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THE METABOLIC SYNDROME IS ASSOCIATED WITH SELF-REPORTED PHYSICAL COMPLAINTS IN PATIENTS WITH BIPOLAR DISORDER

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SUMMARY

Background: *The prevalence of metabolic syndrome (MetS) in patients with bipolar disorder is 35 to 40%. It is, however, not established yet whether MetS influences participation in physical activity, walking capacity and global functioning.*

Subjects and methods: *Sixty-five patients (36 ♀) received a full-fasting laboratory screening, performed a walk test including self-report of pre- and post-test pain, and completed the International Physical Activity Questionnaire and the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16).*

Results: *Patients with (n=24) and without (n=41) MetS did not significantly differ in age, gender, psychotropic medication doses, physical activity, smoking behaviour and global functioning. In contrast, patients with MetS had a significantly (a) longer illness duration, (b) higher BMI, and (c) lower walking capacity. Moreover, patients with MetS scored significantly higher on the QIDS. Patients with MetS reported more pain before and after the walking test and more dyspnea following 6 minutes of walking, indicating the physical health challenges facing people with bipolar disorder and MetS seeking to engage in physical activity.*

Conclusion: *The current data give further credence to the importance of interventions promoting the walking capacity in people with bipolar disorder, in particular in these patients at a high risk for cardiovascular diseases.*

Key words: *metabolic syndrome - bipolar disorder - physical activity – exercise - physical fitness*

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INTRODUCTION

Metabolic and cardiovascular diseases (CVD) have become a major concern in patients with bipolar disorder (Babić et al. 2010, Prieto et al. 2014, Vancampfort et al. 2015a). Patients with bipolar disorder are known to have nearly twice the normal risk of dying from CVD (Osby et al. 2001). Genetic vulnerability (Ellingrod et al. 2012), illness-related inflammatory processes (Rosenblat & McIntyre 2015), cardio-metabolic side-effects of pharmacotherapy (Correll et al. 2015), and lifestyle factors including a sedentary lifestyle (Janney et al. 2014), higher prevalence of substance abuse (Waxmonsky et al. 2005), and a poor diet (Bernstein et al. 2015) all contribute to the increased cardio-metabolic risk.

The metabolic syndrome (MetS) might assist clinicians in identifying and treating patients at an increased risk of CVD. The MetS is defined by a combination of central obesity, high blood pressure, low high-density lipoprotein cholesterol, elevated triglycerides and hyperglycemia (Alberti et al. 2006). Recent meta-analyses demonstrated that the prevalence of MetS in patients with bipolar disorder is approximately 35 to 40% (Vancampfort et al. 2013a, 2015b). A meta-analysis of longitudinal studies reporting associations between MetS and cardiovascular events or mortality in the general population demonstrated that MetS is a predictor of cardiovascular events and death (Mottillo et al. 2010).

Given the potential deleterious nature of MetS in people with bipolar disorder, clinicians should seek to address this risk. Switching psychotropic medications to those with lower metabolic liability and lifestyle changes such as smoking cessation, eating a healthy diet and participating in physical activity should be considered when managing MetS (Dadić-Hero et al. 2010, Vancampfort et al. 2015b). It is however difficult for people with bipolar disorder to adopt and maintain a healthy lifestyle (Vancampfort et al. 2015c). Barriers that are consistently reported in the literature are a lower self-efficacy, a lower educational status and lack of social support (Vancampfort et al. 2013b). Motivating the bipolar disorder subgroup who has MetS towards a more active lifestyle might be even more challenging. It

is known that in high-risk groups, once established, the MetS results often in lower physical activity participation and a reduced walking capacity (Gardner et al. 2006, 2009, Vancampfort et al. 2011). One of the putative mechanisms is that MetS diminishes the peripheral circulation in the lower limbs (Chen et al. 2001). Poor peripheral circulation makes it difficult to participate in physical activities. This, in turn, creates a vicious circle of peripheral pain, physical inactivity, worsening of cardio-metabolic parameters, and progressive decline in walking capacity, deconditioning and consequently an impaired global functioning. For example, due to the physical health consequences of cardio-metabolic diseases, patients may not go to grocery stores, come for appointments, join social activities, engage in vocational activities or follow physical activity prescriptions. However, whilst a plausible relationship might exist, to date, it is not established yet if patients with bipolar disorder and MetS have a lower walking capacity, lower participation in physical activity, physical pain, and a lower global functioning.

Therefore, the aim of this study was to determine if patients with bipolar disorder and MetS have an impaired walking capacity, lower physical activity levels, more self-reported physical pain and a lower global functioning compared with patients with bipolar disorder without MetS.

SUBJECTS AND METHODS

Participants and procedure

Over a 9-month period, in- and outpatients with a DSM 5 diagnosis of bipolar disorder (American Psychiatric Association 2013) admitted to the University Psychiatric Center KU Leuven, campus Kortenberg in Belgium were invited to participate. Reasons for admission were primarily due to either depressive or manic symptoms. Only participants with a clinical global impression severity scale (CGI-S) (Guy 1976) score of five or less, as assessed by a trained psychiatrist during a semi-structured interview were included. The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients (Guy 1976). Patients admitted to the emergency psychiatric ward were excluded. Participants were excluded if they had a current co-morbid DSM 5 diagnosis of substance abuse (American Psychiatric Association 2013) or if they met the absolute somatic contra-indications for exercise testing according to the American College of Sports Medicine (2013) (including evidence of significant cardiovascular, neuromuscular and endocrine disorders). All participants were medically cleared by a general physical examination and baseline electrocardiogram before testing. Participants received a full-fasting laboratory screening, performed a walk test, and completed the International Physical Activity Questionnaire and the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16). The presence of MetS was assessed using the International Diabetes Federation-criteria (Alberti et al. 2006). Illness duration was obtained from the patients' medical records. The study procedure was conform the Declaration of Helsinki and approved by the Scientific and Ethical Committee of UPC KU Leuven, campus Kortenberg, Belgium in accordance with the principles of the Declaration of Helsinki. All participants gave their informed written consent. There was no compensation for participation in the study.

Walking capacity

The 6 minute walk test (6MWT) was performed according to the American Thoracic Society (2002) guidelines in an indoor hallway with a minimum of external stimuli. Two cones 25m apart indicated the length of the walkway. Participants were instructed to walk back and forth around the cones during 6 minutes, without running or jogging. Resting was allowed if necessary, but walking was to be resumed as soon as the participants were able to do so. The protocol stated that the testing was to be interrupted if threatening symptoms appeared, including (a) chest pain, (b) intolerable dyspnea, (c) leg cramps, (d) staggering, (e) diaphoresis, and (f) pale or ashen appearance. The total distance walked in 6 minutes was recorded to the nearest decimetre. Standardised encouragements were provided at recommended intervals. One mental health physical therapist supervised and measured all 6MWTs. The 6MWT has been shown to be a valid and safe exercise test in patients with bipolar disorder (Vancampfort et al. 2015d).

Self-reported pain

Prior to the 6MWT, participants were asked for pain that might interfere with their walking capacity. Specifically, participants were asked whether they experienced any foot problems or pain. Directly after the first test musculoskeletal pain in the lower limbs and dyspnea were recorded.

Physical Activity Participation

The International Physical Activity Questionnaire (IPAQ) (Craig et al. 2003) was used to assess the level of physical activity. The IPAQ asks participants to recall activities for each of the last seven preceding days in morning, afternoon, and evening time periods. On the basis of what activities participants self-reported, the interviewer (a physical therapist) also clarified the perceived intensity of that specific activity. A continuous indicator was calculated as a sum of weekly metabolic equivalent (MET)-minutes per week of physical activity. The MET energy expenditure was

estimated by weighting the reported minutes per week by a MET energy expenditure estimate for each type of activity (low, moderate and vigorous intensity physical activity). The weighted MET-minutes per week were calculated as duration x frequency per week x MET-intensity, which were then summed to produce a weighted estimate of the total physical activity from all reported activities per week as per the IPAQ scoring protocol. Previous research indicated that the IPAQ can be considered as a valid tool to assess differences in levels of physical activity in patients with bipolar disorder, although with caution as active energy expenditure might be overestimated (Vancampfort et al. 2015e).

Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16)

The QIDS-SR16 (Rush et al. 2003) consists of 16 items that assess the nine symptom domains used to diagnose a major depressive episode. The responses for each item range from 0 to 3, with 0 indicating the absence of that symptom in the past week. The total score ranges from 0 to 27.

Global Assessment of Functioning (GAF) score

The GAF (American Psychiatric Association 2000) combines the evaluation of symptoms as well as relational, social, and occupational functioning on a single axis. The scale runs from one to 100 and is divided into 10 equal parts providing defining characteristics, both symptoms and functioning, for each 10-point interval. A low rating reflects worse symptoms and a poorer level of functioning, whereas a high rating reflects less symptoms and a better level of functioning. The GAF was recorded by the treating psychiatrist as a single score reporting only the most severe of the symptom and functioning values. The GAF score is known to be a valid measure of global functioning in patients with severe mental illness (Jones et al. 1995).

Anthropometric assessments

Body weight was measured by the (blinded) research nurse in light clothing to the nearest 0.1 kg using a SECA beam balance scale, and height to the nearest 0.1 cm using a wall-mounted stadiometer.

Smoking behaviour

Participants were asked whether they smoked or not, and if so, how many cigarettes they smoke per day on average.

Medication use

Current antipsychotic medication use was recorded for each patient and the daily dosage of each antipsychotic was converted into a daily equivalent dosage of chlorpromazine following the consensus of Gardner et al. (2010). If patients were treated with a combination of antipsychotics, all obtained equivalent dosages of chlorpromazine were summed together. Next to antipsychotic medication use, we also assessed the daily dosage of mood stabilizers if present in at least 10 participants.

Statistical analysis

Unpaired t-tests were used to assess whether differences in the characteristics existed between bipolar disorder patients with and without MetS. For differences in gender distribution the Fisher Exact Test was used. A Bonferroni correction was applied to adjustment for multiple comparisons by dividing the significance level 0.05 by the number of comparisons, in this case 0.05/20=0.0025. Pearson's correlations were calculated between clinical and demographical variables that differed in those with and without MetS group. Significance for the correlation analyses was set at $p<0.05$. Statistical analyses were performed using the statistical package SPSS version 22.0 (SPSS Inc., Chicago, IL).

RESULTS

Participants

Out of 85 persons with bipolar disorder, 73 met the inclusion criteria of which 8 declined to participate. Reasons for exclusion are presented in Figure 1. The gender distribution of the final included sample was 29 men (45.1±9.8years; BMI=26.7±3.0) and 36 women (43.8±11.6years; BMI=25.8±5.2). Across the entire sample, age ranged from 19 to 64 years. There were 19 outpatients (47.8±7.9years; BMI=26.3±5.2) and 46 inpatients (42.9±11.6years; BMI=26.1±4.0). All individuals were Caucasians.

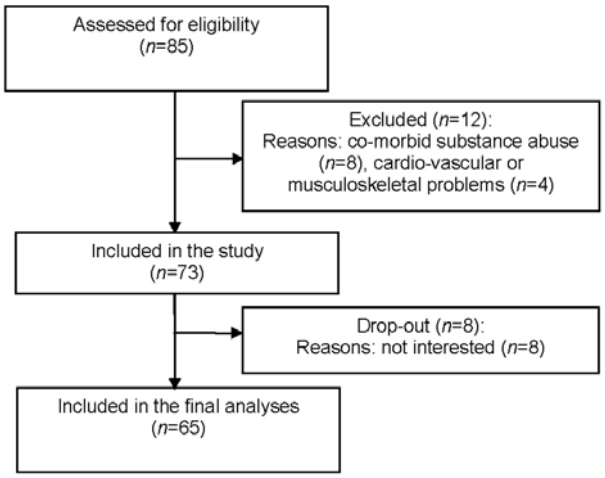

Figure 1. Flow chart of the eligible in- and outpatients with bipolar disorder

Table 1. Clinical characteristics of bipolar disorder patients with and without metabolic syndrome (MetS)

Variables	Non-MetS group (n=41)	MetS group (n=24)	p
Age (years)	42.8±10.3	47.0±11.3	0.140
Gender			0.070
Male	21 (72.4%)	8 (27.6%)	
Female	20 (55.6%)	16 (44.4%)	
Setting			0.100
Inpatients	18 (50%)	18 (50%)	
Outpatients	13 (66.7%)	6 (33.3%)	
Illness duration (years)	12.5±9.0	22.2±10.7	<0.001*
GAF score	59.0±12.7	48.1±16.4	0.004
IPAQ (MET-min/week)	1704.8±1151.9	1014.2±709.4	0.010
QIDS score	5.8±5.1	10.9±5.2	<0.001*
6MWT score (m)	658.0±103.5	543.2±108.9	<0.001*
Foot problems or pain pre (%)			<0.001*
Yes	4 (23.5%)	13 (76.5%)	
Non	37 (80.4%)	11 (19.6%)	
Musculoskeletal problems post			<0.001*
Yes	6 (33.3%	13 (66.7%)	
Non	35 (76.0%)	11 (24.0%)	
Dyspnea post			<0.001*
Yes	0 (0%)	11 (100%)	
Non	54 (100%)	0 (0%)	
Variables	Non-MetS group	MetS group	p
Number of cigarettes (n=22: 16 vs. 6)	16.4±12.2	20.9±12.9	0.51
Chlorpromazine eq (mg/day) (n=52: 34 vs. 18)	381.8±267.5	446.9±296.6	0.42
Lithium carbonate (mg/day) (n=23: 15 vs. 8)	825.0±523.2	833.3±422.8	0.97
Valproic acid (mg/day) (n=14: 8 vs. 6)	1575.0±661.2	1666.7±491.6	0.78

Values expressed as mean ± standard deviation or as otherwise indicated; *Significant when P<0.0025 (Bonferonni-corrected: 0.05/20=0.0025); GAF = Global Assessment of Functioning; IPAQ = International Physical Activity Questionnaire; QIDS = Quick Inventory of Depressive Symptomatology; 6mWT = 6minute walk test; eq = equivalents

Differences between patients with and without MetS

Twenty-four (36.9%) patients with bipolar disorder met the IDF-criteria (Alberti et al. 2006) for MetS. The demographical and clinical characteristics of the patients with and without MetS are presented in Table 1. After Bonferroni correction, there were no significant (p<0.0025) differences between both groups regarding age, gender, psychotropic medication doses, physical activity and smoking behaviour and global functioning. In contrast, patients with MetS had a significantly (a) longer illness duration, and (b) a lower walking capacity. Patients with bipolar disorder and MetS also scored significantly higher on the QIDS. Lastly, patients with MetS reported more physical pain before and after the walking test and more dyspnea following 6 minutes of walking.

Factors associated with walking capacity in patients with MetS

In patients with MetS, the 6MWT was significantly associated with illness duration (r=-0.43, p=0.036), and the QIDS (r=-0.48, p=0.017).

DISCUSSION

To the authors' knowledge this is the first study demonstrating that bipolar disorder patients with MetS have an impaired walking capacity, and more self-reported physical pain compared with patients without MetS. Previous research reported that patients with bipolar disorder walked 16.1% shorter on a 6MWT compared to age and gender matched healthy volunteers (Vancampfort et al. 2015f). The present data add that the presence of MetS places patients with bipolar disorder at an even greater risk for a reduced walking capacity.

The current findings provide several hypotheses for the impaired walking capacity. First, patients with MetS had a higher BMI and reported more physical pain before and after the walk test. Obesity consistently emerges as a key and potentially modifiable risk factor in the onset and progression of musculoskeletal conditions and pain (Wearing et al. 2006), which on its turn impairs the ability to perform weight-bearing activities such as walking. It is known as well that the MetS is associated with an increased incidence of lower extremity peripheral artery disease (Vidula et al. 2015), which is also associated with physical limitations

induced by ambulatory leg pain (McDermott et al. 2001). Second, our data show that bipolar disorder patients with MetS have more depressive symptomatology compared with those not having MetS, and these depressive symptoms were associated with the walking capacity. It might be speculated that those who are depressed are less likely to engage in a healthy lifestyle which on its turn might result in a lower walking capacity. However, after the Bonferroni correction we did not find significant differences in physical activity participation between patients with and without MetS. Also a lower self-efficacy and more negative outcome expectations patients with depression are often confronted with when performing physical fitness tests may result in a worse test performance (Krämer et al. 2014). Next to this psychological hypothesis, low-grade inflammation associated with the manifestation of depressive symptoms (Leboyer et al. 2012) should be tested more in detail. Inflammatory processes may cause pathological microvascular changes that can affect gas transfer across the alveolar-capillary membrane, which in turn may affect the circulatory, respiratory, and muscular systems involved in supplying oxygen to the body (Ostermann et al. 2013). The observation that all patients with dyspnea had MetS offers a strong rationale for this hypothesis. A previous pilot study in patients with schizophrenia already demonstrated that the presence of MetS is associated with an increased prevalence of restrictive lung dysfunction (Vancampfort et al. 2014). The longer illness duration observed in patients with MetS, and consequently a longer lifetime exposure to depressive symptoms in this group, may also point into the direction of a chronic low-grade inflammation hypothesis.

The findings of the present study must be interpreted with caution because of some methodological limitations. An important limitation was the reliance on self-reported physical activity, a method that is prone to both systematic and random errors (Soundy et al. 2014). Secondly, the single-centre nature of our study limits the generalizability. Present findings need to be replicated in a larger multicentre study. Thirdly, data on eating habits and substance abuse as risk factors for MetS and the level of manic symptoms were not assessed. Lastly, the current study had a cross-sectional nature. Thus, the impact of MetS risk and the effects of behaviour modification could not be estimated directly.

This study adds to current knowledge that bipolar disorder patients with MetS have a reduced walking capacity. Patients with MetS may therefore be at greater risk for mobility decline than patients who do not have MetS. Multidisciplinary treatment protocols designed to reduce the risk factors of MetS should not only focus on decreasing CVD risks but should also target physical function improvements in daily life activities. Specifically, we have established that patients with MetS report more musculoskeletal pain in lower limbs. Since patients with bipolar disorder experience a double increased risk for chronic pain (Stubbs et al. 2015a) and pain in the lower limbs seems to be associated with cardio-metabolic and musculoskeletal conditions, strategies to encourage patients with bipolar disorder to become more physically active which do not exacerbate pain are likely to be key in improving the functional outcome of these patients. Physical therapists should lead in the assessment and management of musculoskeletal pain among people with bipolar disorder, who can offer appropriate adaptive and rehabilitation exercises to improve pain symptoms. The importance of addressing pain in people with serious mental illness is rising giving our findings and those of another recent study demonstrating pain is independently associated with worse quality of life and more depressive symptoms (Stubbs et al. 2015b).

Future intervention studies are highly needed to extend the preliminary findings of the current study. Future research should also focus on the possible negative consequences that MetS may have in patients with bipolar disorder on ambulation and especially on the peripheral circulation in the lower limbs. Impaired peripheral circulation could be assessed measuring calf blood flow during a 6MWT by using a mercury strain-gauge plethysmography or by measuring transcutaneous oxygen tension (TcPO2) with a polarographic electrode and a TcPO2 Monitor.

CONCLUSION

The present study demonstrates that the functional exercise capacity is impaired in bipolar disorder patients with MetS. Future research should investigate more in detail underlying mechanisms such as musculoskeletal and cardio-metabolic complications (impaired peripheral circulation) of the MetS and a long-term exposure to depressive symptoms. The current data give further credence to the importance of interventions promoting the walking capacity in people with bipolar disorder, in particular in these patients at a high risk for CVD.

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Conflict of interest: None to declare.

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