Metabolic Syndrome in Bipolar Disorder: A Review With a Focus on Bipolar Depression

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ABSTRACT

Objective: To perform a detailed, qualitative review of existing literature on the co-occurrence of bipolar disorder and metabolic syndrome, the impact of metabolic dysregulation on patients with bipolar disorder, and treatment considerations, with a focus on bipolar depression.

Data Sources: Searches of the PubMed database (October 23, 2012) and Cochrane Library (September 20, 2013) were conducted for English-language articles published from January 1980 onward containing the keywords *bipolar* AND *metabolic, weight, obesity, diabetes, dyslipidemia,* OR *hypertension* in the title or abstract. The searches yielded 1,817 citations from which case reports, conference abstracts, and pediatric studies were excluded.

Study Selection: Abstracts and titles were evaluated for relevance to the stated objectives. Full texts of 176 articles were obtained for further evaluation; additional articles were identified from reference lists.

Results: Metabolic risk factors are highly prevalent yet undertreated in patients with bipolar disorder. Putative factors accounting for the link between bipolar disorder and metabolic syndrome include behavioral/phenomenological features, shared neurobiologic abnormalities, and adverse effects of psychotropic medications. A comprehensive assessment of metabolic risk and regular monitoring of body mass index, waist circumference, lipid profile, and plasma glucose are important for patients with bipolar disorder. Management strategies for the bipolar patient with metabolic risk factors include use of bipolar disorder medications with better metabolic profiles, lifestyle interventions, and adjunctive pharmacotherapy for dyslipidemia, hypertension, and/or hyperglycemia.

Conclusions: Adequate management of metabolic syndrome may improve clinical outcomes in patients with bipolar disorder, as well as prevent adverse cardiovascular events and the development of diabetes.

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With an estimated worldwide prevalence of 2.4%,[1] bipolar disorder is associated with a wide range of detrimental effects on patients' health and functioning and is among the top 20 causes of disability worldwide.[1–3] The burden of bipolar disorder includes higher rates of unemployment and dependence on public assistance,[4,5] reduced work productivity among the employed,[6] reduced quality of life,[4] impaired cognitive function,[7,8] and increased health care costs.[9]

In addition to the substantial psychiatric health care utilization and costs associated with bipolar illness, patients with bipolar disorder have significantly increased nonpsychiatric health care costs.[9–11] The excess costs of bipolar disorder are partly due to high rates of medical comorbidities, especially increased morbidity and mortality related to cardiovascular disease, which is the foremost cause of excess death in bipolar disorder.[12–15] In particular, bipolar disorder is associated with increased occurrence of metabolic syndrome, which has been linked to elevated cardiovascular morbidity.[16–18] A recent meta-analysis of 37 studies (N = 6,983) concluded that 37.3% of patients with bipolar disorder had metabolic syndrome, nearly twice the rate in the general population.[19] This elevated rate of metabolic syndrome has been hypothesized to underlie the increased cardiovascular morbidity and mortality of bipolar disorder.[20,21]

Recent studies suggest that metabolic syndrome is associated specifically with depressive symptomatology.[22] Over the course of their illness, bipolar I and bipolar II patients spend substantially more time in the depressed phase than in the manic/hypomanic or cycling phases.[23,24] We previously reviewed the association of bipolar disorder and obesity and discussed management options for patients with both conditions.[25,26] We noted that several groups showed an association between obesity and depressive burden in patients with bipolar disorder.[26] In this article, we present an overview of the co-occurrence of bipolar disorder and metabolic syndrome, the impact of metabolic dysregulation on patients with bipolar disorder, and treatment considerations, with a focus on bipolar depression. We use the term *bipolar depression* to indicate a major depressive episode or subsyndromal depressive symptoms that occur in the course of bipolar disorder.

METHOD

Data Sources

A search of the PubMed database was conducted on October 23, 2012, for English-language articles, published from January 1980 onward, containing the keywords *bipolar* AND *metabolic, weight, obesity, diabetes, dyslipidemia,* OR *hypertension* in the title or abstract. A similar search of the Cochrane Library was conducted on September 20, 2013. The searches yielded 1,817 unique citations from which case reports, conference abstracts, and pediatric/adolescent studies were excluded.

Clinical Points

- Metabolic syndrome is often inadequately treated in patients with bipolar disorder, despite its high prevalence, association with increased cardiovascular risk, and potential negative impact on psychiatric treatment outcomes.
- All patients with bipolar disorder should be monitored regularly for body mass index, waist circumference, lipid profile, blood pressure, and blood glucose level.
- Therapeutic options for patients with bipolar disorder and metabolic risk factors include lifestyle interventions, use of bipolar disorder medications with better metabolic profiles, and adjunctive pharmacotherapy for dyslipidemia, hypertension, and/or hyperglycemia.

Study Selection

Abstracts and titles were qualitatively evaluated for evidence-based, clinically relevant answers to the following questions:

- How is metabolic syndrome defined clinically and in research studies?
- What is the prevalence of metabolic syndrome in bipolar disorder?
- What is the prevalence of metabolic syndrome in depressive disorders?
- What are the consequences of metabolic syndrome for patients with bipolar disorder?
- What hypotheses have been proposed to account for the association of metabolic syndrome with bipolar disorder? What is the evidence supporting these hypotheses?
- What is the impact of pharmacologic treatments for bipolar disorder on metabolic syndrome and its components?
- What are the best evidence-based strategies for the treatment of patients with bipolar disorder and elevated metabolic risk factors?

Full texts of 176 articles were obtained for further evaluation; additional articles were identified from the reference lists of those articles. In addition, the PubMed database was monitored during the development of this review, with relevant studies incorporated as they were published. We present our findings with the primary objective of providing clinically relevant information to clinicians who manage patients with bipolar disorder.

RESULTS AND DISCUSSION

Overview of Metabolic Syndrome

Metabolic syndrome is not a disorder per se. Rather, it is a constellation of metabolic abnormalities (ie, abdominal obesity, elevated triglyceride level, low high-density lipoprotein cholesterol [HDL-C] level, hypertension, and hyperglycemia) that has been associated with increased risk of cardiovascular disease and diabetes.[18,27,28] Several organizations, including the National Cholesterol Education Program Adult Treatment Panel III (ATP III),[18] International Diabetes Federation (IDF),[29] and World Health Organization (WHO),[30] have developed criteria for the clinical diagnosis of metabolic syndrome. Although some variation across these specific criteria sets exists, all include measures of abdominal obesity, dyslipidemia, hypertension, and hyperglycemia (Table 1).[18,29–32]

On the basis of the ATP III definition, patients who meet any 3 of the 5 criteria have metabolic syndrome; the IDF definition requires the presence of increased waist circumference, plus any 2 of the other 4 criteria. In 2005, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) published updated ATP III clinical criteria for metabolic syndrome (Table 1).[31] Changes from the original ATP III criteria were relatively minor; most notable was the reduction of the threshold for elevated fasting glucose from 110 mg/dL to 100 mg/dL.[31] The ATP III criteria are widely used in studies evaluating metabolic syndrome[31]; however, not all studies cited in this review used these criteria.

On the basis of data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) and the ATP III (2001) definition, the prevalence of metabolic syndrome in the general US adult population was 23.7%.[33] In an update using NHANES data from 2003 to 2006 and the AHA/NHLBI (2005) revised definition, the prevalence of metabolic syndrome was 34.3%.[34]

Insulin resistance, a metabolic disorder in which biological response to insulin is impaired, is recognized as a contributory factor underpinning metabolic syndrome.[18,31] The term *insulin resistance syndrome* was previously used to describe this clustering of metabolic risk factors and is a diagnostic criterion in the WHO definition of metabolic syndrome.[31] However, insulin resistance is not easily measured in clinical settings.[18,31] Therefore, the ATP III and IDF criteria use fasting plasma glucose to assess for hyperglycemia.

Co-occurrence of Metabolic Syndrome and Bipolar Disorder

The association of metabolic syndrome and bipolar disorder applies globally; higher-than-expected rates of metabolic syndrome have been documented in patients with bipolar disorder in 12 countries, including the United States (Table 2).[17,19,35–55] In a recent meta-analysis, the strongest moderator of metabolic syndrome prevalence was the region in which the study was conducted, with the highest rates in New Zealand and Australia (64%), followed by North America (49%), Asia (40%), South America (38%), and Europe (32%).[19] Rates of metabolic syndrome in patients with bipolar disorder were generally similar to those in patients with schizophrenia.[35,38,39] Higher rates of metabolic syndrome were also observed in studies with a higher mean age of patients with bipolar disorder.[19]

Some treatments for bipolar disorder may increase the occurrence of metabolic syndrome. In the recent meta-analysis, metabolic syndrome was significantly more prevalent in patients receiving antipsychotic medications (45.3%; n = 298) than in patients not receiving an antipsychotic agent

Table 1. Criteria for Clinical Diagnosis of Metabolic Syndrome[a]

Clinical Measure	WHO (1999)[30]	ATP III (2001)[18]	IDF (2005)[29]	AHA/NHLBI (2005)[31] Update of ATP III	ATP III/IDF Harmonized (2009)[32]
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity **plus any 2 of the 5 features below:**	None, **but any 3 of the 5 features below:**	None	None, **but any 3 of the 5 features below:**	None, **but any 3 of the 5 features below:**
Abdominal adiposity	Waist-to-hip ratio > 0.90 in men, or waist-to-hip ratio >0.85 and/or BMI > 30 kg/m^2 in women	Waist circumference ≥ 102 cm in men or ≥ 88 cm in women	Elevated waist circumference (population specific) **plus any 2 of the 4 features below:**	Waist circumference ≥ 102 cm in men or ≥ 88 cm in women	Elevated waist circumference relative to population- and country-specific definitions
Lipids	TG ≥ 150 mg/dL and/or HDL-C < 35 mg/dL in men or < 39 mg/dL in women	TG ≥ 150 mg/dL HDL-C < 40 mg/dL in men or < 50 mg/dL in women	TG ≥ 150 mg/dL or on drug treatment for elevated TG HDL-C < 40 mg/dL in men or < 50 mg/dL in women or on drug treatment for reduced HDL-C	TG ≥ 150 mg/dL or on drug treatment for elevated TG HDL-C < 40 mg/dL in men or < 50 mg/dL in women or on drug treatment for reduced HDL-C	TG ≥ 150 mg/dL or on drug treatment for elevated TG HDL-C < 40 mg/dL in men or < 50 mg/dL in women or on drug treatment for reduced HDL-C
Blood pressure	≥ 140/90 mm Hg	≥ 130/85 mm Hg	≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on antihypertensive drug treatment	≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on antihypertensive drug treatment in a patient with a history of hypertension	≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on antihypertensive drug treatment in a patient with a history of hypertension
Glucose	IGT, IFG, or T2DM	> 110 mg/dL (includes diabetes)	≥ 100 mg/dL (includes diabetes)	≥ 100 mg/dL or on drug treatment for elevated glucose	≥ 100 mg/dL or on drug treatment for elevated glucose
Other	Microalbuminuria	…	…	…	…

[a]Adapted with permission from Grundy et al.[31]
Abbreviations: AHA = American Heart Association; ATP = Adult Treatment Panel; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; HDL-C = high-density lipoprotein cholesterol; NHLBI = National Heart, Lung, and Blood Institute; T2DM = type 2 diabetes mellitus; TG = triglycerides; WHO = World Health Organization. Symbol: … = no information available.

(32.4%, n = 339).[19] However, an association of obesity and bipolar depression has been noted since the time of Kraepelin (long before the development of modern psychotropics),[56] and some small studies have suggested that patients with bipolar disorder may be at increased risk for metabolic syndrome before initiation of pharmacotherapy.[57,58] In an Italian study, 40.8% of 76 drug-naive patients with bipolar disorder were overweight, compared with 10.8% of 65 drug-naive patients with obsessive-compulsive disorder.[57] Elevated rates of insulin resistance and dyslipidemia were noted in a small study (N = 11) of unmedicated women with bipolar disorder type II, who were depressed at the time of evaluation.[58] In contrast, a study of drug-naive patients (N = 56) with bipolar disorder type II in Taiwan showed a rate of metabolic syndrome similar to that in the general population.[59] Additionally, in a study of metabolic control in bipolar disorder (N = 381), 51.9% of patients had glycosylated hemoglobin (HbA_{1c}) levels > 7%, and the mean HbA_{1c} level was similar for patients receiving versus not receiving psychotropic medications (7.5% and 7.4%, respectively).[60] It may be that the high prevalence of overweight/obesity, coupled with the iatrogenic effects of medications, has amplified a predisposition for metabolic dysregulation among patients with bipolar disorder into a medical comorbidity.

Increased rates of each individual component of metabolic syndrome have also been observed in patients with bipolar disorder.[44,61] In US patients, the most commonly elevated components, relative to national norms, were triglyceride level and blood pressure (Table 2).[38,39,42–44] In a large national study that included 3,898 patients with bipolar disorder, 54.8% of whom were obese (body mass index [BMI] ≥ 30.0 kg/m^2), 48.4% of 1,109 bipolar patients with available data had hypertriglyceridemia, 61.1% (of 1,102) had low HDL-C, 50.6% (of 3,895) had hypertension, and 31.3% (of 1,107) had fasting hyperglycemia (≥ 100 mg/dL)* on the basis of ATP III/AHA criteria.[39] In that study, elevated triglycerides and abdominal obesity were the strongest predictors of metabolic syndrome in the overall sample of more than 2,500 psychiatric patients with available data (42% with bipolar disorder, 33% with schizophrenia, 66% with depression).[39]

Even though hyperglycemia is generally the least common component of metabolic syndrome in patients with bipolar disorder (Table 2), its occurrence is an important clinical marker, because the prevalence of type 2 diabetes is elevated in bipolar patients.[52,62–64] In a retrospective chart review of 243 older (aged 50–74 years) psychiatric inpatients, diabetes was present in 26.4% of patients with bipolar disorder type I, 18.5% with major depression, 12.7% with schizophrenia, and 50.0% with schizoaffective disorder.[65] The rate of diabetes was significantly elevated relative to the US population (NHANES III data) in patients with schizoaffective and

*Prevalence of elevated waist circumference was not reported.

Table 2. Studies Reporting the Prevalence of Metabolic Syndrome in Patients With Bipolar Disorder

Study	Location	Sample Size/Patient Characteristics	Metabolic Syndrome Definition	Rate of Metabolic Syndrome (%)	Rate of Components of Metabolic Syndrome (%)					Comparison to Reference Group
					WC	TG	HDL-C	BP	Glucose	
Birkenaes et al (2007)[35]	Norway	N = 110 outpatients; 66% on a weight-inducing drug BD-I, BD-II, BD-NOS Mean age = 39 y	ATP III	21.5	54.2	…	23.2	60.8	…	Rate of MetS not compared to reference group. Rates of abdominal obesity and hypertension 1.5 to 2 times those of the Oslo general population
Cardenas et al (2008)[36]	United States	N = 98 patients, predominantly male BD-I, BD-II Mean age = 50 y	ATP III	49.0	…	…	…	…	…	Rate of MetS nearly twice that of the general US population[a]
Chang et al (2009)[37]	Taiwan	N = 117 outpatients (59 with MetS measurement) on lithium, valproate, or both BD type not reported Mean age = 34 y	IDF	33.9	61.0	36.8	53.0	18.6	13.7	Rate of MetS twice that of the general Taiwanese population; significantly higher rates for all components except hypertension
Correll et al (2008)[38]	United States	N = 74 inpatients on SGAs BD type not reported Mean age = 44 y	ATP III/AHA ATP III	54.0 43.2	33.8	46.6	67.6	54.0	32.4 15.1	Rate of MetS markedly higher than that of the general US population[a]
Correll et al (2010)[39]	United States	N = 3,923 inpatients/outpatients at 219 sites (1,139 patients with fasting data) BD type not reported Mean age not reported	ATP III/AHA	53.8	…	48.4	61.1	50.6	31.3	Rate of MetS markedly higher than that of the general US population[a]
de Almeida et al (2009)[40]	Brazil	N = 84 outpatients; 89% on mood stabilizers, 45% on SGAs, and 38% on antidepressants BD-I, BD-II Mean age = 42 y	ATP III/AHA	28.6	46.4	44.0	26.2	45.2	20.2	Rate of MetS similar to that of the Brazilian general population
Elmslie et al (2009)[41]	New Zealand	n = 60 overweight patients on valproate and n = 60 matched controls BD-I, BD-II, BD-NOS Mean age = 42 y	ATP III	50.0	85.0	40.0	63.3	50.0	6.7	Rate of MetS higher than that of the matched control group (31.7%, $P = .06$)
Fagiolini et al (2005)[42]	United States	N = 171 patients; 44% on lithium, 34% on SGAs, 54% on antidepressants BD-I, BD-II, BD-NOS Mean age = 47 y	ATP III	30.2	48.8	48.2	22.6	39.2	7.8	Rate of MetS slightly higher than that of the general US population[a]
Fagiolini et al (2008)[43]	United States	N = 441 patients (update of Fagiolini et al, 2005[42]) BD-I, BD-II, BD-NOS Mean age = 44 y	ATP III/AHA	40	51	47	45	55	19	Rate of MetS slightly higher than that of the general US population[a]
Fiedorowicz et al (2008)[44]	United States	N = 217 outpatients (60 with complete MetS data) BD-I, BD-II, BD-NOS Mean age = 46 y	ATP III[b]	53.3	…	57.5	27.3	67.5	30.3	Rate of MetS twice that of the general US population[a]
Garcia-Portilla et al (2008)[45]	Spain	N = 194 patients taking a mean of 2.9 medications for bipolar disorder BD type not reported Mean age = 47 y	ATP III	22.4	53.8	36.1	38.2	20.9	12.2	Rate of MetS markedly higher than that of the general Spanish population (14.2%)
Grover et al (2012)[46]	India	N = 200 patients; 47% on lithium, 43% on valproate, 35% on olanzapine BD type not reported Mean age = 39 y	ATP III/AHA[c]	41.0	70.5	42.0	41.5	44.5	24.0	Rate of MetS similar to that of the general population in the same catchment area (45.3%)

(continued)

Table 2 (continued). Studies Reporting the Prevalence of Metabolic Syndrome in Patients With Bipolar Disorder

Study	Location	Sample Size/Patient Characteristics	Metabolic Syndrome Definition	Rate of Metabolic Syndrome (%)	Rate of Components of Metabolic Syndrome (%)					Comparison to Reference Group
					WC	TG	HDL-C	BP	Glucose	
Lee et al (2010)[47]	Korea	N = 152 patients; 73% on combination of mood stabilizer and antipsychotic BD type not reported Mean age = 36 y	ATP III/AHA[d]	27.0	47.4	32.9	32.9	25.7	15.1	Rate of MetS twice that of the control group (nonpsychiatric patients); significantly higher rates also for abdominal obesity, hypertriglyceridemia, and low HDL-C
McIntyre et al (2010)[48]	Canada	N = 99 outpatients (those with DM or glucose/insulin dysregulation were excluded) BD-I, BD-II Mean age = 38 y	ATP III	32.6	41.1	38.8	36.4	29.7	…	Despite exclusion of patients with DM, rate of MetS higher than that of the Canadian general population (15%–26%)
Salvi et al (2008)[49]	Italy	N = 99 inpatients; 85% on mood stabilizers, 38% on antipsychotics, 60% on antidepressants BD-I, BD-II, BD-NOS Mean age = 52 y	ATP III	25.3	50.0	34.7	32.3	40.0	11.0	Rate of MetS higher than that of the Italian general population (16%–18%)
Sicras et al (2008)[50]	Spain	N = 178 patients; 30% on lithium, 57% on SGAs BD type not reported Mean age = 50 y	ATP III[e]	24.7	…	23.0	54.5	29.8	16.9	Rate of MetS nearly twice that of the reference group of N = 85,850 non-BD patients in the database (14.4%). Significantly higher rates for hypertriglyceridemia, low HDL-C
Teixeira and Rocha (2007)[51]	Brazil	N = 47 inpatients BD type not reported Mean age = 46 y	ATP III	38.3	…	…	…	…	…	No reference group for MetS, but rate deemed "probably higher than that in the general population" on the basis of Brazilian national prevalence rates of DM and obesity
van Winkel et al (2008)[52]	Belgium	N = 60 patients; 50% on mood stabilizers, 88% on SGAs, 47% on antidepressants BD type not reported Mean age = 45 y	ATP III/AHA ATP III IDF	18.3 16.7 30.0	30.0 60.0	26.7	21.7	48.3	28.3 13.3 28.3	Rate of MetS up to twice that of the general Belgian population
van Winkel et al (2008)[53]	Belgium	N = 112 patients; 48% on mood stabilizers, 89% on antipsychotics, 53% on antidepressants BD type not reported Mean age = 44 y	ATP III/AHA	23.2	33.9	32.1	25.0	50.9	23.2	No comparison to reference group, but rate of MetS similar to rate reported by van Winkel et al[52]
Vuksan-Ćusa et al (2009)[54]	Croatia	N = 40 male patients BD type not reported Mean age = 37 y	ATP III	27.5	…	…	…	…	…	No comparison to reference group
Yumru et al (2007)[55]	Turkey	N = 125 patients; 47% on mood stabilizers, 26% on SGAs, 26% on combination thereof BD-I Mean age = 35 y	ATP III	32.0	…	…	…	…	…	Rate of MetS markedly higher than that of the general Turkish population (17.9%)

[a]US National Health and Nutrition Examination Survey age-adjusted prevalence of metabolic syndrome and individual components. ATP III definition (1988–1994 data): 23.7% MetS, 38.6% abdominal obesity, 30.0% hypertriglyceridemia, 37.1% low HDL-C, 34.0% hypertension, 12.6% hyperglycemia[33]; ATP III/AHA definition (2003–2006 data): 34.3% MetS, 53.6% abdominal obesity, 31.4% hypertriglyceridemia, 25.4% low HDL-C, 30.1% hypertension, 38.4% hyperglycemia.[34]
[b]Body mass index (BMI) ≥ 30 kg/m^2 used as a proxy for abdominal obesity.
[c]Abdominal obesity criteria modified for Asians of > 90 cm for males and > 80 cm for females.
[d]Abdominal obesity criteria modified for Koreans of > 90 cm for males and > 85 cm for females.
[e]BMI ≥ 28.8 kg/m^2 used as a proxy for abdominal obesity.
Abbreviations: ATP III = National Cholesterol Education Program (NCEP) Adult Treatment Protocol III; ATP III/AHA = NCEP ATP III as updated by the American Heart Association and National Heart, Lung, and Blood Institute; BD = bipolar disorder; BP = blood pressure; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; MetS = metabolic syndrome; NOS = not otherwise specified; SGA = second-generation antipsychotic; TG = triglycerides; WC = waist circumference.
Symbol: … = data not available.

bipolar I disorders.[65] In addition, insulin resistance is an early risk factor for vascular disease in patients with bipolar disorder, even in the absence of elevated fasting glucose.[66]

Co-occurrence of Metabolic Syndrome and Depression

The co-occurrence of diabetes and depression is well established,[67] as is the link between depression and elevated cardiovascular risk.[68] In addition, a growing body of evidence has demonstrated an association between depression and metabolic syndrome.[69–71] In an analysis of data from the NHANES study (N = 2,439), overweight adults with abdominal obesity were significantly more likely to have major depressive or moderate-to-severe depressive symptoms than overweight adults without abdominal obesity.[72] Indeed, the association between depression and insulin resistance may be mediated, in part, by abdominal adiposity.[73] In a population of generally healthy US adults (N = 5,125), the presence of depressive symptoms was associated with increased rates of abdominal obesity, hypertriglyceridemia, and low HDL-C level; in women, there was also an association with slightly elevated fasting blood glucose.[74]

Metabolic syndrome may have a particularly strong association with depressive symptoms characterized by neurovegetative features such as fatigue, loss of energy, sleep disruption, and concentration difficulties.[75] Neurovegetative symptoms are highly prevalent among adults with bipolar depression. In a US national survey, fatigue was reported by 80.4% of 1,154 patients with bipolar I depression; sleep disturbance, by 91.2%; and concentration problems, by 90.7%.[76]

In addition to studies showing that metabolic syndrome is more prevalent in people with past or current depressive syndromes, evidence suggests that metabolic syndrome may increase the risk of developing a depressive disorder. In 2 population-based studies (N = 5,232; N = 520), men and women without depressive symptoms at baseline but with metabolic syndrome were more likely to report depressive symptoms at 6- to 7-year follow-up, even after controlling for potential confounders such as age, BMI, education, physical activity, smoking, alcohol use, and antidepressant exposure.[77,78]

In light of the association of metabolic syndrome and depression, it is possible that differences exist in the metabolic profile of patients with bipolar disorder who primarily exhibit symptoms of depression versus primarily hypomania or mania. Mood symptoms and cardiovascular risk, as measured by Framingham scores, were evaluated in a study of US veterans with bipolar disorder (N = 118).[79] Patients with clinically significant depression symptoms (17% of the overall sample) had a 6-fold increased risk of developing cardiovascular disease (Framingham score of > 20%), whereas patients with clinically significant manic symptoms (33% of the overall sample) were not at increased risk.[79] However, the relatively small sample size may have limited the ability to detect increased cardiovascular risk in patients with predominantly manic symptoms. Overall, elevated diastolic blood pressure, fasting glucose, and BMI (but not systolic blood pressure or dyslipidemia) were significantly associated with increased cardiovascular risk. Additional studies are needed to evaluate the relationships between manic versus depressive mood symptoms and metabolic syndrome in patients with bipolar disorder.

Ramifications of Metabolic Syndrome in Bipolar Disorder

In a large US national survey (N = 43,093), people with bipolar disorder type I (n = 1,411) were 5 times more likely than controls (n = 34,851) to have a cardiovascular disease (odds ratio = 4.95; 95% CI, 4.27–5.75); risk was also greater than for patients with major depressive disorder (n = 6,831; odds ratio = 1.80; 95% CI, 1.52–2.14).[80] Among respondents with cardiovascular disease, the age of patients with bipolar disorder was, on average, 13.7 years younger than that of controls.[80] As noted earlier, metabolic syndrome has been identified as a primary contributor to the increased cardiovascular risk in bipolar disorder.[20]

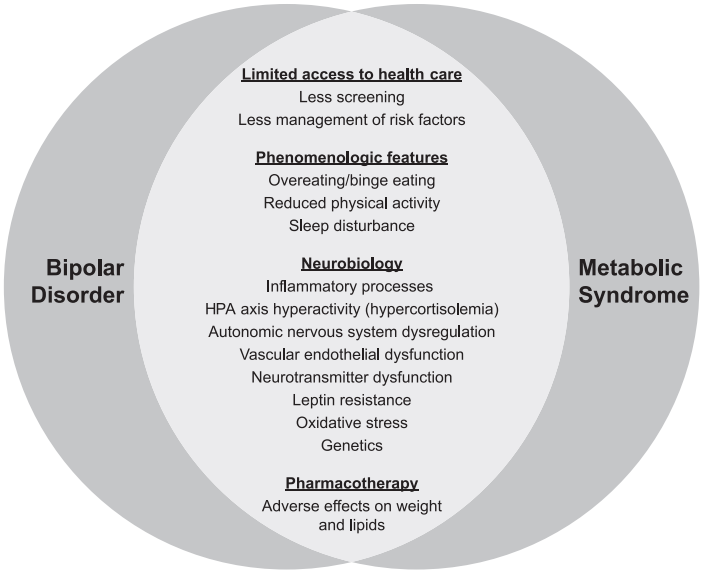
In addition, metabolic dysregulation has been associated with negative psychiatric outcomes for patients with bipolar disorder.[81] In a study of patients with rapid-cycling bipolar disorder (N = 225) treated with lithium and valproate, disorders of the endocrine/metabolic system, including obesity, were associated with greater severity of depression and poorer response to treatment.[82] Abdominal obesity in patients with bipolar disorder has been associated with worse scores on measures of disease severity and global functioning.[43] Research in the United States has indicated that the presence of metabolic syndrome in patients with bipolar disorder is associated with a lifetime history of suicide attempts[42,43]; however, this association has not been confirmed by studies in other countries.[54,83]

Patients with bipolar disorder often have cognitive impairments, which may compromise treatment outcome.[7] Metabolic syndrome has been associated with cognitive decline in older adults,[84] and a recent, large, community-based study showed the greatest cognitive decline in adults who were obese and had metabolic abnormalities.[85] Together, these findings raise concern about the effects of metabolic syndrome on cognitive functioning in patients with bipolar disorder. Indeed, in a post hoc analysis of 67 euthymic adults with bipolar I or bipolar II disorder, BMI was negatively correlated with measures of attention and psychomotor processing, and overweight and obese patients had impaired verbal fluency compared to normal weight patients.[86]

Hypotheses Accounting for the Link Between Bipolar Disorder and Metabolic Syndrome

Several putative explanations exist for the association between bipolar disorder and metabolic syndrome.[87] Hypotheses include reduced access to health care,[88] behavioral/phenomenological features,[61,89,90] shared neurobiologic abnormalities,[62] common genetic susceptibility,[62] and adverse effects of psychotropic medications (Figure 1).[17,26,63] Patients with bipolar disorder are generally more likely to be unemployed or permanently disabled—characteristics

Figure 1. Hypothesized Mechanisms Accounting for the Overlap/Co-occurrence of Bipolar Disorder and Metabolic Syndrome



Abbreviation: HPA = hypothalamic-pituitary-adrenal.

associated with limited access to health care.[88] In addition, unemployment and disability have been associated with poor health habits in general, and obesity in particular.[91–94]

Symptoms of bipolar depression (eg, hyperphagia, fatigue, lethargy, hypersomnia, or insomnia) may lead to overeating and reduced physical activity.[88] Inadequate sleep is associated with hyperphagia and obesity,[95] and bipolar patients often have disturbed sleep.[7] Bipolar I disorder has been associated with increased risk of obstructive sleep apnea,[96] which, in turn, is associated with endothelial dysfunction and cardiovascular risk.[97,98] Binge eating is a frequent comorbidity in patients with bipolar disorder and has been linked with depressive symptoms and obesity.[99–101] Binge-eating disorder in adults and loss-of-control eating in children have been associated with development of metabolic syndrome, and the increased risk was not accounted for by obesity alone.[102,103] Moreover, consumption of certain macronutrients (ie, fat) may induce a proinflammatory response.[104] In contrast, regular exercise may exert a beneficial effect on biochemical markers of inflammation[105,106] and on glucose homeostasis.[107]

Shared pathophysiology. Disruption in metabolic networks (eg, insulin-glucose homeostasis, inflammatory processes, adipokine synthesis) may be a central feature of mood disorders.[108] Inflammation has been identified in several studies as a pathophysiologic link between metabolic dysregulation and both depression and bipolar disorder.[75,109,110] Chronic, subclinical inflammation is associated with metabolic syndrome and decreased insulin sensitivity,[111,112] and preclinical studies indicate that inflammatory cytokines induce insulin resistance.[31] Levels of C-reactive protein (CRP) and other proinflammatory cytokines are elevated in acute bipolar illness and are not entirely normalized during remission.[113,114] Furthermore, elevated CRP levels have been significantly associated with the presence of metabolic syndrome in patients with bipolar disorder (N = 60).[115] Of note, leptin, a peptide hormone secreted by adipocytes, has been identified as a possible link between obesity and depressive disorders.[116] Leptin has shown antidepressant effects in animal models; however, the potentially beneficial effects of leptin on depressive symptoms, food intake, and energy expenditure may be attenuated in obese individuals as a result of leptin resistance.[116,117]

Other overlapping mechanisms include vascular endothelial dysfunction, increased oxidative stress, increased sympathetic activation, increased platelet activation, and stress-related hyperactivity of the hypothalamic-pituitary-adrenal axis.[10,22,63,118–120] In patients with bipolar disorder or major depressive disorder, environmental stressors such as early childhood adversity, and ongoing stressors related to the disease itself, may initiate biological events with long-term effects on mood symptoms and metabolic risk factors.[62,121–123]

Converging evidence supports the role of dopamine in the pathophysiology of both bipolar disorder and metabolic syndrome.[124,125] Reduction in striatal dopamine transporter availability has been observed in a small study of euthymic and depressed patients with bipolar I or bipolar II disorder (N = 11),[126] and dopaminergic agents appear to have therapeutic effects in bipolar depression.[127–131] Dopamine dysregulation has also been implicated in obesity and binge eating.[132–134] Moreover, D_2 receptor agonists have been reported to improve metabolic parameters (eg, blood glucose, resting energy expenditure, systolic blood pressure) in obese patients[135] and lipid levels and glycemic control in those with diabetes.[125] Indeed, the dopamine agonist bromocriptine has recently received regulatory approval for the treatment of type 2 diabetes.[136]

In sum, the association between bipolar disorder and metabolic syndrome is complex and undoubtedly mediated by interactions of multiple mechanistic pathways.

Pharmacotherapy. Pharmacologic therapies approved by the US Food and Drug Administration for the treatment of bipolar disorder include lithium, mood-stabilizing anticonvulsant agents (ie, carbamazepine, lamotrigine, valproate), and atypical antipsychotic agents. Some of these medications are associated with weight gain and unfavorable changes in lipid parameters; however, substantial variation exists among agents regarding degree of liability for weight gain and metabolic disruption (Table 3).[25,127,129,137–148]

Antipsychotic agents can be characterized as conferring higher (eg, clozapine, olanzapine), intermediate (eg, risperidone, quetiapine), or lower (eg, amisulpride, asenapine, aripiprazole, lurasidone, ziprasidone) risks of metabolic abnormalities.[138,141,149–151] Data are mixed, however, as to whether mood stabilizer–antipsychotic combination therapy is more likely to be accompanied by metabolic dysregulation than antipsychotic monotherapy.[55,152]

The weight gain associated with antipsychotic treatment is one contributor to antipsychotic-induced metabolic

Table 3. Metabolic Liability of Medications Used in the Treatment of Bipolar Disorder[a]

Medication	Weight	Dyslipidemia	Blood Pressure	Glucose Level
Mood stabilizers				
Lithium	↑	↔	↔	↔
Valproate	↑	Inconsistent findings	↔	↓ (due to hyperinsulinemia)
Lamotrigine	↔	↔	↔	↔
Carbamazepine	↔	↑	↔	↔
Other anticonvulsants				
Topiramate	↓	↔	↔	↔
Zonisamide	↓	↔	↔	↔
Antipsychotics				
Aripiprazole	↔	↔	↔	↔
Asenapine	↔	↔	↔	↔
Lurasidone	↔	↔	↔	↔
Olanzapine	↑↑	↑↑	↔	↑
Risperidone	↑	↑	↔	Inconsistent findings
Quetiapine	↑	↑	↔	Inconsistent findings
Ziprasidone	↔	↔	↔	↔
Antidepressants				
Bupropion	↓	↔	Inconsistent findings	↔
MAOIs	↑	↑	Orthostatic hypotension, hypertensive crisis	Hypoglycemia with hydrazine MAOIs
SSRIs	Varies by agent	Varies by agent	↔	↔
SNRIs	↔	↔	↑	↔
Tricyclic antidepressants	↑	↑	↑	Inconsistent findings
Dopaminergic agents				
Armodafinil	↔	↔	↑	↔
Modafinil	↔	↔	↑	↔
Pramipexole	↑	Insufficient data	Orthostatic hypotension	Insufficient data
Stimulant				
Lisdexamfetamine	↓	Insufficient data	↑	Insufficient data

[a]Data from references 25, 126, 128, 136–147, and 150.
Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.
Symbols: ↑ = evidence of increase in the specified parameter, ↓ = evidence of decrease in the specified parameter, ↔ = evidence of minor change or neutral effect on the specified parameter.

abnormalities. Other mechanisms for metabolic dysregulation during treatment with antipsychotic agents identified in preclinical research include oxidative stress, direct effects on glucose metabolism, and enhanced lipogenesis.[153–155] The propensity for dyslipidemia among atypical antipsychotic agents parallels that for weight gain (Table 2), although there are reports of antipsychotic-treated patients for whom the association with dyslipidemia was independent of BMI or weight gain.[156,157] Increased blood glucose levels have been observed consistently for olanzapine, but not for many other atypical antipsychotic agents (Table 2).

Weight gain is common during treatment with lithium or valproate; however, adverse effects on lipid and glucose levels are not observed consistently.[143] For example, a 52-week study of lithium or aripiprazole for bipolar disorder type I (N = 63) showed modest weight increases in both treatment groups but small mean changes in lipid, glucose, and insulin levels.[158] Similarly, a study in New Zealand showed lower HDL-C levels but similar frequency of insulin resistance in 60 overweight patients with bipolar disorder treated with valproate and 60 members of the general population matched for age, sex, BMI, and ethnicity.[41] The prevalence of metabolic syndrome was numerically higher in valproate-treated patients (50.0% vs 31.7%), but the difference was not statistically significant.[41] However, in a study in Taiwan, patients with bipolar disorder treated with valproate (n = 52) had significantly higher plasma insulin and triglyceride levels and lower fasting plasma glucose and HDL-C levels than healthy controls (n = 119); metabolic parameters of unmedicated patients did not differ significantly from those of healthy controls.[159]

Lamotrigine appears to have a low risk of causing weight gain and adverse metabolic effects.[143] In two 18-month multicenter placebo-controlled studies that were enriched for lamotrigine response based on a preceding 8-week open-label phase,[160] obese patients with bipolar I disorder (n = 155) lost weight with lamotrigine (mean, −4.2 kg) but gained weight with lithium (mean, +6.1 kg).[161] In clinical trials of carbamazepine for bipolar disorder (N = 239 short-term, N = 77 extension study), minimal weight gain with modest increases in total cholesterol (which included both high-density and low-density lipoproteins) has been observed.[162,163]

Antidepressant medications are used frequently in the treatment of patients with bipolar disorder, although evidence regarding their efficacy and safety in bipolar depression is mixed.[164–168] The effects of antidepressants on weight and other metabolic parameters differ by medication class (Table 3). Tricyclic antidepressants and monoamine oxidase inhibitors tend to produce weight gain, dual serotonin-norepinephrine reuptake inhibitors (SNRIs) have a generally neutral effect, and bupropion may provide weight reduction; the effects of selective serotonin reuptake inhibitors (SSRIs) vary by agent.[25,169] Additionally, some

antidepressants may alter glucose metabolism and insulin sensitivity.[148,170] For example, some tricyclic antidepressants may promote hyperglycemia and impaired insulin sensitivity, whereas some SSRIs may have beneficial effects on glycemic control.[148] SNRIs have no apparent effects on glucose homeostasis.[148] Regarding selective norepinephrine reuptake inhibitors, atomoxetine* may produce weight loss,[171] and reboxetine† may be associated with improvement in metabolic parameters.[172]

Dopaminergic agents, which may be effective for bipolar depression, are generally weight neutral or even associated with weight loss. A randomized, double-blind, placebo-controlled study of modafinil as an adjunct to mood stabilizers in patients with bipolar I or II depression (N = 85) showed weight change similar to placebo during 6 weeks of treatment.[129] Similarly, in an 8-week study of patients with bipolar I depression treated with lithium, valproic acid, or olanzapine, mean weight was essentially unchanged with adjunctive armodafinil (+ 0.1 kg, N = 128), compared with mean weight gain of 1.0 kg with placebo (N = 129).[127] However, information regarding the long-term effects of dopaminergic agents on mood or weight is currently lacking.

Management of Metabolic Syndrome in Patients With Bipolar Disorder

A US national cardiometabolic screening program found that 62.1% of 588 bipolar disorder patients with metabolic syndrome were not receiving treatment for any syndrome component.[39] Among patients receiving treatment for dyslipidemia, hypertension, or hyperglycemia, inadequate symptom control was observed in a substantial proportion.[39] Thus, there is great need for improvement in the treatment of metabolic syndrome in patients with bipolar disorder, particularly because reducing blood pressure and lipid parameters to normal levels in patients with metabolic syndrome has been shown to reduce the occurrence of cardiovascular events by 40%–50%.[173]

There are emerging guidelines on the treatment of common medical and psychiatric comorbidities in patients with bipolar disorder,[174] including recommendations intended to improve the clinical management of metabolic abnormalities.[137,175] However, in the absence of randomized controlled trials in patients with bipolar disorder, it is often necessary to draw recommendations from general treatment guidelines. We have previously proposed an assessment tool for the evaluation of metabolic risk in psychiatric patients,[175] and Table 4 provides a summary of treatment goals and interventions for each metabolic syndrome component.[176] Regular monitoring of BMI, waist circumference, lipid profile, and fasting plasma glucose level is clearly important, especially in patients receiving antipsychotic medications.[26,137,141,177] As the occurrence of dyslipidemia may be independent of BMI,[156] recommendations for regular metabolic monitoring include patients who are normal weight and do not gain weight during treatment.[156,157] However, assessment for and treatment of metabolic syndrome should be tailored to meet individual patients' needs.

Physicians are generally advised to select pharmacologic agents that are efficacious for bipolar disorder symptoms and have a low liability for weight gain and metabolic dysregulation.[25,137] In selecting pharmacotherapies, it has been recommended that physicians conduct a comprehensive risk-benefit analysis considering symptoms and severity of bipolar illness, medical history (including metabolic risk), past medication efficacy, and potential adverse events.[142] However, in an analysis of prescription practices at an academic medical center, factors related to metabolic risk (ie, BMI, diagnosis or treatment for hypertension or diabetes) did not appear to influence psychiatrists' decisions regarding use of atypical antipsychotic agents with moderate-to-high liability for adverse metabolic events.[178]

Lifestyle modifications may have beneficial effects on both cardiovascular risk and depression. Exercise is known to reduce the incidence of metabolic syndrome and cardiovascular disease[179,180] and may improve depressive symptoms in patients with a depressive disorder.[181] The Mediterranean diet has been associated with decreased occurrence of cardiovascular events in older adults (aged 55–80 years; N = 7,447) at elevated risk[182] and with reduced incidence of depression.[183] In a recent study of overweight and obese adults with serious mental illness (eg, schizophrenia, bipolar disorder, or major depressive disorder; N = 291), a behavioral weight loss intervention consisting of nutritional counseling and group exercise produced significantly greater weight loss relative to the control group.[184] Tobacco use has a substantial negative impact on cardiovascular mortality; however, smoking cessation is often associated with weight gain.[185] A recent prospective, community-based study (N = 3,251) found that smoking cessation reduced the risks of cardiovascular disease despite subsequent weight gain (mean of 3.0 kg in 205 recent quitters).[186] Smoking cessation is overlooked as a strategy to reduce cardiovascular risk in patients with bipolar disorder, who are often more amenable to smoking cessation interventions than clinicians assume.[175] Of note, among the available medical treatments for smoking cessation, bupropion and, to a lesser extent, nicotine replacement and varenicline mitigate weight gain associated with smoking cessation.[187]

Weight management in patients with bipolar disorder. Behavioral weight management, also known as lifestyle modification, is the first-line treatment for obesity in bipolar disorder[26,137] and includes stressing the importance of good sleep hygiene for weight management. Reduction in weight and abdominal obesity may also have beneficial effects on other components of metabolic syndrome.[188]

Pharmacologic treatment options for weight management include switching the patient's bipolar disorder medication to one with a lower potential to induce weight gain.[26] However, the possibility of switching medication in a patient who is clinically stable must be carefully considered. Patients

*In the United States, atomoxetine is indicated for the treatment of attention-deficit/hyperactivity disorder.
†Reboxetine is approved in Europe (for treatment of depression) but not in the United States.

Table 4. Monitoring, Treatment Goals, and Interventions for Metabolic Abnormalities[a]

Metabolic Abnormality	Monitoring	Diet and Physical Activity Interventions	Pharmacologic Interventions[b]	Treatment Goal
Abdominal obesity	Initial assessment Quarterly monitoring	Reduce weight Increase physical activity Good sleep hygiene Cognitive-behavioral psychotherapy	Antiobesity pharmacotherapy is indicated as adjunct to lifestyle management for patients with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 if other risk factors[c,d]	Waist size < 102 cm (40 in) in men, < 88 cm (35 in) in women
Hypertriglyceridemia	Initial assessment Annual monitoring On drug therapy, monitoring every 6–8 wk until treatment goal is met and every 4–6 mo thereafter	Reduce weight Increase physical activity Increase intake of foods with low glycemic index Reduce intake of total carbohydrates Increase consumption of omega-3 fatty acids (consider supplementation, especially if triglyceride level > 500 mg/dL) Limit alcohol consumption	Fibrates[e] Reduce fasting and postprandial triglyceride levels (20%–50%) Shift small, dense LDL-C to large, buoyant particles Increase HDL-C particles Nicotinic acid Reduces triglyceride levels (20%–50%) Statins[f] Reduce fasting and postprandial triglyceride levels (7%–30%) Reduce LDL-C particles Increase HDL-C particles Reduce major coronary vascular events	Triglyceride level < 150 mg/dL
Low HDL-C	Initial assessment Annual monitoring On drug therapy, monitoring every 6–8 wk until treatment goal is met and every 6–8 mo thereafter	Reduce weight Increase physical activity Stop smoking Increase intake of monounsaturated fats	Nicotinic acid[e] Increases HDL-C particles (15%–35%) Fibrates Reduce fasting and postprandial triglyceride levels Shift small, dense LDL-C to large, buoyant particles Increase HDL-C particles (10%–35%) Statins[f] Reduce fasting and postprandial triglyceride levels Reduce LDL-C particles Increase HDL-C particles (5%–15%) Reduce major coronary vascular events	HDL-C level > 40 mg/dL in men, > 50 mg/dL in women
Hypertension	Initial assessment Quarterly monitoring On drug therapy, frequency of monitoring depends on severity of hypertension and treatment response	Reduce weight Increase physical activity DASH diet Reduce sodium intake Limit alcohol consumption	ACE inhibitors[e] Decrease CVD events Delay progression of microalbuminuria May slow progression to diabetes Angiotensin receptor blockers Delay progression of albuminuria May improve dyslipidemia associated with metabolic syndrome	Blood pressure < 130/80 mm Hg
Hyperglycemia	Initial assessment Annual monitoring On drug therapy, frequency of monitoring depends on medication used and treatment response	Reduce weight Increase physical activity Reduce intake of total carbohydrates	Metformin[e] Slows progression to diabetes in individuals with insulin resistance (but less effective compared with lifestyle changes) Thiazolidinediones Slow progression to diabetes in individuals with insulin resistance	Fasting glucose level < 100 mg/dL

[a]Adapted with permission from Bermudes.[176]
[b]Pharmacotherapy recommendations are extended from general treatment guidelines, as medications have not been studied specifically in patients with bipolar disorder.
[c]US Food and Drug Administration–approved medications: orlistat, phentermine and topiramate extended release, and lorcaserin.
[d]Bariatric surgery should be considered for patients with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with comorbidities.
[e]Suggested first-line therapy among pharmacologic interventions.
[f]Patients with elevated LDL cholesterol may already be taking a statin.
Abbreviations: ACE = angiotensin-converting enzyme, BMI = body mass index, CVD = cardiovascular disease, DASH = Dietary Approaches to Stop Hypertension, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

respond differently to pharmacologic therapies and may not derive the same benefit from one agent as from another. Thus, when considering a medication switch, the potential for relapse must be evaluated and balanced with expected benefits to the patient's metabolic profile.

Another pharmacologic option for weight management is initiating adjunctive therapy with an agent to reduce weight. Although the effects of pharmacotherapy on the neurovegetative symptoms of bipolar depression have not been formally assessed, it is possible that adjunctive medications that improve symptoms such as fatigue and overeating may promote increased physical activity and weight loss. For example, bupropion, which is considered an "activating antidepressant" because of its mild stimulant-like properties, has been associated with both improvement in depressive symptoms and weight loss in patients with bipolar disorder.[169,189]

Recommended adjunctive medications for weight control include metformin (especially if the patient is taking an antipsychotic agent), orlistat, anticonvulsants (ie, topiramate, zonisamide), and dopaminergic agents (ie, bupropion, modafinil).[137] Bariatric surgery is a highly effective treatment

for severe obesity and may be considered for carefully selected patients with bipolar disorder.[26]

Management of dyslipidemia, hypertension, and hyperglycemia. Lifestyle modification is recommended as first-line treatment for patients with dyslipidemia, hypertension, or hyperglycemia. Whether for weight loss or management of other metabolic risk factors, a multidisciplinary approach to lifestyle modification is generally recommended and may include psychotherapists, nurses, dieticians, and/or self-help groups.[175] Healthy eating habits, appropriate exercise, and good sleep hygiene need to be emphasized. Adjunctive lipid lowering, antihypertensive, or antidiabetic medications should be considered if nonpharmacologic interventions are insufficient (Table 4).[176]

Dyslipidemia. Guidelines for the management of patients with dyslipidemia are available from the ATP III,* the American Association of Clinical Endocrinologists, and other organizations.[18,190–194] Commonly used medications for dyslipidemia include beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), fibric acid derivatives, niacin (nicotinic acid), and bile acid sequestrants (Table 4).[18,137,176,191] Although concerns have been raised about increased risk of depression and suicide associated with statin use, a study of more than 20,000 patients with elevated cardiovascular risk showed no difference in the rate of suicide or attempted suicide in patients receiving statins compared with those receiving placebo.[195] Moreover, statin use was associated with reduced risk of developing depression in a nested case-control analysis (n = 458 cases, n = 1,830 controls).[196]

Nutritional supplementation with omega-3 fatty acids has been shown to reduce triglyceride level and increase HDL-C level[197,198] and may have a beneficial effect on depressive symptoms. A recent meta-analysis of 6 randomized, placebo-controlled studies (N = 291) showed that adjunctive use of omega-3 fatty acids with conventional mood stabilizers may provide improvement in bipolar depression (effect size = 0.34), although the effect on lipid profile was not reported in any of the included studies.[199]

In patients who require treatment with antipsychotics, switching to an agent with lower metabolic liability can provide improvement in lipid levels, including triglycerides, HDL-C, and the triglyceride/HDL-C ratio, as well as reductions in weight and BMI.[200] Lipid-lowering therapy, omega-3 supplementation, or both, may be appropriate in addition to or instead of switching antipsychotic agents. In a 4-year naturalistic prospective study of antipsychotic-treated patients (N = 89), initiation of lipid-lowering therapy was associated with reduction in cardiovascular risk.[201]

Hypertension. Given the well-established links between both bipolar disorder and depressive disorders and cardiovascular disease, adequate treatment of hypertension is of particular importance in these patients. Treatment guidelines regarding dietary and pharmacologic interventions are available from the American Society of Hypertension.[202–205] A key nutritional intervention is the DASH (Dietary Approaches to Stop Hypertension) diet, which emphasizes a diet rich in fruits, vegetables, and low-fat dairy products, with reduced consumption of sodium and saturated fat.[202,206] The DASH diet has been shown to reduce blood pressure in patients with hypertension[207,208] but has not yet been evaluated in hypertensive patients with bipolar disorder.

A broad range of antihypertensive agents are available, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, β-blockers, calcium channel blockers, and aldosterone blockers (Table 4).[175,176,203] Lithium, mood-stabilizing anticonvulsant agents, and atypical antipsychotic agents have no apparent adverse effects on blood pressure.[137] However, clinicians should be aware of the potential for lithium toxicity resulting from drug-drug interactions with thiazide or loop diuretics, ACE inhibitors, and ARBs.[209–212] Of note, despite initial concerns, β-blockers are not associated with increased risk of depression.[213,214]

Hyperglycemia. The American Diabetes Association (2012) guidelines include recommendations regarding testing for diabetes in asymptomatic patients, prevention or delay of diabetes in patients at increased risk, and monitoring and treatment of patients with a diabetes diagnosis.[215] No randomized controlled trials have evaluated the treatment of diabetes in patients with bipolar disorder or the treatment of bipolar disorder in patients with comorbid diabetes, although several studies have evaluated the treatment of depression in patients with diabetes.[216,217] However, as with type 2 diabetes in general, metformin is suggested as first-line therapy for patients with bipolar disorder who have hyperglycemia; a thiazolidinedione may also slow the progression to diabetes in patients with insulin resistance (Table 4).[175,176,215] With the exception of certain atypical antipsychotics, pharmacologic agents used in the treatment of bipolar disorder generally have minimal effects on plasma glucose levels (Table 4).[176] For patients being treated with an atypical antipsychotic agent, metformin may reduce metabolic risks including weight, waist circumference, and insulin resistance.[218] Other pharmacologic options for hyperglycemia and diabetes include sulfonylureas (eg, glipizide), glucagon-like peptide-1 (GLP-1) agonists (eg, exenatide), dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, sitagliptin), and bromocriptine, as well as insulin.[137,215]

Summary of Key Recommendations

- Psychiatrists should conduct a comprehensive assessment of metabolic risk in patients with bipolar disorder. This evaluation should include screening for all metabolic syndrome components. An online tool is available for performing a Framingham cardiovascular risk assessment (http://cvdrisk.nhlbi.nih.gov/calculator.asp).
- Regular monitoring of BMI, waist circumference, lipid profile, and fasting plasma glucose level is important, especially in patients receiving antipsychotic medications.

*An update to the ATP III guidelines is currently in development.

- The patient's psychiatrist and primary care provider should collaborate to provide effective treatment for components of metabolic syndrome, as indicated.
- Selection of pharmacologic treatments for bipolar disorder should take into consideration the presence of or risk for metabolic syndrome and the metabolic liability of the therapeutic regimen. Decisions regarding pharmacotherapy should be customized on the basis of constellation and severity of bipolar symptoms, medical history and comorbidities, and metabolic risk.
- Behavioral management strategies (including dietary changes such as the DASH diet for hypertension and exercise) are first-line treatments for obesity and other components of metabolic syndrome. Good sleep hygiene should be consistently promoted. Smoking cessation is also a first-line strategy for reducing cardiovascular risk. Cognitive-behavioral psychotherapy may help motivate and reinforce behavior change.
- Pharmacotherapy for obesity, dyslipidemia, hypertension, and/or hyperglycemia should be initiated when indicated, and treatment effectiveness should be monitored subsequently.

CONCLUSIONS

Metabolic syndrome is a common but widely under-recognized and undertreated comorbidity in patients with bipolar disorder. Bipolar illness is often characterized by predominance of depressive episodes compared with manic/hypomanic episodes, and metabolic syndrome is particularly associated with depressive symptomatology. Although guidelines are emerging for the clinical management of metabolic syndrome in bipolar disorder, these are not based on randomized controlled trials in patients with bipolar disorder but are typically extended from general guidelines. Psychiatrists should conduct a comprehensive assessment of metabolic risk in patients with bipolar disorder, with regular monitoring thereafter. Selection of pharmacologic treatments for bipolar disorder should take into consideration the patient's risk for metabolic syndrome and the metabolic liability of the therapeutic regimen. Behavioral management strategies are first-line treatments for components of metabolic syndrome and may be supplemented with pharmacologic therapies as necessary. Adequate management of metabolic syndrome may improve clinical outcomes in patients with bipolar disorder, as well as prevent adverse cardiovascular events and the development of diabetes.

Drug names: aripiprazole (Abilify), armodafinil (Nuvigil), asenapine (Saphris), atomoxetine (Strattera), bromocriptine (Parlodel, Cycloset, and others), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), exenatide (Byetta), glipizide (Glucotrol and others), lamotrigine (Lamictal and others), lisdexamfetamine (Vyvanse), lithium (Lithobid and others), lorcaserin (Belviq), lurasidone (Latuda), metformin (Glucophage and others), modafinil (Provigil), olanzapine (Zyprexa), orlistat (Xenical), phentermine (Adipex-P, Suprenza, and others), pramipexole (Mirapex and others), quetiapine (Seroquel), risperidone (Risperdal and others), sitagliptin (Januvia), topiramate (Topamax and others), valproic acid (Depakene, Stavzor, and others), varenicline (Chantix), ziprasidone (Geodon), zonisamide (Zonegran and others).

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