Obesity in Patients With Severe Mental Illness: Overview and Management

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Severe mental illness and obesity are each serious public health problems that overlap to a clinically significant extent. Unfortunately, some of the most effective medications for severe mental illness are associated with the greatest weight gain, and the most effective strategy for severe obesity, bariatric surgery, is a treatment of last resort. First-line medication choices for patients with severe mental illness and obesity should be effective for treating the mental disorder, safe, well-tolerated, and, if possible, weight-neutral or associated with weight loss. If drugs with weight-inducing effects must be used, emerging data indicate that behavioral weight management, if not already in place, should be implemented and that adjunctive pharmacotherapeutic strategies should be considered. Severe mental illness with obesity must be viewed as 2 chronic illnesses that each require long-term management. *(J Clin Psychiatry 2009;70[suppl 3]:12–21)*

Obesity and overweight are growing health concerns for the general population and a rapidly increasing concern for clinical populations, particularly patients with severe mental illnesses such as schizophrenia and bipolar disorder.[1] Body mass index (BMI), expressed as weight (in kilograms) divided by height squared (in meters), is commonly used to classify overweight (BMI = 25.0–29.9) and obesity (BMI ≥ 30).[2]

In the United States, the prevalence of overweight and obesity has grown dramatically over the past 2 decades. A national survey[3] in which adults reported their own weights estimated that, from 1991 to 2001, the incidence of obesity increased by 74%, from 12% to 21%, and overweight increased from 45% to 58%. Similar results were reported by the National Health and Nutrition Examination Survey (NHANES). The prevalence of obesity among adults in the United States over the course of the NHANES increased from 15% in 1976 to 1980 to about 33% in 2003 to 2004.[4] The prevalence of overweight increased as well, from about 47% in 1976 to 1980 to about 66% in 2003 to 2004.[4]

Obesity is a chronic medical disease caused by a persistent excess of energy intake relative to energy expenditure.[5–7] The characteristic pathology is enlarged fat cells, although some people also have an increase in cell number.[6,7] People with obesity have shorter life spans and are at increased risk for a number of general medical conditions, including type 2 diabetes, cardiovascular disease (ie, the combination of cerebrovascular disease, coronary heart disease, and peripheral vascular disease), dyslipidemia, hypertension, and certain cancers (Table 1).[2,6,7] The amount of intra-abdominal or visceral adipose tissue in particular (more so than subcutaneous fat) is correlated with the cardiovascular and metabolic complications of obesity; excess intra-abdominal fat is commonly referred to as abdominal obesity (or visceral or central adiposity) and defined in the United States as a waist circumference > 88 cm in women and > 102 cm in men.[2,6–9] Obesity is also associated with the metabolic syndrome, a constellation of risk factors for cardiovascular disease that include central obesity, glucose intolerance, hypertension, and dyslipidemia. Metabolic syndrome may also predict elevated cardiovascular and all-cause mortality.[10,11]

SEVERE MENTAL ILLNESS AND OBESITY

Increasing evidence suggests that persons with severe mental disorders are at increased risk for overweight,

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FOR CLINICAL USE

- Patients with severe mental illness are at increased risk for obesity, both from the illness itself and from its treatment.
- Obesity may produce not only serious health consequences but also poor outcomes of mental illness treatment.
- Weight management in patients with obesity and mental illness should include prescription of weight-neutral agents to manage psychiatric symptoms, assessment of associated obesity comorbidity and metabolic risk factors, employment of behavioral weight management strategies, and addition of pharmacotherapy for weight loss if necessary.

obesity, and abdominal obesity.[1,12–14] Clinical studies have reported rates of obesity in patients with schizophrenia or bipolar disorder of up to 60%.[1] For example, Dickerson et al[15] compared 169 randomly selected outpatients with serious mental illness (48% with schizophrenia and 52% with a major mood disorder) and a gender-, race-, and age-matched group of 2,404 persons from the NHANES III. Fifty percent of the female psychiatric sample and 41% of the male psychiatric sample were obese compared with 27% of the NHANES female sample and 20% of the NHANES male sample. Similarly, in an analysis of 86,028 subjects in a health management organization database, patients with bipolar disorder had a higher rate of obesity (41%) than those without bipolar disorder (27%; $P = .002$).[16]

Although most studies included patients who were receiving psychotropic medications, some found body weight abnormalities in early onset and/or medication-naive patients, such as abdominal obesity in schizophrenia and obesity in bipolar disorder. Ryan et al[17] found that 17 patients with drug-naive, first episode schizophrenia had a significantly higher amount of intra-abdominal fat than age- and sex-matched control subjects who were also matched for BMI. An Italian study[18] found that almost 41% of untreated patients with bipolar disorder were overweight or obese compared with about 11% of patients with obsessive-compulsive disorder.

Several recent, large community studies[19–23] support the relationship between severe mental illness and obesity observed in clinical populations. Saarni et al[19] examined data from a community survey of 30-year-old Finnish individuals (N = 8,082) and reported that schizophrenia and schizoaffective disorder were associated with obesity (odds ratio [OR] = 2.3, 95% confidence interval [CI] = 1.5 to 3.6), abdominal obesity (OR = 2.2, 95% CI = 1.3 to 3.6), and higher body fat percentage (mean difference = 3.8%, 95% CI = 2.0 to 5.7) when compared with the rest of the sample after adjusting for age and gender. After adjusting for BMI, a statistically significant association with less muscle mass was found. The association between these disorders and both obesity (OR = 1.9, 95% CI = 1.1 to 1.4) and abdominal obesity (OR = 3.8, 95% CI = 1.5 to 9.4) remained after adjusting for current antipsychotic medication use, diet, education, and smoking.

In an analysis of data from a Canadian community survey (N = 36,984), McIntyre et al[20] reported that individuals with a lifetime history of a mood (bipolar or major depressive) disorder were more likely to be obese (19%) than those without a mood disorder (15%, $P < .05$). The age-adjusted rate of overweight or obesity (BMI ≥ 25) in persons with bipolar I disorder was significantly higher than that of the general population (55% vs 48%, $P < .001$).[21] In an analysis of data from 9,125 respondents in the National Comorbidity Survey-Replication, Simon et al[22] reported that obesity was significantly associated with a lifetime diagnosis of bipolar disorder (OR = 1.5, 95% CI = 1.1 to 1.9); this association was greater for bipolar disorder present in the last 12 months (OR = 1.6, 95% CI = 1.1 to 2.4). Evaluating data from 41,654 respondents in the National Epidemiological Survey on Alcohol and Related Conditions, Petry et al[23] found that obesity was associated with any mood disorder, including a manic episode (OR = 1.6, 95% CI = 1.3 to 1.9 for obesity and OR = 2.7, 95% CI = 2.0 to 3.7 for severe obesity). The relationships remained after controlling for psychotropic medication use.

Persons with severe mental illness also have elevated rates of some of the generalized medical conditions that are related to obesity, including type 2 diabetes and cardiovascular disease.[24–30] They are also at increased risk for metabolic syndrome.[16,31,32] Thus, compared with their NHANES counterparts, male and female schizophrenia patients participating in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) were 138% and 251% more likely, respectively, to have metabolic syndrome.[32] A Spanish study of patients receiving treatment for bipolar disorder reported a significantly higher prevalence of metabolic syndrome in these patients (about 25%) than in a control group without bipolar disorder (about 14%; $P = .013$), and this difference was largely due to higher BMI, increased triglyceride levels, and decreased high-density lipoprotein cholesterol levels.[16] Indeed, like

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Table 1. Physical Health Complications of Obesity[a]

Cancers
Breast
Uterine
Cervical
Colon
Esophageal
Pancreatic
Kidney
Prostate
Cardiovascular disorders
Coronary heart disease
Stroke
Peripheral vascular disease
Dermatological problems
Skin infections (candidiasis)
Dermatitis
Pressure ulcers
Endocrine disorders
Type 2 diabetes
Dyslipidemia
Metabolic syndrome
Gynecological problems
Abnormal menses
Infertility
Polycystic ovary syndrome
Pregnancy complications
Pulmonary disease
Hypoventilation syndromes
Obstructive sleep apnea
Other conditions
Osteoarthritis
Gout
Gallbladder disease
Nonalcoholic fatty liver disease
Hypertension
Phlebitis
Severe pancreatitis

[a]Reprinted with permission from McElroy et al.[1]

Table 2. Weight Liability of Psychotropic Agents Used in Severe Mental Illness[a]

Drug Class	Weight Loss	Weight Neutral	Weight Gain
Antidepressants	Fluoxetine	Sertraline	Amitriptyline
	Bupropion	Nefazodone	Nortriptyline
		Duloxetine	Imipramine
		Citalopram	Mirtazapine
		Escitalopram	Paroxetine
		Venlafaxine	
Anticonvulsants/ Mood Stabilizers	Topiramate	Lamotrigine	Valproate
	Zonisamide	Oxcarbazepine	Carbamazepine
			Gabapentin
			Lithium
Antipsychotics		Ziprasidone	Clozapine
		Aripiprazole	Olanzapine
		Haloperidol	Quetiapine
		Fluphenazine	Risperidone
		Molindone	Thioridazine
		Perphenazine	Chlorpromazine

[a]Adapted with permission from McElroy et al.[1]

obese persons, persons with schizophrenia and bipolar disorder have shorter life spans and elevated mortality from medical causes, with cardiovascular disease being the most common cause of death.[30,33–35] However, it is as yet unknown to what degree obesity contributes to this elevated mortality.

PREDISPOSING FACTORS FOR OBESITY IN THE SEVERELY MENTALLY ILL

Treatment-Related Factors

It is well-established that some antipsychotic, mood-stabilizing, and antidepressant agents cause weight gain (Table 2),[1,12,13,36] and at least 1 community survey found an association between antipsychotic drug use and obesity.[20] Growing evidence indicates that psychotropic treatment may be associated with obesity in the severely mentally ill. For example, a recent French study[37] of 5,756 patients with schizophrenia reported that obesity occurred more often in patients taking antipsychotic medication (clozapine, olanzapine, risperidone, or amisulpride) than in those not receiving antipsychotic treatment. A Chinese study showed that atypical antipsychotics may increase abdominal obesity in treatment-naive schizophrenia patients.[38]

A study of inpatients in South Korea[39] found that obesity increased from 25% to 36% in the first 4 weeks of acute treatment of 179 consecutive patients with bipolar I disorder. Notably, atypical antipsychotics were associated with more weight gain than other monotherapy treatments (typical antipsychotics and mood stabilizers), but patients treated with a combination of atypical antipsychotic and mood stabilizer agents (eg, olanzapine and valproate) showed the greatest weight gain.

Further supporting a link between obesity and antipsychotic medication are findings that obesity is a risk factor for noncompliance with antipsychotic medication. In a survey[40] of 304 schizophrenia patients, obese individuals were more than twice as likely as those with normal weight to report missing their medications (OR = 2.5, 95% CI = 1.1 to 5.5).

Other Factors

Obesity in patients with severe mental illness is also associated with factors associated with obesity in the general population as well as illness-related factors. Regarding the former, female gender, unhealthy lifestyle habits, and binge eating have been associated with obesity in both schizophrenia and bipolar disorder.[1,41,42] In CATIE, for example, 72% of women had abdominal obesity versus 37% of men. Regarding illness-related factors, obesity has been associated with poorer outcome in bipolar disorder.[43] Finally, as genetic factors contribute to both obesity and severe mental illness, specific genetic factors may also predispose certain individuals to the co-occurrence of obesity and severe mental disorders.[44,45] By contrast, one community study[21] found an inverse relationship between the presence of comorbid overweight or obesity and substance use disorders in bipolar I disorder.

Conclusion

Clinical and community studies suggest that severe mental illness and its treatment are associated with obesity. They also suggest that the medical complications of obesity, such as cardiovascular disease, type 2 diabetes, and metabolic syndrome, are more common in patients with severe mental disorders than in other populations. Causes of obesity in the mentally ill are likely to include treatment, and illness-related factors.

NONPHARMACOLOGIC APPROACHES TO MANAGING WEIGHT

An increasing number of guidelines have been proposed for monitoring patients with severe mental illness and obesity or obesity-related medical comorbidities.[24,25,27,28,46] Most of these guidelines recommend regular monitoring of BMI, waist circumference, lipid profile, and fasting plasma glucose level in patients with psychotic disorders, especially those receiving antipsychotics. Some have made similar recommendations for patients with bipolar disorder.

The guidelines proposed by Marder et al[25] recommend recording the patient's BMI before medication initiation or a change in medication and at every visit for the first 6 months thereafter. Importantly, rapid weight gain in the first month of treatment may be a risk factor for further substantial weight gain.[47] After the first 6 months of treatment, as long as the BMI remains stable and the patient is not overweight, the guidelines specify that the BMI can be monitored quarterly. By contrast, a weight gain of 1 BMI unit indicates the need for an intervention, unless the patient was underweight. Some of the interventions suggested by Marder et al[25] include closer monitoring of the patient's weight, engaging the patient in a weight management program, switching the patient's antipsychotic medication to an agent with less weight-gain liability, and using an adjunctive medication to reduce weight.

Behavioral Weight Management

Behavioral weight management remains the cornerstone of obesity treatment.[2,5–7] It consists of 3 goals for the individual: decreasing caloric intake, increasing physical activity, and learning cognitive-behavioral strategies to reinforce positive changes in dietary habits and physical activity. Importantly, patients with schizophrenia have expressed interest in losing weight and willingness to participate in weight loss programs.[48] Several reviews have concluded that patients with severe mental illness can safely lose weight with behavioral weight-loss strategies.[1,14,49,50] For example, a recent meta-analysis[50] assessed the effectiveness of such interventions to treat antipsychotic-induced weight gain in patients with either first-episode or chronic schizophrenia. Randomized controlled trials comparing "a specific nonpharmacologic adjunctive intervention aimed at preventing or controlling antipsychotic-induced weight gain"[50(p101)] with treatment as usual were included. At least 75% of participants had to have been diagnosed with schizophrenia spectrum disorders per DSM or ICD criteria. The 10 trials that met these criteria comprised 482 patients. Interventions included cognitive-behavioral therapy (n = 6), nutritional counseling (n = 3), and the combination of nutritional counseling with exercise (n = 1). Five trials tested group interventions, and 5 tested individual interventions. Six trials aimed to reduce weight and 4 aimed to prevent weight gain. The primary outcome measures were mean change in body weight and BMI by the end of the intervention (at 8 weeks through 6 months), with follow-up at 2 to 3 months after the end of the intervention. Results showed a statistically significant reduction in mean body weight for those in the nonpharmacologic treatment groups compared with those who received treatment as usual (weighted mean difference [WMD] = –2.6 kg, 95% CI = –3.2 to –1.9 kg, $P < .001$). Similar significant results in favor of nonpharmacologic treatments were seen for mean change in BMI (WMD = –0.9 kg/m^2, 95% CI = –1.1 to –0.7 kg/m^2, $P < .001$). Pooling treatment effects of mean changes in body weight and BMI showed that the statistically significant advantages of the behavioral interventions were maintained at follow-up (WMD = –4.1 kg, 95% CI = –5.8 to –2.5, $P < .001$). Trials that aimed to prevent weight gain showed a slightly larger effect on mean body weight change than those designed to reduce weight. The authors concluded that adjunctive behavioral interventions were effective in reducing antipsychotic-associated weight gain when compared with treatment as usual. They further suggested that using such approaches in the early stages of antipsychotic treatment had the potential to be more effective than employing them after the patient was already obese.

Diet Versus Exercise

Two critical components of behavioral weight management are modifying diet and enhancing exercise. Few empirical studies of these individual components have been conducted in severely mentally ill populations.

Diet. Epidemiologic evidence[51,52] suggests that diets low in fish consumption may be associated with increased risk of developing mood disorders and depressive symptoms and with poorer outcome of schizophrenia. Further, double-blind, placebo-controlled studies[53,54] suggest that omega-3 essential fatty acid supplements may be effective adjunctive treatments for medication-resistant bipolar disorder, major depression, and possibly schizophrenia. Until further data are available, however, diets high in fruits, vegetables, and whole grains and low in saturated fats are recommended.[1,2]

An established weight loss program that was modified for obese patients with schizophrenia or schizoaffective

disorder was used successfully in a randomized controlled pilot trial using a food reimbursement program.[55] Patients were reimbursed up to $25/wk for choosing healthy foods; these included fruits, vegetables, lower fat dairy products, whole grain breads and cereals, and lean cuts of meat and poultry. Snack foods and desserts were not reimbursable. The patients experienced weight loss and improvement in fasting blood glucose, which continued after the program ended according to 6-month follow-up.

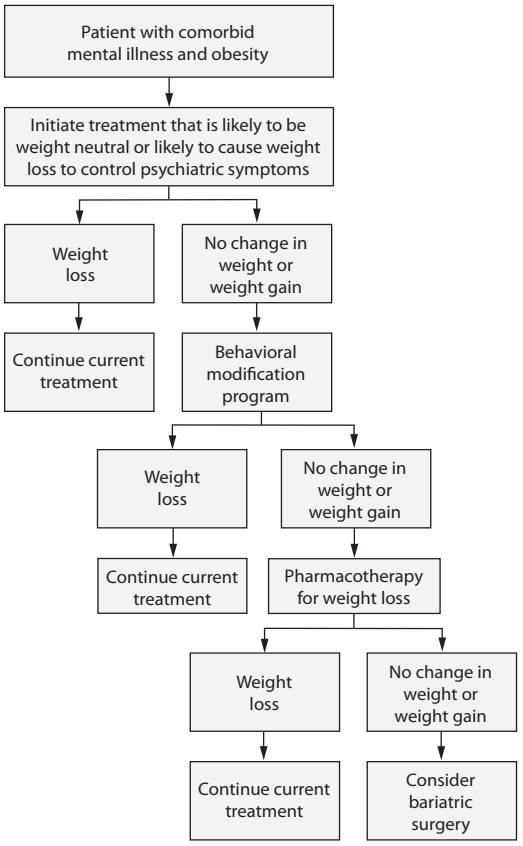
Exercise. The few controlled trials of exercise in patients with severe mental illness and obesity have had positive results.[56–58] In a Taiwanese study,[57] 53 clozapine-treated, obese inpatients with schizophrenia were randomly assigned to a 6-month regimen of diet and exercise or no intervention for weight gain. The study group (N = 28) was placed on a reduced calorie diet and participated in physical activity (level walking and walking on stairs) for 1 hour 3 times per week. Anthropometric, metabolic, and hormonal parameters were measured at 3 and 6 months. Relative to the control group, the study group showed significant decreases in body weight, BMI, and waist and hip circumferences at both time points as well as improvement in insulin, triglyceride, and insulin-like growth factor-binding protein-3 profiles.

A naturalistic Australian study[58] examined the effectiveness of an exercise program in 110 patients with bipolar disorder, schizophrenia, and schizoaffective disorder who were taking antipsychotic medication. The intervention group (N = 59) received education about diet and exercise and participated in a structured, supervised physical activity program for 18 months, while the control group did not. By endpoint, the intervention group had significantly lower body weight, BMI, and waist circumference than at baseline, as well as significantly improved lipid and fasting glucose profiles. The control group had experienced significant increases since baseline in weight, BMI, waist circumference, low-density lipoprotein cholesterol levels, and triglyceride levels. Further study of the effects of both diet and exercise in severely mentally ill patients is warranted.

PHARMACOTHERAPY TO CONTROL WEIGHT GAIN

As noted earlier, many of the medications commonly used to treat severe mental illness are associated with weight gain, and this weight gain may exacerbate or even cause obesity. Other medications, however, are weight neutral and some are associated with weight loss (see Table 2). The general approach to treating the severely mentally ill patient with obesity is to choose pharmacologic agents that are efficacious for the patient's primary mental disorder and that are weight neutral or, if available, associated with weight loss. If weight loss cannot be accomplished through adjusting the psychotropic drug regimen and using behavioral modification, then switching to antipsychotics with less weight gaining liability or adding pharmacotherapy specifically for weight loss may be considered; bariatric surgery is a last resort (Figure 1).[1]

Figure 1. Treatment Considerations for Patients With Mental Illness and Comorbid Obesity[a]

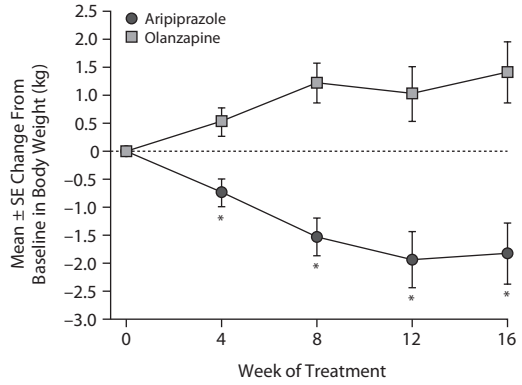


[a]Adapted with permission from McElroy et al.[1]

Switching Antipsychotic Agents

Switching antipsychotic medications to promote weight loss is an important treatment approach for the management of obesity in the severely mentally ill.[59,60] For example, clinical data have shown that patients may successfully be switched for weight loss from olanzapine to risperidone[61] and from various antipsychotics to either ziprasidone[62] or aripiprazole.[63] Patients switched to ziprasidone or aripiprazole may also have improvement in metabolic measures such as hyperlipidemia.[64,65] Newcomer et al[66] recently examined the effects of aripiprazole in overweight patients switched from olanzapine and found improvements in both body weight and triglyceride levels. The difference between the weight decrease with aripiprazole (–1.8 kg [n = 56]) versus the increase with olanzapine (+1.4 kg [n = 62]) was statistically significant ($P < .001$; Figure 2). A secondary outcome was the

Figure 2. Change in Body Weight From Baseline to Week 16[a]



[a]Reprinted with permission from Newcomer et al.[50] Mean ± SE baseline body weight: aripiprazole (n = 81), 91.3 + 2.1 kg; olanzapine (n = 77), 92.7 ± 2.1 kg.
*$P < .001$, aripiprazole versus olanzapine.

change in fasting triglyceride levels, which were also statistically significantly improved with aripiprazole versus olanzapine from baseline to week 16 (–14.5% [n = 54] vs. +5.3% [n = 61], respectively; $P = .002$). While resulting weight loss and metabolic changes may be favorable, careful monitoring must be used during any switch to ensure that symptoms are not destabilized.

Antidepressants

Some antidepressants, such as fluoxetine and bupropion, have been associated with weight loss, including in obesity.[67] Moreover, the combination of bupropion with naltrexone is associated with greater weight loss than either drug alone and is presently being evaluated as a treatment for obesity.[68] Although neither bupropion alone nor bupropion plus naltrexone has been evaluated in severely mentally ill patients with obesity or psychotropic drug-related weight gain, adjunctive bupropion was associated with weight loss in a single blind, 8-week comparator trial in patients with bipolar depression.[69] In addition, the selective norepinephrine reuptake inhibitor antidepressant reboxetine was superior to placebo in attenuating weight gain in 26 patients with schizophrenia.[70]

By contrast, fluoxetine was not effective in preventing weight gain among patients with schizophrenia[71] or patients with bipolar depression receiving olanzapine.[72] Nor was fluoxetine effective in reducing weight in olanzapine-treated schizophrenia patients (baseline mean BMI 25–27) when given at a relatively high dose (60 mg/d).[73] However, a randomized, 12-week study in 68 patients with treatment-resistant schizophrenia suggested adjunctive fluvoxamine may attenuate clozapine-related weight gain and metabolic disturbances (glucose and triglyceride abnormalities), possibly in part by inhibiting clozapine metabolism and decreasing norclozapine levels.[74]

Anticonvulsants

Topiramate, zonisamide, and lamotrigine have all been shown in controlled trials to have weight loss properties or to decrease BMI in obese patients without severe mental illness.[75–78] Topiramate has been associated with weight loss in randomized, placebo-controlled trials in patients with bipolar I mania when given as monotherapy,[79] and in patients with bipolar I disorder and schizoaffective disorder when given adjunctively.[80,81] It was also associated with weight loss in a single-blind, 8-week comparator trial in bipolar depression.[69] Moreover, in a post hoc analysis of 2 randomized, placebo-controlled studies comparing lamotrigine and lithium in bipolar disorder, lamotrigine monotherapy was associated with weight loss in obese patients who responded to the drug.[82]

Two randomized, placebo-controlled studies[83,84] have evaluated topiramate for weight control in patients with severe mental illness. In the first study,[83] 66 inpatients with schizophrenia and excessive weight received topiramate at either 100 mg/d or 200 mg/d or placebo in addition to their antipsychotic medication. After 12 weeks, patients in the 200 mg/d topiramate group had greater weight loss than the 100 mg/d topiramate group and the placebo group. In the second study,[84] 43 women with mood or psychotic disorders who had gained weight with olanzapine were randomly assigned to receive topiramate or placebo for 10 weeks. The treatment group lost more weight and had greater improvement in quality of life and psychological impairments than the placebo group.

No other controlled trials of anticonvulsants as weight loss agents in severely mentally ill patients have been published. However, 2 open-label trials[85,86] found that initiating treatment with the combination of topiramate and either risperidone or olanzapine successfully stabilized mood in patients with bipolar disorder while preventing weight gain. In addition, 2 open-label trials[87,88] suggest adjunctive zonisamide may have weight loss effects in overweight or obese patients with bipolar disorder who are receiving mood stabilizers and/or antipsychotics. Of the 62 outpatients with bipolar disorder who entered the first study,[87] 32 patients completed an initial 8-week acute trial and entered a subsequent 48-week continuation trial. Significant weight loss was found in both trials ($P < .001$), but 20 patients (32%) discontinued zonisamide because their mood symptoms worsened. In the second study,[88] a 6-month trial of 25 euthymic, overweight outpatients with bipolar disorder, significant weight loss was again seen, but 18 patients (72%) discontinued zonisamide, 11 (44%) because of emergent mood symptoms requiring treatment.

Further studies of anticonvulsants with weight loss properties for weight reduction in severe mentally ill patients with obesity, including randomized, placebo-controlled trials, would be informative.

Adjunctive Weight Loss Pharmacotherapy

Stimulants and dopamine agonists. Virtually all stimulants, such as methylphenidate, are associated with appetite suppression and weight loss, and some (phentermine, diethylpropion, benzphetamine, and phendimetrazine) are approved by the US Food and Drug Administration (FDA) as short-term weight loss agents.[67] However, no stimulant is approved by the FDA for the treatment of a psychotic or mood disorder, although there are reports of stimulants being helpful for negative and depressive symptoms.[1,89,90] Similarly, no dopamine agonist has been approved for the treatment of psychotic or mood disorders, although some of these agents have been reported to have weight loss effects in obese patients (bromocriptine)[91] and to decrease depressive symptoms in patients with bipolar depression (pramipexole).[92,93] When used adjunctively in patients with severe mental disorders, stimulants and dopamine agonists might not only alleviate weight gain but also have therapeutic effects on negative and/or depressive symptoms.

Unfortunately, most of the studies of stimulants and dopamine agonists in patients with psychotic or mood disorders do not report effects on weight. Studies of weight reduction with the stimulants chlorphenetermine and phenmetrazine[94] and dextroamphetamine[95] in schizophrenia patients with obesity were negative. A study[96] of phenylpropanolamine in patients who gained weight during clozapine treatment was also negative. Two controlled trials[97,98] of the dopamine agonist amantadine in patients with schizophrenia, schizoaffective disorder, or bipolar disorder who had gained weight with olanzapine, however, found efficacy for amantadine in reducing weight gain.

Sibutramine. Sibutramine is a selective serotonin norepinephrine reuptake inhibitor approved for weight loss and weight maintenance in persons with obesity.[67] In a double-blind, 12-week study,[99] adjunctive sibutramine was superior to placebo for weight loss in 37 overweight or obese patients with schizophrenia or schizoaffective disorder who were receiving olanzapine. The drug was also associated with greater decreases in waist circumference and glycosylated hemoglobin levels. In a study[100] of 46 patients with bipolar disorder who were overweight or obese and receiving psychotropic medication, sibutramine (n = 18) and topiramate (n = 28) were comparably effective for weight loss, but only 22% of patients taking sibutramine and 21% of those taking topiramate completed the 24-week trial. By contrast, in another study,[101] sibutramine was not found to promote weight loss or metabolic improvement compared with placebo in obese, clozapine-treated patients with schizophrenia or schizoaffective disorder, but the negative findings may have been due to small sample size (N = 21) or inadequate trial duration (12 weeks). Sibutramine, like stimulants and antidepressants, should be used cautiously in patients with severe mental illness, since there have been reports of exacerbations of psychotic and manic symptoms associated with the drug.[1]

Orlistat. Orlistat is a lipase inhibitor approved for weight loss and weight maintenance in obesity. In a 16-week study[102] of adjunctive orlistat or placebo in 71 overweight or obese patients receiving clozapine or olanzapine, orlistat had no effect on weight or metabolic variables in the study population as a whole or in women. However, significant weight loss was seen in men (–2.4 kg vs +0.6 kg on placebo).

Metabolic Drugs

Metformin. Three controlled trials[103–105] have shown that antipsychotic-associated weight gain and insulin resistance may be attenuated with adjunctive metformin, an insulin-sensitizing medication used for type 2 diabetes. In the first study,[103] metformin was superior to placebo over 16 weeks of treatment in reducing weight gain, decreased insulin sensitivity, and abnormal glucose metabolism in 39 children or adolescents with severe mental disorders whose weight had increased by ≥ 10% during less than 1 year of olanzapine, risperidone, or quetiapine therapy (baseline mean BMI = 27–29). In the second study,[104] 40 patients were randomly assigned to 12 weeks of treatment with olanzapine, 15 mg/d, plus metformin, 750 mg/d, or olanzapine plus placebo. Weight and insulin parameters were significantly better in the metformin group. In addition, metformin was well tolerated, and 92.5% of patients completed the 12 weeks of treatment. Of note, most of the patients in this study were normal weight; baseline mean BMI was 21 to 22. In the third study,[105] 128 first-episode patients with schizophrenia who had gained ≥ 10% of their pre-treatment weight (baseline mean BMI = 25) were randomly assigned to 12 weeks of placebo, metformin alone, metformin and lifestyle intervention, or lifestyle intervention plus placebo. Metformin alone, lifestyle intervention alone, and the 2 treatments together were all efficacious for antipsychotic-induced weight gain. The combination was superior to metformin alone and lifestyle intervention alone for weight loss. Metformin alone was more effective than lifestyle intervention alone for weight loss and improving insulin sensitivity. However, a 12-week placebo-controlled trial[106] found that the combination of metformin and sibutramine in 28 olanzapine-treated patients produced weight loss similar to placebo (–2.8 ± –3.2 kg vs –1.4 ± –2.6 kg, respectively); the only difference between active and placebo groups was prevention of triglyceride level increase in the active drug group.

Other Agents

H_2 antagonists. One randomized, placebo-controlled, 8-week trial[107] found that nizatidine significantly reduced weight in patients receiving olanzapine (N = 35). However, 2 other placebo-controlled trials found that nizati-

dine did not significantly reduce weight in schizophrenia patients receiving quetiapine (N = 28)[108] or olanzapine (N = 54)[109] after 8 or 12 weeks of treatment, respectively. Similarly, the 2 controlled trials that evaluated H_2 antagonists for the prevention of antipsychotic-induced weight gain in schizophrenia found no benefit after 6 weeks of treatment with famotidine (N = 14)[110] or 16 weeks of treatment with nizatidine (N = 175).[111]

CONCLUSION

Obesity and mental illness are overlapping public health concerns, and mental health providers must be familiar with this overlap. For patients with severe mental illness and obesity, first-line treatments include psychotropic medications that are effective for treating the mental disorder, safe, well tolerated, and, if possible, weight-neutral or associated with weight loss. Because some of the most effective drugs for severe mental illness are associated with the greatest weight gain, however, some severely mentally ill patients with obesity will require treatment with these agents. Behavioral weight management strategies, if not already in place, should be implemented and adjunctive pharmacotherapy considered; bariatric surgery is a last resort. When severe mental illness and obesity co-occur, they must be viewed as 2 chronic illnesses that each require long-term management.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), benzphetamine (Didrex and others), bromocriptine (Parlodel and others), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), dextroamphetamine (Dexedrine, Dextrostat, and others), diethylpropion (Tenuate and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), famotidine (Pepcid, Fluxid, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), metformin (Riomet, Glucophage, and others), methylphenidate (Daytrana, Ritalin, and others), mirtazapine (Remeron and others), molindone (Moban), naltrexone (Vivitrol, Revia, and others), nizatidine (Axid and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), orlistat (Xenical), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), phendimetrazine (Bontril and others), phentermine (Adipex-P and others), pramipexole (Mirapex and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), sibutramine (Meridia), topiramate (Topamax), venlafaxine (Effexor and others), ziprasidone (Geodon), zonisamide (Zonegran and others).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, amantadine, fluvoxamine, metformin, nizatidine, orlistat, phenylpropanolamine, and reboxetine are not approved by the US Food and Drug Administration for the treatment of antipsychotic-induced weight gain; bromocriptine, bupropion, lamotrigine, and zonisamide are not approved for the treatment of weight loss in obesity; chlorphentermine, dextroamphetamine, and phendimetrazine are not approved for the treatment of weight loss in schizophrenia with obesity; pramipexole is not approved for the treatment of bipolar depression; sibutramine is not approved for the treatment of psychotropic-induced weight gain; fluoxetine is not approved for the treatment of weight loss in obesity and antipsychotic-induced weight gain; and topiramate and zonisamide are not approved for the treatment of weight loss in obesity, psychotropic-induced weight gain, and bipolar disorder.

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