Somatic monitoring of patients with mood and anxiety disorders

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Metabolic syndrome at an outpatient clinic for bipolar disorders: a case for systematic somatic monitoring

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ABSTRACT

Objective

Considering the lack of systematic somatic monitoring to detect metabolic syndrome and other somatic complications in psychiatric outpatients, the objectives of this study were to assess the feasibility of introducing the monitoring program 'Monitoring Outcomes of psychiatric Pharmacotherapy' (MOPHAR) at an outpatient clinic for bipolar disorders, and the frequency of metabolic syndrome in this population after introduction of the MOPHAR program.

Methods

The frequencies of physical examinations and laboratory tests before (retrospectively) and after the active introduction of MOPHAR (prospectively) were compared in adult patients from three locations of an outpatient clinic for bipolar disorders in The Netherlands. The MOPHAR screening assessed the presence of metabolic syndrome according to the Adult Treatment Protocol III (ATP-III) criteria.

Results

One hundred fifty-five patients were included. Implementation of the MOPHAR program was feasible and showed to be valuable; a median of 3.0 measurements (range 0-19) per patient was performed before introduction of MOPHAR, compared to a median of 24 measurements (range 3-24) afterwards ($p<0.0001$). As expected, MOPHAR implementation yielded somatic abnormalities that were previously unknown to treating physicians, with metabolic syndrome being present in 62/116 patients (53.4%). In 61 of 62 (98.4%) this was not known before the introduction of MOPHAR. Of the patients with metabolic syndrome, 46.8% did not receive pharmacological treatment for metabolic syndrome.

Conclusions

Introduction of a monitoring program largely improved knowledge regarding amongst others metabolic abnormalities. This study shows high frequencies of metabolic syndrome in bipolar disorder outpatients, that were initially unknown to treating physicians and patients.

INTRODUCTION

Patients with a severe mental illness (SMI), including bipolar disorders, have a 13-30 year shorter life expectancy compared to the general population.[1,2] Approximately 60% of this excess mortality can be explained by somatic co-morbidities like cardiovascular, nutritional and metabolic diseases.[1,3-5] Several factors contribute to this increased somatic morbidity and mortality, such as an unhealthy lifestyle and disparities in health care access, both associated with mental illness.[1,6] In addition, the use of psychotropic drugs may cause and/or increase the vulnerability of psychiatric patients to (metabolic) side effects.[1,7] In order to detect somatic complications and psychotropic drug-induced adverse effects, several guidelines and consensus documents have suggested to monitor essential somatic parameters as part of routine clinical practice in among others patients with schizophrenia, bipolar disorder and major depressive disorder or using specific (classes of) psychotropic drugs.[8-13]

Apart from the recognition that serum lithium levels, renal function and thyroid function should be regularly monitored during lithium therapy, more recently monitoring of other parameters including those of metabolic syndrome has been advocated in guidelines for bipolar disorder.[8,10,14-19] According to the updated 2005 Adult Treatment Protocol III (ATP-III) criteria from the National Cholesterol Education Program, metabolic syndrome is diagnosed if three of the following five features are present and/or pharmacologically treated in the patient: elevated waist circumference, elevated triglyceride concentrations, reduced High-Density Lipoprotein (HDL) cholesterol levels, elevated blood pressure and elevated fasting glucose (Table 1).[20] A recent meta-analysis of 37 studies (n=6,983) found that 37,3% of patients with bipolar disorder fulfilled criteria of metabolic syndrome - nearly twice the rate of the general population.[21] Antipsychotics, and to a lesser extent antidepressants and mood stabilizers, are associated with an increased risk for metabolic dysregulation.[7] The high prevalence of metabolic syndrome in patients with bipolar disorder may therefore partly be explained by treatment with psychotropic drugs.[1,7] However, presence of bipolar disorder in itself, longer illness duration and higher illness severity also independently affect metabolic parameters.[1,7,22]

Relevant interventions and treatments can only be initiated and tailored to meet individual patient's needs if test results on metabolic and other parameters are available. However, a recent meta-analysis on international monitoring practices in psychiatric clinics has shown poor adherence to metabolic monitoring guidelines.[23] Fully in line with this, previous research by our group in mood and anxiety disorder outpatients indicated that somatic monitoring is not part of daily clinical practice in the Netherlands either: less than 50% of psychiatric outpatients (n=324) were monitored for somatic parameters during a median treatment period of 7.3 months.[24] Given the high prevalence of somatic co-morbidities such as metabolic syndrome in bipolar disorder patients, suboptimal monitoring puts these patients at considerable risk for both physical and psychiatric harm.[25]

Table 1. Presence of metabolic syndrome components according to the ATP III criteria[20] after introduction of MOPHAR (n=116)

Metabolic syndrome component (any 3 of 5 constitute diagnosis of metabolic syndrome)	Presence of metabolic syndrome components (n, (%))		Drug treatment for dyslipidaemia, hypertension and/or hyperglycaemia (n, (%))		Presence of metabolic syndrome components corrected for successful treatment (n, (%))	
	n	%	n	%	n	%
Elevated waist circumference[a]	79	68.1	N/A	N/A	79	68.1
Elevated triglycerides[b]	51	44.0	19	16.4	49	42.2
Reduced HDL-cholesterol[c]	47	40.5			45	38.8
Elevated blood pressure[d]	70	60.3	28	24.1	67	57.8
Elevated fasting glucose[e]	49	42.2	10	8.6	49	42.2
Total for metabolic syndrome	62	53.4	33	28.4[f]	59	50.9

[a] ≥102 cm in men, ≥88 cm in women
[b] ≥1.7 mmol/L or on drug treatment for elevated triglycerides
[c] <1.03 mmol/L in men, <1.3 mmol/L in women or on drug treatment for reduced HDL-cholesterol
[d] ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or on antihypertensive drug treatment
[e] ≥5.6 mmol/L or on drug treatment for elevated glucose
[f] The 33 patients treated for dyslipidaemia, hypertension and/or hyperglycaemia make up 53.2% of the 62 patients with a diagnosis of metabolic syndrome.
ATP-III (National Cholesterol Education Program) Adult Treatment Protocol III;
HDL High-Density Lipoprotein; N/A not applicable.

In previous research, the introduction of guidelines/consensus statements, education materials, or (national) quality improvement programs alone appeared minimally effective in improving somatic monitoring rates.[23,26-29] Therefore, we developed a monitoring program for psychiatric patients, 'Monitoring Outcomes of psychiatric Pharmacotherapy (MOPHAR)', which is actively implemented at all outpatient clinics of Mental Health Service (MHS) Drenthe, the Netherlands, a large regional specialized mental health care institution. In this program, structured somatic monitoring of psychiatric outpatients has been incorporated in routine clinical practice at the outpatient clinic. The objective of this monitoring program is to prevent, detect, monitor and treat somatic co-morbidities and adverse effects of psychotropic drugs, including metabolic syndrome, in psychiatric patients.

The objectives of the current prospective study were to assess the feasibility of introducing the MOPHAR screening program at psychiatric outpatient services specialized in bipolar disorders by retrospective comparison, and the frequency of occurrence of metabolic syndrome in this population with the aid of MOPHAR.

METHODS

Setting and study population

MOPHAR was implemented at the three locations of the regional secondary outpatient clinic for bipolar disorders of MHS Drenthe, The Netherlands. At this outpatient clinic approximately 200 adult patients are in treatment at any moment. We implemented the general somatic screening from the MOPHAR program at the outpatient clinics for bipolar disorders at first appointment and yearly thereafter.

The MOPHAR screenings of this study took place between January 2016 and June 2017. Patients above age eighteen already in treatment at the clinic of bipolar disorders were invited consecutively to take part in the MOPHAR program.

MOPHAR research has been registered with the Nederlands Trial Register (NTR4918; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4918). The independent medical ethics committee in Leeuwarden, the Netherlands (rTPO Leeuwarden; RTPO 928) reviewed and approved the study protocol. After providing complete verbal and written information about the MOPHAR program and research, the MOPHAR nurses asked for written informed consent to participate in the study.

Design of the MOPHAR monitoring program

The aims, outline and contents of the MOPHAR monitoring program are described in more detail elsewhere (see chapter 5; manuscript submitted, 2018). In short, the structured MOPHAR monitoring program consists of four pillars:

1. A general somatic screening for every patient at the first appointment and yearly thereafter, irrespective of psychiatric diagnosis or medication use. This screening includes among other elements a physical examination, laboratory tests and medication reconciliation.[30] Table 2 shows the full set of parameters of the physical examination and laboratory tests. This set of measurements has been composed by a multidisciplinary working group consisting of psychiatrists, (hospital) pharmacists and a clinical chemist from the northern part of The Netherlands in 2014. The protocol is based on available monitoring recommendations from guidelines and consensus documents, literature and expert opinion.[12,31-34] It serves to screen for potential existing somatic comorbidities, side effects of psychotropic drugs (e.g. metabolic disturbances) and potential somatic (additional) causes of mental illness (e.g. thyroid dysfunction for depression). In addition, it may serve as a baseline screening before the start of psychotropic drug treatment if applicable. The focus of this study will be on this general somatic screening.
2. Monitoring of therapeutic effect with disorder-specific questionnaires and monitoring of subjective and objective somatic adverse effects using a combination of questionnaires, physical examination and laboratory measurements. Monitoring of adverse effects is performed according to pre-specified protocols for psychotropic drugs used as determined by regular medication reconciliation.

Table 2. The MOPHAR physical examination and laboratory tests

Physical examination	Laboratory tests (in blood)
Body Mass Index (BMI)	Haemoglobin
Waist circumference	Haematocrit
Blood pressure	Leucocytes
Heart frequency	Leucocyte differentiation[b]
Temperature	Thrombocytes
Electrocardiogram (ECG)[a]	Sodium
	Potassium
	Calcium
	Albumin
	Creatinine
	Estimated Glomerular Filtration Rate (eGFR)
	Alkaline Phosphatase (AP)
	Alanine Transaminase (ALT)
	Gamma-glutamyl Transferase (GT)
	Thyroid-stimulating Hormone (TSH)
	Free thyroxine (T_4)[c]
	Triglycerides
	Cholesterol
	Low-density Lipoprotein (LDL)
	High-density Lipoprotein (HDL)
	Fasting glucose[d]
	Vitamin B12[e]
	Folic acid[e]
	Prolactin[f]
	Bèta-human chorionic gonadotropin (hCG)[g]

[a] With cardiac anamnesis, age >60 years or use of ≥1 QTc-prolonging drugs
[b] Only with an aberrant leucocyte count
[c] Only with an aberrant TSH level
[d] Add HbA_{1C} in case of a non-fasting glucose
[e] When indicated, definitely with age >65 years
[f] When indicated, definitely in case of young adults and for example with a history of (congenital) aberrant prolactin levels
[g] In case of uncertainty about a possible pregnancy with women of childbearing age

3. Generating a concise summary of monitoring information within the electronic medical records to provide the medical and nursing staff with complete up-to-date information on medication use and monitoring parameters.
4. Weekly multidisciplinary meetings, in which all results from the MOPHAR screening are discussed and recommendations for interventions and follow-up are formulated for each patient

Objectives

For the current study, we focused on the physical examination and laboratory tests from the general somatic screening for their renewed first assessment after introduction of MOPHAR.

First, as a feasibility and quality indicator, we investigated whether the introduction of the MOPHAR program improved monitoring practices "as usual", by comparing the numbers of available physical examinations and laboratory tests as collected through the MOPHAR screening retrospectively with the somatic monitoring data gathered around the first appointment with the current primary treatment officer in the same patients.

Of all 31 measurements in the general somatic screening protocol (Table 2), 24 measurements are performed in every outpatient. Weight and length are represented by BMI. Data are presented per measurement as a percentage of all patients in whom the measurement was performed. We included records within one month before and after the general somatic screening appointment. This time lag was applied to take into account the time between the day of blood withdrawal and the appointment and the time for the analysis and report of the results. Similarly, we assessed the monitoring practices around the start of treatment at the outpatient clinic for bipolar disorders in order to compare the percentage of physical examination and laboratory measurements before and after introduction of the MOPHAR screening.

Second, to determine the frequency of occurrence of metabolic syndrome and whether patients were pharmacologically treated for metabolic symptoms, we cross-sectionally assessed the results of the physical examination, laboratory tests and medication reconciliation of the MOPHAR general somatic screening for each patient. Presence of metabolic syndrome was assessed using the National Cholesterol Education Program ATP-III criteria (updated 2005).[20] A patient was classified as having metabolic syndrome if three or more of the five metabolic parameters were outside the normal range (Table 1), or if the patient received pharmacological treatment for these parameters. We calculated the frequency of occurrence of metabolic syndrome before and after the introduction of MOPHAR in order to investigate whether metabolic abnormalities were known by treating psychiatrists before MOPHAR.

In addition, to assess the frequency of metabolic syndrome despite pharmacological treatment, we recalculated the prevalence of metabolic syndrome components after correction for successful pharmacotherapeutic treatment if the measurement result was within reference ranges while the patient used one or more drugs registered for dyslipidaemia, hypertension or hyperglycaemia. No systematic lifestyle treatments (e.g. lifestyle therapy groups) were in place at the outpatient clinic. We were unable to correct for the effects of lifestyle training or nonpharmacological treatments of metabolic syndrome, because we had no reliable information on such treatment.

Statistical analyses

We performed descriptive and statistical analyses using Excel 2013 (Microsoft, Redmond, Washington, USA) and IBM SPSS (version 25 for Windows; IBM Corp., Armonk, New York, USA). For the descriptive analyses, we report only medians (range) when distributions are non-normally distributed. For comparison of paired (before/after the introduction) differences in continuous variables we used paired t-tests. We investigated the potential associations of gender and duration of disease with the presence of metabolic syndrome in univariate logistic regression models. In all analyses, differences were considered statistically significant when $p<0.05$.

RESULTS

Participants

A total of 189 consecutive patients were invited for the MOPHAR somatic screening program during the study period. Of those, sixteen patients refused to undergo MOPHAR monitoring care and eighteen patients refused to give informed consent for use of their data for research. The remaining 155 patients were included. Table 3 shows their characteristics. Female patients were slightly overrepresented (56.8%), as expected in a psychiatric population. Patients were on average 50.1 years old; the majority had a primary diagnosis of a bipolar I or II disorder (78.1%) and had been mentally ill for more than 10 years (63.2%). We did not collect information on race or ethnicity, which appears irrelevant for our research aims.

Monitoring practices before and after introduction of the MOPHAR program

After introduction of the MOPHAR monitoring program a mean±standard deviation of 20.3±6.8 standard measurements were performed out of the maximum of 24 measurements, with a median of 24 (range 3-24). In contrast, a median of 3.0 (range 0-19) measurements were performed per patient at the first appointment before introduction of MOPHAR ($p<0.0001$). For 67 patients (43.2%) no standard monitoring measurements were available around the first appointment. Each measurement was performed in 0-43% of the patients before and in 67-100% of the patients after introduction of MOPHAR (Figure 1).

Frequencies of metabolic syndrome

Metabolic syndrome could be determined in 62/116 patients after the introduction of the MOPHAR program (53.4%; Table 1).[20] Elevated waist circumference was present most often (in 79 patients (68.1%)), while reduced HDL-cholesterol was least often present (in 47 patients (40.5%); Table 1). In 39 out of the total 155 patients, we were unable to establish presence or absence of metabolic syndrome, because (fasting) results on one or more of the parameters were unavailable. The presence of metabolic syndrome was not associated with gender (OR 1.82, 95% confidence interval (CI) 0.26-1.20) or with duration of disease (OR 1.82, 95%CI 0.97-3.42).

Table 3. Characteristics of the study population (n=155)

Characteristic	Value
Female, n (%)	88 (56.8%)
Age, mean±standard deviation, years	50.1±9.7
Primary diagnosis, n (%)	
Bipolar I disorder	79 (51.0%)
Bipolar II disorder	42 (27.1%)
Cyclothymic disorder	2 (1.3%)
Unspecified bipolar or related disorder	1 (.6%)
Other primary (non-bipolar) disorder	31 (20.0%)
Duration of disease, n (%)	
0-5 years	11 (7.1%)
5-10 years	46 (29.7%)
>10 years	98 (63.2%)
Duration of outpatient treatment since first appointment with current main treatment officer, mean±standard deviation, months	10.0 ±4.7
Outcome Questionnaire-45 (OQ45) score (n=137), median (range)	46 8-117
Physical complaints and general functioning: >55 indicates symptoms of clinical significance	
DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult (n=145), n (%)	
Score above threshold for depression	65 (44.8%)
Score above threshold for mania	35 (24.3%)
Score above threshold for >2 domains	80 (55.2%)
Patients without monitoring measurements at first appointment, n (%)	67 (43.2%)

DSM Diagnostic and Statistical Manual of Mental Disorders.

Of the 62 patients with metabolic syndrome, 29 (46.8%) were not treated with any drugs registered for dyslipidaemia, hypertension or hyperglycaemia at the time of screening and 30 patients (48.4%) were not treated to target (Table 1). After correction for current successful pharmacotherapeutic treatment of individual metabolic parameters, the frequency of occurrence of metabolic syndrome was thus reduced by only 3 patients to 50.9% (Table 1).

In 61 of the 62 patients with metabolic syndrome (98.4%), this was not known around their first appointment: metabolic syndrome could be determined in only one patient. For the remaining 154 patients, it was not possible to assess the presence of metabolic syndrome around the first appointment due to missing variables.

DISCUSSION

This study shows that introduction of the MOPHAR systematic somatic monitoring program substantially improved the availability of monitoring results for clinically relevant somatic comorbidities that otherwise remain undetected. Introduction of MOPHAR at outpatient clinics for bipolar disorders increased the number of patients in whom metabolic

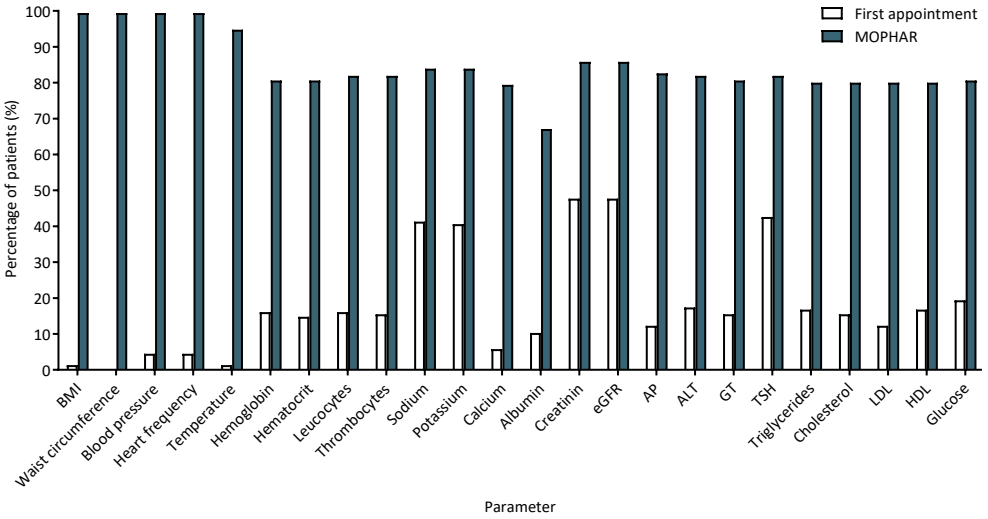

Figure 1. Performance of monitoring measurements before (at first appointment) and after introduction of the MOPHAR general somatic screening (n=155). BMI Body Mass Index, eGFR estimated Glomerular Filtration Rate, AP Alkaline Phosphatase, ALT Alanine Transaminase, GT Gamma-glutamyl Transferase, TSH Thyroid-Stimulating Hormone, LDL Low-Density Lipoprotein, HDL High-Density Lipoprotein.

syndrome could be determined from 1 to 116 patients. A significant proportion, 53.4% of these patients, fulfilled criteria for the presence of metabolic syndrome. In addition, 46.8% of these 62 participants did not receive pharmacotherapeutic treatment for any of the individual components of metabolic syndrome and only three were treated to target for their metabolic risk. Increased availability of monitoring parameters enables potential subsequent prevention and/or treatment of clinically relevant metabolic comorbidities.

Treatment of psychiatric patients with an increased metabolic risk in an attempt to reduce the impressive excess mortality warrants monitoring of parameters of somatic diseases and side effects of psychotropic drugs. However, previous research shows that such monitoring most often is not part of daily clinical routine.[8,35] The introduction of new guidelines/consensus statements, education materials, or a (national) quality improvement program for somatic monitoring at psychiatry outpatient clinics have brought about only minimal improvements in monitoring practices.[23,26-29] We therefore performed an active implementation that led to larger improvements in monitoring practices than in most previous studies. In the United Kingdom, increased awareness and education in combination with appointments at a mobile physical health clinic increased the number of patients with a physical health check from 0 to 48%, with blood tests from 6 to 56% and with ECG's from 4 to 24%.[36] After the introduction of a monitoring program for chronic psychotic patients in The Netherlands, a net 20% reversal of metabolic syndrome was reported in one year follow-up.[37] The results of these studies and the current study justify

putting effort, time and money in active introduction of monitoring programs at outpatient clinics for psychiatry.

Previous studies – in most cases using the ATP-III criteria- report frequencies of metabolic syndrome in bipolar disorder patients between 10-54%.[19-22,25,38] Our study results are in line with the high end of this range. Apart from the setting in different countries and differences in criteria, the differences between studies may also partly be explained by differences in duration and severity of illness and treatment with psychotropic drugs. These factors have been shown before to affect metabolic parameters independently[1,7], although we did not find an association of duration of disease with the presence of metabolic syndrome in our population.

Our results clearly demonstrate the need for metabolic screening in patients with bipolar disorder. Importantly, before MOPHAR, in only one patient the presence of metabolic syndrome could be determined based on the variables available around the first appointment. Apparently, although we could not determine whether the high frequency of metabolic syndrome found in MOPHAR was a result of initiated treatment or was pre-existent, the mental health care providers were not aware of this increased metabolic risk until our MOPHAR assessment.

However, knowledge of aberrant (metabolic) monitoring parameters is only useful if relevant interventions are initiated too. As a future innovation, we intend to define standardized interventions and a responsible health care provider (e.g. psychiatrist or general practitioner) in MOPHAR, as this may facilitate treatment of and follow-up on deviating test results. In the current study, 46.8% of the patients with metabolic syndrome were not treated with drugs registered for dyslipidaemia, hypertension or hyperglycaemia at the time of screening and 48.4% were not treated to target – both despite an apparent indication. Although we could not verify whether patients had been offered lifestyle modification - the recommended first-line treatment for metabolic syndrome components - potential undertreatment of metabolic syndrome appears presumable. In a Dutch outpatient population with psychotic disorders from the PHAMOUS monitoring program, half of the patients were not treated for their metabolic risk factors, despite reported prevalences of metabolic syndrome >50% at three yearly assessments.[5] These Dutch figures are comparable to a US national cardiometabolic screening program: 62.1% of 588 bipolar disorder patients with metabolic syndrome did not receive treatment.[39]

Finally, apart from being an important risk factor for adverse cardiovascular events and the development of diabetes, metabolic syndrome has also been shown to negatively affect psychiatric outcomes in patients with bipolar disorder in many[22,40-43] although not all studies[44,45]. Adequate management of metabolic syndrome may therefore improve both somatic and psychiatric clinical outcomes in patients with bipolar disorder.

Two limitations of our study need consideration. First, although patients are asked to go to the laboratory in the week before the MOPHAR general somatic screening appointment, we may have been very strict using the one-month margin in the laboratory records. Using a three-months margin, we found at least one laboratory test result from

the MOPHAR protocol for 16 of the 18 patients with initially missing laboratory test results. This post-hoc analysis shows the underestimation of the monitoring measurements performed in MOPHAR as we found in the current study and underscores the importance of communicating measurements. Second, during part of the study time, at two of the three locations, copies of laboratory request forms were used with all tests requested individually resulting in repeatedly missing requests. A few months before the end of the observation period, a dedicated MOPHAR laboratory request form that ensured all blood tests was introduced on these two locations as well.

Conclusions

Our study shows that the introduction of a general somatic screening program substantially improves monitoring frequencies in bipolar disorder patients. In addition, the current study shows high frequencies of metabolic abnormalities in patients with bipolar disorders, which before MOPHAR remained unnoticed by the mental health care providers and which were pharmacologically treated, although mostly unsuccessfully, in only half of the patients. Monitoring programs such as MOPHAR may thus support detection and follow-up of physical co-morbidities and side effects such as metabolic syndrome in psychiatric patients. To what extent introduction of a monitoring program improves treatment of metabolic syndrome and the psychiatric illness, decreases somatic complications and increases life quality and expectancy remains to be determined in future studies.

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III

Somatic monitoring beyond the MOPHAR monitoring program