Sex differences need to be considered when treating women with psychotropic drugs

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the stabilization of these systems in several animal models as well as in small studies of patients with mood disorders[3]. Further testing of the circadian effects of such medications, and the potential for treatment-relevant subtyping, is highly warranted[2,9].

There are major hurdles to the wider application of these new insights. Accurate, real-time, and repeated detection of the true timing of the internal circadian clock, and its alignment with the external light-dark cycle, remains a major goal. Current measures are largely limited to either intensive, expensive, in-lab methods, or indirect inferences from wearable recordings of the 24-hour patterns of motor activity and sleep. Hence, a clear research focus is the development of novel methods based on 24-hour patterns of gene expression, metabolic activity, and peripheral blood or urinary markers. More sophisticated modelling techniques, based on tracking symptom clusters and objective markers earlier in the course of illness, and then longitudinally, are also required to unpick the direction of causation between these phenomena.

Increased and coordinated global investment in this research area is timely, and may well lead to genuine new therapeutic insights.

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In a period in which they keep on struggling for equal chances in several fields, women still need to strive for a medical treatment which takes sex differences into account. Medical practice has long been implicitly led by the notion that only reproductive organs differ between the sexes. Yet, significant sex differences have been clearly documented in blood, immune system, liver, kidneys, stomach, gut, heart and brain[1]. Such differences can impact pharmacokinetic and pharmacodynamic mechanisms[2].

For example, women have a less acidic stomach[3], which increases the absorption of weak acids but decreases that of weak bases. Gastric and colonic emptying is slower, lending pharmaceuticals more time to be absorbed. The levels of protein-transporter p-glycoprotein are two-fold lower in women of fertile age than in men: as this transporter pumps substances out of the cell, a lower activity increases absorption in the body and the brain, while decreasing renal excretion[3]. Blood volume and blood protein fraction are lower in women, decreasing dilution and binding capacity compared to men. Women, on average, have more fat tissue, which can lead to stacking of lipophilic pharmaceuticals. In gut and liver, many cytochrome P450 (CYP) enzymes are influenced by estrogens, which can lead to higher (for CYP3A4, and to a lesser degree for CYP2D6) or lower (for CYP1A2 and CYP2C19) metabolic activity in women of reproductive age. Renal blood flow, glomerular filtration, tubular secretion and resorption are all lower in women. These sex differences are not only numerous; they are also sizable – a 10-50% sex difference per mechanism – and can significantly affect the efficacy and tolerability of pharmacotherapy.

In 1977, the US Food and Drug Administration (FDA) recommended that women of childbearing age should be excluded from phase 1 and early phase 2 clinical trials. This directive, intended to protect women, did quite the opposite: it halted the understanding of pharmacotherapy in the female body and widened the knowledge gap in women's health. In 1993, the US National Institutes of Health policy made the inclusion of women and minorities in trials mandatory, but drugs already registered at that time were never retested in large female study populations. At present, only a handful of drugs (such as alosetron, desmopressin and zolpidem) have different dosing recommendations for women, while there are over 100 commonly prescribed drugs with unequal pharmacokinetics between men and women[2]. This suggests that women are at high risk for both over- and under-dosing of many drugs across medical specialties.

For psychotropic drugs, sex differences in pharmacodynamics further contribute to inequalities in efficacy and tolerability. Dopamine release regulation and synaptic elimination are influenced by sex hormones and differ significantly between men and women[4]. Although less well studied, such sex differences in neurotransmitter trafficking are also described in the serotonergic, GABAergic and glutamatergic circuitry[5].

Many of the above mechanisms – such as increased or reduced activity of CYP enzymes or p-glycoprotein, gastric acid production, gastric and colonic emptying, and dopaminergic and serotonergic trafficking – are estrogen-dependent[3,5]. This means that changes in pharmacokinetics and pharmacodynamics occur over the phases of the menstrual cycle, affecting the efficacy and tolerability of psychotropic drugs. Robust changes in efficacy and safety occur when hormonal changes are large, such as during pregnan-

cy and menopause. With menopause, pharmacokinetic and pharmacodynamic mechanisms may both reduce the bioavailability of drugs, inducing a dramatic reduction in their efficacy. We recently demonstrated a massive increase in rehospitalization after menopause in women with schizophrenia spectrum disorders using commonly prescribed antipsychotics[6].

Olanzapine is absorbed more readily from the gastrointestinal tract in women, whereas renal clearance is lower. As this antipsychotic is predominantly metabolized by CYP1A2, which is inhibited by estrogens, blood levels may be about two-fold higher in pre-menopausal women than in men with equal dosing[7]. In addition, the pre-menopausal female brain is more sensitive to olanzapine treatment, with women achieving similar receptor occupancy rates at a 50% lower dose than men[3]. After menopause, gastric acidity and emptying equals that of men, and CYP1A2 is no longer inhibited by estrogens, so that the blood levels of the drug decrease. At the same time, declining estrogen levels reduce the sensitivity of the brain to olanzapine[3], which leads to much lower receptor occupancy and efficacy in post-menopausal women.

Quetiapine is mainly metabolized by CYP3A4, whose activity is induced by estrogens, while excretion in women is lower than in men. In pre-menopausal women, these mechanisms work in opposite directions, leading to approximately similar blood levels in men and women with the same dose of the drug[7]. After menopause, quetiapine metabolism slows down and blood levels rise, which may cause a rapid increase in side effects[7].

Imipramine is absorbed better in women than in men. Its main metabolizing enzyme, CYP2C19, is inhibited by estrogens and, with equal dosing, blood levels in women may be much higher. In practice, toxic serum levels are often corrected, as therapeutic drug monitoring is the standard of care for imipramine. After menopause, CYP2C19 inhibition stops and, with the same dose, bioavailability of imipramine decreases significantly, increasing the risk for relapse of depression.

Fluoxetine is transported by p-glycoproteins and metabolized by several CYP enzymes, including CYP2C19. In pre-menopausal women, serum levels are much higher than in men receiving the same dose. As therapeutic drug monitoring is not the standard for this medication, many young female patients are expected to be overdosed.

Zolpidem yields an about 30% higher exposure in women, especially after menopause[8]. The risk of morning drowsiness prompted the FDA to request sex-specific dose recommendations. The manufacturers now recommend prescribing half the male dose for women, without taking menopausal status into account[8].

Simply treating women with half the male dose of a psychotropic drug, as the manufacturers of zolpidem recommend, is not sufficient, as sex differences can be hormone-dependent and drug-specific. In order to provide women with a dose that fits their body and hormonal status, each psychotropic drug would need to be examined for its sex- and hormone-specific pharmacokinetic and pharmacodynamic mechanisms. Detailed knowledge of sex-specific dosing for all psychotropic drugs should be expanded rapidly, to stop over- and under-treatment of female patients, which now occurs for many of these drugs[2].

Female patients are a heterogeneous group. As many mechanisms are estrogen-dependent, hormonal status – especially during pregnancy and menopause – needs to be considered. We currently cannot oversee all sex- and hormone-dependent pharmacokinetic and pharmacodynamic mechanisms for each psychotropic drug, as this is a quite complicated matter. Therefore, therapeutic drug monitoring – when available – is recommended for female patients, especially during pregnancy and menopausal transition.

There are factors – such as age, body mass index, percentage of fat tissue, and genetic polymorphism of CYP enzymes – whose importance in determining the correct dosage of psychotropic drugs is widely acknowledged. However, sex and hormonal status also have a large impact on the efficacy and tolerability of many psychotropic drugs. It is now time to take them into account.

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The need to focus on perfectionism in suicide assessment, treatment and prevention

Perfectionists are people who not only want to be perfect; they also need to seem perfect. Several decades of global research on perfectionism have identified a host of worrisome realities. First, meta-analytic evidence indicates that perfectionism is on the rise among young people[1]. Second, perfectionism is associated with mental health problems, but also with physical health issues and early mortality[2]. Third, perfectionism is associated with heightened risk for suicide[3], as illustrated by the results of a comprehen-