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REVIEW

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Metabolic Syndrome and Bipolar Disorder: What Should Psychiatrists Know?

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SUMMARY

This paper reviews the association between bipolar disorder (BD) and metabolic syndrome (MetS), focusing on the etiopathogenetic and pathophysiological aspects of this association and on the recommendations for preventing and managing MetS in patients with BD. We conducted a nonsystematic literature review by means of a MEDLINE search. The exact causal relationship between MetS and BD is still uncertain. The side effects of psychotropic medications may be a major contributor to the increased rates of MetS in patients with BD. Other factors such as unhealthy lifestyles, common neuroendocrine and immuno-inflammatory abnormalities, and genetic vulnerability may also play a role in explaining the high rates of MetS in BD. Strategies to prevent and treat the MetS and its cardiovascular consequences in patients with BD include accurate screening and monitoring of the patient and appropriate psychoeducation on weight control, healthy nutrition, and increased physical activity. When deciding on pharmacological therapy for the treatment of the components of the MetS, drug interactions and the effects of the medications on mood must be taken into account.

Introduction

Bipolar disorder (BD) is a mental illness associated with negative social and occupational consequences, with a potentially devastating impact on patients' well-being, morbidity and mortality, and significant health care costs [1,2]. However, the burden of the BD is not limited to symptoms and dysfunction related to the illness. Individuals with BD are at greater risk than the general population for several medical conditions and have a life span 25 to 30 years shorter due primarily to premature cardiovascular disease (CVD) [3–6].

Metabolic syndrome (MetS) is a constellation of metabolic abnormalities that has been identified as a risk factor for the development of CVD and diabetes type 2 [7,8]. International studies have shown high prevalence of MetS among patients with BD [9].

This article reviews the association between BD and MetS, focusing on the etiopathogenetic and pathophysiological aspects of this association and on the recommendations for preventing and managing MetS in patients with BD.

Methods

We conducted a nonsystematic literature review by means of a MEDLINE search using combinations of the key words: MetS, BD, insulin resistance (IR), obesity, atypical antipsychotics (AA), lithium, and valproate. We augmented this search with manual review of references. Criteria used to select articles included (1) English language, (2) published studies in peer-reviewed journals, (3) studies that assessed the prevalence of MetS in subjects with BD, and (4) studies that had relevant and good quality information on the association of MetS and BD, its etiopathogenetic, and pathophysiological aspects as well as the prevention and treatment of MetS in patients with BD.

Definitions of MetS

Since the publication of Reaven's 1988 lecture about IR as the underlying cause of metabolic changes leading to CVD, clinicians and researchers have been interested in a collection of CVD risk factors characterized by visceral adiposity, IR, dyslipidemia, elevated blood pressure (BP), and a systemic proinflammatory state, first coined as Syndrome X by Reaven, and now named MetS [10,11]. The etiological basis for the syndrome and its pathophysiological mechanism are not completely known, and there is no unifying pathophysiological explanation for the MetS. Nevertheless, it's well established that abdominal adiposity and IR are core features of its pathophysiology [12]. Changes in the insulin

sensitivity result in glucose and lipid metabolism abnormalities, enhanced sodium reabsorption, and increased sympathetic nervous system activity [13]. In addition, substantial evidence has been accumulated to suggest that the visceral adipose depot contributes to increased free fatty acid turnover and IR [12]. Another mechanism by which adipose tissue contributes to the pathophysiology of the MetS is through the excessive release of proinflammatory cytokines. The adipose tissue is an active secretory organ that elaborates a variety of inflammatory molecules, known as adipocytokines, that may mediate many of the metabolic changes observed in the MetS [14].

MetS can be diagnosed in a number of ways using a variety of criteria developed by various groups (Table 1) [8,15–19]. The several definitions have similarities; they all tend to agree that MetS core components include obesity, IR, dyslipidemia, and hypertension. However, they are not identical; microalbuminuria, for example, is listed only in the World Health Organization (WHO) criteria, and there are differences in waist measurement and cut-offs

Table 1 Definitions of metabolic syndrome

Clinical measure	WHO (1998) [15]	EGIR (1999) [16]	ATP III (2001) [17]	AACE (2003) [18]	IDF (2005) [19]	AHA/NHLBI (2005) [8]
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on clinical judgment	None	None, but any 3 of the following 5 features
Body weight	Men: waist-to-hip ratio > 0.90; women: waist-to-hip ratio > 0.85 and/or BMI > 30 kg/m^2	WC ≥ 94 cm in men or ≥ 80 cm in women	WC ≥ 102 cm in men or ≥ 88 cm in women	BMI ≥ 25 kg/m^2	Increased WC (population specific) plus any 2 of the following	≥ 102 cm (≥ 40 inches) in men ≥ 88 cm (≥35 inches) in women
Lipid	TG ≥ 150 mg/dL and/or HDL-C < 35 mg/dL in men or < 39 mg/dL in women	TG ≥ 150 mg/dL and/or HDL-C < 39 mg/dL in men or women	TG ≥ 150 mg/dL HDL-C < 40 mg/dL in men or < 50 mg/dL in women	TG ≥ 150 mg/dL and HDL-C < 40 mg/dL in men or < 50 mg/dL in women	TG ≥ 150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or < 50 mg/dL in women or on HDL-C Rx	TG ≥ 150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglycerides HDL-C < 40 mg/dL (1.03 mmol/L) in men or < 50 mg/dL (1.3 mmol/L) in women or on drug treatment for reduced HDL-C
BP	≥140/90 mmHg	≥140/90 mmHg or on hypertension Rx	≥130/85 mmHg	≥130/85 mmHg	≥130 mmHg systolic or ≥ 85 mmHg diastolic or on hypertension Rx	≥130 mmHg systolic BP or ≥ 85 mmHg diastolic BP or on antihypertensive drug treatment in patient with a history of hypertension
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)	≥100 mg/dL (includes diabetes) or on drug treatment for elevated glucose
Other	Microalbuminuria			Other features of insulin resistance		

Adapted from Grundy et al. [8].

WHO, World Health Organization; EGIR, European Group for Study of Insulin Resistance; ATP III, Adult Treatment Panel III; AACE, American Association of Clinical Endocrinologists; IDF, International Diabetes Foundation; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute.

IGT, impaired glucose intolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; BP, blood pressure; BMI, body mass index; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

Table 2 Prevalence of metabolic syndrome and its components in patients with bipolar disorder

Author/Country	Criteria	MetS	WC	↓HDL	↑TG	↑Glucose	↑BP
Fagiolini et al., 2005, USA [22]	ATP III	30%	49%	23%	48%	8%	39%
Yumru et al., 2007, Turkey [23]	ATP III	32%	_	_	_	_	_
Birkenaes et al., 2006, Norway [24]	ATP III	30% (male) 17% (female)	_	_	_	_	_
Garcia-Portilla et al., 2007, Spain [25]	ATP III	22.4%	54%	38.2%	36.1%	12.2%	20.9%
Teixeira et al, 2007, Brazil [26]	ATP III	38.3%	_	_	_	_	_
Salvi et al., 2008, Italy [27]	ATP III	25.3%	50%	32.3%	34.7%	11%	40%
	IDF	30%					
Fagiolini et al., 2008, USA [28]	ATP III	40%	51%	45%	47%	19%	55%
Cardenas et al., 2008, USA [29]	ATP III	49%	_	_	_	_	_
Van Winkel et al.,2008, Belgium [30]	ATP III	16.7%	30%	21.7%	26.7%	13.3%	48.3%
	ATP III + FG $\geq$ 100	18.3%				28.3%	
	IDF	30%	60%			28.3%	
Fiedorowicz et al., 2008, USA [31]	ATP III	53%	_	27%	48%	28%	63%
Correll et al., 2008, USA [32]	ATP III	43.2%	33.8%	67.6%	46.6%	32.4%	54%
	ATP III + FG $\geq$ 100	54%					
Sicras et al., 2008, Spain [33]	ATP III	24.7%	_	54.5%	23%	16.9%	29.8%
Yumru et al., 2008, Turkey [34]	ATP III	36.7%	_	_	_	_	_
Almeida et al., 2009, Brazil [35]	ATP III/AHA	28.6%	46.4%	26.2%	44%	20.2%	45.2%
Vuksan-Cusa et al., 2009, Croatia [36]	ATP III	27.5%	_	_	_	_	_
Chang et al., 2009, Taiwan [37]	IDF	33.9%	61%	53%	36.8%	13.7%	18.6%
Lee et al., 2010, South Korea [38]	AHA (FG $\geq$ 100)	27%				5.3%	
	ATP III	25%	47.4%	32.9%	32.9%	15.1%	25.7%
	IDF	25.7%				5.3%	
Kemp et al., 2010, USA [39]	ATP III	36%	_	_	_	_	_

ATP III, Adult Treatment Panel III; IDF, International Diabetes Foundation; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute. FG, fasting glucose; BP, blood pressure; WC, waist circumference; TG, triglycerides; HDL, high-density lipoprotein cholesterol.

among the definitions. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition appears to be most widely used and cited in the general literature and more specifically in studies evaluating patients with BD.

Prevalence of MetS in Patients with BD

The prevalence of obesity and MetS in the general population is increasing to epidemic proportions not only in the United States and other developed countries but also in developing nations [20,21]. Following this trend, cross-sectional studies assessing patients with BD have showed that MetS is highly prevalent among patients with BD all over the world (Table 2) [22–39].

Etiopathogenetic and Pathophysiologic Aspects of the Association between MetS and BD

The increased rates of MetS in patients with BD suggest that they co-occur to a greater degree simply by chance alone. It is known that both conditions share some pathophysiological and lifestyle risk factors [40]. However, the exact causal relationship between them is still uncertain.

The side effects of psychotropic medications may be a major contributor to the increased rates of MetS in patients with BD [34]. Lithium, valproic acid, and AA (mostly, olanzapine, and clozapine) are associated with significant weight gain [41,42]. In addition, valproate has been also associated with insulin and lipid abnormalities in patients with epilepsy [43]. Furthermore, a study published in 2008 showed that first-episode psychosis subjects had significant weight increase and negative changes in glucose and lipid profiles than controls after 6 months of treatment with AA [44]. Although weight, glucose and lipid-related effects of psychotropic medications may account for the increasing rates of MetS in BD, it is worth noting that the cooccurrence of BD with obesity and abnormal glucose metabolism was observed even before the existence of modern psychotropic medications [45,46]. Therefore, other factors such as unhealthy lifestyles, common neuroendocrine and immunoinflammatory abnormalities, and genetic vulnerability may also play a role in explaining the high rates of MetS in BD.

Prospective research has demonstrated that depressive symptoms predict onset of the MetS in healthy women [47]. Patients with BD, particularly during depressive episodes, may have increased appetite and poor eating behaviors, may be less likely to exercise, and may have lower ability to care for themselves [48]. In addition, BD is associated with increased rates of tobacco and alcohol abuse/dependence, which may negatively impact MetS and CVD risk [49].

Several common neuroendocrine and immunoinflamatory abnormalities have been associated with MetS and BD, suggesting

biological correlates of these conditions [40]. Biological abnormalities that may help to explain the development of MetS in BD include hyperactivity of the hypothalamic–pituitary–adrenal axis, which is the most prominent neuroendocrine abnormality in major depression and seems to be implicated in the neurobiology of the switch process in BD as well as in the euthymic, depressive, and manic phases [50–53]. Glucocorticoid resistance has also been reported in patients with BD [54]. The dysregulation of cortisol has been associated with abdominal obesity, IR, hyperlipidemia, diabetes, and hypertension, which are components of the MetS [55].

Abnormalities in the immune system are another potential biological correlate of BD and MetS [40]. Studies have shown increased proinflammatory cytokine production across manic and depressive phases of BD [56,57]. Citokines may lead to glucocorticoid resistance through direct effects on glucocorticoid receptor expression and function [58]. As previously mentioned, adipose tissue produces several inflammatory cytokines, which can induce IR. Therefore, abnormalities in the inflammatory system are also involved in the underlying etiology for some of the MetS factors.

It is worthwhile noting that cigarette smoking and heavy alcohol use are associated with increased systemic inflammation, and physical fitness has been associated with smaller inflammatory responses to acute mental stress [59–61]. Therefore, the extent to which these biologic abnormalities are mediated or moderated by the weight gain related to the medication use and/or by unhealthy lifestyles remains unclear.

On the other hand, a study recently published compared biologic pathways and processes involved in seven different diseases (including BD) pathogenesis, by means of pathway-based approaches of Genome Wide Association data, and found a strong genetic correlation between BD and coronary artery disease as well as diabetes type 2. These three conditions were shown to have basic pathways in common, such as lipid metabolism, suggesting shared genetic bases among them [62].

Prevention and Treatment of the MetS in Patients with BD

Recently, the concept of MetS has been the target of some criticism. Critics have argued that the cluster of risk factors for the MetS does not offer more than the sum of its parts in terms of diagnosis and management [63]. In addition, some of the criteria used for defining MetS are considered ambiguous or incomplete and most of the guidelines do not measure inflammation features, oxidant stress, and genetics related to the MetS [63]. This has led the WHO to review the utility of the MetS concept [64]. The WHO Expert Consultation concluded that while the MetS may be considered useful as an educational concept, it has limited practical utility as a diagnostic or management tool. It stated that evidence suggests that the MetS concept has educated health professionals on the importance of risk factor clustering and the need to assess related risk factors when one risk factor is detected [64]. As Cornier et al. pointed out, the importance of the concept of MetS is that the identification of the syndrome "is undeniably an opportunity to encourage patients to make lifestyle changes that will attenuate their chances for CVD and metabolic disease later in life" [12]. In the field of BD research, that is exactly what we have seen in the last 5 years, since Fagiolini et al. published the first article on the prevalence of MetS in patients with BD [22]. This publication put the association between MetS and BD into appropriate scientific and clinical perspective. In addition, recommendations have been provided to mental health practitioners on the prevention and treatment of the MetS and each of its components, CVD and diabetes [65]. The psychiatrists have been encouraged to be familiar with basic primary prevention and routine diagnostic screening of the MetS, with special attention to the role of iatrogenic factors that may account for its increasing prevalence in patients with BD, as can be seen on the International Society for Bipolar Disorder (ISBD) guidelines published in 2009 [66].

In 2005–2006, studies were conducted to assess the awareness of metabolic issues among American and European psychiatrists, and how this awareness influences their management of BD [67,68]. Ninety-four percent of the American psychiatrists and 72% of the European psychiatrists endorsed that the MetS poses a significant health risk for which patients should be monitored and treated. However, less than one third of the American and European psychiatrists correctly identified all the MetS criteria. After initiating pharmacotherapy for BD, the majority of the psychiatrists surveyed monitored weight or BMI, BP, and plasma glucose levels, but less than half of the European psychiatrists monitored lipid profiles and only 10% monitored waist circumference. Most of the respondents reported they recommend dietary changes and exercise for those patients with MetS. However, 39% of the European psychiatrists said they rarely or never stop or switch therapies for their patients due to worsening metabolic symptoms. The European study concluded that it seems psychiatrists still need to be better educated on the syndrome, its diagnostic criteria and monitoring practices, as well as on the prevention and treatment that should be implemented in patients with BD and MetS. Little is currently known about this issue regarding psychiatrists from developing countries.

The first step on the prevention and treatment of MetS in BD is the accurate screening of the patient for metabolic and CVD risks. The ISBD guideline for the safety monitoring of BD treatments suggest that personal and family history of CVD and diabetes, smoking status, alcohol use, BMI, waist circumference, BP, fasting glucose, and lipid profile should be investigated in every patient prior to treatment, as part of a minimum standard of care [66]. Those patients under medications with potentially weight gain and metabolic abnormalities side effects, which include not only AA but also lithium and valproic acid, must have weight and metabolic parameters evaluated routinely. The ISBD proposes as minimum monitoring standards for patients under AA therapy: monthly weight measurements for the first 3 months, followed by measures every 3 months for the duration of treatment; BP and fasting glucose at 3-month intervals for the first year, then annually; and fasting lipid profile at 3 months after initiation of AA therapy, to be repeated at annual intervals thereafter (Table 3). For those under treatment with lithium, weight should be measured after 6 months and then annually. Patients receiving valproic acid should have their weight assessed more frequently, every 3 months for the first year, then annually. Fasting glucose and lipid profile should be obtained if risk factors are detected [66].

Table 3 Weight and metabolic monitoring protocol for patients with BD on atypical antipsychotics [65]

	Baseline	1st month	2nd month	3rd month	Quarterly	Annually
Weight	x	x	x	x	x*	
Blood pressure	x			x	x	x
Fasting glucose	x			x	x	x
Fasting lipid profile	x			x		x

* For the duration of the treatment.

The second step on the prevention and treatment of MetS in BD is the appropriate psychoeducation of the patient regarding modifiable risk factors, such as unhealthy lifestyles. Recommendations for managing the MetS are not specific due to the absence of randomized controlled trials conducted with this aim [12]. Nevertheless, several authors highlight that lifestyle interventions aimed to prevent or treat the excess adiposity and IR associated with the MetS may have beneficial effects on all of the syndrome components [12,63]. Therefore, psychiatrists should give their patients advice on weight control, healthy nutrition, and increased physical activity, "what is now a fundamental tenet of medicine" [63].

Psychiatrists should recommend their patients to have a diet high in complex, unrefined carbohydrates with an emphasis on fiber, and low in added sugars. Patients should also be stimulated to have a diet rich in unsaturated fatty acids and low in saturated fatty acids [12].

Exercise is particularly effective at reducing IR and has also been shown to improve dyslipidemia and hypertension [12]. Psychiatrists should strongly encourage their patients to follow the American Heart Association and American College of Sports Medicine recommendation to engage in a moderate-intensity aerobic physical activity for at least 30 min/day 5 days of the week [69]. Simple recommendations such as doing more household chores or gardening and taking stairs instead of the elevator contribute to decrease sedentary time [70].

Of note, studies have showed that fitness and diet may serve a neuroprotective function and may have positive influence on brain plasticity and beneficial effects on cognitive function in humans and animals [71–74]. Therefore, patients should know that exercise and healthy diet may improve both physical and mental states.

Although many studies have stressed the importance of advising people about eating well balanced meals and exercising in order to get in a good health, lifestyle changes seems to be hard to achieve for anyone and even more difficult for patients with BD since the illness is associated to a greater degree of sedentarism and poor dietary habits [48]. Studies have suggested that the implementation of psychoeducational programs and cognitive behavioral interventions for weight control and lifestyle changes have beneficial effects in improving weight control, nutrition, and activity levels in patients with psychiatric disorders, although there are no published trials to date that have specifically targeted patients with BD [75–77].

When deciding on pharmacological therapy for the treatment of the components of the MetS, drug interactions and the effects of the medications on mood must be taken into account.

Pharmacotherapy for weight loss: studies have demonstrated that sibutramine, orlistat, and topiramate show some efficacy in inducing weight loss [78,79]. Reports of high number of cardiovascular events in patients taking sibutramine has led to a review of the safety of this medication and restrictions to its prescription in the USA and marketing suspension of the substance in Europe [80,81]. There is one case report of depression induced by orlistat in a patient with BD type 2 [82]. As diarrhea is frequently seen as a side effect of orlistat, caution must be taken to prevent lithium intoxication [83]. In addition, orlistat may reduce the absorption of lipophilic drugs, such as lamotrigine and valproic acid [84]. Therefore, patients receiving these anticonvulsants may need close monitoring. A study found no clinically relevant changes in plasma concentrations of haloperidol, clozapine, or carbamazepine over an 8-week period in orlistat recipients [85]. Topiramate has been associated with high risk for depression in patients with epilepsy [86]. A randomized, controlled trial compared topiramate to sibutramine in the treatment of obesity in patients with BD [87]. Both medications produced similar rates of weight loss and high rates of drug discontinuation. Topiramate showed exacerbation of depression as one of the most frequent adverse effects leading to early discontinuation. On the other hand, a study designed to investigate the efficacy and safety of topiramate versus placebo as adjunctive therapy for the management of patients with BD found that topiramate reduced body weight significantly relative to placebo without worsening depressive or manic symptoms [88].

Pharmacotherapy for IR, dislypidemia, and hypertension: there are no studies designed to specifically target the effects of metformin or thiazolidiones in mood stabilization of patients with BD and MetS. There is a case report of antidepressant response with pioglitazone in a patient with resistant depression [89]. There are no reports of negative drug interactions between medications for BD and agents that target IR, such as metformin and thiazolidinediones. However, caution is warranted regarding liver toxicity resulting from concurrent use of medications that have been occasionally implicated in liver injury, that is, some antidiabetics, antihypertensives, statins, and anticonvulsants commonly used in the treatment of BD [90]. Statins have also been involved in case reports of ataxia in two patients with BD; rhabdomyolysis in patients with schizophrenia and dysthymic disorder; and a report of QTC interval prolongation in a woman with schizophrenia [91–94].

Thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors may also increase lithium levels. Loop and potassium-sparing diuretics are considered to have lower likelihoods of increasing lithium levels [95]. However, ISBD suggests close monitoring for a period of 2 months of patients under lithium and not

only thiazide diuretics and/or ACE inhibitors but also loop and potassium-sparing diuretics [66].

As a last resort, in order to prevent or treat the MetS, psychiatrists may have to face the challenge of changing medication regimen. Among the AA, a large body of data suggests that clozapine and olanzapine have the highest propensity to produce weight gain and metabolic abnormalities, followed by quetiapine and risperidone. Aripiprazole and ziprasidone have the lowest propensity to cause this type of adverse effect [96]. Among the mood stabilizers, there has been little systematic research regarding metabolic side effects in patients with BD. Carbamazepine and lamotrigine seems to be less likely to cause significant weight gain [97,98]. Although switching medications may reverse weight gain and metabolic abnormalities it can be a major problem when the patient has experienced a good clinical response to the current treatment regimen. This approach requires careful assessment of benefits versus risks of each medication and which one is essential for BD stabilization as well as the evaluation of differential levels of its efficacy [65].

In conclusion, in spite of any criticism on the utility of the concept of MetS, the association between that condition and BD has been well established. Therefore, psychiatrists should be aware of not only the higher risks of morbidity and mortality patients with BD and MetS are exposed to, but also of the need of early interventions using strategies to prevent and treat the MetS and its cardiovascular consequences in that specific population.

Disclosures

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