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REVIEW ARTICLE

The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid metabolic disorders

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BACKGROUND: One goal of the Canadian Network for Mood and Anxiety Treatments (CANMAT) is to develop evidence-based and best practice educational programs and recommendations. Our group conducted a comprehensive literature review to provide evidence-based recommendations for treating metabolic comorbidity in individuals with major depressive disorder (MDD) and bipolar disorder (BD).

METHODS: We searched PubMed for all English-language articles published January 1966 to November 2010 using BD and MDD cross-referenced with *metabolic syndrome*, *obesity*, *diabetes mellitus*, *hypertension*, and *dyslipidemia*. That search was augmented by a review of articles reporting outcomes of an intervention targeting components of metabolic syndrome in individuals with MDD or BD.

RESULTS: Consensus exists for the recommendation that individuals with MDD and BD should be routinely screened for risk factors that increase risk for metabolic syndrome. For excess weight, the best-studied pharmacologic approaches are metformin and topiramate, with emerging evidence for liraglutide and modafinil. For binge eating disorder, the best evidence in mood disorders was for cognitive-behavioral therapy as well as topiramate, zonisamide, and in select cases selective serotonin reuptake inhibitors. For dysglycemia, dyslipidemia, and hypertension, evidence supports cognitive-behavioral interventions and anti-diabetic, antilipidemic, and antihypertensive treatments.

CONCLUSIONS: Comprehensive care of individuals with mood disorders should include routine evaluation of the risk and presence of metabolic syndrome and its components. Systematic evaluation of preventative and targeted treatments of metabolic syndrome in mood disorder populations is insufficient.

KEYWORDS: bipolar disorder, diabetes mellitus, major depressive dis-

order, obesity, cardiovascular disease, hypertension, dyslipidemia

INTRODUCTION

Metabolic illness—including obesity, metabolic syndrome, and insulin resistance—has been amply documented during the past decade to differentially affect individuals with major depressive disorder (MDD) and bipolar disorder (BD).[1,2] The co-occurrence of metabolic syndrome in the mood disorder population is associated with a more complex affective presentation and less favorable course and outcome.[3,4] The considerable phenotypic overlap between mood disorders and metabolic syndrome provides the framework for hypothesizing that these conditions, albeit discrete, may have overlapping pathophysiology.[5-7]

Practitioners often encounter individuals with mood disorders who are overweight/obese and/or have evidence of dyslipidemia, dysglycemia, and/or hypertension. Prevention, screening, timely detection, treatment, and management of co-occurring metabolic abnormalities is a widely accepted recommendation for individuals with mood disorders.[8] Emerging evidence also suggests that components of metabolic syndrome (eg, hypertension, obesity) are associated with negative effects on memory function in individuals with psychotic disorders.[9,10] Moreover, mortality studies indicate that excess death in the mood disorder population is largely the result of excess cardiovascular disease, a consequence of the metabolic syndrome.[11] Notwithstanding the salience and hazards posed by metabolic comorbidity in mood disorder populations, relatively few resources are available to inform treatment decisions in individuals with mood disorders when co-occurring metabolic syndrome or its components are present.

Relatively few studies have aimed primarily to evaluate the effect of metabolic syndrome or its components on the treatment of individuals with mood disorders (and vice versa). As in other sections of these treatment recommendations, we aim to synthesize and summarize extant study results pertaining to this topic. The tabular presentation of data is intended to foster accessibility and organizational clarity, as well as highlight gaps in the evidentiary base. This paper is organized into 3 sections: introduction, evidence review, and conclusions.

METHODS

We conducted a PubMed search of all English-language articles published between January 1966 and November 2010. Search terms were *bipolar disorder* and *major depressive disorder* cross-referenced with: *metabolic syndrome, obesity, diabetes mellitus, hypertension*, and *dyslipidemia*. The search was augmented with a manual review of article reference lists and conference proceedings; the overarching aim was to identify all original articles reporting on the outcomes of an intervention targeting metabolic syndrome or its components in individuals with MDD or BD.

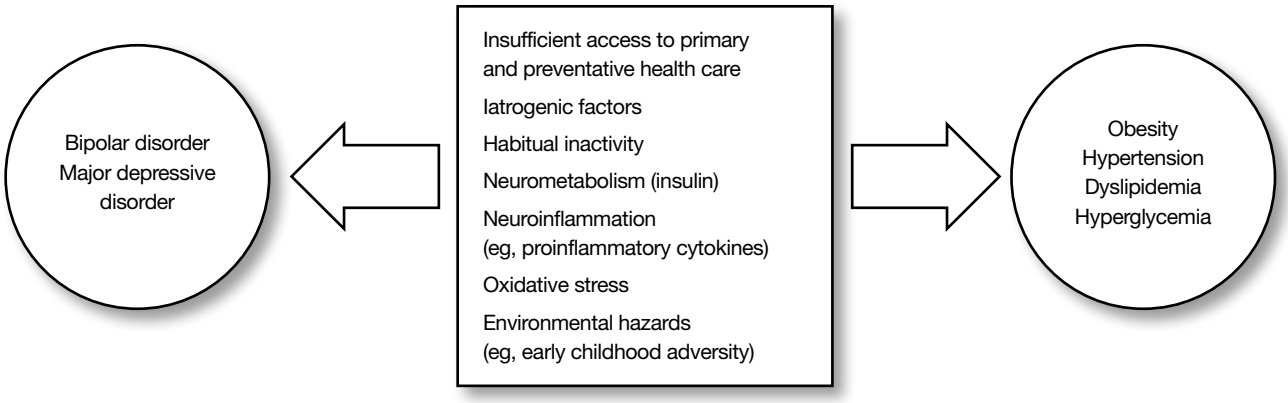
Evidence review

Metabolic syndrome in MDD and BD. Metabolic syndrome comprises a cluster of clinical and biochemical risk factors for cardiovascular disease, diabetes mellitus, and premature mortality.[12] Although several definitions have been proposed for metabolic syndrome, the most often cited is the Third Report of the U.S. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III).[13] All schemas for defining metabolic syndrome emphasize obesity and insulin resistance as primary pathophysiologic processes. According to ATP-III, the clinical features defining metabolic syndrome are abdominal adiposity, hypertension, impaired fasting glucose or diabetes mellitus, and atherogenic dyslipidemia.

The age-adjusted prevalence of ATP-III-defined metabolic syndrome in American adults is 23.7%, according to data from the Third National Health and Nutrition Examination Survey.[14] The risk for metabolic syndrome increases with age and is highest among women and Hispanic populations.[2] The age-adjusted prevalence of World Health Organization (WHO)-defined metabolic syndrome in Europe is relatively lower (15.7% for men, 14.2% for women).[15,16]

The major underlying risk factors for metabolic syndrome are abdominal obesity and insulin resistance.[17] Habitual inactivity, aging, and hormonal imbalances also are considered to be pathogenic factors.[18] Metabolic syndrome predisposes an affected individual to type 2 diabetes mellitus and is considered to be a multidimensional risk factor for atherosclerotic cardiovascular disease. Other conditions associated with metabolic syndrome are fatty liver, polycystic ovarian syndrome, sleep apnea, and lipodystrophies.[19]

FIGURE 1
Factors that predispose and portend mood disorder populations to metabolic syndrome



Before the widespread use of modern psychotropic agents, individuals with mood and psychotic disorders were documented to be at increased risk for obesity, hypertension, and diabetes mellitus when compared with unaffected populations.[20] During the past decade, replicated evidence indicates that individuals with MDD and BD are differentially affected by metabolic syndrome. Interpretations and inferences that can be drawn from the existing data are limited by heterogeneity in study design (longitudinal vs cross-sectional), sample composition (epidemiologic vs clinical), treatment, diagnostic criteria for mood disorder and metabolic syndrome, and measurement of affective symptoms. Nevertheless, the reported rate of metabolic syndrome in MDD and BD ranges between 20% and 65%.[22]

In a clinical trial population, a similar prevalence of metabolic syndrome was reported in 125 stabilized outpatients with bipolar I disorder, where the rate of metabolic syndrome was 36%. Elevated waist circumference was identified as the most commonly encountered criterion (>60% of the population).[22]

Several factors predispose and portend mood disorder populations to metabolic syndrome (**FIGURE 1**). Medication-associated adverse events are the most replicated causative factor. Other evidence supports habitual inactivity, insufficient access to primary and preventative health care, and low socioeconomic status as contributing variables. The psychobiology of mood disorders (eg, hypothalamic-pituitary-adrenal [HPA] axis dysregulation, inflammatory cytokines, oxidative stress) may be a pathophysiologic nexus with metabolic syndrome and its components.[5] Relatively few studies have reported on contributing effects of early childhood adversity on metabolic syndrome in mood disorders. Environmental insults are associated with several components of metabolic syndrome in nonpsychiatric samples and are more likely to occur in individuals with MDD or BD when compared with the general population.[21]

For clinicians, identifying metabolic syndrome in persons with mood disorders is important because of the complex interrelationship between metabolic syndrome and mood disorders.[22] Comorbidity with metabolic syndrome is associated with a more complex illness presentation, lower probability of recovery, and more frequent episodes and suicide attempts. For example, the first report describing an association between metabolic syndrome and BD evaluated 171 individuals enrolled in the Bipolar Disorder Center for Pennsylvanians.[23] Fagiolini et al reported that 30% of their sample met ATP-III criteria for metabolic syndrome. They also reported that abdominal obesity was associated with suicidality.

The only study to include euthymic patients also reported an increased rate of metabolic syndrome. Data from 99 euthymic BD patients (51 female, 48 male) were included for the analysis. The sample mean age (SD) was 38 years (11.2). Thirty-one patients (32.6%) met criteria for metabolic syndrome, with no significant differences as a function of sex. Thirty-seven (41.1%) met the waist circumference criterion; 26 (27.6%) and 28 (29.7%) met diastolic and systolic blood pressure criteria; 31 (36.4%)

met the high-density lipoprotein (HDL) criterion; and 33 (38.8%) met the triglyceride criterion. Five (6.1%) met the criterion for elevated fasting glucose, even though diabetes mellitus or glucose/insulin dysregulation were exclusion criteria at screening.[24]

Other studies in BD have observed an inverse correlation between cardiometabolic illnesses and the probability of achieving remission from depressive symptoms.[25] Overweight and obese patients receiving conventional mood stabilizers such as lithium and valproate have been reported consistently to exhibit greater chronicity and severity of depression as well as lower psychosocial functioning.[25,26]

Mortality studies in mood disorders indicate that cardiometabolic disorders are the most common causes of premature death.[27] In addition, individuals with BD have an increased prevalence of diabetes mellitus and higher rate of early mortality subsequent to the diagnosis of diabetes.[28] Identifying risk factors (eg, metabolic syndrome) that increase risk for cardiovascular disease and diabetes therefore is a priority research objective in the mood disorder population.

Treating the obese patient with MDD or BD. Overweight and obesity are the most common nutritional disorders in the United States.[29] In adults, an epidemic rise in the prevalence of self-reported overweight (body mass index [BMI] >25 kg/m^2) and obesity (BMI ≥30 kg/m^2) has occurred in the past 2 decades.[30,31] Moreover, the prevalence of obesity in child and adolescent populations has almost tripled since 1970.[32] The medical complications of overweight and obesity are well-established: osteoarthritis, type 2 diabetes mellitus, cardiovascular disease, and some forms of cancer.[33] All of these maladies are relatively more common in the mood disorder population.[27,34-36] Many of the causes of overweight and obesity are potentially modifiable with behavioral and preventative treatment, which is recommended as first-line treatment (**TABLE 1**).[37]

No approved pharmacologic agent for MDD or BD has been purposefully studied in overweight/obese individuals. When selecting and sequencing pharmacotherapy in the overweight/obese mood disorder patient, the clinician needs to consider both short- and long-term weight-gain potential and the psychotropic agent's effect on adipose tissue distribution. Most atypical antipsychotics cause varying degrees of weight gain, as shown in acute and continuation studies. Weight gain with some antidepressants (eg, mirtazapine, paroxetine) often is slow but inexorable. The only approved agent for MDD or BD that is associated with weight loss is bupropion.[38] Lamotrigine also has been associated with moderate weight loss in patients with bipolar I disorder and obesity but does not appear to be associated with weight loss in nonobese patients.[39]

Pharmacokinetics need to be considered when prescribing and monitoring the effects of psychotropic agents for overweight/obese individuals. Nonalcoholic steatohepatitis (NASH), a common cause of liver inflammation, is associated with obesity, insulin resistance, and hyperlipidemia. An estimated 10% to 15% of patients with histologically proven NASH progress to cirrhosis and its complications, such as liver failure and hepatocellular carcinoma.[40] The effect of fatty infiltration of the liver on psychotropic agents' pharmacokinetics has not been sufficiently evaluated. Moreover, drug development programs do not require sponsors to report on the pharmacokinetics of agents as a function of percentage of adipose tissue. Whether NASH represents a form of pharmacokinetic variability in overweight patients remains a testable hypothesis.

The initial approach to managing overweight/obese affective disorder patients is to prevent further weight gain, increase in BMI (kg/m^2), or visceral adipose tissue. Behavioral strategies, dietary modification, and increased aerobic activity are considered general recommendations for persons with mood disorders. Although a rationale for aerobic exercise as salutary in mood disorders is available for both MDD and BD, much of the available evidence has reported a modest beneficial effect of exercise in MDD.[41-43]

Symptomatic remission and functional recovery are the therapeutic objectives in managing the mood disorder patient. Replacing a weight-gain offending agent with a weight-neutral/favorable medication is recommended if the index agent's overall therapeutic value is unfavorable or equivocal. In many circumstances, however, psychotropic agents associated with weight gain should be continued if the clinician judges that the index agent provides optimal illness control. If behavioral strategies or substitution for a psychotropic agent associated with less weight gain prove unsuccessful, clinicians may consider using bariatric medicine.

The WHO recommends using bariatric medicine to control weight in an individual with a BMI of ≥27 with weight-related morbidity (eg, diabetes mellitus) or a BMI of ≥30 without weight-related morbidity.[44] FDA-approved agents for weight loss are phentermine and

TABLE 1
Levels of evidence supporting treatments for overweight/obesity in patients with bipolar disorder or major depressive disorder

Overweight/obesity	Bipolar disorder	Major depressive disorder
Behavioral/diet modification/cognitive interventions	III; A	III; A
Metformin	I; B	III; B
Topiramate	II; B	III; B
Modafinil	III; B	III; B
Orlistat	NS; B	III; B
Zonisamide	III; B	III; C
Liraglutide	III; C	III; C
Nizatidine	III; C	III; C
Amantadine	III; C	III; C
Naltrexone/bupropion	NS	NS
Phentermine	III; NR	III; NR

I: 2 RCT and/or meta-analysis; II: 1 RCT; III: open-label/case-series; NS: not studied.
A: first-line recommendation; B: second-line recommendation; C: third-line recommendation; NR: not recommended. Recommendations were adjudicated by the authors.
RCT: randomized controlled trial.

orlistat. Phentermine, a sympathomimetic agent, has not been studied in mood disorder populations and has the potential to induce hypomania/mania.[45] Although phentermine may help alleviate depressive symptoms in binge eating disorder, it has not been established as safe or efficacious in mood disorder populations.[46] The elevated rate of cardiovascular disorders in mood disorder populations is an additional concern with sympathomimetics in this population.[47]

Orlistat is a pancreatic lipase inhibitor and is not known to alter the pharmacokinetics of psychotropic agents. This medication has no central activity, so the potential for drug-drug interaction with centrally acting psychotropic medications is small. Orlistat often is not acceptable to patients, however, because of adverse abdominal effects such as loose stools, possible uncontrolled bowel movements, flatulence with discharge, and abdominal pain.[48]

A naltrexone-bupropion combination also has been studied in individuals with obesity. The hypothesized mechanism of this agent's weight-loss effect is the hypothalamic melanocortin system, which integrates input related to energy balance and produces anorexigenic signalling.[49] Moreover, both naltrexone and bupropion modulate the mesolimbic reward system implicated in reward value and goal-oriented behavior. The rationale for combining naltrexone with bupropion was based on observations that bupropion stimulates hypothalamic pro-opiomelanocortin neurons, whereas naltrexone blocks opioid-mediated pro-opiomelanocortin auto-inhibition. Contemporary models of obesity have implicated excess food intake as a behavioral consequence of addiction.[49-51]

Results from the largest of 4 Phase III studies with bupropion 360 mg/naltrexone 32 mg reported on 2 primary efficacy endpoints at 56 weeks: percent change in body weight and proportion of participants who achieved a ≥5% decrease in body weight.[49] Mean change in body weight was –1.3% with placebo, and –6.1% with the naltrexone/bupropion combination. Sixteen percent of participants assigned to placebo had a decrease in body weight of ≥5% compared with 48% assigned to naltrexone/bupropion. The most frequent adverse event in participants assigned to combination treatment was nausea. A transient increase of approximately 1.5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of approximately 1 mm Hg below baseline in the naltrexone/bupropion group. (The naltrexone-bupropion combination is not FDA-approved for weight loss; January 2012).

Modafinil is a stimulant-like wake-promoting agent that has shown utility as an adjunctive agent in treating bipolar depression.[52] Emerging evidence indicates it also may promote weight loss through reduced food intake.[53] Further studies will be needed to confirm this property.

Other agents have been used off-label for managing

obesity in patients with mood disorders, often as a secondary prevention strategy for psychotropic-associated weight gain. These include topiramate, metformin, reboxetine, zonisamide, nizatidine, and amantadine.[54-56] Liraglutide, a glucose lowering agent and glucagon-like peptide-1 (GLP-1) analogue, also has been evaluated as a weight loss agent in patients with obesity.[57] The mechanisms that mediate liraglutide's weight reduction effects include appetite suppression and delayed gastric emptying.[58] In a double-blind, placebo-controlled, 20-week trial, with open-label orlistat as an active comparator, participants taking liraglutide lost significantly more weight than did those taking placebo or orlistat. Seventy participants (76%) receiving liraglutide, 3 mg/d, lost >5% of baseline body weight compared with 29 (30%) receiving placebo and 42 (44%) receiving orlistat.[57] To our knowledge, liraglutide has not been studied specifically in individuals with mood disorders.

Taken together, available evidence provides the greatest support for metformin as a pharmacologic treatment of weight gain. Most studies of metformin have attempted to mitigate antipsychotic-associated weight gain. A substantive body of evidence also exists in support of topiramate. The naltrexone/bupropion combination, although insufficiently studied, may be applicable particularly to individuals with mood disorders. A meta-analysis of pharmacologic treatments for obesity concluded that sibutramine, orlistat, phentermine, and probably diethylpropion, fluoxetine, bupropion, and topiramate promote weight loss for at least 6 months when given along with recommendations for diet and exercise. The additional weight loss attributable to these medications is modest (>5 kg at 1 year) but clinically significant.[59]

Bariatric surgery is recommended for individuals with BMI of 35 to 39 with ≥1 obesity-associated comorbidity requiring medical treatment or BMI ≥40 with or without obesity-associated comorbidity.[60] The 3 most common bariatric procedures are Roux-en-Y gastric bypass, adjustable gastric banding, and sleeve gastrectomy.[61] The effects of bariatric surgery on the pharmacokinetics of psychotropic medications have not been sufficiently evaluated. Because these procedures change the GI tract's surface area and transit time, postsurgical serum level monitoring and dosage adjustments may be warranted for many patients, notably those taking controlled-release or long-acting medications.

The impact of bariatric surgery on mood disorder outcomes also is understudied.[62] Nevertheless, a 6-year follow-up analysis suggests that BMI reductions are associated with stable improvement in employment, reduced severity of anxiety and depressive symptoms, and improved health-related quality of life.[63] Patients with actively treated depression likely could expect gastric bypass surgery outcomes equivalent to those of individuals without identifiable psychiatric illness or treatment.[64] Available evidence suggests that a current diagnosis of an Axis I or II condition was not associated with gastric bypass outcomes at 6 months, but the presence of a lifetime mood or anxiety disorder was associated with a smaller decrease in BMI over 6 months.[65,66] Most trials of gastric bypass in psychiatric populations are limited by short follow-up and small sample size.

Binge eating disorder. Eating disorders are more likely to co-occur in BD than in MDD,[67] and individuals with BD I and II are affected similarly by eating disorders. In the BD population, the presence of a comorbid eating disorder is associated with female sex, younger age, early age at onset of BD, mixed episodes, rapid cycling, suicide attempts, severe obesity, alcoholism, and drug abuse.[68] The high frequency of binge eating as a separate diagnosable disorder (ie, binge eating disorder [BED]) or as part of bulimia nervosa warrants special consideration in the mood disorder population.

BED may compound the risk of metabolic syndrome over and above the risk attributable to obesity alone.[69] Anticonvulsants and antidepressants have been the most studied agents in treating eating disorders (**TABLE 2**). Topiramate has the broadest spectrum of action, demonstrating anti-binge eating, anti-purging, and weight-loss effects, as demonstrated in 2 placebo-controlled trials in bulimia nervosa and 3 placebo-controlled trials in BED with obesity.[70] Topiramate also has shown beneficial effects in night-eating syndrome and in sleep-related eating disorder.[70]

Zonisamide has demonstrated efficacy in treating BED and obesity. Topiramate and zonisamide are limited by GI- and CNS-related adverse events.[70] Contrasting results are available for phenytoin in compulsive or binge-eating behavior, and for the few studies of carbamazepine or valproate. Lithium has been evaluated as an augmentation of topiramate in individuals with BD and comorbid BED and obesity.[71] Negative data exist for lamotrigine in BED with obesity.[69] Positive controlled data exist for escitalopram, citalopram, and atomoxetine across variable measures such as binge episodes, binge days, weight, BMI, and global severity of illness scores.[72-74] Open-label data are available for sodium oxybate.[75] No

TABLE 2
Levels of evidence supporting treatments for bulimia nervosa/binge eating disorder in patients with bipolar disorder or major depressive disorder

Bulimia nervosa/binge eating disorder	Bipolar disorder	Major depressive disorder
Behavioral/diet modification/cognitive interventions	III; A	III; A
Topiramate	III; A	III; A
Escitalopram	III; B	III; A
Citalopram	III; B	III; A
Fluoxetine	III; B	III; A
Zonisamide	III; B	III; B
Lamotrigine	II; C	III; C
Sodium oxybate	III; C	III; C
Divalproex	III; C	NS; C

II: 1 RCT; III: open-label/case-series; NS: not studied.
A: first-line recommendation; B: second-line recommendation; C: third-line recommendation. Recommendations were adjudicated by the authors.
RCT: randomized controlled trial.

existing pharmacologic treatment strategy has been primarily examined in individuals with bulimia nervosa/BED in BD or MDD.

Treating the hypertensive patient with MDD or BD. MDD and depressive symptoms are well-established risk factors for incident and recurrent coronary artery disease (CAD), decreased quality of life, and all-cause mortality in individuals with pre-existing heart disease.[76] The risk attributable to depressive symptoms is independent of other known prognostic markers of CAD.[76] Moreover, epidemiologic studies indicate that MDD is a risk factor for incident heart disease in populations initially free of heart disease.[77] The association between mood disorders and cardiovascular disease is moderated and mediated by economic, behavioral, physiological, and iatrogenic factors.[78] Results from cross-sectional and prospective studies have reported an association between depression and transient increases in blood pressure, as well as hypertension and hypotension.[79]

Available evidence also indicates that depressive symptoms may be more difficult to treat in patients with comorbid CAD. For example, in the Sertraline Anti-Depressant Heart Attack Trial, which evaluated sertraline in patients with acute myocardial infarction or unstable angina, the overall effect size of sertraline on the depression endpoint was small and only significant in the subset of patients with recurrent depression.[80] Likewise, treatment with sertraline did not provide greater reduction in depression or improved cardiovascular status compared with placebo among patients with heart failure and depression (this may be due to a low event rate).[81]

Nevertheless, SSRIs may be tried as a therapeutic modality and are generally considered "blood pressure neutral" despite reports of hypo- and hypertension associated with their use (**TABLE 3**). Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, and duloxetine are associated with dose-dependent elevations in systolic/diastolic blood pressure and sustained diastolic hypertension in a relatively small number of treated individuals. Hypertension has been reported with bupropion, although randomized, placebo-controlled, dose-dependent studies of bupropion's vasopressor effects have reported neutral and/or minimal effects on blood pressure.

Mirtazapine, nefazodone, and trazodone exhibit minimal effect on blood pressure, although orthostatic hypotension has been reported. Taken together, the tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are associated with orthostatic hypotension. The possibility for malignant hypertension is increased when MAOIs or moclobemide are coadministered with other monoaminergic-based agents or tyramine-rich foods. Vasopressor effects are not noted with atypical antipsychotics, lithium, or anticonvulsant mood stabilizers.

Treating the dyslipidemic patient with MDD or BD. Dyslipidemia is an independent risk factor for incident and recurrent CAD.[13] ATP-III indicates that low-density lipoprotein cholesterol (LDL-C) is the primary factor pre-

TABLE 3
Levels of evidence supporting treatments for hypertension, dyslipidemia, and dysglycemia in patients with bipolar disorder or major depressive disorder

Hypertension	**Bipolar disorder**	**Major depressive disorder**
Behavioral/diet modification/cognitive interventions	III; A	III; A
Dyslipidemia		
Behavioral/diet modification/cognitive interventions	III; A	III; A
Dysglycemia		
Behavioral/diet modification/cognitive interventions	III; A	I; A
Conventional antidepressants	III; C	I; A
Pioglitazone	III; C	III; C

I: 2 RCT and/or meta-analysis; III: open-label/case-series.
A: first-line recommendation; C: third-line recommendation. Recommendations were adjudicated by the authors.
RCT: randomized controlled trial.

dicting CAD risk.[13] A direct association between LDL-C (and total cholesterol) and new-onset CAD or recurrent coronary events has been reported in population-based studies.[82] The CAD risk associated with atherogenic LDL-C levels (>100 mg/dl; 2.59 mmol/L) is greater in the presence of other established CAD risk factors.[13,83] Recent meta-analyses indicate that elevated triglyceride levels are an independent risk factor for CAD.[84,85]

Broadly sketched, some (notably weight-gain promoting) antidepressants exert a clinically significant effect on lipid homeostasis that is yoked to alterations in body weight. Compelling evidence is lacking that some antidepressants significantly alter lipid levels independent of their effects on body weight, BMI, nutrition, and energy expenditure. On the other hand, antidepressants' effect on glucose-insulin homeostasis has been documented. Antidepressants directly affect tissue sensitivity to insulin (with increased insulin and glucose levels), and antipsychotics exert a variety of adverse effects on body anthropometrics and metabolic parameters.[86-88] The effect of anticonvulsant mood stabilizers on lipid levels is more variable. For example, a neutral effect on lipid homeostasis has been reported for lamotrigine. In patients taking divalproex, observations of circulating lipid levels have been mixed: increased, no change, and decreased.

Abnormal lipid homeostasis in individuals receiving atypical antipsychotics most often is associated with weight gain. Although atypical antipsychotics as a class have been consistently implicated in promoting weight gain and cardiometabolic complications, recent evidence suggests a differential risk profile in the long-term treatment of BD. Maintenance studies in BD have reported clinically significant weight gain with most atypical antipsychotics, notably clozapine and olanzapine, with less weight gain and consequently metabolic abnormalities, in individuals receiving asenapine, aripiprazole, lurasidone, and ziprasidone.[89-92]

Aripiprazole and ziprasidone generally are regarded as having more favorable metabolic profiles compared with other atypical antipsychotics, although longer-term data have become available only recently. Aripiprazole can be used both short- and long-term without compromising patients' metabolic status, as no significant difference was observed between aripiprazole and placebo during 26 weeks of treatment. However, clinically significant weight gain occurred in a higher proportion of patients receiving aripiprazole (13%) compared with individuals receiving placebo (0%).[93] In a randomized, double-blind, placebo-controlled maintenance trial of ziprasidone adjunctive to a mood stabilizer (lithium or valproate), overall changes in weight, lipids, or other metabolic parameters were relatively small and similar to those seen with placebo. This lack of significant change may reflect a continuing neutral and/or minimal effect of ziprasidone over time on these parameters (asenapine and aripiprazole also exert minimal effect on these parameters in long-term BD studies).[94]

Even though dyslipidemia is the second-most commonly encountered metabolic syndrome criterion, no studies have evaluated the effect of an antilipidemic therapy in mood disorder populations. Behavioral and dietary strategies for weight management are encouraged as first-line approaches.

Medications for dyslipidemia are HMG-CoA reductase inhibitors ("statins"), fibrates, niacin, and resins. All

can reduce hypercholesterolemia. The statins (eg, atorvastatin, simvastatin, rosuvastatin, pravastatin) exert a robust effect on lowering LDL-C and also reduce very low-density lipoprotein cholesterol production. Statins' benefits include salutary effects on endothelial function, inflammatory signalling, foam cell formation/cholesterol accumulation, plaque stabilization, thrombosis formation, and antioxidation.

Adverse events associated with statins are largely GI-related. Increases in liver function tests commensurate with Hy's rule (ie, aspartate aminotransferase/alanine aminotransferase >3 times upper limits of normal [ULN] and bilirubin >2 times ULN) occur in approximately 2% of statin-treated patients. In addition, myopathy and rhabdomyolysis have been associated with statin therapy. Coadministration of agents that inhibit the 3A4 family of cytochrome P450 enzymes may increase the risk for liver and/or muscle toxicity with statin therapy. The use of statins and other lipid-lowering drugs does not appear to be associated with an increased risk of depression or suicide. In a nested case-control analysis, individuals with current statin use had a lower risk of developing depression, perhaps reflecting an improved quality of life because of decreased risk of cardiovascular events or greater attention to health maintenance.[95]

Some studies suggest an association between mood symptoms and abnormally low levels of cholesterol, although definitive evidence does not exist as to whether this represents a state or trait phenomenon. In one small study, lower cholesterol levels appeared to predispose individuals with BD to greater manic (but not depressive) symptomatology.[96] Some studies also have found that individuals who use more violent methods to attempt suicide have lower cholesterol levels than those who use less violent methods.[97]

Treating the dysglycemic patient with MDD or BD. Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[98] The estimated prevalence of diabetes mellitus in adults in the United States is 8%, with higher rates in older populations and some racial and ethnic groups (eg, African-Americans, Hispanics, and Southeast Asians).[99] Persons with diabetes mellitus are at risk for acute life-threatening consequences such as hyperglycemia associated with ketoacidosis and nonketotic hyperosmolar syndrome.[98,99] Long-term medical complications of diabetes mellitus include blindness, cardiovascular disease, end-stage renal disease, nontraumatic limb amputation, cognitive impairment, and peripheral and autonomic neuropathy.

Available evidence suggests that diabetic disorders and dysglycemia are more commonly encountered in individuals with MDD and BD than in general populations. Evidence is growing that conditions caused by abnormalities in insulin regulation, such as insulin resistance and type 2 diabetes mellitus, may increase the risk of age-related cognitive decline.[100,101] Recently, a 4- and 10-year prospective study determined that metabolic syndrome and its individual components (ie, hyperlipidemia, hyperglycemia, hypertension, and abdominal obesity) significantly increased the risk of developing dementia, mild cognitive impairment, and decreased performance on global cognitive test scores.[102,103] Moreover, the link between depression and dementia may be mediated in part by disturbances in insulin/glucose homeostasis. Insulin is a regulatory peptide and is hypothesized to play a critical role in both physiologic (eg, neurotrophism, neuroplasticity, neuromodulation, neuroprotection) and pathophysiologic CNS processes (eg, Alzheimer's disease [AD]).[104] A derivative of these observations is the hypothesis that the prevention and comprehensive treatment of depressive symptoms and insulin/glucose abnormalities would have the largest impact on reducing the incidence of dementia, possibly outweighing the effect of removing the ApoE4 genotype, which represents the best known risk factor for AD.[105]

Taken together, evidence indicates that successful treatment outcomes can be expected for both diabetes and mood disorders. A recent meta-analysis indicated that the combined effect of all antidepressant therapies in individuals with diabetes mellitus is moderate; a large effect is noted for psychotherapeutic interventions combined with diabetes self-management and moderate for pharmacologic treatment.[106] No controlled trials have evaluated the effect of antidiabetic treatment in individuals with BD.

Psychotropic medications commonly disrupt glucose homeostasis; the most replicated evidence exists for weight-gain promoting antidepressants and atypical antipsychotics. Abnormal glucose homeostasis often is associated with decreased kidney function, which may affect the clearance of several psychotropic agents (eg, lithium). The commonly employed antidiabetic agents are insulin, sulfonylureas (eg, glipizide), biguanides (eg, metformin), thiazolidinediones (eg, pioglitazone), GLP-1 (eg, exenatide), and dipeptidyl peptidase-4 inhibitors (eg, sitagliptin).

Given the pathophysiologic overlap between metabolic syndrome and depressive disorders, a small pilot study evaluated the use of pioglitazone, an insulin sensitizer of the thiazolidinedione class, as monotherapy or adjunctive therapy for the treatment of major depressive episodes that co-occurred with abdominal obesity or metabolic syndrome.[107] The study's primary objective was to test whether improving insulin sensitivity with pioglitazone would be accompanied by an antidepressant response.

Pioglitazone treatment over an acute 12-week period was found to significantly reduce depression severity. Pioglitazone also was associated with improvement in measures of glucose homeostasis and dyslipidemia, including a significant reduction in fasting glucose, triglycerides, LDL-C, and HDL-C. Levels of highly sensitive C-reactive protein, a biomarker of inflammation implicated in the risk of first incident and recurrent cardiovascular events, also decreased during pioglitazone treatment. Similar to metformin, pioglitazone may represent a treatment strategy to help prevent diabetes from developing in high-risk patients, such as those receiving atypical antipsychotics.[107]

Among the glucose-lowering agents, the largest quantity of evidence exists for metformin as an adjunctive agent to mitigate weight gain. Most metformin studies are short-term and have focused on nonwhite populations (ie, Han Chinese) or patients receiving concomitant olanzapine therapy. The drug appears to be effective as a weight prevention or reduction agent among individuals with psychiatric disorders taking antipsychotics when used in combination with a lifestyle program.[108] The effect of metformin on anthropometrics and insulin sensitivity are beneficial but modest, with one meta-analysis finding a mean weight difference of 3.16 kg.[109]

CONCLUSIONS

A comprehensive evaluation of patients with mood disorders includes assessing medical and behavioral factors associated with metabolic syndrome. Screen all patients for exercise habits, eating patterns, comorbid BED, bulimia nervosa, caffeine dependence, smoking, and thyroid dysfunction. Obtain baseline weight and BMI measurements; waist-to-hip ratio is an optional measure but a reliable proxy of visceral adipose tissue. Measure fasting blood glucose and lipid fractionation at baseline, and provide ongoing surveillance of anthropometrics and metabolic parameters. Despite consensus on the need for baseline and systematic monitoring, evidence indicates that most individuals with mood (and psychotic) disorders are not monitored on a regular basis.

Individuals with a mood disorder and metabolic syndrome ideally should receive care from a multidisciplinary coordinated team, with patients assuming an active role in their care. In patients with pre-diabetes (impaired fasting glucose/impaired glucose tolerance) lifestyle modification is strongly recommended.[98]

American Diabetes Association guidelines on the treatment of diabetes mellitus recommend earlier screening and more frequent monitoring of high-risk patients.[110] The basic principles of managing metabolic syndrome in diabetic individuals are similar in mood disorder and nonpsychiatrically affected populations. Unique, however, to diabetic individuals with mood disorders is their vulnerability to depression (ie, associated with poor diabetes compliance), propensity for impulsivity and suicidal behavior, comorbidity with alcohol and substance use disorders, higher prevalence of cardiovascular disease and smoking, frequent overeating and inactivity, and exposure to weight-gain promoting psychotropic agents. ■

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