Objective: Dopamine neurotransmitter systems have been associated with reward-related and novelty-seeking personality traits. We investigated the possible relationship between the personality traits measured by the Temperament and Character Inventory (TCI) and the TaqI A and −141C Ins/Del polymorphisms in the dopamine D2 receptor gene (DRD2).

Methods: The sample consisted of 1084 healthy Japanese medical students and medical staff (age = 29.0 ± 9.7 years), each of whom completed the TCI. Their genomic DNA was isolated from whole blood and genotyped using the TaqMan allele-specific assay method. The associations between gene polymorphisms and the scores for TCI were statistically analyzed by one-way analysis of covariance (ANCOVA) adjusting age. Males and females were analyzed separately. Epstatis was assesses using two-way ANCOVA between the DRD2 and ANKK1 genes.

Results: Men with the Ins/Del genotype of the −141C Ins/Del polymorphism had significantly higher self-directedness scores than those with the Ins/Ins genotype ($p = 0.021$). None of the TCI scores differed among women with regard to the three genotype groups of the −141C Ins/Del polymorphism. The DRD2/ANKK1 Taq1 A polymorphism did not affect any TCI factor for either men or women. An epistatic analysis did not reveal main effects of the two genes with regard to TCI scores, but an ANKK1 × DRD2 interaction significantly predicted TCI scores.

Conclusion: These findings suggest the possibility that the −141C Ins/Del polymorphism and the DRD2/ANKK1 Taq1 A polymorphism are not strongly linked to personality traits directly, but influences them under the interaction between the DRD2 and ANKK1 genes.

P-23-014 Exercising autonomy

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Objective: The concept of autonomy occupies a central role in both the legal and ethical frameworks governing clinical practice. In the latter half of the twentieth century this new ethical principle has emerged, resulting in many changing in patient centered models of care, shared decision making processes and stricter requirements for consent processes. One important change is from long term inpatient, to daycare patient to outpatient, the balance between individual and public interests.

Methods: Participants were patients with diagnosis of severe mental disorders treated in psychiatric clinic in Constantza by a psychiatrist at list six months, with good compliance to treatment, with good therapeutic alliance and good improvement on CGI scale. During a period of four years clinical, demographic and routinely collected outcome data was obtained from clinical case notes for people who were patients with diagnosis of severe mental disorders. They received letters from psychiatrists to their family doctors, and they where asked to change the visit from psychiatrist to family doctor. Outcome and engagement data were collected on 79 service-users who were included in the study.

Results: Data was collected over three distinct time periods, first contact until transfer, time under the care of family doctor, and time under the care of psychiatrist or in-patient, during a period of four years. Findings suggested that some factors were associated with less admittance and less bed days, for example treatment compliance determined by perception of usefulness of treatment, quality of therapeutic interactions and openness.

Conclusion: Clinical and demographic variables associated with good outcome were single service users, longer than three years and those who did not use substances and who were well engaged in change. Better engaged clients might more easily accept the need for early or even voluntarily admission, which in turn has been shown to reduce length of hospitalization. The engagement once developed is fairly stable over several years and collaboration with treatment increases over time.

P-23-015 The effects of modafinil on 'cold' cognition, creativity, and motivation in healthy volunteers

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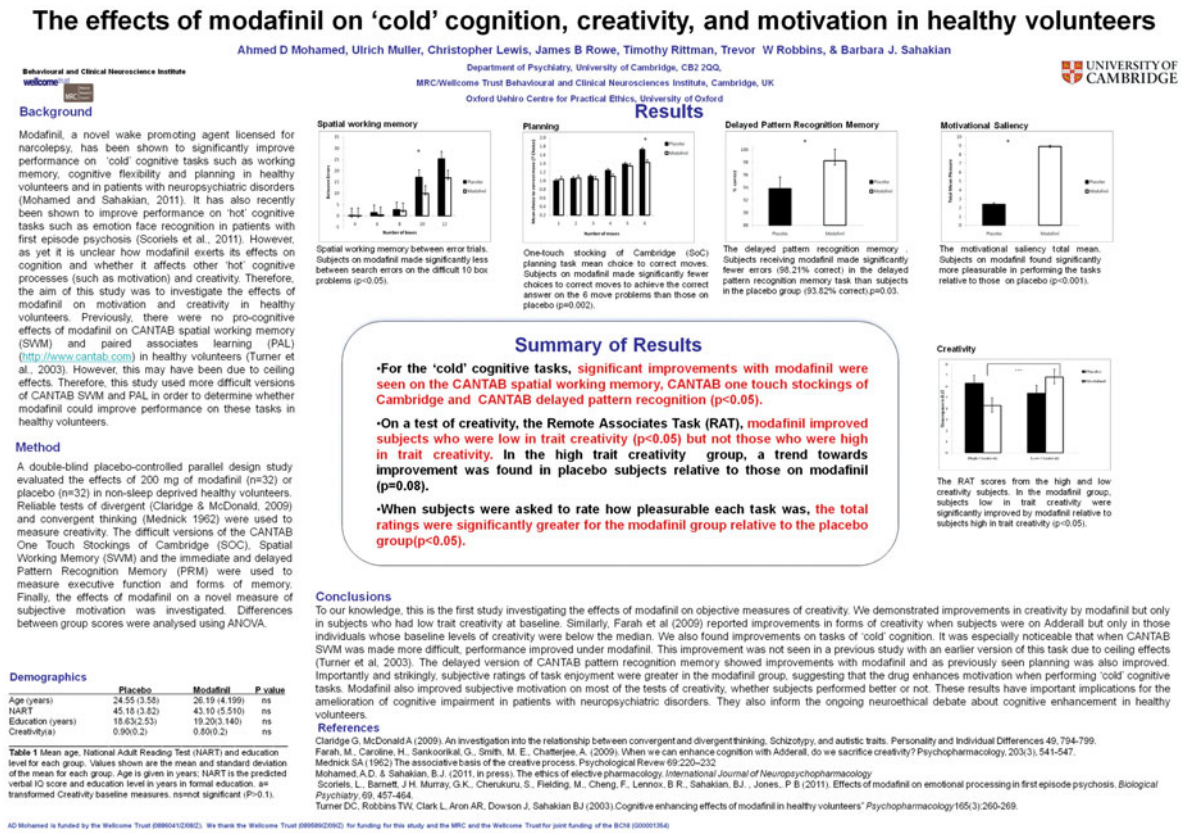
Objective: The aim of this study was to investigate the effects of modafinil on cognition, motivation and creativity in healthy volunteers.

Methods: A double-blind placebo-controlled parallel design study evaluated the effects of 200 mg of modafinil ($n = 32$) or placebo ($n = 32$) in non-sleep deprived healthy volunteers. Reliable tests of divergent and convergent thinking were used to measure creativity. The difficult versions of the CANTAB tasks were used to measure executive function. Finally, subjective effects were measured using a novel motivational salience task.

Results: For the CANTAB tasks, significant improvements with modafinil were seen on a load dependent manner ($p < 0.05$). On a test



of creativity, the Remote Associates Task, modafinil improved subjects who were low in trait creativity ($p < 0.05$) but impaired those who were high in trait creativity. In the high trait creativity group, a trend towards improvement was found in placebo subjects relative to those on modafinil ($p = 0.08$). Modafinil induced significant increase in salience of pleasure as the total ratings were significantly greater for the modafinil group relative to the placebo group ($p < 0.05$).

Conclusion: This is the first study investigating the effects of modafinil on objective measures of creativity and motivation. We demonstrated improvements in creativity by modafinil but only in subjects who had low trait creativity at baseline. We also found improvements on tasks of 'cold' cognition. It was especially noticeable that when CANTAB SWM was made more difficult, performance improved under modafinil. Due to ceiling effects, this improvement was not seen in a previous study with an earlier version of this task. Importantly and strikingly, subjective ratings of task pleasure were greater in the modafinil group, suggesting that the drug increases salience of pleasure independent of the performance of all tasks. These results have important implications for cognitive enhancement practices among healthy individuals and they inform the ongoing neuroethical debate.

P-23-016 Pharmacotherapy in pregnancy and breastfeeding: Clinical database

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Objective: Decision on drug treatment of mental disorders in pregnancy and breastfeeding poses a clinical problem. Psychiatrists have to weigh the potential risks of drugs for the fetus and infant versus known risks of untreated disorder. Treatment discontinuation during pregnancy frequently results in a relapse of mental illness. Controlled clinical trials provide little guidance; females of fertile age are rarely included in the early phases of clinical testing, the Phase IIb and III trials have a standard provision to use a reliable contraception. Pregnancy during drug trial is considered as a 'serious adverse event' with subsequent study discontinuation. The available information on teratogenic effects, neonatal toxicity, withdrawal symptoms, or long-term neurobehavioral effects of drugs on fetus and infant is based mostly on anecdotal case vignettes, case series, drug registries, and epidemiological studies.

Methods: In the Prague Psychiatric Center, a specialized outpatient clinic for treatment of mental disorders in pregnancy and lactation was established in 2005. The Clinic provides treatment, counseling, and consultation services. We present an overview of our clinical experience and summarize treatment recommendations.

Results: Our clinical database currently includes 148 patients (54% diagnosed with anxiety disorders, 24% psychotic, 9% depressive, 7% bipolar, 5% personality disorders, and 1% behavioral syndromes. Approximately 20% pregnant patients were without drug treatment. Clinical complications were observed in 14% cases. Experience with administration of psychotropic drugs and the most frequent adverse outcomes are reviewed, including the use of alternative non-pharmacological interventions (psychotherapy, ECT, rTMS).

Conclusion: In general, monotherapy is recommended, changes in prescription should be avoided. Preferred are drugs with low number of metabolites, higher protein binding affinity and low potential for drug-drug interactions. Our results support the notion that the cautious use of psychotropic drugs in pregnancy and breastfeeding may be associated with a low number of drug-induced complications. Supported by the research project MZ0PCP2005.

P-23-017 Comparison of pharmaceutical treatment in patients hospitalised in different acute departments of psychiatric hospital of Attica

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Objective: Despite the constant recommendations for avoiding antipsychotic polypharmacy and the absence of a convincing reasoning in such pharmaceutical treatment, the combination of antipsychotic drugs remain a common and widespread practice. The aim of this audit is calculating the prevalence of polypharmacy in hospitalized patients, and finding out if there are any differences concerning medication options among the 9 acute departments of Psychiatric Hospital of Attica.

Methods: Participants (423 inpatients) were selected randomly among the 9 acute departments of Psychiatric Hospital of Attica. The statistical program SPSS was used in the analysis.

Results: Participants (423 inpatients) had the following characteristics: Age of 45.9 years on average (SD = 13.1), 60.8% males, 63.7% involuntarily hospitalized, onset age of disease 28.4 years (SD = 12.1), with a diagnosis of schizophrenic disorder in 72.1%, bipolar disorder in 16.8%, and depression in 11.1%. Use of illegal substances in 18.7% with cause of hospitalization: destructive or self-destructive behaviour in 24.3%, disease recurrence in 46.1%, and discontinuation of drug treatment in 27%. During their hospital admission, their aggressiveness decreased to 22.9% with verbal aggression estimated to be the main type (14.4%). 41.9% of patient treatment involved more than one antipsychotic. Despite the similar profiles of patients hospitalized in different acute departments of the Psychiatric Hospital of Attica revealed great differences concerning the treatment options and the use of multiple concomitant formulations.

Conclusion: There is a concern about the balance between the risks and the benefits of polypharmacy in psychiatry. The combination of several drugs should be the last option for treatment of resistant psychiatric disorders. In future, prospective observational studies on this issue should be conducted among the different acute departments of the Psychiatric Hospital of Attica in order to decide about the best practices for the treatment of mentally ill patients.

P-23-018 Medication used in aggression in a sample of involuntarily hospitalized patients at the psychiatric hospital of Attica

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Objective: Violent behavior and psychiatric disorder such as schizophrenia seem to be strongly associated with the involuntary hospitalization in the mind of people outside the mental health system. The aim of the present research is to study the choice of pharmaceutical drugs in patients who were involuntarily hospitalized in the psychiatric hospital of Attica and have exhibited aggression or/and violent behavior while either arriving to the emergency department of the hospital or throughout their hospitalization.

Methods: Data collection was made by randomly selected 532 patients who were involuntarily hospitalized in the psychiatric hospital of Attica from 01/08/08 to 03/09/10. The statistical program SPSS was used for the data analysis.

Results: Our sample consists of 532 patients, mean age 43.64 yrs (SD = 13.7), 64.3% male, 63.3% of which diagnosed with the schizophrenic spectrum disorders, 10.8% with bipolar disorder, 5.1% with depression and 24.1% with other diagnoses. Our research showed that 92.7% of the patients were escorted by the police, while 1.1% was escorted by an ambulance, and 6.2% by relatives. That wasn't justified by the absence of any kind of aggression in 46.4% of them, as 12.6% were in need to be placed under protective restrain. In 32.7% of them typical antipsychotics were administered, in 59.4% of them atypical antipsychotics were used and in 5.1% of the patients a combination of both typical and atypical antipsychotics. There was a need to administer intramuscular antipsychotics in 34.4% of our sample.

Conclusion: In patients who are hospitalized involuntarily, have no capacity to decide for their self and show increased aggression, the need for intramuscular antipsychotic drug treatment and protective restrain is decreased after their involuntary admission in the hospital.

P-23-019 Tinnitus co-morbid with insomnia: A significant interrelationship and implications

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Objective: Tinnitus is a prevalent medical disorder (10–20%), frequently resulting in compromised daily-life functioning and insomnia (Langguth, 2010). We hypothesized that tinnitus and co-morbid insomnia (symptom and diagnosis) negatively effect each other leading to added distress. Our paper will review the tinnitus co-morbid literature and present our prospective tinnitus study evaluating this co-morbidity.

Methods: 14 studies evaluating insomnia in tinnitus were reviewed addressing the criteria of insomnia used (symptom vs. diagnosis), the questionnaire utilized, etc. In addition, we screened 72 prospective patients responding to an advertisement for a tinnitus treatment study. We used a semi-structured questionnaire addressing issues of tinnitus (e.g. constant vs. intermittent), specific sleep disturbances, daytime functioning, and total sleep time. Diagnosing insomnia followed ICSD-2 and DSM-IV-TR criteria.

Results: 14 studies were reviewed examining co-morbid insomnia; unfortunately, only the prevalence of insomnia symptoms (versus a diagnosis) was presented (19%–79%). Most only asked whether tinnitus disturbed a patients' sleep while a few assessed a full range of sleep disturbances. Our tinnitus sample consisted of 72 subjects; 69.4% endorsed at least 1 insomnia symptom (See Tables 1 and 2 for demographics and specific sleep disturbances). 59.7% had a diagnosis of insomnia secondary to tinnitus. Tinnitus patients with co-morbid insomnia had a more severe illness, e.g., bilateral vs. unilateral tinnitus.

Conclusion: Although previous studies found that insomnia was frequently co-morbid with tinnitus (19–79%), they were inadequate asking as few as 1–3 insomnia questions. They only identified insomnia as a symptom and did not clarify whether insomnia as a diagnostic category existed. Our current study provided for a more in-depth evaluation of insomnia. Our data confirmed that not only is insomnia a prevalent co-morbid symptom-70%- but is also a prevalent co-morbid diagnosis in approximately 60% of tinnitus patients. Furthermore, co-morbid insomnia was associated with more severe tinnitus. Implications of this possible bidirectional interrelationship will be discussed.

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Table 1: Demographics of Tinnitus Population(n=72)

Age	33Years – 83 Years (Range) 55.9 Years (Mean)
Gender:	Male: 49 Female: 23
Duration of Tinnitus:	1Month – 50Years (Range) 8.9 Years (Mean)
Type of Tinnitus:	Pulsatile: 15 Non-Pulsatile: 57
Constant Vs. Non-Constant:	Constant: 64 Patients Non-Constant: 8 Patients
Hearing Loss:	50 Patients
Hearing Aids Used:	5 Patients
Unilateral Vs Bilateral	Unilateral: 37 Patients Bilateral: 35 Patients

P-23-020 Exploding head syndrome – case study and therapeutic approaches

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Objective: Exploding head syndrome (EHS) is a relatively rare type of parasomnias characterised by a sense of an explosive loud banging noise in the head usually in the twilight stage of sleep. The sudden awakening due to this loud noise shortly after falling asleep is occasionally accompanied by the sensation of a flash light. Abrupt electroencephalographic and electromyographic changes during polysomnography indicate suddenly increasing alertness in stage N1 or stage N2 sleep at the time of the attacks. Although EHS attacks are usually quite painless, however, they may precede migraines in certain cases.

Methods: The authors present the case of a 47-year-old female patient suffering for EHS attacks for 4 years. The painless attacks were characterised by auditory sensations as if noisy lorries would quickly pass by. In roughly one third of the cases sparking flash light was simultaneously perceived. After a sudden awakening palpitation and excessive sweating was often reported by the patient. However, migraine or other type of headache has never been related to the attacks.

Results: EHS patients are mostly reported to require getting reassured about the benign nature of the rush. Beyond that, treatment with clomipramine is suggested by some authors. Thus, in our case 75 mg clomipramine has been administered as a first therapeutic approach. Due to disturbing adverse effects (blurred vision, drowsiness, and constipation), however, clomipramine medication had to be ceased and topiramate therapy (50 mg in the evening) has been gradually launched. From the third week of the treatment on, no EHS attacks could have been observed any more.

Conclusion: The aetiology of EHS is still unclear. A detailed analysis of polysomnographic data could probably help in understanding the underlying pathophysiology. The plausible link to migraine may encourage clinicians to choose new therapeutic strategies, administering for example topiramate or some other second- or third-generation antiepileptic drugs.

P-23-021 Elevated levels of serum plasminogen activator inhibitor-1 are associated with moderate to very severe sleep disturbances in individuals with a history of elevated depressive symptoms

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Objective: Plasminogen activator inhibitor type 1 (PAI-1) is an acute-phase reactant and an inhibitor of intravascular fibrinolysis, and its increased levels lead to pathological intravascular fibrin deposition (Aso, 2007). Elevated PAI-1 levels have been reported to associate with sleep-disordered breathing, but not with self-reported sleep quality (Matthews et al., 2010). Furthermore, depressive symptoms also modulate PAI-1 levels (Lahlou-Laforet et al., 2006). We sought to examine the association between sleep disturbance and the serum levels of PAI-1 in a population-based sample with a history of elevated depressive symptoms.

Methods: A total of 136 general population study participants, who reported elevated depressive symptoms (Beck Depression Inventory (BDI) <9; Beck et al., 1961) at least once during the earlier study phases (1998, 1999, or 2001), participated the clinical part of the study in 2005. They rated their sleep disturbances as none or mild and occasional ($n=90$) vs. moderate to very severe ($n=46$), and provided data on socioeconomic status and lifestyle. They were also examined to diagnose metabolic syndrome. Circulating PAI-1 levels were analysed with a human serum adipokine LincoPlex kit using a Bio-Plex Suspension Array System.

Results: Individuals with moderate to very severe sleep disturbance had elevated levels of PAI-1, and each 1 standard deviation increase in the level of PAI-1 was associated with an almost doubled likelihood of belonging to the disturbed sleep group (OR 1.91, 95% CI 1.22–2.98, $p=0.004$) in a logistic regression model adjusted for age, gender, BDI scores and metabolic syndrome. No differences between the sleep disturbance groups were observed with regard to socioeconomic or lifestyle variables.

Conclusion: Elevated circulating levels of PAI-1 were independently associated with disturbed sleep, which may lead to increased vulnerability to adverse vascular events in this group.

P-23-022 Effect of valerian on sleep quality in menopausal women: A randomized placebo-controlled clinical trial

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Objective: Sleep problems, can lead to low quality of life in Menopausal women. There are a wide variety of pharmacologic and non- pharmacologic methods for solving it. Some of Herbal Medicine, which have low side effect, may be useful for management of sleep disturbance during this time. Aim: To evaluate effects of valerian extract on improvement of sleep quality in menopause women.

Methods: Material and Methods: In this randomized, triple- blind, controlled trials 100 volunteer menopause women with age 50–60, who had insomnia and selected from 250 volunteers, had been visited in Public clinics of West of Tehran. Instrument includes demographic form and Pittsburg sleep quality index (PSQI). Samples randomly divided to two groups. Each group received twice a day for four weeks 530 mg of concentrated Valerian extract or 50 mg Starch as placebo in capsules.

Results: Equality of personal characteristics and sleep quality before intervention were checked and there were no differences in two groups. Valerian led to significant decrease in average of PSQI in compared to placebo (Valerian before intervention: 9.8 ± 3.6, after one month intervention: 6.02 ± 2.6) (Placebo before intervention: 11.14 ± 4.3, after one month intervention: 9.4 ± 3.9) ($p=0.000$). Also 30% of valerian group and 4% of placebo group had important improvement in sleep quality, which was decreasing of 5 score of PSQI. There were significant difference between two groups ($p=0.00$).

Conclusion: Findings from this study add to the scientific evidence that support use of valerian in the clinical management of insomnia especially in menopausal women.

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P-23-023 Insomnia and ADHD self-reported symptomatology: A comparison in adult ADHD and chronic insomnia likely individuals

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Objective: To compare self-reported sleep parameters and quality in individuals likely to suffer from adult attention deficit hyperactivity disorder (ADHD) and insomnia disorder.

Methods: We conducted a web-based survey with a battery of tests consisted in Sleep Condition Indicator (SCI), Sleep Disorders Questionnaire (SDQ), Sleep Timing Questionnaire (STQ), Adult ADHD Self-Reporting Scale (ASRS) and Barkley Adult ADHD Self-Reporting Scale (BAARS-IV). About six hundred participants were recruited from psychology students (in two cities) and from general population across Romania via adverts in mass media. We identified 46 participants likely to suffer from ADHD (mean age 27 ± 10.32) and 60 individuals likely to suffer from insomnia disorder (without comorbid ADHD, average age 32.35 ± 13.52). Less than 30% were men.

Results: ADHD likely reported significant later going to bed and going out of bed times (particularly in a rest day), as well as shorter sleep durations (n.s.) Insomnia likely reported significantly more frequently needing more than 45 minutes for falling asleep and being awake for more than 45 minutes per night. Ten ADHD likely (21.7%) met the criteria for comorbid insomnia disorder, too. Higher scores in impulsivity ($rho=-.410$) and inattention ($rho=0.488$) were significantly linked with poor sleep in ADHD group only.

Conclusion: While not as severe, insomnia is common in ADHD likely and appears to be linked positively with inattention and negatively with impulsivity.

P-23-024 REM-sleep behavior disorder in psychiatry- a case control study

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Objective: REM sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal REM-related muscle atonia with enactment of violent dreams and sleep-related injury. In recent years, RBD variants have been reported in young population, women and psychiatric population. While early case reports suggested that RBD symptoms in psychiatric patients were secondary to antidepressant treatment, we found that the lifetime prevalence of RBD symptoms in psychiatric out-patients was 5.8% and the risk of developing RBD symptoms among those taking selective serotonin reuptake inhibitor (SSRI) was only 1 out of 20.

Methods: This is a case-control study, aimed at establishing the clinical and polysomnographic features of RBD in psychiatric populations. Two age-, sex-matched control groups were selected: 1) one from psychiatric clinic (also psychiatric diagnosis matched) and 2) healthy control from general population. All cases and control subjects undergo standard measurements, including self-reported questionnaires, structural clinical interviews, overnight polysomnography, neuro-cognitive tests and neurological examinations.

Results: 40 subjects were recruited for each arm. (Total number of subjects: 120). Results showed that patients with RBD reported more core features of RBD, including nightmares, dream enactment and resultant sleep-related injury. They also scored higher marks in anxiety scale ($p < 0.05$) when comparing with the controls. For the PSG features, the cases had a higher REM-related muscle activities and loss of REM related muscle atonia ($p < 0.05$). Despite there was no significant difference over the use and dosage of antidepressants between the cases and psychiatric control group, the cases still had a significant higher degree of loss of REM atonia. ($p < 0.01$).

Conclusion: This study suggested that RBD exists in psychiatric populations and antidepressant per se could not fully account for the clinical and polysomnographic features.

P-23-025 Alcohol use among Indigenous group in Gombak, Malaysia

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Objective: To investigate the pattern of alcohol use and psychiatric orbidity among the indiginous people in Malaysia and their psychosocial correlates.

Methods: The cross sectional study conducted among 18 years and above of 201 Orang Asli settlement in Tekala river village of Gombak district, Malaysia in year 2010. We interviewed every third house after house mapping procedures based on previous studies using systematic sampling. The study was approved by the ethic committee board of the University hospital. The alcohol use were measured using ASSIST-BI and psychiatric comorbidity using MINI Ver 5.0.

Results: The study population consist of 201 respondents from 76 households. The respondent mean age is 37.3 years, almost three quaters are married, more than half are females and 84.1% are employed at the time of study. We found the lifetime and current prevalence of alcohol use are 14.4% and 13.4% respectively. The number of respondents fulfilled at least one psychiatric diagnosis is 4.0%. There was significance negative correlation between Islamic religion and alcohol use even after adjusted with gender and marital status. However, there was no significance correlation found between psychiatric morbidity and alcohol use in this study.

Conclusion: The prevalence of alcohol use among orang asli Gombak is higher as compared to the general population group in Malaysia. Islamic religion seems to have protective factors against alcohol use. There is a need for further study to proove the causal relationship of Islamic religion and alcohol use in this population.

P-23-026 Mass psychogenic illness-temporal spread and containment- a south east Asian story

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Objective: Mass hysteria, also known as mass psychogenic illness (MPI), has been reported for hundreds of years in different socio-cultural settings. MPI has been characterized by a group of symptoms that usually mimic an organic disease, but without any identified cause, and occurs in those who share a common belief that those symptoms constitute a definite illness.

Methods: Few months back in a wedding party in Jharkhand, India, a lady had a sudden death and among the guests it spread that the death was caused due to henna or mehendi poisoning. Henna is used to colour the hands of the bride and other women during wedding in India. This news spread more through mobile and sms service than through mass media and a particular brand of henna was discussed as the cause. For the next 2 weeks more than 500 young women were admitted in various hospitals and nursing homes across Jharkhand and West Bengal with conversion symptoms similar to poisoning.

Results: Recently in October 2010, there was an epidemic of Koro in West Bengal which spread to Assam, Mumbai and Delhi which is an area of more than 1500 km of epidemic like spread in temporal fashion. The name Koro means ''shrinking penis''. Other local languages in South-East Asia also have similar names for the condition. The classic syndrome in South-East Asia is culture-bound and is characterized by the belief that the penis is shrinking; it will disappear into the abdomen and it will cause death. These beliefs are accompanied by an intense fear and by preventive manoeuvres such as tying, clamping or grasping the penis.

Conclusion: This poster addresses the issues on factors affecting the origin and spread of Mass Psychogenic Illness and its containment.

P-23-027 Caffeine counteracts impairments in task-oriented psychomotor performance induced by chlorpheniramine: A double-blind placebo-controlled crossover study

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Objective: The combined effects of chlorpheniramine and caffeine on task-oriented psychomotor function have not been systematically evaluated. This study aimed to evaluate the effects of chlorpheniramine on psychomotor performance and the counteracting effects of caffeine on those sedative antihistamine actions.

Methods: Sixteen healthy young men participated in this study. Using a double-blind placebo-controlled crossover design, each subject was administered one of the following conditions in a random order with a 1-week interval: 'placebo-placebo', 'chlorpheniramine-placebo', 'placebo-caffeine', or 'chlorpheniramine-caffeine'. Before and after the treatments, psychomotor functions were assessed using a battery of tests. Additionally, subjective responses were assessed using a visual analogue scale (VAS).

Results: Psychomotor performance changed over time in different ways according to the combination of study medications. In the 'chlorpheniramine-placebo' condition, reaction times of the compensatory tracking task were significantly impaired compared with the other three conditions. In addition, the number of omission errors of the continuous performance test were significantly greater compared with the 'placebo-caffeine' condition. However, the response pattern of the 'chlorpheniramine-caffeine' condition was not significantly different from that of the 'placebo-placebo' condition. Changes of VAS for sleepiness were significantly greater in the 'chlorpheniramine-placebo' condition compared with the other three conditions. Blood pressures significantly increased in conditions that included caffeine compared with the conditions that did not.

Conclusion: Chlorpheniramine significantly increases subjective sleepiness and objectively impairs psychomotor reactions to a

stimulus. However, caffeine counteracts these sedative effects and psychomotor impairments.

P-23-028 Plants used in popular medicine for treatment of atherosclerosis: The experience of Dhaka city in Bangladesh

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Objective: Today a person is very much preoccupied. Modern lifestyle has contributed to serious increases in killer diseases like atherosclerosis. Currently, most medications or therapies for treatment of atherosclerosis have serious side-effects, which sometimes can be more life-threatening than the diseases itself. It is important, therefore, to turn to plant sources for discovery of novel yet safe compounds, which has less or no side-effects to treat atherosclerosis. We accordingly conducted a survey of several areas within Dhaka city of Bangladesh to learn more about plants used by the traditional medicinal practitioners to treat atherosclerosis.

Methods: Interviews were conducted with the help of a semi-structured questionnaire and plant specimens as pointed by the traditional medicinal practitioners were collected, deposited, and identified at the Bangladesh National Herbarium.

Results: The plant names obtained in our survey included Morus alba L., Coccinia grandis (L.) Voigt, Saccharum officinarum L., Bacopa monnieri (L.) Pennell, Arachis hypogaea L., Terminalia arjuna (Roxb. ex DC.) Wight & Arn., Abrus precatorius L., Withania somnifera (L.) Dunal, Maranta arundinacea L., Allium sativum L., Zea mays L., Psidium guajava L., Sorghum bicolor (L.) Moench, Cicer arietinum L., Hemidesmus indicus (L.) R. Br., Swertia chirata (Wall.) C. B. Clarke, Nigella sativa L., Ocimum tenuiflorum L., Carica papaya L., Aloe vera (L.) Burm F., Euphorbia thymifolia L., Citrullus vulgaris Schrad. ex Eckl. & Zeyh., Cocos nucifera L., Prunus communis (L.) Arcang., Olea europaea L., Strychnos nux-vomica L., Aegle marmelos (L.) Corrêa, Ficus racemosa L., Rosa achburensis Chrshan., Punica granatum L., Vitis vinifera L., Sterculia foetida L., and Cinnamomum verum J. Presl.

Conclusion: Since the Dhaka city patients appeared to be generally satisfied with the treatment offered through these plants, it is important to conduct proper scientific studies towards discovery of compounds of interest in these plants, which can be used as safe and effective medicines.

P-23-029 Manic episode after malaria prophylaxis with mefloquine: Case report

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Objective: Mefloquine (Lariam) is the drug of choice as malaria prophylaxis for travel to countries with chloroquine-resistant malaria. Severe Neuropsychiatric side effects are rare. We report a clinical case of mood disorders: manic episode with psychotic characteristics in a patient with mefloquine antimalarial prophylaxis.

Methods: A 31 years old man has taken Mefloquine at a rate of 250 mg /week as malaria prophylaxis for his mission in Democratic Republic of Congo. He developed mania with psychotic symptoms after taking 5 tablets of 250 mg of Mefloquine. He was very unstable; he exhibited an elevated mood and also developed delusions of grandeur, reference and persecution, with auditory hallucinations. The physical examination and the blood laboratory tests were normal. The patient was treated with atypical neuroleptic (olanzapine 20 mg/d) giving a complete resolution of symptomatology at the end of 3 weeks.

Results: Mefloquine is widely accepted as a safe and effective treatment and a prophylactic agent for cholorquine- resistant malaria. Common Neuropsychiatric sequelae of mefloquine can occur in up to 40% of patients. Other more serious adverse reactions are rare. they are represented primarily by attacks of panics, acute psychosis, suicidal ideation, disorders of mood: major depressive episode and the excitation maniac. The incidence of such neuropsychiatric effects is 1/10 000 to 1/15 000 during the prophylactic treatment. The causal mechanism for the side effects is not known. Several risk factors increasing the neurotoxicity of mefloquine can be identified, the patient with personal or familial antecedents of psychiatric disorders are more frequently concerned. Alcohol and the association with other drugs (like quinine) are two other risk factors.

Conclusion: It is pertinent for medical practitioners to be aware of the severe neuropsychiatric side effects of mefloquine as malaria prophylaxis. It requires to investigate the risk factors such personnal or familial history of psychiatric disorders.

P-23-030 Criminal poisoning with scopolamine and psychiatric symptoms

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Objective: In Colombia and other Latin American countries, intoxications with delictive intention are common in the emergency room of general and psychiatric hospitals and scopolamine is a substance frequently used. The present work aims to identify psychiatric symptoms secondary to criminal anticholinergic poisoning in exposed patients victims of theft.

Methods: Analysis of two cases and literature review.

Results: The first patient was evaluated in the emergency department during the first 24 hours of intoxication and the second one was evaluated two months later, in both cases we applied the Minimental State Examination (MMSE), Hamilton Rating Scale For Anxiety and the Hamilton Rating Scale for Depression as well as a narrative description taken from several interviews. These patients had no previous psychiatric history. The first case showed a severe cognitive impairment in Minimental test scoring 18/30, additional identification of depressive and anxiety symptoms was found on the scales. The second case was evaluated two months later and we found similar scores in the Minimental (MMSE) and in the scales for anxiety and depression.

Conclusion: Scopolamine- induced deficits in cognitive and motor processes have been widely demonstrated in animals and humans, although the role of acetylcholine in working memory is not well understood. There is little information in the current literature about psychiatric symptoms related to criminal anticholingergic poisoning that can occur with scopolamine, antihistamines, tricyclic antidepressants, antiparkinsonian agents and fenotiazines among others. From the neuropsychiatric point of view, descriptions of changes are evident at the level of memory besides affective symptoms, therefore protocols for collaborative care that include an integrative approach are required for patients affected with delictive intoxication.

P-23-031 The lithium archives project: The role of lithium in the protection of neurodegenerative and cardiovascular disease

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Objective: Since the 1950's Lithium has been used in the successful treatment of bipolar disorder. Advancements in neuroscience suggest that Lithium increases gray matter volume and therefore may also have neuro-protective properties. Lithium has also been shown to have a low incidence of suicide attempts when compared to other medications but little exists in the literature showing any relationship between lithium and cardiovascular disease. The Lithium Archives Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression over the past 40 years. This is a retrospective naturalistic study which includes over 100 variables that can be analyzed collectively or autonomously.

Methods: The Lithium Archives Project is a retrospective, random electronic chart review conducted by a research scientist. Patient charts are examined for over 100 variables including neurological and cardiovascular diseases, eye disorders, medication history, side effects, demographics and patient histories. The current sample of over 800 charts was analyzed by a statistician using standard SPSS statistical software. Mean, standard deviation and significance of cerebrovascular disease, myocardial infarction, brain tumors, stroke, and seizures of patients treated with lithium and patients treated without lithium were compared and analyzed. Multivariate analysis was

performed to analyze group (lithium/no lithium) and incidence of disease. The means of disease incidence in the lithium versus non-lithium groups were then charted.

Results: Analysis of the current data shows that group is a significant variable in the incidence of diseases analyzed (Pillai's Trace $F=2.926$, $df=11.416$, $p=0.004$). The patients treated with lithium show less incidence of myocardial infarction ($p=0.014$), seizures ($p=0.091$, stroke ($p=0.014$) and brain tumors ($p=0.072$).

Conclusion: The current analysis indicates that in this patient population, lithium may have played a role in protection from developing both cardiovascular and neurodegenerative diseases.

P-23-032 In utero exposure to lithium, fetal biometry and neonatal outcomes

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Objective: To determine the effect of in-utero exposure to lithium on fetal biometry and neonatal outcomes.

Methods: Prospective observational study including 18 pregnant women on maintenance treatment with lithium alone ($n=13$) or polytherapy ($n=5$) during late pregnancy, which were treated at the Perinatal Psychiatry Program CLÍNIC between 2007 and 2011. We evaluated sociodemographic data, lithium plasma concentrations in maternal blood and umbilical cord, fetal biometry and neonatal outcomes.

Results: Women did not fulfill diabetes or obesity criteria pre-pregnancy and during pregnancy. Mean maternal age (SD) 32.71 (4.02), 66% primiparaes, 95% Caucasian and 100% married or with partner. Tetuses exposed to lithium had a mean (SD) waist circumference of 291.84 mm (18.1), which was lower than those exposed to polytherapy [317.8 mm (27.93)]. Statistical significant differences were not found ($p=0.055$); fetuses exposed to lithium had a mean femur length of 62.69 mm (3,82) compared to polytherapy that had a femur length of 69 mm (5.15), which was statistical significant ($p=0.018$). Estimated fetal weight by percentile, adjusted for sex and gestational age, was higher in the polytheraphy group compared to lithium monotherapy [61.62 (32.16) vs. 78.00 (27,94)], but it did not have clinical significance. Infant exposed to polytherapy had on average a higher birth weight (3773.3 vs. 3079.6), but not in terms of percentile. They had higher gestational age (40 vs. 38.29 weeks), were longer (51.8 vs. 48, 89 cm), had increased head circumference (35.6 vs. 33.43). There not were differences in umbilical cord/maternal plasma lithium levels in both groups (0.95 vs. 0.98).

Conclusion: Lithium crosses the placental barrier almost completely. The fetuses that were exposed to lithium had a lower waist circumference and femur length, lower weigth, gestational age and head circunference compared to polytherapy group. Foetal growth surveillance is recommended in pregnancy.

P-23-033 The relationship between temperament and the efficacy of lamotrigine augmentation therapy for refractory depression

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Objective: We showed that lamotrigine (LTG) augmentation was effective for the treatment of treatment-resistant mood disorder (TRMD). The combined model of the brief version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire (TEMPS-A), which assesses 5 affective temperaments (depressive, cyclothymic, irritable, hyperthymic and anxious) and the Munich Personality Test (MPT), which examines other 2 personality traits (schizoid and melancholic), is suggested to be an useful pretreatment tool for the screening of baseline temperaments without a time-consuming interview process. This study investigated the relationship between therapeutic response to LTG augmentation treatment and the patients' temperamental features assessed by TEMPS-A/MPT in TRMD.

Methods: The subjects were 39 depressive patients who had already shown insufficient response to at least 3 antidepressants or mood stabilizers despite enough therapeutic doses and durations. LTG was added to the ongoing antidepressants or mood stabilizers for 8 weeks. The daily dose of LTG was titrated by the clinician's decision. Treatment response was assessed by MADRS before and after the 8-week treatment. Responders were defined as 50% or more symptom reduction from baseline, and complete remitters were defined as less than 4 of MADRS score for more than 2 weeks. The TEMPS-A/MPT was administered to the subjects.

Results: Twenty (51%) patients were responders, and 5 (13%) of them were complete remitters. 19 (49%) were non-responders. There were no significant differences in the 7 temperaments between responders and non-responders.

Conclusion: The present result suggests that therapeutic response to LTG augmentation in TRMD cannot be predicted by the patients' temperaments by using the TEMPS-A/MPT.

P-23-034 The effect of valproic acid on excessive dopamine release in the amygdala in response to conditioned fear stress: An in vivo microdialysis study in methamphetamine-sensitized rats

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Objective: Emotional hypersensitivity in handling the event may play a role in patients with schizophrenia, therefore, it is meaningful to study dopamine dynamics in the amygdala. In our series of studies, we have found that dopamine release in amygdala was increased significantly higher in the methamphetamine (MAP)-sensitized rats than in un-sensitized ones under conditioned fear stress application. The hypersensitivity of dopamine release was considered to be a biochemical marker of vulnerability to psychosis. We also demonstrated this excessive dopamine release was inhibited by antipsychotics (Oshibuchi et al., 2009). Meanwhile, valproic acid (VPA) is used for augmentation therapy, in the treatment of schizophrenia and other emotional disorders. But there is no biochemical evidence of the difference of pharmacological effect on psychological stress. Therefore, in order to examine the differential effect between VPA and antipsychotic agents on fear response, the effect of VPA on the basal dopamine release and on dopamine response to the conditioned stress in amygdala in this model rats was measured.

Methods: Male Sprague-Dawley rats were used. Rats were administrated 2 mg/kg/day of MAP for 10 days to develop MAP-sensitization. The fear conditioning was conducted to develop psychological stress. Dopamine changes to conditioned fear stress in amygdale were measured by microdialysis and high-performance liquid chromatography (HPLC).

Results: As a result, VPA showed similar effect to antipsychotics on dopamine dynamics in amygdala.

Conclusion: Our results exhibit the partial mechanism of VPA in dopamine change in amygdala of emotional disorders.

P-23-035 Prescription of mood stabilizers: Lithium vs. valproate – what clinicians expect for them

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Objective: Although both lithium and valproate are used as classical mood stabilizer, the real world prescriptive condition is not well known. Our study aimed to explore how common the use of lithium and valproate in psychiatric conditions of Japanese outpatients and to describe the difference of characteristics of the patients. Because Japanese Society of Mood Disorders described the guideline for bipolar disorder in 2011, we surveyed the patients before 2011 to exclude the influence of the guideline.

Methods: We investigated prescriptions for lithium and for valproate given for psychiatric conditions to the first visit from 2005 till 2010 in Showa University Fujigaoka Hospital, Japan. Psychiatrist who sees new outpatients changed depending on the day of the week. DSM-IV and ICD-10 were used for diagnosis of psychiatric disorders.

Clinical records were assessed retrospectively. As valproate is also used as antiepileptic drug, subjects with diagnosis of epilepsy were excluded from the analysis.

Results: The numbers of the patients with prescription of lithium and valproate at the date of the first visit were 39 and 48, respectively. 2 patients were prescribed both lithium and valproate. There was no significant difference of age and sex between the groups. Patients with lithium prescription showed significantly more frequency of diagnosis of bipolar disorder (rate of bipolar disorder: lithium 71.8%; valproate 31.3%, $p<0.001$). Among bipolar subjects, patients prescribed lithium were significantly younger compared with those prescribed valproate (50.08 ± 16.82 years old vs. 63.62 ± 12.63 years old, $p=0.020$).

Conclusion: Lithium appears to be more expected as mood stabilizer for bipolar disorder rather than valproate in clinical practice.

P-23-036 The transcultural concept of epilepsy in beliefs

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Objective: The prevalence of epilepsy is 1.1%. But despite the high number of patients, epilepsy is still unknown and care is lacking. The point about this disease too long remained mysterious.

Methods: Traditional beliefs reinforce the public on the idea that epilepsy is a disease caused by evil spirits. Besides the names we give this evil in language Moroccan dialect are revealing: jnoun, maskoun, krina, msalmin, ladam, riah. Unfortunately these beliefs are behind the delay in diagnosing the disease and hence the bad disease and poor social integration of the patient. This is very expensive. The stigma associated with epilepsy are very numerous. Sometimes patients suffer much more than their disease. Sometimes it is claimed that epilepsy is contagious, that patients with epilepsy are ''abnormal'', dangerous or having mental retardation and even doors misfortune.

Results: All these ideas are false and exacerbate the isolation of patients with epilepsy. Epilepsy affects people of all ages but especially children and adolescents, and because of the weight of prejudice and delay diagnosis, these patients outside the circuit of the school, vocational training, and social life (marriage…) and are completely marginalized. The scientific advances in recent years, it is now possible to improve the plight of epilepsy. The anxiety generated by the onset of the crisis, can lead to emotional dependency relationships with parents and inhibit the acquisition of emotional or intellectual autonomy of a child or young person.

Conclusion: These difficulties autonomy may themselves be a source of pain or symptoms (emotional immaturity, self disorders, disturbances, aggressiveness) The loss of self-control during the crisis, dependence with regard to others cause an injury which in turn, affects self-confidence. Thus, the real trauma of the disease in addition to the psychological trauma that deserves to be considered.

P-23-037 Safety and efficacy of sustained release lamotrigine as monotherapy/add on therapy in the treatment of epilepsy

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Objective: Our aim was to determine the safety and efficacy of the LTG(SR) in Indian patients of epilepsy.

Methods: Total 20 patients were enrolled. All patients completed the full (12 weeks) duration of the study. Patients in the age range of 16–70 years with diagnosis of Epilepsy, as defined in ICES were selected. Patient-categories included were: Category-I: Newly diagnosed patients (h/o>2 seizures in last 3 months), Category-II: Patients who did not achieve adequate seizure control (>4 seizures in last six weeks) with other AED. Category-III: Patients who were on Lamotrigine Conventional release (IR) formulation, followed by exclusion criteria.

Results: LTGSR treatment reduced seizure frequency in all patient-categories. Statistically significant reduction in seizure frequency (per 4 weeks) was seen in patient-Category – II. QOLIE-31 total score also significantly improved, in each patient-category. No serious adverse event (AE) was reported during the study.

Conclusion: It can be concluded that the LTGSR is safe and effective in the Indian patients of Epilepsy. It offers the advantage of a better tolerability profile as compared to conventional LTG. It also offers a safe switchablility from conventional preparation at the same molar dose.

P-23-038 Involvement of the nicotinic acetylcholine system in the cognitive impairment induced by electroconvulsive seizures in rats

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Objective: Epilepsy is a chronic neurological condition characterized by recurrent seizures. The seizures are frequently comorbid with psychiatric disorders, including cognitive disorders. We recently reported that seven consecutive electroconvulsive shock (ECS)-induced seizures markedly impaired spontaneous alternation behavior in a Y-maze test, indicating impairments in short-term working memory. The involvement of the nicotinic acetylcholine system in these ECS-induced behavioral impairments remains incompletely understood.

Methods: Wistar rats were administered ECS (100 V, 50 mA, 0.2 sec, 60 Hz) once daily for 7 days. The Y-maze test was conducted 24 h after the last ECS administration. Physostigmine, cholinesterase inhibitor, 0.5 and 1 mg/kg; anabasine, α7 nicotinic acetylcholine receptor (nAChR) agonist, 0.3 and 3 mg/kg; and ABT-418, α4β2 nAChR agonist, 0.1 and 0.5 mg/kg, were administered i.p. to ECS-treated rats 30 min before the test. For immunohistochemical analysis, α4 nicotinic acetylcholine receptor-positive cells were quantified 24 h after the last administration of ECS.

Results: ECS reduced spontaneous alternation behavior in the Y-maze test as reported previously. Increasing acetylcholine levels with physostigmine (0.5 and 1 mg/kg) prevented this impairment, whereas α7 receptor activation by anabasine treatment had no significant effect. The impairment of spontaneous alternation behavior was significantly improved by the α4β2 nAChR agonist ABT-418 (0.5 mg/kg). In addition, the ECS administration caused a reduction in the number of α4 nicotinic acetylcholine receptor-positive cells in the prefrontal prelimbic cortex and the hippocampal areas CA1 and CA3, compared with the sham group.

Conclusion: These results suggest that impairment of the α4β2 nAChR underlies cognitive impairments induced by seizures, and that the positive effect of α4β2 nAChR activation on spontaneous alternation behavior may be linked to the medial prefrontal cortex or hippocampus.

P-23-039 Assessement of comorbidity in post-neurosurgical patients with epilepsy

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Objective: The depressive comorbidity in epileptic patients is more frequent than in the general population and other chronic diseases. In this cross-sectional study, we investigated the prevalence and clinical features of interictal depressive symptomatology in a cohort of neurosurgical patients.

Methods: The study was carried out in 54 post-neurosurgical epilepsy patients (PNS), 53 with 'no-postneurochirurgical' epilepsy (NPNS) and 52 healthy control subjects. The majority of patients were receiving antiepileptic monotherapy, and had no prior history of mood disorders. Screening for depressive disorder (DD) was conducted by means of a self-assessment scale, the CES-D (Center for Epidemiologic Studies-Depression Scale), as validated in Italian, and already used in similar studies.

Results: In the group of PNS the total score for the individual CES-D scale value (mean+SD) was 12.15 ± 9.42. The 45.40% of patients had a scor >16, indicative of DD. The total score on the individual CES-D was 13.98 ± 8.90. The 54.55% of patients had a scor >16, indicative of DD. In control subjects the total score on the individual CES-D was 9.11 ± 5.3, with scores indicative of DD in 17.30% of cases. A further stratification of patients with satisfactorily controlled frequency of seizures or less did not show any relationship with the presence of DD.

Conclusion: The results of the study showed no differences in the prevalence of comorbid interictal depression in neurosurgical patients, according to the type of epilepsy. However, the prevalence of

depression ranged between 45.40% and 54.55% of cases and suggest the need for careful assessment of this comorbid condition in patients with epilepsy.

P-23-040 Enhancement of morphine-induced antinociception by electroconvulsive shock

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Objective: Electroconvulsive therapy (ECT) is a widely used method for treating drug-resistant depression and schizophrenia, and reportedly has a positive effect on neuropathic pain. Interestingly, some studies have reported that an amount of opioid to relieve pain is reduced after a series of ECT. In the present study, we administered electro-convulsive shocks (ECS) to mice, since mice are supposed to have a similar response pattern to ECS as humans have to ECT, in order to clarify the effect of ECT on morphine-induced antinociception and to elucidate its mechanism.

Methods: Hot plate tests were performed to study morphine-induced antinociception in mice that were treated with ECS 24 hours before the administration of morphine.

Results: Results demonstrated that the dose-response curve for morphine-antinociception in ECS-pretreated mice was shifted left and the EC50 of morphine in ECS-pretreated mice was 30% decreased compared to it in mice which were not pretreated with ECS. Additionally, we administrated morphine twice with 24 hours interval to develop an acute tolerance to clarify the effect of ECS on the tolerance. Mice pretreated with ECS 21, 23, and 25 hours before the second administration of morphine did not develop acute morphine tolerance, while those pretreated with ECT 1 to 6 hours before did. Western blotting was performed with a specific antibody to detect mu-opioid receptors in the thalamus. The expression level of mu-opioid receptors was significantly higher in the thalamus of the morphine- and ECS-treated mice compared to that of the mice only treated with morphine.

Conclusion: These results indicate that ECS may facilitate the antinociceptive effects of morphine and counteract the development of a tolerance to morphine, possibly due to increased expression of mu-opioid receptors, suggesting that similar mechanisms may underlie the effect of ECT on opioid-induced analgesia in humans.

P-23-041 Comparative characterization of ADX71653 and ADX71943, novel CNS- and peripherally-targeted GABAB receptor positive allosteric modulators

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Objective: There is evidence that the orthosteric GABAB agonist baclofen has anxiolytic- and analgesic- like profile, albeit showing narrow therapeutic window, rapid onset of side-effects, with signs of tolerance, withdrawal and rebound. Here we compared efficacy and side-effect profiles of a CNS-targeted GABAB positive allosteric modulator (PAM) ADX71653 to that of a peripherally-targeted PAM ADX71943.

Methods: Efficacy of ADX71653 was evaluated in the mouse marble burying (MB) test of anxiety while efficacy of ADX71943 was evaluated in the mouse MB and in the acetic acid writhing (AAW) test of visceral pain. Side-effect profile of each compound was assessed in the mouse locomotor activity (LMA), rotarod and body temperature (BT) tests.

Results: ADX71653 reduced numbers of buried marbles (MED 3 mg/kg), indicative of its anxiolytic-like effect. However, it also reduced LMA, body temperature and impaired rotarod activity from 10 mg/kg. ADX71943 reduced the number of acetic acid-induced writhes (MED 3 mg/kg), indicative of antinociceptive-like efficacy. However, it failed to have an effect in MB when tested at up to 100 mg/kg. ADX71943 had no effect in the mouse LMA, rotarod and BT tests when tested at up to 100 mg/kg.

Conclusion: Thus, peripherally-targeted GABABR PAMs offer a wide therapeutic margin when evaluating indications with peripheral mechanisms, while being inactive in centrally-mediated conditions. However, centrally-targeted PAMs offer a narrow margin, similar to that seen with baclofen. Therefore, GABABR PAMs with a balanced central/peripheral profile may offer the potential for development of novel non-opioid alternative for chronic osteoarthritis (OA) pain and a non-muscarinic alternative for overactive bladder (OAB) with a wider therapeutic margin. Recently we develop a novel, orally-bioavailable GABABR PAM with a balanced central/peripheral profile which offers efficacy in models of anxiety, OAB and pain, with ameliorated side-effect liability. It is currently advancing toward the IND.

P-23-042 Vitamin D in pediatric patients with chronic non-malignant pain

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Objective: Vitamin D deficiency (25[OH]D < 20 ng/mL)has been found to contribute to both medical and psychiatric conditions. The association with chronic pain has been noted in adult patients with chronic non-malignant pain (Turner 2008), with a 26% prevalence of hypovitaminosis D. Antiel et al., (2011) studied a group of adolescent patients with postural orthostatic tachycardia syndrome (POTS) and found that 22% of those patients met the criteria of Vitamin D deficiency with serum 25[OH]D < 20 ng/mL. To date there has been no report of the prevalence of Vitamin D deficiency in a population of adolescents with chronic non-malignant pain which is the purpose of this study.

Methods: This study reviewed the records of 333 adolescent and young adult (ages 11–21 years old) patients with chronic non-malignant pain who participated in a three week outpatient Pediatric Pain Rehabilitation Program. As part of the standard admission process, serum 25[OH]D level was measured in all patients at the start of the program. Supplementation of vitamin D is provided to those patients who are vitamin D deficient as part of the rehabilitation.

Results: In this group of pediatric patients with chronic non-malignant pain, we found a prevalence of 21.6% (72/333 patients) with Vitamin D deficiency. Of those with Vitamin D insufficiency/deficiency, mean serum 25[OH]D was 28 ng/mL. Female patients (n = 250) had a 25[OH]D level of 30.7 ng/mL; male patients (n = 83) had a mean of 20 ng/mL. Of the African American patients (n = 5), mean serum 25[OH]D level was 17; Asian patients (n = 5) demonstrated a mean level of 28 ng/mL. The remainder were Caucasian patients (n = 323) with a mean level of 28.2 ng/mL.

Conclusion: Supplementation of vitamin D may help improve pain and physical functioning in adolescent populations with chronic non-malignant pain.

P-23-043 Sadness enhances the experience of pain and affects brain regions associated with pain

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Objective: Pain is a multidimensional experience. Human pain perception can be modulated by subjective emotional responses. We examined this association by using functional magnetic resonance imaging (fMRI) (15 healthy subjects) and magnetoencephalography (MEG) (19 healthy subjects).

Methods: Pain-inducing stimuli were presented during different emotional contexts, which were induced via the continuous presentation (5 s) of sad, happy or neutral pictures of faces. Subjects also rated their subjective pain intensity.

Results: We found: 1) The intensity of subjective pain ratings increased in the sad emotional context, 2) pain-related activation in the anterior cingulate cortex (ACC) was more pronounced in the sad context, and we demonstrated amygdala to ACC connections during the experience of pain in the sad context, and 3) event-related desynchronization (ERD) of lower beta bands in the right hemisphere after pain stimuli was larger in the sad emotional condition.

Conclusion: These results show that sadness can modulate neural responses to pain stimuli, and that it may be relevant to

understanding the broader relationship between somatic complaints and negative emotion. We also consider that further research is needed to understand this relationship from the clinical viewpoint including the psychiatric treatment.

P-23-044 Association between smoking and plasma brain-derived neurotrophic factor (BDNF) levels in healthy workers

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Objective: Brain-derived neurotrophic factor (BDNF) had been reported to play an important role in the development of nicotine dependence (ND). Chronic nicotine intake increased BDNF mRNA expression in rat hippocampus. In addition, human plasma BDNF level was found significantly increased after nicotine abstinence, but same result cannot be reconfirmed in another study using serum sample. In other words, the issue is controversial. In the present study, we investigate the plasma BDNF concentration between smoker and non-smoker using health samples from industrial workers.

Methods: 85 never smokers and 220 current smokers from a major industrial company were enrolled in this study. Plasma was quickly separated in a centrifuge and stored at −80 degrees Celsius until it was used for assay. Plasma BDNF levels were assayed using ELISA methods following to the manufacturer's instructions. All the statistics were performed using SPSS v16.0 Japanese version.

Results: The mean plasma BDNF concentration in smokers is 1636.31 (SD = 1250.33) pg/mL and, it is 1601.17 (SD = 1699.06) pg/mL in never smoker. We found a significant difference in the Log-transferred BDNF concentration between smokers and never smokers ($p = 0.035$). After adjusting age, the smoking behavior still increase the plasma BDNF concentration ($p = 0.029$).

Conclusion: Our results suggested that the plasma BDNF concentration in smoker is higher than that in non-smoker which is in line with a research in male schizophrenia patients. However, it was inconsistent with other human researches which revealed the lower BDNF concentration in smokers. The inconsistency between our and other human studies might due to different settings of participant fs background. Unfortunately, we still had some limitations in this study, such as BMI, excise and disease information of the workers. Association between smoking and the plasma BDNF level remains controversial. Further studies are needed to draw a firm conclusion.

P-23-045 Smoking cessation in patients with chronic schizophrenia

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Objective: To examine whether smoking cessation is associated with psychotic symptom severity and antipsychotics side effects in smoking patients with chronic schizophrenia.

Methods: A total of 100 smoking patients with chronic schizophrenia were recruited at a Taiwan chronic mental hospital for the 8-week smoking secession program using nicotine patch replacement therapy (NRT). Medication adjustment was allowed during the NRT. All subjects were evaluated for the clinical psychotic symptoms and antipsychotic side effects at baseline and after the NRT. Psychotic symptom severity and antipsychotic side effects were measured by the Positive and Negative Syndrome Scale (PANSS) and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, respectively. The differences before and after the NRT were analyzed by multiple logistic regression analysis.

Results: After adjusting for age and hospitalization day, the clinical psychotic symptoms signifiantly improved after the NRT (PANSS score at baseline and after the NRT: 63.77 ± 1.72; 60.85 ± 1.55), especially in general and positive subdivisions. The antipsychotic side effects, however, were not significantly different (UKU Side Effect Rating Scale at baseline and after the NRT: 5.46 ± 0.38; 5.09 ± 0.39); items including fatigue, rigidity, and constipation significantly improved after the NRT, while blurred vision and drooling significantly worsened (p-value < 0.05).

Conclusion: Smoking cessation is beneficial for smoking patients with chronic schizophrenia in reduction of clinical psychotic symptoms and certain side effects of antipsychotics.

P-23-046 Genome-wide association study identified susceptibility loci associated with nicotine dependence in a Japanese population

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Objective: Many genetic and environmental factors can be involved in the etiology of nicotine dependence. To date, several candidate genetic variations have been identified to be associated with smoking behaviors and vulnerability to nicotine dependence. These were found mostly by investigating single nucleotide polymorphisms (SNPs) on each gene related to phenotypes of concern or by genome-wide association studies (GWAS), which treat genetic markers in the whole genome, conducted for subjects with European ancestry. However, genetic factors have not been reportedly investigated for Japanese population utilizing whole-genome genotyping arrays. We comprehensively explored genetic contributors to nicotine dependence by GWAS in Japanese.

Methods: Subjects were 300 patients who visited Iwata City Hospital. A number of participants involved in this study had various smoking habits and filled in a questionnaire leaflet containing various questions. Whole-genome genotyping was performed with iScan System (Illumina K.K.) and the BeadChip HumanCytoSNP-12.

Results: In association study between over 200,000 marker SNPs and scores of the Fagerström Test for Nicotine Dependence (FTND), a test that yields a continuous measure of nicotine dependence, the Tobacco Dependence Screener (TDS), consisting of 10 questions, and the numbers of cigarettes smoked per day (CPD), none of the SNPs were found to reach the genome-wide significant level and the P-values were no less than 10–6 in all analyses. However, several potent SNPs were found in loci that have not been highlighted, as well as in loci that include known candidate genes resulted from previous GWAS. Among them was CSMD1, CUB and Sushi multiple domains 1, which appeared in top ranks of our GWAS results for all the three phenotypes examined.

Conclusion: Although future studies with larger sample size is required, these results will serve to discover genetic factors contributing to nicotine dependence and smoking behavior specific to Japanese population in addition to those common to other populations.

P-23-047 Effects of smoking cessation on reward processing

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Objective: Research on nicotine addiction indicates greater ventral striatal activity in smokers compared to non-smokers in response to smoking-associated cues but blunted reactivity to non-drug rewards (David et al., Biol Psychiatry 2005, 58: 488–494; Martin-Soelch et al., Eur J Neurosci 2003, 18: 680–688). However, it is still unclear how reward processing changes after smoking cessation. The aim of the present study was to examine effects of long term smoking abstinence on neural correlates of reward anticipation and cue reactivity.

Methods: Thirty-three smokers and 30 non-smokers performed two paradigms on a 1.5 T scanner: Monetary and social reward anticipation were investigated using the Monetary and Social Incentive Delay task (Knutson et al., Neuroimage 2000, 12: 20–27; Spreckelmeyer et al., SCAN 2009, 4: 158–165). The second paradigm examined cue reactivity by presenting blocks of smoking-related, neutral or sexually arousing pictures. All smokers took part in a smoking cessation course. Fifteen smokers who succeeded in staying abstinent for three months underwent a second fMRI scan with the same paradigms.

Results: During both monetary and social reward anticipation smokers showed weaker striatal activity compared to non-smokers. However, in response to smoking-associated pictures stronger neural responses were found in the caudate nucleus. For both reward

anticipation and cue reactivity no effect of smoking cessation could be detected.

Conclusion: The data implies that striatal activation during anticipation of non-smoking rewards is decreased in smokers while reactivity is increased for smoking-associated pictures. The findings further suggest that neural activation during reward processing is not affected by smoking abstinence. The data points towards a general dysfunction of the reward system in nicotine-dependent smokers. A subsample of 22 smokers and 12 nonsmokers in this study underwent [18F]FDOPA PET scans parallel to the fMRI scans. These data is currently being analyzed and will be available at the meeting.

P-23-048 The amnesic effects of benzodiazepines: A science or media concern?

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Objective: This study highlights the history and logic of the discovery and study of the amnesic effect of benzodiazepines, and how information about it is relayed in different sources, from research journals to the medical and lay media. Benzodiazepines are the most-prescribed drugs worldwide, thanks to their effects on anxiety and insomnia, but in some circumstances trigger amnesic episodes. Almost 20 years elapsed (at least in France) between when these effects were discovered and when general practitioners and users were told about them.

Methods: The written media are important for disseminating information about drugs. Unlike information relating to other fields of research, however, information about drugs has many different written sources (research and medical journals, rules and regulations, magazines and lay media). This study explored how information about them was relayed in the written media, and why it took so long to reach those who prescribe or use them.

Results: The amnesic properties of benzodiazepines were discovered by anaesthetists, who considered them useful, and the relevant information was first confined to anaesthesia journals. The molecules were later used by fundamental cognitive researchers to investigate memory processes and again considered useful tools. Gradually, however, medical and lay journals began to describe benzodiazepine-induced amnesic episodes, for the most part drug-induced aggressive disinhibition behaviour accompanied by amnesia. Since then, benzodiazepines have become unpopular with other segments of the population, namely the general practitioners who prescribe them, and users who take them to alleviate anxiety or insomnia.

Conclusion: This study demonstrates why physicians remained in the dark for such a long time, and how a beneficial effect became an undesirable effect, partly due to media coverage of a trial.

P-23-049 Development of a short questionnaire for the assessment of the onset and latency to treatments in psychiatric disorders

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Objective: Psychiatric disorders are prevalent and disabling conditions often undiagnosed and untreated for several years [1,2]. To date, little is known about causal mechanisms that determine different latency to treatments [3], given that few questionnaires focused on the onset and latency to treatments are available. From this perspective, our Department of Mental Health has recently developed a brief questionnaire on the topic: the psychopathological onset and latency to treatment questionnaire (POL-Q).

Methods: 316 patients with any psychiatric diagnosis were required to complete the questionnaire. Statistical analyses were performed using SPSS.

Results: The sample showed the following demographic variables in terms of age (47.58 years ±14.7), occupation (56% unemployed) and family history for psychiatric disorders (48.1%). Clinical variables included: age at onset (30.6 years ±14.6), age at first diagnosis (35.5 years ±18.7), age at first drug treatment (34.6 years ±14.6) and duration of untreated illness (47.2 months ±95.9), showing that, on average, patients received the first pharmacological treatment before having received a specific diagnosis. The most common symptoms at onset were related to anxiety spectrum (29.4%), depression (19.9%) or both (28.5%) then to psychotic spectrum (13.6%). Most frequent primary diagnoses were major depressive disorder (25.3%), bipolar disorder (13.3%) and generalized anxiety disorder (11.7%). Mean latency to the first visit was 31.4 months. In the 45.6% of the sample the first contact was with a psychiatrist, in the 27% with the general physician and in the 13% with a psychologist. The 76.9% of the sample was treated with drugs as first treatment, while 11.4% with psychotherapy.

Conclusion: In a first group of 316 patients affected by different psychiatric disorders, the POL-Q resulted to be a useful and reliable instrument in order to collect information on the psychopathological onset and latency to treatments.

P-23-050 Conduction abnormalities and associated factors in Korean patients with eating disorders

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Objective: QT interval prolongation and dispersion known as the indicators of an increased risk for ventricular arrhythmias and sudden death, have been reported to be prolonged in patients with anorexia nervosa. The aims of this study were to compare conduction abnormalities in Korean patients with anorexia nervosa and bulimia nervosa, and to examine its relation with clinical and laboratory factors.

Methods: We retrospectively examined 45 women with anorexia nervosa and 75 women with bulimia nervosa who were assessed 12-lead electrocardiogram as a baseline assessment. Conduction abnormalities were measured as QT interval and corrected QT interval, QT dispersion of the difference between the longest and shortest QT intervals, and abnormal U wave.

Results: QT interval was significantly longer in patients with anorexia nervosa compared with patients with bulimia nervosa. There were no differences in QTc, QTd and abnormal U wave between patients with anorexia nervosa and patients with bulimia nervosa. QTd was significantly correlated with the lowest ever lifetime body mass index (kg/m^2) as well as the serum amylase level in patients with anorexia nervosa.

Conclusion: These results suggest some conduction abnormalities reported in patients with anorexia nervosa are also found in patients with bulimia nervosa. It appears severity of weight loss and purging behavior could affect on the cardiac arrhythmia in patients with eating disorders. Appropriate attention should be paid to cardiac involvement in patients with eating disorders.

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P-23-051 Adverse effects of zolpidem and lorazepam in three-week treatment of primary insomnia

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Objective: Objective of this work was to establish differences in adverse effects of zolpidem and lorazepam during the three-week treatment of primary insomnia.

Methods: Forthy one patients with primary insomnia were included in double-blind randomized research, out of which 21 were treated with 10 mg/d of zolpidem and 20 mg/d of lorazepam during three weeks. Examinees received the medication each night during the first week, 5 times a week during the second week, and during the third week they received one of the investigated drugs 3 times a week. The most common adverse effects were recorded in patients at the beginning, then after the first, the second and the third week of treatment by using the list of adverse effects (AECL), and their intensity was estimated with visual analogue scale (VAS).

Results: Our results show that the examinees on zolpidem had total statistically significantly less adverse effects than examinees on

lorazepam ($U = 82$; $p = 0.001$), and that they also had less total intensity of adverse effects ($U = 58.5$; $p < 0.002$) and intensity by individual adverse event ($U = 45$; $p < 0.008$). In both groups of examinees there is statistically significant difference in time, that is, both examinees on zolpidem and lorazepam had decrease of adverse events and by number ($F = 29{,}805$; $p < 0.001$; $F = 24{,}968$; $p < 0.001$) and by intensity ($F = 27{,}335$; $p < 0.001$; $F = 28.423$; $p < 0.001$), during the course of treatment.

Conclusion: Based on results obtained, we can conclude that from the point of adverse events, zolpidem is safer drug than lorazepam, as well as that during the time there is a decrease of number and intensity of adverse events in both drugs.

Monday 4 June 2012

SA-01. Managing depression: Agomelatine a landmark treatment supported by an educational grant from Servier

SA-01-001 Circadian rhythm dysfunction and severity of depression

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Circadian rhythms control many biological, physiological, and behavioral parameters such as variations in the daily pattern of mood, body temperature, and secretion of various hormones. Animal as well as human data support the assumption that dysfunction of the circadian system may underlie the pathophysiology of depression as well as other psychiatric diseases. Disruption of circadian rhythms affect mood, day-time functioning, concentration, energy, sleep-wake cycle, and cognition, and predispose individuals to a wide range of mood disorders including depression, mania, and impulsivity. Recent data established the correlation of circadian misalignment and depression symptom severity, indicating that the clinical expression of some core symptoms of depression reveal circadian rhythm deregulation and pointing out therefore the importance of a chronobiological approach to depression treatment. Among the established strategies such as sleep deprivation, circadian phase advance, entrainment by light therapy, and social rhythms, the development of drugs that target the circadian system appears to be the most promising approach. The novel antidepressant agomelatine acts as an agonist of MT1/MT2 receptors, as well as an antagonist of 5-HT2C receptors, and has been shown to resynchronize altered circadian rhythms in both animal models and humans. Agomelatine was shown to increase the flattened amplitude and to phase advance the circadian timing of several psychological parameters in healthy volunteers and depressives and to resynchronize the impaired circadian system in depressed patients. In particular, agomelatine rapidly improves daytime functioning, quality of sleep, and as a critical measure of circadian functioning the circadian rest-activity cycle. Its antidepressant efficacy has been demonstrated in a great number of clinical trials versus placebo and comparator drugs. Its robust antidepressant efficacy in severe depression, versus placebo and comparators, suggests that agomelatine can reduce unmet therapeutic needs in the treatment of depressed patients, thanks to the resynchronization of disturbed circadian rhythms in these patients.

SA-01-002 Synergistic mechanisms involved in the antidepressant effects of agomelatine

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Major depression is considered as a complex disorder resulting from interactions between genetic, physiological, psychological, and environmental factors. The clinical manifestations of depression include affective, cognitive, somatic, and behavioral symptoms. Despite their variety, current antidepressants still have limitations in terms of efficacy, onset of action, and tolerability. In particular, none of them can alleviate all the symptoms of depression. Since the core symptoms of depression reveal disturbance of circadian rhythms in their clinical expression, an antidepressant with resynchronizing effects would be of value. The new antidepressant agomelatine is an agonist of melatonergic MT1/MT2 receptors as well as an antagonist of serotonergic 5-HT2C receptors. Both properties contribute to agomelatine's antidepressant activity, which has been proven in several animal models of depression and in patients with major depressive disorder. Moreover, agomelatine was shown to resynchronize disturbed circadian rhythms in several animal models and in patients. Given the action of agomelatine through these receptors, it was important to investigate how agomelatine really works: through a modulation or a synergistic interaction between MT1/MT2 and 5-HT2C receptors. Recent data on the cellular processes involved in the mechanisms of antidepressants have demonstrated that agomelatine increases the expression of brain-derived neurotrophic factor in the prefrontal cortex and hippocampus, as well as the expression of activity-regulated cytoskeleton-associated protein (arc) in the prefrontal cortex. Moreover, chronic agomelatine therapy increases neurogenesis in the hippocampus, via enhancement of neuronal cell survival, and attenuates stress-induced glutamate release in the cortex. 5-HT2C antagonists or melatonin alone fail to reproduce these effects. These data suggest therefore that agomelatine acts through a synergistic action on MT1/MT2 and 5-HT2C receptors. This novel pharmacological profile translates into a distinctive antidepressant efficacy demonstrated in depressed patients.

SA-01-003 Agomelatine: A new insight into antidepressant efficacy

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Several clinical challenges associated with the management of major depressive disorder contribute to the poor performance of established antidepressant treatments: delayed onset of perceived improvement, side effects, and residual symptoms. Agomelatine is differentiated from conventional antidepressants by its pharmacology MT1, MT2 receptor agonism and 5-HT2C receptor antagonism which modulates circadian function and has no action on serotonergic brain levels, unlike most other antidepressants. In double-blind, randomized clinical trials versus placebo and comparators, there was promise of early efficacy. Thus in one 8-week study versus placebo, agomelatine reduced HAM-D scores significantly from the first week of treatment, remaining statistically significant until week 8, and in a head-to-head comparison with sertraline, the HAM-D response rate was significantly higher (20% versus 10.9%, $P = 0.027$) at the first (2-week) assessment visit. In comparison with venlafaxine, agomelatine improved alertness and daytime functioning at week 1. Clinical experience with agomelatine has confirmed early benefits, beyond reduced side effect burden, also evident in double-blind trials. In experimental studies of healthy volunteers, agomelatine improved positive affective memory and decreased recognition of sad facial expressions more selective effects on the processing of emotional information than conventional antidepressants such as citalopram or reboxetine. Our hypothesis, that this could lead to less blunting of emotional experience in depressed patients, has also received preliminary confirmation: in comparison with escitalopram, agomelatine improved some items of blunted emotional reactivity from week 2 to week 24. Taken together, these results confirm that, in responding patients, agomelatine's novel mode of action leads to early improvement of the core symptoms of depression and potentially to less blunting of ordinary emotional experience.

SA-01-004 Agomelatine in real life: practical experience with agomelatine

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Agomelatine is an innovative antidepressant, an MT1, MT2 receptor agonist and a 5-HT2C antagonist, which is being investigated in noninterventional studies to assess its efficacy and tolerability in daily practice. The French D-CHANGE trial assessed in daily practice the efficacy of agomelatine in depressed patients who were either not treated before for this episode (naïve population) or previously treated with another antidepressant (switch population). In this

6-week prospective study, more than 2700 depressed patients received agomelatine (25–50 mg) once daily at bedtime. In order to detect early clinical markers predictive of clinical response after 6 weeks, assessments were performed at day 0, week 2, and week 6: severity of symptoms using the Quick Inventory of Depressive Symptomatology by Clinicians (QIDS-C) and the Clinical Global Improvement Severity (CGI-S) scale, the level of mood with a VAS, sleep complaints with the Leeds Sleep Evaluation Questionnaire (LSEQ), social functioning (SDS), and emotional state (MATHYS). The balance between sensitivity and specificity for each parameter was assessed using ROC curves. The early improvement at week 2 with agomelatine, perceived by both clinicians (QIDS and CGI-EI) and patients (VAS), was the criterion most predictive of response later (week 6). The severity of symptoms was similarly reduced after just 2 weeks in the total population and both subpopulations, confirming the clinical benefit of agomelatine in the naïve and switch populations. All noninterventional trials conducted in real daily practice conditions, ie, representing the heterogeneous depressed population with severe symptoms and symptoms of anxiety, confirmed the antidepressant efficacy and good tolerability profile of agomelatine. Taken together, the converging data observed in both randomized clinical trials and prospective trials make agomelatine a treatment of choice for a large spectrum of depressed patients.

SA-02. Asenapine, a multifunctional antipsychotic. Beyond symptom control in schizophrenia and bipolar disorder supported by an educational grant from Lundbeck

SA-02-001 Improving patient outcomes in schizophrenia and bipolar I disorder

A. Gonzales-Pinto. *Spain*

Psychiatric disorders are frequently misdiagnosed due to overlapping symptomatology and comorbidities. Early and accurate diagnosis is essential to ensure that the correct treatment is received at the earliest opportunity and that the benefits are maintained over the long-term. There is also a need for diagnostic markers that may allow earlier, accurate diagnosis. Despite important advances in pharmacotherapy for bipolar I disorder, a substantial number of individuals do not achieve full remission, experiencing treatment-resistant symptoms, frequent relapse, and poor functioning. There remains a need for more effective, and better tolerated, antipsychotic, antidepressant, and mood-stabilising therapies with faster onset of action, including improved treatment of comorbid psychiatric and medical disorders, and of cognitive deficits. Successful management of bipolar I disorder may be further hindered by poor treatment adherence due to intrinsic disease symptoms (e.g., poor insight), problems with intolerable side effects, use of numerous concomitant medications, and poor social support systems. Non-adherence to treatment regimens is generally reported to range from 40 to 60%. An ideal treatment for bipolar I disorder should be able to rapidly control symptoms and achieve clinical, as well as functional, remission.

SA-02-002 Asenapine, a multifunctional antipsychotic

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Asenapine is a new treatment option with some specificproperties. It is derived from a tetracyclic chemical class that is different from other antipsychotics, and has a unique sublingual mode of administration. Asenapine has a unique multi-functional human receptor pharmacology with three distinctive components. It is a potent D2-receptor antagonist and, like other antipsychotics, has a high 5-HT2A/D2 binding affinity ratio – a key driver for antimanic and antipsychotic efficacy. Additionally, asenapine has 'untypical' receptor properties, such as the combination of potent 5-HT2A/β2 and 5-HT7/5-HT6 receptor antagonism, when compared to first- and second-generation antipsychotics, at therapeutic doses. This triple action multi-functional pharmacology has driven hypotheses for potential additional therapeutic benefits of asenapine. For example, 5-HT2A/β2 receptor blockade may contribute towards alleviating depressive symptoms. Furthermore, the preclinical pharmacology of asenapine provides a rationale for enhancing cognition. Unlike the tricyclic antipsychotics, asenapine does not have excessive antihistaminic or appreciable antimuscarinic activity, which are linked with development of metabolic dysfunction and anticholinergic effects, respectively. Efficacy of asenapine has been demonstrated in the management of bipolar disorder, but translation of asenapine's unique pharmacology into additional therapeutic benefits should be determined in patients. The pre-clinical profile provides rationale for study in depressive symptoms.

SA-02-003 Effective remission with asenapine for patients with bipolar I disorder

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Asenapine is a novel, tetracyclic antipsychotic medication delivered in a fast-dissolving sublingual tablet. In two 3-week, double-blind, randomised, placebo-controlled studies in patients with bipolar I disorder experiencing manic or mixed episodes, asenapine-treated patients showed a significantly greater reduction than placebo-treated patients in the Young Mania Rating Scale (YMRS) total score, as early as Day 2. A subsequent 9-week, double-blind, head-to-head, non-inferiority extension study demonstrated that over 12 weeks of treatment asenapine maintained efficacy and was comparable to olanzapine in terms of improving YMRS total score, and in rates of response and remission. A further 40-week, double-blind, extension study showed that the efficacy of asenapine treatment (secondary endpoint) was maintained up to 1 year. A post-hoc analysis was performed to assess the effect of asenapine on depressive symptoms experienced by patients during an acute manic phase. In patients with significant depressive symptoms (baseline MADRS total score $\geqslant$20) a highly significant improvement in MADRS total score with asenapine treatment relative to placebo was observed; an effect that was not shown in patients in the olanzapine group. Asenapine offers a new treatment option for patients with bipolar I disorder. The strong clinical efficacy of asenapine has been demonstrated in acute manic and mixed episodes. Asenapine efficacy is comparable to olanzapine over 12 weeks and is maintained up to 1 year. Furthermore, reduction of depressive symptoms was shown in a post-hoc analysis.

Wednesday 6 June 2012

SA-04. Designing new antidepressants: A focus on multimodality supported by an educational grant from Lundbeck

SA-04-001 What is the rationale for designing multimodal antidepressants?

J. A. Den Boer. *University Medical Center, Department of Psychiatry, Groningen, Netherlands*

Major depressive disorder (MDD) is characterised by aberrations in many intertwined pathways: monoaminergic dysfunctions; inflammatory pathways (increased levels of proinflammatory cytokines); hypothalamic-pituitary-adrenal (HPA) axis abnormalities; impairments in neuroplasticity markers; and disturbances in circadian rhythmicity. Monoaminergic dysfunctions have dominated clinical development of antidepressant drugs, as witnessed by the role of selective serotonin reuptake inhibitors (SSRIs) and dual-action antidepressants during recent decades [1]. However, treatments with improved response and tolerability are needed. Several attempts have been undertaken to develop antidepressants based on pathogenetic principles related to hyperactivity of the HPA axis, such as CRH1, glucocorticoid and vasopressin1B receptor antagonists [2]. So far, these developments have been disappointing. Candidate targets have been identified that reduce the increased signs of neuroinflammation in MDD [3]. Based on this, new targets could include cytokine antagonists, Cox-2 inhibitors, acetylsalicylic acid, ketamine and

antioxidants. Clinical evidence for these candidate compounds is, however, still circumstantial. In clinical practice, recent studies have shown that augmentation of SSRIs with atypical antipsychotics leads to enhanced antidepressant response [4]. There is increasing clinical evidence for the augmentation strategy involving combination of an SSRI and mirtazapine [5, 6]. This response could be explained by assuming a synergistic effect between inhibiting reuptake of 5-HT and adding an antidepressant that is a 5-HT2A/2C and 5-HT3 receptor antagonist. From preclinical studies, there is evidence for the efficacy of multi-target serotonergic compounds, such as combination of an SSRI with 5-HT1A agonism, 5-HT2C antagonism, 5-HT3 antagonism, 5-HT6 agonism and 5-HT7 antagonism in different varieties [7]. When studied in isolation, 5-HT1A agonists may have modest antidepressant effects, as may 5-HT2C and 5-HT3 antagonists. There is a rationale for combining these two pharmacological modes of action into one molecule, constituting a multimodal drug. This may lead to synergistic effects and a strong antidepressant response.

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SA-04-002 Optimising receptor activity and reuptake inhibition in multimodal antidepressants – examining the evidence to date

C. Sanchez. *USA*

The new multimodal compounds vilazodone and Lu AA21004 are thought to work via a combination of both receptor activity and reuptake inhibition. Vilazodone combines serotonin (5-HT) transporter (SERT) inhibition and 5-HT1A receptor partial agonism, increases extracellular 5-HT in vivo in the rat frontal cortex and ventral hippocampus, and is active in preclinical models of anxiety and depression [1]. Lu AA21004 functions as a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the SERT in vitro [2]. In vivo non-clinical studies have demonstrated that Lu AA21004 dose-dependently occupies these targets [2] and enhances extracellular levels of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in the prefrontal cortex [3, 4]. In a rat progesterone-withdrawal model, Lu AA21004 produced an antidepressant-like response, whereas fluoxetine was inactive at corresponding SERT occupancies [5]. Lu AA21004 is effective in animal models of cognitive function, enhancing episodic memory in the rat novel object recognition (NOR) test and contextual memory in the rat fear conditioning test [4]. In contrast to the selective serotonin reuptake inhibitor (SSRI) escitalopram, Lu AA21004 normalises deficits in episodic and spatial memory induced in rats by 5-HT depletion, as measured in the NOR test and spontaneous alteration test, respectively [6]. Thus, Lu AA21004 exerts both its antidepressant-like activity and memory-enhancing effects via mechanisms beyond SERT inhibition [5,6]. Overall target occupancies, neurotransmitter levels and behavioural models, as well as quantitative EEG analyses [7], point towards a unique preclinical profile for Lu AA21004 compared to both vilazodone and current SSRIs.

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SA-04-003 Potential clinical benefits of Multimodals in depression

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The ability of the new multimodal compounds vilazodone and Lu AA21004 to target receptors and enhance neurotransmitters in specific brain areas is expected to have particular clinical benefits, including fewer side effects than are associated with serotonin-noradrenaline reuptake inhibitors. It is anticipated that the multimodal effects of Lu AA21004 could reduce treatment-emergent sexual dysfunction (TESD) (via 5-HT3 antagonism and 5-HT1A agonism) and improve cognitive function (via 5-HT3 and 5-HT7 antagonism) [1–4]. Vilazodone is an effective treatment for adults with MDD, as shown by significant improvements compared with placebo in the MADRS and HAM-D-17 in two pivotal, 8-week, randomised, double-blind, Phase III studies [5, 6]. Vilazodone was generally well tolerated, with diarrhoea and nausea being the most common treatment-emergent AEs, and had minimal impact on sexual functioning. In a proof-of-concept study, Lu AA21004 was comparable to a high-dose venlafaxine in improving depressive symptoms (MADRS and CGI-S/I at 6 weeks) [7]. Lu AA21004 also significantly reduced the risk of relapse compared with placebo in a long-term study in patients with MDD (24–64 weeks) [8]. In elderly patients ($\geqslant$65 years) with MDD, Lu AA21004 significantly improved depressive symptoms (HAM-D-24) and cognitive performance (DSST and RAVLT) compared with placebo at 8 weeks [9]. Lu AA21004 was well tolerated in the short-term and maintenance studies [7, 8], with placebo-level TESD [7]. In elderly patients, the AE profile was similar to placebo for Lu AA21004, with nausea being the only AE that was significantly higher [9]. Several AEs were significantly higher than placebo with the active comparator duloxetine. To date, vilazodone and Lu AA21004 have shown evidence of efficacy in improving depressive symptoms, together with a lack of serotonin-related AEs such as TESD. Ongoing clinical trials will further assess the potential benefits of their multimodal pharmacological profiles.

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