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Somatic monitoring of patients with mood and anxiety disorders

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GENERAL INTRODUCTION

MIND THE BODY

The Greek philosopher and writer Plato (±427 B.C. – 347 B.C.) has probably been one of the first to have posed the question of how the human mind and body causally interact, i.e. the mind-body problem. Plato believed the non-physical mind and physical body were two distinct entities, but they should be studied as a whole – a mind-body complex.¹ René Descartes (1596 – 1650), a French philosopher and mathematician, more extensively described the dualist theory.¹ Descartes too was firmly convinced of the possibility and importance of reciprocal interaction between mental and physical (bodily) substances.² Many philosophers since Descartes have thought about the mind-body problem. Today, many health care professionals, in mental health care in particular, are still confronted with the mind-body problem in clinical practice. Unlike for example infectious disease specialists, whose practice has a significant overlap with internal medicine, psychiatrists and their mental health team have traditionally focused mainly on their patients' mental status, mental rehabilitation, home life and occupational situation.³ The attention for the physical health needs of their patients may vary in clinical practice and may sometimes be limited to some well-defined treatment-related adverse effects (e.g. white blood cell count with clozapine or thyroid and kidney function with lithium).

In the last few decades, it has become more and more clear that the segregation of psychiatric care from other medical care may not be justified. It is well known that many physical diseases, including nutritional and metabolic diseases, cardiovascular diseases, viral diseases, respiratory diseases, musculoskeletal diseases, and sexual dysfunction, have a higher prevalence among drug-naïve people with severe mental illness (SMI) than among the general population.⁴ In addition to the increased risk of somatic comorbidities in drug-naïve psychiatric patients, which are sometimes not recognised by health care workers, the side effects of psychotropic drugs, such as weight gain and associated metabolic disturbances, movement disorders, and haematological abnormalities are important reasons for combined somatic-psychiatric care. In fact, physical illness provides a major contribution (about 60%) to the two to three times higher mortality in people with SMI compared to the general population.^{4,5} This translates to a 13-30 year shortened life expectancy – even in countries with generally acknowledged high quality health care such as The Netherlands and the Scandinavian countries.^{4,5} Furthermore, common health threats and individual unhealthy lifestyle choices, such as cigarette smoking, little physical exercise and an unhealthy diet are highly prevalent in this population.⁴ These aspects warrant integrated somatic care for psychiatric patients with the aim to prevent, monitor and treat somatic co-morbidities and side effects of psychotropic drugs. However, general consensus on how to design and structure the efforts to capture the physical aspects of psychiatric treatment is lacking and it has not always been properly implemented. In this thesis, we focused on monitoring, with the goal to prevent somatic complications or detect them at an early stage.

Different health care providers should ideally organize the care for psychiatric patients in a patient-centered fashion (see Figure 1). The reciprocal relationships between patients and health care providers may all play a role when an outpatient receives somatic monitoring care during their psychiatric treatment. In this introduction, we will follow the patient during their treatment for a mental illness at an outpatient department for psychiatry. With respect to somatic monitoring, available guidelines and the current standard of care will be discussed at the two stages of the psychiatric outpatient treatment: the baseline assessment (here referred to as 'intake') and subsequent monitoring during treatment. Furthermore, a monitoring program as a potential solution to the shortcomings of the current standard of care will be introduced.

SOMATIC SCREENING AT INTAKE OF PATIENTS AT OUTPATIENT DEPARTMENTS FOR PSYCHIATRY

The referral of a new patient to an outpatient department for psychiatry is not only the start of psychiatric treatment, but may also be the start of somatic monitoring. A baseline screening may be useful in different ways. First, it may serve to detect potential (additional) causes of the mental illness (e.g. thyroid dysfunction for depression) in the diagnostic phase. Second, by screening for existing somatic co-morbidities and side effects of psychotropic drugs already in use at intake (e.g. metabolic disturbances), untreated or high-risk individuals may be identified and selected for adequate care and/or (intensified) monitoring. Also, it may serve to establish baseline measures of physical and mental health in order to monitor

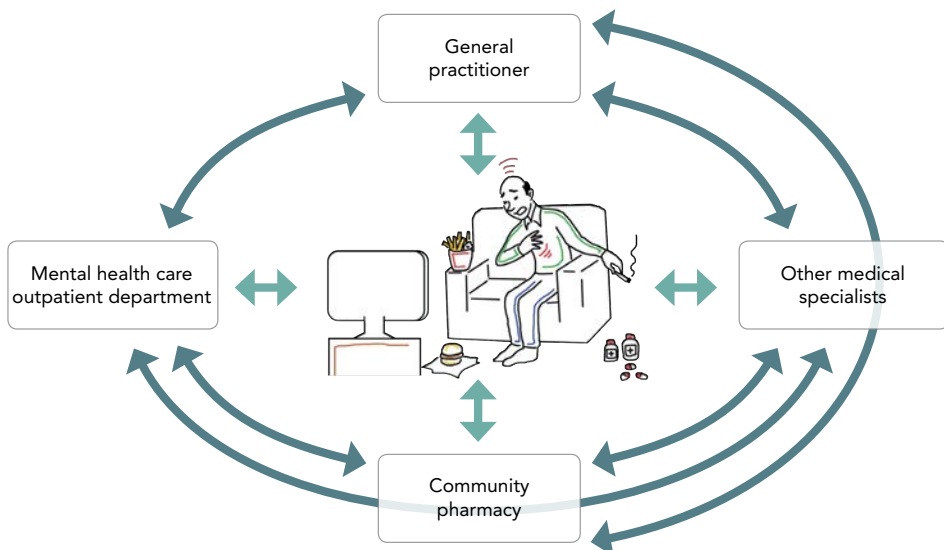


Figure 1. Different health care professionals providing care for psychiatric patients in a patient-centred fashion

overall treatment effects, side effects and safety. A baseline measurement may thus be of added value in order to determine whether any treatment that may be initiated after intake has a deteriorating or beneficial effect on the baseline status of any pre-existent condition at intake. Without a baseline measurement, the treating psychiatrist cannot determine whether deviating measurements during treatment are the result of (drug) treatment or was pre-existent at intake.

Several guidelines address the need for a baseline screening including aspects of both mental and physical health. There are guidelines with baseline screening recommendations for patients with specific psychiatric diagnoses (e.g. bipolar disorder, schizophrenia) and for patients using specific (classes of) psychotropic drugs (e.g. antidepressants or lithium). In 2015, the Dutch guideline on somatic screening in SMI patients was published. This guideline suggests an elaborate baseline somatic screening in all SMI patients, irrespective of the specific psychiatric diagnosis.⁶ The available guidelines differ somewhat in their specific recommendations, but generally agree that the personal and familial medical history of the patient, smoking status, alcohol and illicit substance use, medication use, exercise and dietary habits, physical examination (e.g. weight (BMI), waist circumference and blood pressure) and laboratory tests (e.g. plasma glucose and blood lipids) should be included.⁶⁻¹¹ Some guidelines also consider ECG parameters necessary, but recommendations vary from all patients to patients with specific characteristics.⁶⁻¹¹

A baseline somatic screening at intake for a mental health treatment as described in this chapter is considered basic health care by health insurance companies, policy makers and the government, including the healthcare inspectorate.^{6,12} This may reflect the expected clinical relevance of somatic monitoring in patients with (severe) mental illness. However, it is unclear whether current standards of daily clinical psychiatric practice always meet these proposed and expected standards.

SOMATIC MONITORING DURING PSYCHIATRIC OUTPATIENT TREATMENT

After the start of treatment, the values for each parameter from the baseline screening may vary with time, as a consequence of the mental illness or the treatment. Therefore, it is necessary to perform repeated screenings, i.e. somatic monitoring, to ensure that somatic complications and adverse drug effects are detected and treated in a timely manner.

Several guidelines and consensus documents have suggested parameters for somatic monitoring as part of routine clinical practice after the baseline screening in among others patients with schizophrenia, bipolar disorder and major depressive disorder.^{8,10,11} Similarly, guidelines have been published for somatic monitoring during the use of specific classes of psychotropic drugs.^{8-11,13} The previously mentioned 2015 Dutch guideline on somatic screenings in SMI patients advises a yearly somatic screening in all SMI patients, irrespective of the specific psychiatric diagnosis, plus extra monitoring if the patient starts psychotropic drugs.⁶ Naturally, somatic monitoring consists of many of the parameters

that are in the baseline screening as well, such as physical examination (anthropometrics), laboratory tests and medication reconciliation.

Describing monitoring standards in guidelines, has the advantage of increasing awareness of the need for somatic monitoring by mental health care providers and raising an expectation that somatic monitoring should be incorporated in routine practice. However, although many of the suggested somatic monitoring parameters such as weight and blood pressure are simple, easy to perform and inexpensive, monitoring practices may not meet the proposed standards from the guidelines yet. For example, monitoring of serum lithium level, renal function and thyroid function in patients with bipolar disorder using lithium in the United Kingdom showed only 30-55% compliance to the available guideline.¹⁴ A meta-analysis of 39 studies (n=218940) on metabolic screening in patients with predominantly schizophrenia or related disorders using antipsychotics, showed that routine baseline metabolic screening before start of pharmacotherapy was suboptimal and above 50% only for blood pressure and triglycerides.¹⁵ Given the high prevalence of somatic co-morbidities (e.g. metabolic syndrome, pooled prevalence of 32.6% in a large cohort of SMI patients (n=52,678)¹⁶), suboptimal monitoring might put patients at considerable risk for iatrogenic harm, regardless of the specific psychiatric diagnosis. Metabolic disturbances and other somatic complications are not limited to patients with schizophrenia or specific parameters in patients using lithium. Mood disorders are increasingly treated with combinations of lithium, antipsychotics, mood stabilizers and antidepressants.^{17,18} Therefore, these patients are at risk for somatic complications as well.

Another essential element for somatic monitoring is medication reconciliation. An incomplete or erroneous medication overview may lead to failure to detect cause and consequence of side effects and somatic complications, prescribing errors and iatrogenic harm. Most research on medication reconciliation quality has been conducted in non-psychiatric patients. Previous studies at outpatient departments such as for hemodialysis or internal medicine, found on average 0.97 to 3.4 discrepancies per patient.^{4,10-14} A systematic review examining the clinical relevance of such errors after general hospital admission, showed that approximately 11%-59% of the medication discrepancies were clinically important.⁵ However, little is known about the clinical importance of medication discrepancies in psychiatric populations. A single study investigating psychiatric inpatients after admission to a geriatric psychiatric clinic showed discrepancies in 78% of 50 patients with a median of two discrepancies per patient.⁶ Of all discrepancies, 82% were considered clinically relevant.⁶ To our knowledge, there are no studies reporting medication discrepancies and their clinical relevance in psychiatric outpatients.

MOPHAR: SOMATIC MONITORING IN A STRUCTURED MONITORING PROGRAM

Poorly controlled somatic conditions have been shown to lead to potentially preventable medical hospitalizations and excess morbidity and mortality.^{4,5,19} The poor monitoring

rates for somatic parameters in psychiatry as described in the preceding paragraphs therefore must improve in order to prevent and treat somatic co-morbidities and side effects. However, the introduction of new guidelines, education materials, consensus statements, or (national) quality improvement programs alone is only minimally effective in improving monitoring rates.^{15,20-23} Factors contributing to the lack of physical health care for psychiatric patients might be the perception that physical health and lifestyle are matters for general practitioners or the belief that patients are uninterested or unwilling to change.²⁴⁻³⁰ However, a recent study showed that SMI patients' actually want to have their somatic health screened and monitored, as their ability to survey their own physical health interest is reduced.³¹ In addition, there is increasing evidence that disparities not only in health care access and utilization, but also in health care provision contribute to the poor physical health outcomes.²⁴⁻³⁰ Therefore, to our opinion, the active implementation of a more structured monitoring program is warranted, which includes (at minimum): physical examination, laboratory tests and medication reconciliation.

In the northern part of The Netherlands, we developed the innovative care path 'Monitoring Outcomes of Psychiatric Pharmacotherapy (MOPHAR)', which is currently actively implemented as a restructured routine practice for outpatient care at all outpatient departments from Mental Health Services (MHS) Drenthe.³² In this program, somatic monitoring of psychiatric outpatients is incorporated in routine clinical practice at the outpatient department. Primary objective of this program is to prevent, monitor and treat somatic co-morbidities and adverse effects of psychotropic drugs. A nurse conducts and coordinates general somatic screenings with each patient at intake and yearly thereafter. In addition, recommended monitoring (among others of therapeutic effect and somatic adverse effects of psychotropic drugs) is performed according to pre-specified protocols per drug used as determined by regular medication reconciliation. Mental health care providers have immediate access to this up-to-date information and minimal burden to pursue these protocols. In addition, patients are asked for their informed consent to use the MOPHAR data and an extra blood sample for research purposes.

The MOPHAR monitoring protocol comprises a set of elements based on literature, expert consensus and clinical experience from MHS Drenthe and health care providers from the northern part of the Netherlands. This set is dynamic and should be submitted to a process of continuous scrutiny and adaptation based on, among others, altered criteria for monitoring or parameters that can be in- or excluded for reasons of (in)efficiency.

In addition, the results of the monitoring measurements need to be communicated to other health care providers involved. It is currently unclear to which extent monitoring measurements are shared between for example the outpatient department for psychiatry and the general practitioner, which warrants investigation and - if necessary - adjustment of communication practices. Furthermore, in order to take full advantage of the information from somatic monitoring, the results from monitoring measurements should be translated to interventions if necessary with subsequent follow-up. These issues too are relevant

aspects of a monitoring program for psychiatric outpatients, in order to provide the patient with a complete somatic monitoring care path that can be added to the mental treatment.

OBJECTIVES OF THIS THESIS

The primary objective of this thesis was to investigate the need for, the construction of and the effects after introduction of a structured somatic monitoring program (MOPHAR) for psychiatric patients visiting an outpatient department of MHS Drenthe. The secondary objectives were to evaluate the criteria for included parameters in MOPHAR and to explore potential new monitoring parameters.

OUTLINE OF THE THESIS

This thesis consists of three parts. In Part I, the lack of structured medication and somatic monitoring is quantified and associated risks for patients are described. Chapter 2 describes a cross-sectional study in which discrepancies between the actual medication use by patients and the medication overviews of their outpatient departments for mood and anxiety disorders, general practitioners and community pharmacies are determined. In addition, the clinical relevance of these discrepancies for the patients' medication safety was investigated. In chapter 3, monitoring practices at outpatient departments for mood and anxiety disorders are quantified – in general and with a specific focus on metabolic monitoring in patients using atypical antipsychotics, lithium monitoring in patients using lithium and ECG monitoring. In chapter 4, current standards of between-health-care-provider communication of monitoring measurements are discussed with the *CYP2D6* genotyping as an example. We investigated the availability of the genotyping test results in the medical records of psychiatric patients that had undergone *CYP2D6* genotyping in the course of their treatment.

Part II concerns the monitoring program 'Monitoring of Psychiatric Pharmacotherapy' (MOPHAR) at outpatient departments for psychiatry at MHS Drenthe. In chapter 5, the design and methods of the MOPHAR monitoring program are presented. Chapter 6 describes the first implementation of the somatic screening at intake from the MOPHAR monitoring program, at the outpatient department for bipolar disorders of MHS Drenthe. The results of the physical examinations and laboratory tests after implementation of the MOPHAR monitoring program are compared to the monitoring practices at the original intake before MOPHAR in outpatients with bipolar disorders.

In part III of this thesis, studies on monitoring parameters that in the future may become a standard measurement in MOPHAR and their implications for clinical practice are described. In addition, a consensus view on ECG monitoring recommendations is presented. Chapters 7 is a systematic review and meta-analysis of the relative risks of antidepressants for prolongation of the QTc-interval on the ECG. In chapter 8, literature on risk factors associated with proarrhythmia and sudden (cardiac) death is reviewed and Dutch consensus recommendations on ECG monitoring of patients using antidepressants

are presented. In chapter 9, as an example of a potential study that could be performed with the infrastructure provided by MOPHAR, the potential modification of the association between paroxetine serum concentration and SERT-occupancy by four *ABCB1* (P-glycoprotein) single nucleotide polymorphisms (SNPs) is investigated in patients with major depressive disorder.

Finally, in the general discussion presented in chapter 10, the main findings are put in a broader perspective. Implications and considerations for both clinical practice and future studies will be discussed.

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