Somatic monitoring of patients with mood and anxiety disorders

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Design and methods of the MOPHAR monitoring program

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ABSTRACT

Background

At many outpatient departments for psychiatry worldwide, standardized monitoring of the safety of prescribed psychotropic drugs is not routinely performed in daily clinical practice. Therefore, it is unclear to which extent the drugs used by psychiatric outpatients are prescribed effectively and safely. These issues warrant structured monitoring of medication use, (pre-existing) co-morbidities, effectiveness and side effects during psychiatric outpatient treatment. Improvement of monitoring practices provides an opportunity to ensure that somatic complications and adverse drug effects are detected and dealt with in a timely manner. Structural support for data collection and follow-up tests seems essential for improvement of monitoring practices in psychiatric outpatients. The implementation of a structured monitoring program including somatic monitoring as part of routine clinical practice may be a solution.

Methods

In order to address these issues, we developed the innovative program 'Monitoring Outcomes of psychiatric Pharmacotherapy (MOPHAR)'. MOPHAR is an infrastructure for implementation of standardized routine outcome monitoring (ROM; including standardized monitoring of treatment effect), monitoring of adverse psychotropic medication effects in psychiatric outpatients, encompassing both somatic adverse effects (e.g. metabolic disturbances) and subjective adverse effects (e.g. sedation or sexual side effects) and medication reconciliation.

Discussion

In the MOPHAR monitoring program, a nurse performs general and psychotropic drug-specific somatic screenings and provides the treating mental health care providers with more and better information on somatic monitoring for treatment decisions. Given our experience regarding implementation of the MOPHAR program, we expect that the MOPHAR program is feasible and beneficial for patients in any MHS organisation. This paper describes the objectives, target population, setting and the composition and roles of the treatment team. It also indicates what measurements are performed at which time points during outpatient treatment in the MOPHAR monitoring program, as well as the research aspects of this project.

INTRODUCTION

Patients with a severe mental illness have a 13-30 year shorter life expectancy compared to the general population.[1,2] Approximately two-thirds of this excess mortality can be explained by somatic co-morbidities like cardiovascular disease, nutritional and metabolic diseases and pain.[1,3,4] Several factors may contribute to this increased risk of somatic morbidity and mortality, such as an unhealthy lifestyle (directly or indirectly associated with psychopathology of the patient) and disparities in health care access that are associated with mental illness.[1,5] In addition, the use of psychotropic drugs may cause and/or increase the vulnerability of psychiatric patients to somatic complications due to iatrogenic adverse effects.[1,6] Metabolic disturbances and other somatic complications are not limited to patients with schizophrenia or patients using antipsychotics. Mood disorders are also known to negatively influence lifestyle.[7,8] Moreover, these disorders are commonly treated with combinations of lithium, mood stabilizers, antipsychotics and antidepressants. Therefore, these patients are at risk to develop somatic complications too.[9,10] In addition, psychiatric patients are generally less inclined to use health care services and have a decreased perception of illness compared to the general population.[11]

Worldwide, at many specialized outpatient clinics for psychiatric disorders, systematic monitoring of the safety of prescribed drugs is not routinely performed in daily clinical practice. Previous research from our group has indicated that medication reconciliation[12] and monitoring of somatic parameters[13] are not routine clinical practice at outpatient departments for mood and anxiety disorders in The Netherlands. Likewise, in a large benchmarking audit in lithium-treated patients from The United Kingdom, no weight or body mass index (BMI) or waist circumference had been recorded in 72% of 2,976 patients, no (follow-up) tests had been performed on kidney and thyroid function in 19% and 18% of patients respectively, and no lithium serum concentration had been taken in 9%.[14] A meta-analysis of 39 studies (n=218,940) on metabolic screening in patients with predominantly schizophrenia or related disorders using antipsychotics, showed that routine baseline metabolic screening before the start of pharmacotherapy was suboptimal and in more than 50% of patients only blood pressure and triglycerides blood concentrations were checked.[15] Research in somatic departments shows that between 90-100% of HIV patients are regularly screened on hypertension, diabetes and dyslipidaemia, which is considerably higher than 40-70% in psychiatric outpatients taking antipsychotics. This suggests particularly poor monitoring in patients with psychiatric problems.[16] Furthermore, there may be considerable medication discrepancies between the medication overview at the psychiatric outpatient clinic and the actual drug use by the patient.[12] In conclusion, monitoring of side effects (associated with prescribing psychotropic medication) and medication use has generally not been systematically implemented in daily psychiatric practice. Therefore, it is unclear to which extent the drugs used by psychiatric outpatients are prescribed safely. These issues warrant systematic somatic monitoring of (pre-existing) co-morbidities, side effects and medication use, during psychiatric outpatient treatment.

Improvement of monitoring practices provides an opportunity to ensure that somatic complications and adverse drug effects are detected and treated in a timely manner. Unfortunately, the introduction of new guidelines, consensus statements, education materials or (national) quality improvement programs alone have appeared to be only minimally effective in improving monitoring practices.[15,17-20] Structural support for data collection and follow-up testing seems essential for improvement of monitoring practices in psychiatric outpatients. The implementation of a structured monitoring program in which somatic monitoring is ensured as part of routine clinical practice may be a solution.[21] In order to address these issues, we developed the innovative care path 'Monitoring Outcomes of psychiatric Pharmacotherapy (MOPHAR)'. MOPHAR is an infrastructure for implementation of standardised routine outcome monitoring (ROM; including standardised monitoring of treatment effect), monitoring of objective somatic adverse effects including metabolic disturbances as well as subjective symptoms such as sedation or sexual side effects of psychiatric pharmacotherapy and medication reconciliation in outpatients.

This paper describes the objectives, target population, setting and the composition and roles of the treatment team and indicates what measurements are performed at which time points during outpatient treatment in the MOPHAR monitoring program as well as research aspects of this project.

METHODS

Objectives of MOPHAR

The primary objective of the MOPHAR monitoring program is to systematically provide mental health care providers with more and better information for treatment decisions and to facilitate monitoring of the treatment effect and adverse effects of psychiatric pharmacotherapy in psychiatric outpatients. Secondary objective is to enable routine collection of longitudinal monitoring data of daily psychiatric practice for research purposes.

Target population and setting

The MOPHAR monitoring program targets adult patients (≥18 years) referred to mental health care outpatient clinics for any psychiatric diagnosis. MOPHAR accommodates patients either at intake or already in treatment at the outpatient clinic at the time of implementation.

The MOPHAR monitoring program is currently implemented at a large secondary community mental health care outpatient department. However, in its current form, it can be implemented at any mental health care outpatient clinic serving a broad population of persons with a (severe) mental illness. While a core set of elements and monitoring measurements is provided in MOPHAR, the current program as described in this paper does not preclude access to other somatic services or program amendments fitted to

specific populations (e.g. disease-specific measurements or questionnaires or paper-based instead of online questionnaires for elderly patients).

The MOPHAR treatment team

The MOPHAR treatment team is multidisciplinary. The MOPHAR team comprises the regular treatment team with at least one psychiatrist, at least one psychiatric nurse trained in the somatic screening of MOPHAR and a secretary. However, usually more than one person per discipline is involved, as well as a psychologist and a nursing specialist. There is a flexibility in the size and composition of the team.

The roles of the different team members can be described as follows. The secretary plans the appointments and invites the patient, which marks the start of the MOPHAR monitoring program for individual patients. The psychiatric nurse performs the MOPHAR screenings. To this end, in a one-day session the psychiatric nurses are trained in the logistics of the MOPHAR monitoring program and how to perform medication reconciliation, to enter the medication use in the electronic prescribing system and to register the MOPHAR screening results. The medication prescriber (i.e. psychiatrist or nursing specialist) is responsible for decisions on and execution of interventions and follow-up based on the results of the MOPHAR screenings along with the psychiatric treatment. The team must identify a clear workflow regarding the communication of results with other relevant health care professionals (e.g. general practitioner).

Members of the MOPHAR treatment team may have collateral responsibilities to MOPHAR patients or other non-MOPHAR (inpatient) teams. In addition, the nurses can be scheduled interchangeably for different outpatient teams to perform MOPHAR screenings if necessary. This flexibility may be a major appeal of the MOPHAR model of somatic monitoring for mental health care institutions. Implementation and project support are provided by a project manager and a pharmacist to ensure project progress and resolve practical issues. The pharmacist is responsible for the quality assurance of the established monitoring protocols.

The MOPHAR monitoring process and protocols

Figure 1 shows the general process of the MOPHAR monitoring program. MOPHAR is an addition to the established routine clinical practice at the outpatient clinics. Because outpatients are simultaneously treated for their psychiatric disorder by different mental health care providers (e.g. a psychiatrist, psychologist, nursing specialist and/or psychiatric nurse), the appointments for a MOPHAR screening and the invitations for online questionnaires are planned together as much as possible, shortly before the appointments with the mental health care provider(s).

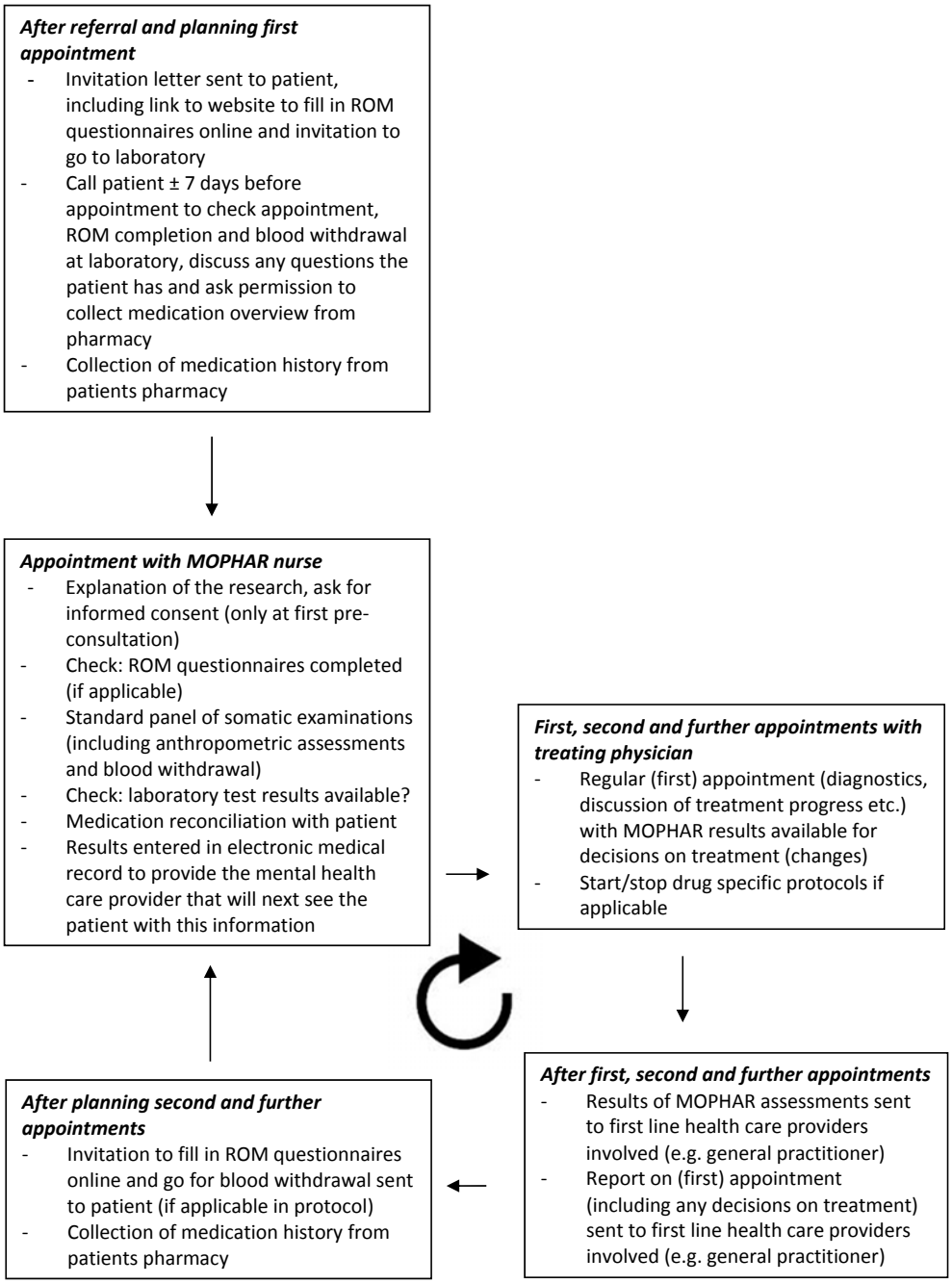

Figure 1. Schematic presentation of health care and study procedures in MOPHAR. All procedures shown are performed as a part of routine daily clinical practice. Routine Outcome Monitoring (ROM; online patient-filled questionnaires) has to be completed at certain time points, but not with all MOPHAR appointments.

Somatic screening at first appointment

A general somatic screening is performed at the first appointment, irrespective of (differential) diagnosis or medication use. This general somatic screening serves to screen for existing somatic comorbidities, side effects of drugs already in use (e.g. metabolic disturbances), and potential (additional) causes of the mental illness (e.g. thyroid dysfunction for depression). In addition, it may serve as a baseline screening before start of psychotropic drug treatment if applicable.

Online patient-filled questionnaires

In the invitation letter for the first appointment, patients are asked to fill in questionnaires about their demographics, family history of psychiatric disease, smoking, alcohol and illicit substance use and previous psychiatric (pharmacotherapeutic) treatments. These questionnaires have been developed by the department of Psychiatry of the University Medical Centre Groningen, The Netherlands (HGR).[22] In addition, the World Health Organisation Disability Assessment Schedule (WHO-DAS) 2.0[23] and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5-level 1-questionnaire[24] on general psychiatric symptoms are filled in. The WHO-DAS 2.0 is a generic assessment of a patient's health and disability, and with the results of the DSM-5-level 1-questionnaire the psychiatrist can assess in which mental health domains a patient experiences symptoms that need further examination because they may have a significant influence on the treatment and prognosis. The Outcome Questionnaire (OQ)-45 is added for non-elderly adult patients, to monitor treatment outcomes and general functioning.[25] Furthermore, an 18-item questionnaire is filled in about the presence of subjective symptoms and potential drug side effects. This questionnaire, called the Somatic Mini Screen (SMS), is developed by MHS Central, The Netherlands, and is in the process of validation (internal validity has been confirmed, inter- and intra-rater reliability is currently investigated). Lastly, at least one disorder-specific questionnaire is added to the set, depending on the patient population (e.g. the patient-completed self-report of the Inventory of Depressive Symptomatology (IDS-SR) in mood disorder patients). All questionnaires can be filled in by the patient through an online secured patient portal, that is integrated with the electronic medical records. We currently use RoQua, which is a patient portal that is accessible via the electronic medical records and is used by several associated mental health care institutions.[26]

Screening appointment with MOPHAR nurse

During the MOPHAR screening visit, roughly four types of monitoring information are collected by the trained nurse (Figure 1). First, a basic physical examination, including measurements of body mass index (BMI), waist circumference, blood pressure and heart rate. An electrocardiogram (ECG) can be added on indication.

Second, laboratory measurements. The nurse can perform the venepuncture, but patients from most teams are asked in the invitation for the appointment to go to

the laboratory for blood withdrawal in the week before the screening. The total set of physical and laboratory measurements collected is shown in Supplemental table 1. This protocol has been written by a Dutch multidisciplinary working group, consisting of psychiatrists (including BD and HGR), (hospital) pharmacists (HM, MS) and a clinical chemist. The monitoring recommendations were based on the available relevant monitoring guidelines to start with[27-31], but since there was a paucity thereof, the protocol was mostly based on clinical experience and expert opinion of the members of the working group.

Third, two questionnaires regarding history of somatic disease for the patient and first-degree family members and regarding the patient's lifestyle, including physical exercise and diet. The nurse completes these with the patient through the online portal in the electronic medical records.

Last, medication reconciliation. This is performed by the nurse through a combination of the pharmacy records and patient counselling. Medication reconciliation provides an up-to-date and complete medication overview including all drugs currently in use and all medication allergies or intolerances. In case of relevant medication discrepancies (compared to the pharmacy records), the MOPHAR nurse will notify the psychiatrist/ nursing specialist.

Availability of the screening results

The information collected via questionnaires beforehand and during the MOPHAR screening is immediately available to the mental health care provider via the patient portal and serves as a starting point for the anamnesis, psychiatric examination and a (semi-) structured interview for diagnostic purposes. The patient portal generates a summary of all information collected at the MOPHAR appointment. This summary selects a set of pre-specified most relevant parameters for a quick assessment of the clinical status of the patient, together with the information on medication use and laboratory tests.

Yearly somatic screenings

The general somatic screening at the first appointment is repeated yearly in all patients, irrespective of psychiatric diagnosis or medication use. However, with respect to the patient-filled online questionnaires, only the smoking/alcohol/illicit substance use questionnaire, the WHO-DAS 2.0, the DSM-5 screener, and the SMS are repeated at the yearly screening as well as the disorder-specific questionnaire and OQ45 (if applicable).

Psychotropic drug-specific monitoring

In addition to the general somatic screenings at the first appointment and yearly thereafter, the MOPHAR nurse conducts additional screenings according to drug-specific monitoring protocols if a patient starts with or already uses one or more psychotropic drugs. To this end, the abovementioned multidisciplinary working group has additionally written MOPHAR monitoring protocols per psychotropic drug (class). The monitoring protocols are shown in the Supplemental tables 2-12.[27,29,30,32-37] The time points for the follow-up

measurements differ per drug because of the different timeline of occurrence of side effects, but have been clustered as much as possible within each drug and between drugs to reduce the number of appointments and venepunctures. This makes the protocols uniform and enables clustering of follow-up measurements in patients using multiple psychotropic drugs.

In order to monitor subjective side effects, the SMS questionnaire is repeated three monthly when psychotropic medication is used. The physical exercise and lifestyle questionnaire (filled in by the nurse during a MOPHAR appointment) may also be repeated in the course of monitoring of psychotropic drug use.

Medication reconciliation is performed by the nurse at MOPHAR appointments or by the medication prescriber (i.e. psychiatrist or nursing specialist) if medication is prescribed, stopped or changed.

Interpretation and follow-up of MOPHAR results

The summary generated from the patient portal, the medication overview from the electronic prescribing system and the laboratory test results together provide a full picture of the patient for the weekly to monthly multidisciplinary meeting where interventions and follow-up are planned. A recent study by Bruins et al. (2016) showed that despite prevalences of the metabolic syndrome in >50% at three yearly assessments in the PHAMOUS monitoring program for schizophrenia patients, half of the patients were not treated for their metabolic risk factors.[38] We will propose standardized interventions to facilitate the treatment of and follow-up on deviating test results by the responsible health care provider.

Protocol evaluation

Apart from the abovementioned adjustments to fit specific populations, the core set of monitoring program elements will be adjusted over time. There is on ongoing debate regarding the necessity and appropriate frequency of monitoring of parameters such as the ECG[39,40], liver function[41] and blood counts[42]. Also, monitoring items might be added to the program. For example, pharmacogenetics testing is not part of the protocol but the multidisciplinary group might decide to add pharmacogenetics testing to the program in the future.[43] The protocol therefore needs a yearly evaluation in a plan-do-check-act cycle to keep it up-to-date and adjusted to best clinical practices and new guidelines.

DISCUSSION

MOPHAR current status and future perspectives

The MOPHAR monitoring program is currently incorporated in routine psychiatric care at the outpatient departments of MHS Drenthe after the assignment and approval for the implementation from the general board of MHS Drenthe. Eventually, all approximately 5700 adult patients with a (differential) diagnosis of a psychiatric disorder who are annually

referred to a psychiatrist or psychologist at the MHS Drenthe outpatient departments will be asked to participate in MOPHAR.

Implementation of MOPHAR started at the outpatient department for bipolar disorders. First appointment somatic screenings took place from January 2016 onward and yearly somatic screenings from November 2016 to synchronize MOPHAR with the individual yearly treatment evaluation schemes for patients that were already in treatment. Results of the first appointment somatic screenings for the outpatient department for bipolar disorders are reported separately.[44]

At this moment a general practitioner is not part of the treatment team. In the near future we would like to add this professional in order to ensure patient-centred care. Other potential future innovations of the program are a digital assurance system to ascertain protocol adherence and standardized interventions on aberrant test results where possible. In addition, the monitoring program may be adjusted for implementation in first-line health care-organizations, thereby serving the target population throughout the continuum of relevant (mental) health care providers for psychiatric outpatients.

MOPHAR research

Apart from a somatic monitoring care path for routine clinical practice, the MOPHAR monitoring program also provides the opportunity for a long-term (longitudinal) prospective observational cohort study. The large amount of information collected in this patient-registry of MOPHAR can be used for research: many questions may be answered in retrospective studies, including association studies and prediction models on the effect and side effects of psychotropic drugs. Because all new patients are asked for informed consent to be included in MOPHAR, the sample size will increase in time.

Next to retrospective studies, MOPHAR also gives the perspective for future prospective studies. After implementation of MOPHAR there is a structured program in place with uniform moments for evaluation by a MOPHAR nurse. These moments can be used for future prospective interventions as well. Furthermore, patient and treatment characteristics are gathered systematically thereby allowing selection of patients suited for specific prospective studies.

The general research objectives are:

1. To investigate the association between patient characteristics and outcomes (e.g. (cost)effectiveness, adverse effects) of psychiatric pharmacotherapy. Amongst others the association between pharmacogenetic determinants/biomarkers and the prevalence of adverse events of antidepressants will be investigated.
2. To investigate the association between the use of specific psychotropic drugs and adverse outcomes like metabolic abnormalities in selected samples and the unselected population (population-based research). In addition, we will be able to set up intervention studies targeting such adverse outcomes.

Our research objectives reflect both the aim to investigate how we can most efficiently detect the relevant signals for somatic complications and the aim to investigate how we can predict which patients will probably benefit from specific psychotropic drugs and/or are vulnerable for specific side effects. Results of these studies can be used to prevent, monitor and treat adverse effects in the near future.

Informed consent

MOPHAR research has been registered with the Netherlands Trial Register (NTR4918; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4918). The research aspects of MOPHAR were approved by the independent medical ethics committee (RTPO 928, rTPO Leeuwarden, The Netherlands), and all participants provide written informed consent. We ask general informed consent to conduct research on the data collected in the MOPHAR monitoring program including the linkage of the clinical data with an extra blood sample obtained for MOPHAR research (see below under 'extra blood sample'). Subjects can withdraw from further participation in the MOPHAR research cohort at any time for any reason without any consequences regarding their treatment and MOPHAR monitoring care.

Study population

For every research question addressed in MOPHAR, the appropriate study population will be determined within the MOPHAR cohort from the patient registry. In general, eligible patients meet the following inclusion criteria: older than eighteen years of age and visiting an outpatient department of MHS Drenthe (first time or follow-up visit, i.e. newly referred and current patients) are eligible for inclusion in MOPHAR). There are no general exclusion criteria for inclusion in the MOPHAR patient registry.

Extra blood sample

For research purposes, an extra blood sample (20 ml) will be taken from each subject. This blood sample will be taken at the same time as one of the blood sample withdrawals for routine clinical practice. Therefore, no additional venepuncture is necessary, and no additional risks are associated with this single study procedure. This blood sample can be used for future research (for example, pharmacogenetics and biomarker research) to investigate associations between drug or patient characteristics and treatment success and/or the prevalence of somatic side effects concerning scientific questions related to psychiatric health issues for which the patient visited the outpatient department.

Conclusion

Psychiatric patients are vulnerable for somatic co-morbidities and side effects of psychotropic medication. However, current monitoring frequencies of somatic health of these patients may be low. There is a need for structural support for improvement of somatic monitoring practices in psychiatric outpatients in line with available monitoring

guidelines. The active implementation of a structured monitoring program in which somatic monitoring is ensured as part of routine clinical will provide be a possible solution. In the MOPHAR monitoring program, a nurse performs general and psychotropic drug-specific somatic screenings and provides the treating mental health care providers with more and better information on somatic monitoring for treatment decisions. Given our experience regarding implementation of the MOPHAR program, we expect that the MOPHAR program is feasible and beneficial for patients in any MHS organisation.

REFERENCES

1. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011 Feb;10(1):52-77.
2. Hjorthoj C, Sturup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry 2017 Apr;4(4):295-301.
3. Romera I, Fernandez-Perez S, Montejo AL, Caballero F, Caballero L, Arbesu JA, et al. Generalized anxiety disorder, with or without co-morbid major depressive disorder, in primary care: prevalence of painful somatic symptoms, functioning and health status. J Affect Disord 2010 Dec;127(1-3):160-168.
4. Vaccarino AL, Sills TL, Evans KR, Kalali AH. Prevalence and association of somatic symptoms in patients with Major Depressive Disorder. J Affect Disord 2008 Oct;110(3):270-276.
5. De Hert M, Cohen D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndetei DM, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 2011 Jun;10(2):138-151.
6. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015 Jun;14(2):119-136.
7. Rahe C, Baune BT, Unrath M, Arolt V, Wellmann J, Wersching H, et al. Associations between depression subtypes, depression severity and diet quality: cross-sectional findings from the BiDirect Study. BMC Psychiatry 2015 Mar 4;15:38-015-0426-9.
8. Pearsall R, Hughes S, Geddes J, Pelosi A. Understanding the problems developing a healthy living programme in patients with serious mental illness: a qualitative study. BMC Psychiatry 2014 Feb 14;14:38-244X-14-38.
9. Fjukstad KK, Engum A, Lydersen S, Dieset I, Steen NE, Andreassen OA, et al. Metabolic Abnormalities Related to Treatment With Selective Serotonin Reuptake Inhibitors in Patients With Schizophrenia or Bipolar Disorder. J Clin Psychopharmacol 2016 Dec;36(6):615-620.
10. de Wit LM, van Straten A, Lamers F, Cuijpers P, Penninx BW. Depressive and anxiety disorders: Associated with losing or gaining weight over 2 years? Psychiatry Res 2015 Jun 30;227(2-3):230-237.
11. Bijl RV, Ravelli A. Psychiatric morbidity, service use, and need for care in the general population: results of The Netherlands Mental Health Survey and Incidence Study. Am J Public Health 2000 Apr;90(4):602-607.
12. Simoons M, Mulder H, Risselada AJ, Wilmink FW, Schoevers RA, Ruhé HG, et al. Medication Discrepancies at Outpatient Departments for Mood and Anxiety Disorders in the Netherlands: Risks and Clinical Relevance. J Clin Psychiatry 2016;77(11):1511-1518.
13. Simoons M, Mulder H, Doornbos B, Schoevers RA, van Roon EN, Ruhe HG. Monitoring of somatic parameters at outpatient departments for mood and anxiety disorders. PLoS One 2018 Aug 21;13(8):e0200520.
14. Collins N, Barnes TR, Shingleton-Smith A, Gerrett D, Paton C. Standards of lithium monitoring in mental health trusts in the UK. BMC Psychiatry 2010 Oct 12;10:80-244X-10-80.
15. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychol Med 2012 Jan;42(1):125-147.
16. Jennex A, Gardner DM. Monitoring and management of metabolic risk factors in outpatients taking antipsychotic drugs: a controlled study. Can J Psychiatry 2008 Jan;53(1):34-42.

17. Dhamane AD, Martin BC, Brixner DI, Hudson TJ, Said Q. Metabolic monitoring of patients prescribed second-generation antipsychotics. J Psychiatr Pract 2013 Sep;19(5):360-374.

18. Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. Arch Gen Psychiatry 2010 Jan;67(1):17-24.

19. Paton C, Adroer R, Barnes TR. Monitoring lithium therapy: the impact of a quality improvement programme in the UK. Bipolar Disord 2013;15(8):865-75.

20. Brody RS, Liss CL, Wray H, Iovin R, Michaylira C, Muthutantri A, et al. Effectiveness of a risk-minimization activity involving physician education on metabolic monitoring of patients receiving quetiapine: results from two postauthorization safety studies. Int Clin Psychopharmacol 2016 Jan;31(1):34-41.

21. Najim H. Monitoring cardiometabolic risk in schizophrenia. Br J Psychiatry 2012 Jul;201(1):75-6; author reply 76-7.

22. Peeters FP, Ruhe HG, Wichers M, Abidi L, Kaub K, van der Lande HJ, et al. The Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD): an extension of the Maudsley Staging Method. J Affect Disord 2016 Nov 15;205:365-371.

23. World Health Organization. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). 2017; Available at: http://www.who.int/classifications/icf/whodasii/en/. Accessed November 1st, 2017.

24. American Psychiatric Association. DSM-5 Online Assessment Measures. 2017; Available at: https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures. Accessed November 1st, 2017.

25. Lambert M, Morton J, Hatfield D, Harmon C, Hamilton S, Reid R, et al. Administration and scoring manual for the Outcome Questionnaire-45 OQ Measures. Orem, UT: American Professional Credentialing Services; 2004.

26. RoQua. RoQua - Routine Outcome Monitoring. Available at: https://www.roqua.nl/. Accessed November 1st, 2017.

27. Spijker J, Bockting CLH, Meeuwissen JAC, Vliet van IM, Emmelkamp PMG, Hermens MLM, et al. Multidisciplinary Guideline Depression (third revision). 2013; Available at: https://www.ggzrichtlijnen.nl/depressie. Accessed July 19th, 2018 - Article in Dutch.

28. National Institute for Health and Care Excellence (NICE). Depression in adults: recognition and management (CG 90). 2009; Available at: https://www.nice.org.uk/guidance/cg90. Accessed July 19th, 2018.

29. Dodd S, Malhi GS, Tiller J, Schweitzer I, Hickie I, Khoo JP, et al. A consensus statement for safety monitoring guidelines of treatments for major depressive disorder. Aust N Z J Psychiatry 2011 Sep;45(9):712-725.

30. Nolen WA, Kupka RW, Schulte PFJ, Knoppert-van der Klein EAM, Honig A, Reichart CG, et al. Guideline Bipolar Disorders (second revision). 2008; Available at: http://www.med-info.nl/Richtlijnen/Geestelijk%20-%20Gedragsstoornissen/Bipolaire%20stoornissen.pdf. Accessed November 28th, 2017.

31. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 2010; Available at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 19th, 2018.

32. Cahn W, Ramlal D, Bruggeman R, de Haan L, Scheepers FE, van Soest MM, et al. Prevention and treatment of somatic complications arising from the use of antipsychotics. Tijdschr Psychiatr 2008;50(9):579-591.

33. Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009 Sep;11(6):559-595.

34. ClozapinePlusWerkgroep. Guideline for the use of clozapine. 2013; Available at: https://www.clozapinepluswerkgroep.nl/

publicaties/richtlijn-voor-het-gebruik-van-clozapine/. Accessed November 28th, 2017.

35. Blom MJ, Birkenhäger TK, van den Broek W, Hugenholtz GWK, Kok RM, Nolen WA, et al. Protocol for the use of classic MAO-inhibitors. 2009; Available at: http://hulpgids.nl/files/mao_protocol.pdf. Accessed November 28th, 2017.
36. Les Laboratoires Servier. Summary of Product Characteristics of Valdoxan (agomelatine). 2013; Available at: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000915/WC500046227.pdf. Accessed November 28th, 2017.
37. Alphen van C, Ammeraal M, Blanke C, Boonstra N, Boumans H, Bruggeman R, et al. Multidisciplinairy guideline Schizophrenia. 2012; Available at: https://assets-sites.trimbos.nl/docs/06b5fc38-cf0b-4e43-bac9-7aef4b67a9c5.pdf. Accessed November 28th, 2017.
38. Bruins J, Pijnenborg GH, van den Heuvel ER, Visser E, Corpeleijn E, Bartels-Velthuis AA, et al. Persistent Low Rates of Treatment of Metabolic Risk Factors in People With Psychotic Disorders: A PHAMOUS Study. J Clin Psychiatry 2017 Apr 11;78(8):1117-1125.
39. Sheeler RD, Ackerman MJ, Richelson E, Nelson TK, Staab JP, Tangalos EG, et al. Considerations on safety concerns about citalopram prescribing. Mayo Clin Proc 2012 Nov;87(11):1042-1045.
40. Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. Am J Psychiatry 2013 Jun 1;170(6):642-650.
41. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-Induced Liver Injury: A Review for Clinicians. Am J Psychiatry 2013 Dec 20.
42. Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. Hum Psychopharmacol 2008 Jan;23 Suppl 1:27-41.
43. Wilffert B, Swen J, Mulder H, Touw D, Maitland-Van der Zee AH, Deneer V, et al. From evidence based medicine to mechanism based medicine. Reviewing the role of pharmacogenetics. Int J Clin Pharm 2011 Feb;33(1):3-9.
44. Simoons M, Mulder H, Doornbos B, Raats CC, Bruggeman R, Cath DC, et al. Metabolic syndrome at an outpatient clinic for bipolar disorders: a case for systematic somatic monitoring. Psychiatr Serv 2018;in press.

SUPPLEMENTAL MATERIALS

Supplemental table 1. MOPHAR protocol for baseline/yearly screening

Anthropometrics	
Length	X
Body weight	X
BMI	X
Waist circumference	X
Cardiovascular measurements	
Blood pressure (sitting/supine/standing)	X
Heart rate	X
Electrocardiogram	X[1]
Blood cells	
Haemoglobin	X
Haematocrit	X
Leucocytes + differential	X[2]
Thrombocytes	X
Electrolytes	
Sodium	X
Potassium	X
Calcium	X
Kidney function	
Creatinine	X
Estimated Glomerular Filtration Rate (eGFR)	X
Liver function	
Alkaline phosphatase	X
Alanine transaminase	X
Gamma-glutamyl transferase	X
Thyroid function	
Thyroid-stimulating hormone + free thyroxine 4 (FT4)	X[3]
Blood lipids	
Triglycerides (fasting)	X
Cholesterol	X
Low Density Lipoprotein	X
High Density Lipoprotein	X
Glucose	
Fasting glucose	X[4]
Other measurements	
Albumin	X
Vitamin B12	X[5]
Folic acid	X[5]
Prolactin	X[6]
Temperature	X

Supplemental table 1. (continued)

Pregnancy test	X[7]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs,
[2] Differential only in case of a deviating leucocyte count,
[3] FT4 only in case of a deviating thyroid-stimulating hormone level,
[4] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined,
[5] On indication, in any case with age >65 years,
[6] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations,
[7] In case of uncertainty about a potential pregnancy with women of child-bearing age.

Supplemental table 2. MOPHAR monitoring protocol tricyclic antidepressants (TCAs)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X	X		X	
BMI	X		X	X	X		X	
Waist circumference	X		X	X	X		X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X		X	X	X		X	
Heart rate	X		X	X	X		X	
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							X[3]
Haematocrit	X							X[3]
Leucocytes	X							X[3]
Differential	X							X[3]
Thrombocytes	X							X[3]
Electrolytes								
Sodium	X		X		X		X	
Potassium	X		X		X		X	
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X							X
Alanine transaminase	X							X
Gamma-glutamyl transferase	X							X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[4]	X							

Supplemental table 2. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X				X		X	
Cholesterol	X				X		X	
Low Density Lipoprotein	X				X		X	
High Density Lipoprotein	X				X		X	
Glucose								
Fasting glucose[5]	X				X		X	
Therapeutic drug monitoring								
TCA trough level, 12±1 hour after last (evening) dose		X[6]						X[7]
Other measurements								
Albumin	X							
Vitamin B12	X[8]							
Folic acid	X[8]							
Prolactin	X[9]							
Temperature	X							
Pregnancy test	X[10]							X[10]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see 1)
[3] Structural monitoring is recommended in patients with a history of blood dyscrasia or with a rechallenge; monitor at least on T=0 with one follow-up measurement during dose adjustment and/or one measurement between T=3 weeks and T=2 months, then on T=6 months and yearly
[4] FT4 only in case of a deviating thyroid-stimulating hormone level
[5] HbA1C (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[6] During dose adjustments:
- 7-10 days after the first dose
- then 7-10 days after every dose adjustment and after starting/stopping of interacting drugs
- repeat until two consecutive measurements show constant levels in the therapeutic window

[7] After reaching a stable target level; for example with side effects, therapy adherence issues, dose adjustments, etc.
[8] On indication, in any case with age >65 years
[9] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[10] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 3. MOPHAR monitoring protocol selective serotonin reuptake inhibitors (SSRIs)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X	X		X	
BMI	X		X	X	X		X	
Waist circumference	X		X	X	X		X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X							
Heart rate	X							
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							X[3]
Haematocrit	X							X[3]
Leucocytes	X							X[3]
Differential	X							X[3]
Thrombocytes	X							X[3]
Electrolytes								
Sodium	X		X		X		X	
Potassium	X		X		X		X	
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X							X
Alanine transaminase	X							X
Gamma-glutamyl transferase	X							X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[4]	X							

Supplemental table 3. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X				X		X	
Cholesterol	X				X		X	
Low Density Lipoprotein	X				X		X	
High Density Lipoprotein	X				X		X	
Glucose								
Fasting glucose[5]	X				X		X	
Therapeutic drug monitoring								
SSRI trough level, 12±1 hour after last (evening) dose								X[6]
Other measurements								
Albumin	X							
Vitamin B12	X[7]							
Folic acid	X[7]							
Prolactin	X[8]							
Temperature	X							
Pregnancy test	X[9]							X[9]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] Structural monitoring is recommended in patients with a history of blood dyscrasia or with a rechallenge; monitor at least on T=0 with one follow-up measurement during dose adjustment and/or one measurement between T=3 weeks and T=2 months, then on T=6 months and yearly
[4] FT4 only in case of a deviating thyroid-stimulating hormone level
[5] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[6] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[7] On indication, in any case with age >65 years
[8] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[9] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 4. MOPHAR monitoring protocol selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X	X		X	
BMI	X		X	X	X		X	
Waist circumference	X		X	X	X		X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X		X	X	X		X	
Heart rate	X		X	X	X		X	
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							X[3]
Haematocrit	X							X[3]
Leucocytes	X							X[3]
Differential	X							X[3]
Thrombocytes	X							X[3]
Electrolytes								
Sodium	X		X		X		X	
Potassium	X		X		X		X	
Calcium	X							
Kidney function[4]								
Creatinine	X		X		X		X	
Estimated Glomerular Filtration Rate (eGFR)	X		X		X		X	
Liver function								
Alkaline phosphatase	X							X
Alanine transaminase	X							X
Gamma-glutamyl transferase	X							X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[5]	X							

Supplemental table 4. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X				X		X	
Cholesterol	X				X		X	
Low Density Lipoprotein	X				X		X	
High Density Lipoprotein	X				X		X	
Glucose								
Fasting glucose[6]	X				X		X	
Therapeutic drug monitoring								
SNRI trough level, 12±1 hour after last (evening) dose								X[7]
Other measurements								
Albumin	X							
Vitamin B12	X[8]							
Folic acid	X[8]							
Prolactin	X[9]							
Temperature	X							
Pregnancy test	X[10]							X[10]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] Structural monitoring is recommended in patients with a history of blood dyscrasia or with a rechallenge; monitor at least on T=0 with one follow-up measurement during dose adjustment and/or one measurement between T=3 weeks and T=2 months, then on T=6 months and yearly
[4] Consider measuring a 24-hour urine after consulting a general practitioner/internist in case of a deviating eGFR
[5] FT4 only in case of a deviating thyroid-stimulating hormone level
[6] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[7] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[8] On indication, in any case with age >65 years
[9] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[10] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 5. MOPHAR monitoring protocol monoamine oxidase inhibitors (MAOIs)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X	X		X	
BMI	X		X	X	X		X	
Waist circumference	X		X	X	X		X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X	X	X	X	X		X	
Heart rate	X		X	X	X		X	
Electrocardiogram	X[1]							
Blood cells								
Haemoglobin	X							X[2]
Haematocrit	X							X[2]
Leucocytes	X							X[2]
Differential	X							X[2]
Thrombocytes	X							X[2]
Electrolytes								
Sodium	X							
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X							X
Alanine transaminase	X							X
Gamma-glutamyl transferase	X							X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[3]	X							

Supplemental table 5. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X				X		X	
Cholesterol	X				X		X	
Low Density Lipoprotein	X				X		X	
High Density Lipoprotein	X				X		X	
Glucose								
Fasting glucose[4]	X				X		X	
Therapeutic drug monitoring								
MAOI trough level, 12±1 hour after last (evening) dose								X[5]
Other measurements								
Albumin	X							
Vitamin B12	X[6]							
Folic acid	X[6]							
Prolactin	X[7]							
Temperature	X							
Pregnancy test	X[8]							X[8]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] Structural monitoring is recommended in patients with a history of blood dyscrasia or with a rechallenge; monitor at least on T=0 with one follow-up measurement during dose adjustment and/or one measurement between T=3 weeks and T=2 months, then on T=6 months and yearly
[3] FT4 only in case of a deviating thyroid-stimulating hormone level
[4] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[5] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[6] On indication, in any case with age >65 years
[7] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[8] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 6. MOPHAR monitoring protocol other antidepressants (trazodone, mianserin, mirtazapine, bupropion, vortioxetine, agomelatine, hypericum)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X	X		X	
BMI	X		X	X	X		X	
Waist circumference	X		X	X	X		X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X		X	X	X		X	
Heart rate	X		X	X	X		X	
Electrocardiogram	X[1]							
Blood cells								
Haemoglobin	X							X[2]
Haematocrit	X							X[2]
Leucocytes	X							X[2]
Differential	X							X[2]
Thrombocytes	X							X[2]
Electrolytes								
Sodium	X		X		X		X	
Potassium	X		X		X		X	
Calcium	X							
Kidney function[3]								
Creatinine	X		X		X		X	
Estimated Glomerular Filtration Rate (eGFR)	X		X		X		X	
Liver function								
Alkaline phosphatase	X	X[4]	X[4]	X[4]	X[4]			X
Alanine transaminase	X	X[4]	X[4]	X[4]	X[4]			X
Gamma-glutamyl transferase	X	X[4]	X[4]	X[4]	X[4]			X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[5]	X							

Supplemental table 6. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X				X		X	
Cholesterol	X				X		X	
Low Density Lipoprotein	X				X		X	
High Density Lipoprotein	X				X		X	
Glucose								
Fasting glucose[6]	X				X		X	
Therapeutic drug monitoring								
Antidepressant trough level, 12±1 hour after last (evening) dose								X[7]
Other measurements								
Albumin	X							
Vitamin B12	X[8]							
Folic acid	X[8]							
Prolactin	X[9]							
Temperature	X							
Pregnancy test	X[10]							X[10]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] Structural monitoring is recommended in patients with a history of blood dyscrasia or with a rechallenge; monitor at least on T=0 with one follow-up measurement during dose adjustment and/or one measurement between T=3 weeks and T=2 months, then on T=6 months and yearly
[3] Consider measuring a 24-hour urine after consulting a general practitioner/internist in case of a deviating eGFR
[4] With agomelatine. Perform this monitoring with the same frequency after an increase in dose including a measurement before increasing the dose
[5] FT4 only in case of a deviating thyroid-stimulating hormone level
[6] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[7] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[8] On indication, in any case with age >65 years
[9] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[10] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 7. MOPHAR monitoring protocol antipsychotics other than clozapine

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X						X	X
Body weight	X		X	X	X		X	X
BMI	X		X	X	X		X	X
Waist circumference	X		X	X	X		X	X
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X			X	X		X	X
Heart rate	X			X	X		X	X
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							X[3]
Haematocrit	X							X[3]
Leucocytes	X							X[3]
Differential	X							X[3]
Thrombocytes	X							X[3]
Electrolytes								
Sodium	X							
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X							X[3]
Alanine transaminase	X							X[3]
Gamma-glutamyl transferase	X							X[3]
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[4]	X							

Supplemental table 7. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X			X	X		X	X
Cholesterol	X			X	X		X	X
Low Density Lipoprotein	X			X	X		X	X
High Density Lipoprotein	X			X	X		X	X
Glucose								
Fasting glucose[5]	X			X	X		X	X
Therapeutic drug monitoring								
Antipsychotic trough level, 12±1 hour after last (evening) dose								X[6]
Other measurements								
Albumin	X							
Vitamin B12	X[7]							
Folic acid	X[7]							
Prolactin	X[8]		X[3,8]	X[3,8]				X
EEG								X[9]
Temperature	X							
Pregnancy test	X[10]							X[10]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] For example monitoring of blood cell parameters in case of a history of blood dyscrasia, monitoring of liver function in case of a history of liver disease, and monitoring of prolactin in case of congenital or historic prolactin level deviations
[4] FT4 only in case of a deviating thyroid-stimulating hormone level
[5] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[6] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[7] On indication, in any case with age >65 years
[8] Required in young adults
[9] For example with insults during use of antipsychotics
[10] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 8. MOPHAR monitoring protocol clozapine

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							X
Body weight	X		X	X	X			X
BMI	X		X	X	X			X
Waist circumference	X		X	X	X			X
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X		X	X	X			X
Heart rate	X		X	X	X			X
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							
Haematocrit	X							
Leucocytes	X	X[3]	X					
Differential	X	X[3]	X					
Thrombocytes	X							
Electrolytes								
Sodium	X							
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X						X[4]	X
Alanine transaminase	X						X[4]	X
Gamma-glutamyl transferase	X						X[4]	X
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[5]	X							

Supplemental table 8. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X			X	X		X	X
Cholesterol	X			X	X		X	X
Low Density Lipoprotein	X			X	X		X	X
High Density Lipoprotein	X			X	X		X	X
Glucose								
Fasting glucose[6]	X			X	X		X	X
Therapeutic drug monitoring								
(Nor)clozapine trough level, 12±1 hour after last (evening) dose		X[7]						X[8]
Other measurements								
Albumin	X							
Vitamin B12	X[9]							
Folic acid	X[9]							
Prolactin	X[10]							
Temperature	X							X
EEG								X[11]
C-reactive protein								X
Troponin	X		X					X
Pregnancy test	X[12]							X[12]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] Weekly leucocyte- and granulocyte counts for the first 18 weeks, then four-weekly
[4] In case of a history of liver disease
[5] FT4 only in case of a deviating thyroid-stimulating hormone level
[6] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[7] Therapeutic drug monitoring can be performed 6 days after the last dose adjustment; many patients reach steady state after three days, so from the fourth day onward a trough level can be measured. Furthermore, therapeutic drug monitoring moments during dose adjustments can be for example after reaching the 100 mg dose, with unexpected severe adverse effects and after reaching the target dose
[8] For example 14 days after addition or tapering interacting drugs; starting/quitting smoking of excessive caffeine use; in addition, immediate therapeutic drug monitoring in case of dose dependent adverse effects or toxicity (mainly insults, drooling, sedation, hypotension); fever as a consequence of an inflammatory response; check on drug adherence; (danger of) psychotic decompensation
[9] On indication, in any case with age >65 years
[10] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[11] For example with insults during use of antipsychotics
[12] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 9. MOPHAR monitoring protocol lithium

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X			X	
BMI	X		X	X			X	
Waist circumference	X		X	X			X	
Cardiovascular measurements								
Blood pressure (sitting/supine/ standing)	X						X	
Heart rate	X							
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X							
Haematocrit	X							
Leucocytes	X			X				X
Differential	X			X				X
Thrombocytes	X							
Electrolytes								
Sodium	X			X		X		
Potassium	X			X		X		
Calcium	X			X		X		
Kidney function[3]								
Creatinine	X			X		X		
Estimated Glomerular Filtration Rate (eGFR)	X			X		X		
Liver function								
Alkaline phosphatase	X							
Alanine transaminase	X							
Gamma-glutamyl transferase	X							
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[4]	X			X		X		

Supplemental table 9. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Thyroperoxidase antibodies								X
Blood lipids								
Triglycerides (fasting)	X						X	
Cholesterol	X						X	
Low Density Lipoprotein	X						X	
High Density Lipoprotein	X						X	
Glucose								
Fasting glucose[5]	X						X	
Therapeutic drug monitoring[6]								
Lithium level[7]		X[8]				X[9]		
Other measurements								
Albumin	X			X		X		
Vitamin B12	X[10]							
Folic acid	X[10]							
Prolactin	X[11]							
Temperature	X							
Pregnancy test	X[12]							X[12]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] Consider measuring a 24-hour urine after consulting a general practitioner/internist in case of a deviating eGFR
[4] FT4 only in case of a deviating thyroid-stimulating hormone level
[5] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[6] Correction factor for lithium level in case of dosing other than twice a day: 0,9 in case of once a day dosing, 1.2 in case of three times a day dosing
[7] Blood withdrawal for therapeutic drug monitoring 12±1 hour after the last (evening) dose (12-hours level); <1 hour before the next dose in case of three or four times a day dosing (trough level).
[8] During dose adjustments:
- 3 days after the first dose
- then 5-7 days every dose adjustment and after starting/stopping of interacting drugs
- repeat until two consecutive measurements show constant levels in the therapeutic window, then every 3-6 months (see [9]).

[9] After reaching a stable target level; at least every six months
[10] On indication, in any case with age >65 years
[11] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[12] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 10. MOPHAR monitoring protocol carbamazepine

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X							
BMI	X							
Waist circumference	X							
Cardiovascular measurements								
Electrocardiogram	X[1]		X[1]					X[2]
Blood cells								
Haemoglobin	X		X	X				X
Haematocrit	X		X	X				X
Leucocytes	X		X	X				X
Differential	X		X	X				X
Thrombocytes	X		X	X				X
Electrolytes								
Sodium	X		X	X			X	
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X		X	X			X	
Estimated Glomerular Filtration Rate (eGFR)	X		X	X			X	
Liver function								
Alkaline phosphatase	X							
Alanine transaminase	X							
Gamma-glutamyl transferase	X							
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[3]	X			X			X	
Blood lipids								
Triglycerides (fasting)	X							
Cholesterol	X							

Supplemental table 10. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Low Density Lipoprotein	X							
High Density Lipoprotein	X							
Glucose								
Fasting glucose[4]	X							
Therapeutic drug monitoring								
Carbamazepine trough level		X[5]						X[6]
Other measurements								
Albumin	X							
Vitamin B12	X[7]							
Folic acid	X[7]							
Prolactin	X[8]							
Temperature	X							
Pregnancy test	X[9]							X[9]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] At least with significant dose alterations in patients with risk factors (see [1])
[3] FT4 only in case of a deviating thyroid-stimulating hormone level
[4] HbA_{1C} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[5] During dose adjustments:
- 5-7 days after the first dose
- then 5-7 days after every dose adjustment
- 4-6 weeks after start of treatment (because of possible level decrease because of enzyme induction)
- The dose has been correctly adjusted when two consecutive measurements show constant levels in the therapeutic window; thereafter, therapeutic drug monitoring is only performed on indication (see [6])

[6] After reaching a stable target level; for example with side effects, therapy adherence issues, dose adjustments, etc.
[7] On indication, in any case with age >65 years
[8] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[9] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 11. MOPHAR monitoring protocol valproic acid

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X		X	X			X	
BMI	X		X	X			X	
Waist circumference	X		X	X			X	
Cardiovascular measurements								
Blood pressure	X						X	
Heart rate	X							
Electrocardiogram	X[1]							
Blood cells								
Haemoglobin	X			X				X
Haematocrit	X			X				X
Leucocytes	X			X				X
Differential	X			X				X
Thrombocytes	X			X				X
Electrolytes								
Sodium	X			X			X	
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X		X	X			X	
Alanine transaminase	X		X	X			X	
Gamma-glutamyl transferase	X		X	X			X	
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[2]	X							

Supplemental table 11. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X						X	
Cholesterol	X						X	
Low Density Lipoprotein	X						X	
High Density Lipoprotein	X						X	
Glucose								
Fasting glucose[3]	X						X	
Therapeutic drug monitoring								
Valproic acid trough level		X[4]						X[5]
Other measurements								
Albumin	X							
Vitamin B12	X[6]							
Folic acid	X[6]							
Prolactin	X[7]							
Temperature	X							
Pregnancy test	X[8]							X[8]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[2] FT4 only in case of a deviating thyroid-stimulating hormone level
[3] HbA_{1c} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[4] During dose adjustments:
- 5-7 days after the first dose
- then 5-7 days after every dose adjustment
- The dose has been correctly adjusted when two consecutive measurements show constant levels in the therapeutic window; thereafter, therapeutic drug monitoring is only performed on indication (see [5])

[5] After reaching a stable target level; for example with side effects, therapy adherence issues, dose adjustments, etc.
[6] On indication, in any case with age >65 years
[7] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[8] In case of uncertainty about a potential pregnancy with women of child-bearing age

Supplemental table 12. MOPHAR monitoring protocol lamotrigine

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Anthropometrics								
Length	X							
Body weight	X							
BMI	X							
Waist circumference	X							
Cardiovascular measurements								
Blood pressure	X							
Heart rate	X							
Electrocardiogram	X[1]							
Blood cells								
Haemoglobin	X							X
Haematocrit	X							X
Leucocytes	X							X
Differential	X							X
Thrombocytes	X							X
Electrolytes								
Sodium	X						X	
Potassium	X							
Calcium	X							
Kidney function								
Creatinine	X							
Estimated Glomerular Filtration Rate (eGFR)	X							
Liver function								
Alkaline phosphatase	X		X	X			X	
Alanine transaminase	X		X	X			X	
Gamma-glutamyl transferase	X		X	X			X	
Thyroid function								
Thyroid-stimulating hormone + free thyroxine 4 (FT4)[2]	X							

Supplemental table 12. (continued)

	T = 0	During dose adjustment	At least one measurement between T=3 weeks and T=2 months	T = 3 months	T = 6 months	Every 3 months	Yearly	On indication
Blood lipids								
Triglycerides (fasting)	X							
Cholesterol	X							
Low Density Lipoprotein	X							
High Density Lipoprotein	X							
Glucose								
Fasting glucose[3]	X							
Therapeutic drug monitoring								
Lamotrigine trough level								X[4]
Other measurements								
Albumin	X							
Vitamin B12	X[5]							
Folic acid	X[5]							
Prolactin	X[6]							
Temperature	X							
Pregnancy test	X[7]							X[7]

[1] With cardiac anamnesis, age >60 years of use of one or more QTc-prolonging drugs
[3] FT4 only in case of a deviating thyroid-stimulating hormone level
[3] HbA_{1c} (combined with a non-fasting glucose) in case a fasting glucose cannot be determined
[4] For example with side effects, therapy adherence issues, dose adjustments, etc. A SSRI level with stable drug taking and effectiveness can be useful as an intraindividual reference
[5] On indication, in any case with age >65 years
[6] On indication, in any case with young adults and for example in case of congenital or historic prolactin level deviations
[7] In case of uncertainty about a potential pregnancy with women of child-bearing age