Weight Gain in the Treatment of Mood Disorders

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Overweight and obesity have become an urgent public health problem in the United States: approximately 61% of the adult population (97 million adults) are overweight or obese, where overweight is defined as a body mass index (BMI) ≥ 25 and obesity is defined as a BMI ≥ 30. Overweight and obesity increase the risk for developing many serious chronic diseases such as cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, and certain cancers. Increased morbidity due to obesity-related disorders begins within the normal weight range. Weight gain in adulthood per se, even in individuals who are normal weight, has deleterious health effects. Medications, particularly those commonly used in psychiatry and neurology, are a significant iatrogenic source of overweight and obesity. The weight gain potential of prescription medications should be considered in order to enhance patient compliance and reduce the risk of metabolic sequelae of weight gain. This article provides an overview of the weight-gain potential of several classes of drugs commonly used in psychiatric practice and considerations for clinicians in prescribing these medications.

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Approximately 97 million adults in the United States (~61% of the population) are overweight or obese, where overweight is defined as a body mass index (BMI) ≥ 25 and obesity is defined as a BMI ≥ 30.[1] The burden of overweight and obesity is enormous and includes increased risk for developing many chronic diseases such as cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, sleep apnea, and certain cancers.[2–4] Obesity in the United States is responsible for approximately 300,000 deaths per year[5] and has direct (medical expenses) and indirect (value of lost productivity) costs that exceed $100 billion/year.[6]

Weight gain during adulthood represents an additional risk factor for medical complications beyond those associated with obesity. Epidemiologic data indicate that a gain of 5 kg (11 lb) or more in body weight after the age of 18 to 20 years increases the risk of developing diabetes, hypertension, and coronary heart disease in both men and women, even in those who are initially lean adults (BMI of 18.5–24.9 kg/m^2).[7–9]

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Recent guidelines from the National Institutes of Health and other experts recommend weight gain prevention to minimize health risks from overweight and obesity.[2,3] This prevention entails preventive and public health initiatives beginning in childhood and an understanding of factors that contribute to the risk of weight gain in adulthood. Prescription medications, including those commonly used in psychiatry and neurology, are a significant iatrogenic source of overweight and obesity. Accordingly, the weight-gain potential should be considered when prescribing these medications.

IMPLICATIONS FOR CLINICAL PRACTICE

The health risks of overweight and obesity, the poor success rate of long-term maintenance of weight loss, and the documented benefits of modest weight loss[10–11] suggest that preventing or minimizing weight gain are important health care interventions. The first step in this process is establishing a patient's baseline weight and determining if a weight problem already exists. Guidelines for evaluating body weight are described in detail elsewhere.[2] Second, it is important to identify patients who are at potential risk for further weight gain, such as those for whom concomitant illnesses and the treatment for those illnesses are associated with weight gain.

Psychiatrists can play an important role in managing overweight and obesity by recognizing that substantial weight gain is a side effect of a number of psychotropic drugs. This weight gain impairs adherence to the treatment regimen, but it also has deleterious health consequences

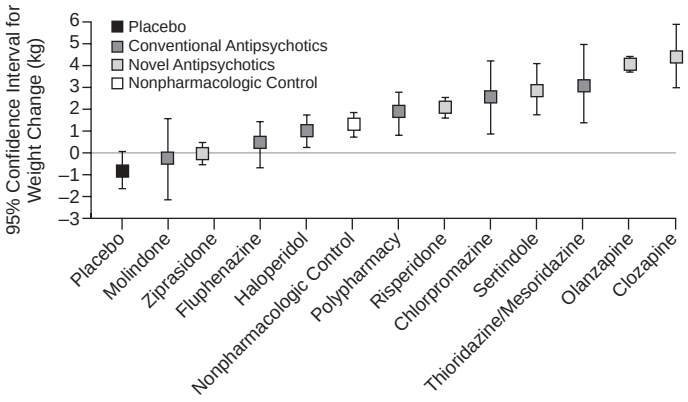
such as increased risk of developing obesity-related comorbid conditions such as type 2 diabetes and hypertension. Weight gain exacerbates these conditions in patients who are already affected by them. Therefore, the weight-gaining or weight-reducing effects of centrally acting agents should be considered in the selection of medications. When appropriate, medications that are weight neutral or could promote weight loss should be considered.

ANTIPSYCHOTIC AGENTS

Although better tolerated than the older antipsychotic agents because of the lack of extrapyramidal side effects, many of the new atypical antipsychotic agents have weight gain as a common side effect.[12] This weight gain is of clinical concern because it impedes patient compliance and has deleterious health consequences.[12–13] The differential effect of atypical antipsychotics on antihistamine (H_1) receptors, anticholinergic effects, and serotonin 5-HT_{2C} antagonistic effects may explain differences in weight gain among the drugs. Moreover, the prevalence of overweight and obesity in patients with schizophrenia—without regard to therapy—may be as high as or higher than in the nonschizophrenic population, while the complications of obesity (e.g., diabetes, dyslipidemias, and hypertension) may be underdiagnosed and undertreated in these patients.[12] Weight gain contributes substantially to treatment noncompliance, but it also confers the additional health risks associated with obesity.[12–14] Recent studies document these risks: Henderson et al.[15] demonstrated that weight gain associated with clozapine treatment continued for as long as 46 months and was accompanied by a significant increase in triglyceride levels and a 37% increase in the incidence of type 2 diabetes over the 5-year period of observation. Allison and Casey[12] noted the effects of switching patients from olanzapine to ziprasidone: patients lost weight when switched to ziprasidone, and this weight loss was associated with improvements in their serum lipid profile and glucose tolerance.

Allison et al.[16] reviewed and compared the effects of a broad range of antipsychotic agents on body weight. This meta-analysis of 81 reports estimated the weight change after 10 weeks of treatment at the standard dose for each agent. Compared with placebo treatment, which was associated with a mean weight reduction of 0.74 kg (1.64 lb), the mean weight changes with conventional antipsychotic agents ranged from a loss of 0.39 kg (0.87 lb) (molindone) to a gain of 3.19 kg (7.08 lb) (thioridazine/mesoridazine). Among the newer agents, clozapine produced the greatest weight increase and ziprasidone produced the least increase (Figure 1). Quetiapine was not included in the analysis because of limited data; however, a later report noted that 25% of patients gained at least 7% of their initial body weight.[13]

Figure 1. 95% Confidence Intervals for Estimated Weight Change After 10 Weeks of Treatment With Standard Drug Doses[a]



[a]Reprinted with permission from Allison et al.[16]

Pairwise comparisons among all of the antipsychotic agents indicated statistically significant differences among the drugs.[16] The key point is that with the exception of ziprasidone, all of the newer agents were associated with significantly greater weight gain than placebo after just 10 weeks of therapy. There is marked variation in the reported weight gain associated with long-term use of these atypical antipsychotic agents, ranging from virtually zero gain with ziprasidone to an average gain of 12 kg (27 lb) after 1 year of treatment with olanzapine.[16] Risperidone produced less weight gain than sertindole, olanzapine, or clozapine.

Clinical Implications of Weight Gain Associated With Antipsychotic Medications

Fontaine et al.[17] estimated the expected impact of varying degrees of weight gain associated with use of antipsychotic medications on health (impaired glucose tolerance and hypertension) and mortality rate and compared the increased risk of mortality due to weight gain of 10 kg (22 lb) with the reduced risk of mortality from suicide in the population of schizophrenic patients. The investigators estimated that 492 suicide deaths per 100,000 schizophrenic patients would be prevented over the course of 10 years with the use of clozapine compared with the occurrence of 416 additional deaths due to antipsychotic-induced weight gain of 10 kg (22 lb).

Because of the medical significance of this weight gain,[3,5] efforts should be made to minimize weight gain in the schizophrenic patient population. While further research is needed to provide specific guidelines on the management of weight gain in patients taking antipsychotic drugs, Allison and Casey[12] provide the following recommendations: (1) assess baseline body weight—a subgroup of patients with schizophrenia will be thin enough to tolerate some weight gain, others will not, (2)

consider agents associated with a lesser degree of weight gain in patients with an average or higher BMI when it is appropriate therapeutically, and (3) determine if the degree of risk from weight gain is more important than the antipsychotic benefits of the specific drug.

ANTIDEPRESSANT AGENTS

Weight changes in patients undergoing treatment for depression are complicated by several factors. First, weight gain can represent an improvement in those who may have lost weight as a result of their depression. Second, ongoing weight gain may be a residual symptom of depression. Last, it can be a side effect of treatment. This last possibility may be most likely when substantial weight gain occurs during the acute phase of treatment or when it continues following complete remission of depressive symptoms. As is the case with antipsychotic medications, weight gain associated with use of antidepressant medications is an important source of treatment noncompliance and may also contribute to the increased health risks associated with overweight and obesity. The relative risk for weight gain associated with antidepressant therapy has been reviewed by Fava.[18] That analysis suggests that tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are more likely to cause weight gain than the selective serotonin reuptake inhibitors (SSRIs) or some of the newer antidepressants.

Weight gain induced by TCAs has been recognized for many years, and amitriptyline in particular may be associated with the greatest weight gain. Several reports suggested that weight gain with TCAs ranged from 0.57 kg (1.27 lb) to nearly 1.4 kg (3.1 lb) per month of treatment.[18] Within the class of SSRIs, paroxetine may be more likely to cause weight gain than other agents.[19] Interpretation of these findings is complicated by confounding variables such as possible return of depressive symptoms and the lack of placebo-controlled trials. Frequently, weight gain reported with SSRI use does not differ from that reported with placebo in other studies and may reflect the restoration of prior body weight loss due to depressive illness.

The atypical antidepressants bupropion and nefazodone appear to cause less weight gain in the long term. Nefazodone is relatively weight neutral,[19] and bupropion may be associated with weight loss.[20] Fava et al.[21] reported that more patients treated with paroxetine compared with either fluoxetine or sertraline gained ≥ 7% of their baseline weight during 26 to 32 weeks of treatment. Sussman et al.[19] noted that published data on newer antidepressants and treatment-emergent changes in weight are somewhat limited and that many reports of unexpected weight gain with SSRIs were anecdotal or from small uncontrolled trials. These investigators conducted a retrospective analysis of data from trials comparing nefazodone with various SSRIs and with the TCA imipramine. Medications were considered to cause clinically significant weight change if the patients gained or lost at least 7% of their baseline weight. Acute effects were assessed after 6 or 8 weeks of treatment. Long-term effects of treatment were evaluated from 16 to 46 weeks. SSRIs were associated with greater weight loss than nefazodone during acute treatment: 4.3% of SSRI-treated patients lost weight compared with 1.7% of nefazodone-treated patients ($p = .017$).[19] In contrast, during long-term treatment, 17.9% of SSRI-treated patients gained weight compared with 8.3% of nefazodone-treated patients ($p = .003$). Imipramine produced greater weight gain than nefazodone during both the acute treatment phase (4.9% vs. 0.9%, respectively; $p = .027$) and long-term treatment (24.5% vs. 9.5%, respectively).

In a controlled, long-term study of bupropion sustained release (SR) in depressed patients, weight change was evaluated as one of the safety measures.[20] Patients with recurrent major depression received bupropion SR for 8 weeks in an open-label phase, and responders were then randomly assigned to continue with bupropion SR or placebo for 44 additional weeks. At the end of the 8-week open-label phase, an overall mean weight loss of 1.4 kg (3.1 lb) was observed.[20] Patients with higher baseline BMIs had a greater mean weight loss than did patients with lower baseline BMIs. During the double-blind treatment phase, more bupropion-treated patients experienced a greater-than-5% weight loss than did placebo-treated patients. During the long-term treatment phase, the maximum mean loss was 1.7 kg (3.8 lb) in patients with an initial BMI < 22, 2.1 kg (4.7 lb) in patients with a baseline BMI ≥ 27, and 2.4 kg (5.3 lb) in patients with a baseline BMI ≥ 30. Thus, it was concluded that bupropion SR resulted in a small mean weight loss that was maintained over the long term.

Masand[22] evaluated the relative risk of weight gain associated with drugs within the major classes of antidepressant medications. As shown in Table 1, the antidepressants vary considerably with respect to their long-term weight-gain potential.

MOOD STABILIZERS (LITHIUM)

Lithium has been used widely since 1970 for treating bipolar disorder despite a number of side effects, a narrow therapeutic window, and limited effectiveness in some patients. Weight gain is a common side effect of lithium therapy,[23,24] occurring in one third to two thirds of patients. The weight gain associated with the use of lithium can range from 5 kg (11 lb) within 1 to 2 years to 4.5 to 15.6 kg (10.0–34.6 lb) over 2 years.[24]

ANTIEPILEPTIC DRUGS

Antiepileptic drugs have been used in a number of therapeutic categories in both neurology and psychiatry.

Table 1. Relative Risk of Weight Gain Associated With Antidepressant Drugs[a]

Class/Drug	Estimated Risk/Potential
Tricyclic antidepressants	
Amitriptyline	3
Imipramine	2
SSRIs	
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimeldine	0–1
MAOIs (nonselective)	
Isocarboxazid, phenelzine, tranylcypromine	2–3
MAOI-As	
Brofaromine, moclobemide	0
MAOI-B	
Selegiline	0
Novel antidepressants	
Bupropion, nefazodone, venlafaxine	0
Mirtazapine	4

[a]Reprinted with permission from Masand.[22] For estimated risk/potential, 0 = lowest risk and 4 = highest risk.
Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

The broad usage of some of these agents may be attributed to their relatively wide-ranging mechanisms of action in the central nervous system. These actions include prolonged inactivation of sodium channels, potentiation of γ-aminobutyric acid (GABA) transmission, and, in some cases, actions on glutamate receptors.[25] In addition to their primary indications in epilepsy, a number of these agents have been proven safe and effective in mood stabilization in bipolar disorder as well as migraine and cluster headache prevention and painful diabetic neuropathy.

Most older antiepileptic drugs and some of the newer ones—with the exceptions of topiramate, lamotrigine, and the infrequently used drug felbamate—are associated with weight gain. The most commonly used antiepileptic drugs are valproate, which has broad indications, and the newer agents lamotrigine and topiramate. Until recently, weight change in patients treated for neurologic or psychiatric conditions was not regarded as essential information in evaluating therapy. As a result, weight change has not been evaluated consistently in clinical trials with antiepileptic drugs or other psychoactive drugs. In addition, many trials with weight change data are not well controlled: they may be retrospective analyses or have inadequate baselines and not have controlled for an underlying trend to increase body weight over time.

Valproate

Valproate in its various formulations is indicated for seizure disorders, manic episodes associated with bipolar disorder, and migraine prevention.[25] Weight gain has been reported as a side effect of valproate.[26,27] One retrospective analysis suggested that approximately 50% of patients receiving long-term valproate treatment for epilepsy gained weight during treatment.[27] Obesity and endocrine disorders (polycystic ovaries and hyperandrogenemia) have been reported in women receiving valproate therapy for epilepsy, and obesity-induced insulin resistance and hyperinsulinemia have been proposed as the underlying cause of the endocrine dysfunctions.[27] In that study, 13 (59%) of 22 women treated with valproate had a BMI greater than 25. In comparison, only 5 (12%) of 43 healthy women who served as controls had a BMI greater than 25 ($p < .001$). Fifty percent of the women gained a substantial amount of weight. The authors also suggested that weight gain with valproate treatment could continue for years.[27] Of the valproate-treated women, 14 (64%) had polycystic ovaries, hyperandrogenemia, or both ($p < .001$ vs. controls). Weight gain in 10 of these 14 women averaged 22 kg (49 lb) (range, 8–49 kg [18–109 lb]). Valproate-treated patients also exhibited high fasting serum insulin concentrations and low levels of serum insulin-like growth factor binding protein.[27]

The long-term safety of valproate in migraine prevention was assessed in a study by Silberstein and Collins.[28] Overall, 19% of patients reported weight gain. Patients on valproate therapy gained significant amounts of weight by week 10 of treatment ($p < .002$), and body weight continued to increase throughout the study. Unlike other side effects, this weight gain did not diminish over the course of the study.

Gidal et al.[29] evaluated the contributions of energy intake and energy expenditure to weight gain in subjects treated with valproate monotherapy and observed an inappropriately low resting metabolic rate but not excessive food intake in patients who gained more than 5 kg (11 lb) after 6 months of therapy compared with both healthy controls and with valproate-treated subjects who did not gain weight.

Considerable evidence thus suggests that valproate has substantial weight gain potential that is also associated with metabolic effects. Therefore, clinicians should consider therapeutic alternatives when weight is a concern or may become a concern, particularly in younger women who appear to be at risk for developing polycystic ovarian syndrome.

Gabapentin

Although indicated to reduce seizure frequency, gabapentin is often used for nonepileptic indications, such as migraine prevention, neuropathic pain, bipolar disorders, and other conditions.[30] Weight change was not reported in studies of the use of gabapentin in painful neuropathy.[30,31] DeToledo et al.[32] evaluated weight changes associated with chronic, high-dose gabapentin therapy for seizure disorders. The authors reviewed weight changes in 44 gabapentin-treated patients for a period of at least 12 months. The minimum gabapentin dosage was 1800 mg/day; 28 of the patients received more than 3000 mg/day. Overall, 57% of patients gained more than 5% of

their baseline body weight; of these, 10 patients (23%) gained more than 10% of their baseline weight.[32] The mean weight gain was 1.9 kg (4.2 lb) at 6 months and 2.9 kg (6.4 lb) at 12 months. In most cases, weight gain became apparent between 2 to 3 months and stabilized after 6 to 9 months of treatment. Neither a previous history of weight gain with valproate nor concomitant therapy with other antiepileptic drugs predicted weight gain with gabapentin. Weight gain had not been reported in earlier studies of gabapentin, and the authors suggest that the observations in this study could have been related to the higher doses.

Lamotrigine

Like other antiepileptic drugs, the efficacy of lamotrigine for nonseizure disorders is under investigation.[33] Currently indicated for seizure disorders, lamotrigine is considered to be weight neutral, as demonstrated by a review of published studies.[34] This retrospective analysis evaluated weight data from 463 patients in 32 clinical trials conducted with lamotrigine. All patients were adults with epilepsy. The mean duration of lamotrigine therapy was 318 days at a mean daily dose of 259 mg. Most patients were receiving concomitant therapy with at least 1 other antiepileptic drug. The mean change in body weight was 0.4 ± 5.0 kg (0.9 ± 11.1 lb) in women and 0.6 ± 5.0 kg (1.3 ± 11.1 lb) in men and followed a normal distribution. These data suggested that lamotrigine had no significant impact on body weight. These findings were confirmed in a recent double-blind, placebo-controlled trial.[35]

Biton et al.[35] evaluated weight changes associated with valproate and lamotrigine monotherapy in patients with epilepsy. Patients underwent up to 2 weeks of screening, followed by an 8-week dose escalation phase and a 24-week maintenance phase. Clinically relevant weight gain was defined as a gain of at least 4.0 kg (8.9 lb) or 10% or more of baseline body weight. Weight remained relatively stable in patients receiving lamotrigine. Although baseline BMI was similar in the 2 treatment groups, by the end of the study (week 32), mean weight gain in valproate-treated patients (12.8 ± 9.3 lb [5.8 ± 4.2 kg]) was significantly greater compared with that in lamotrigine-treated patients (1.3 ± 11.9 lb [0.6 ± 5.4 kg]; $p < .002$). Furthermore, 38% of the valproate-treated patients gained > 10% of their initial weight compared with 8% of the lamotrigine-treated patients. Weight gain occurred in both men and women with no significant gender differences. In this study, no predictors of weight change were identified. These results suggest that lamotrigine may be a suitable alternative to valproate when body weight is a concern.

Topiramate

Topiramate is associated with weight loss or weight stability rather than weight gain in the majority of patients. Like other antiepileptic drugs, topiramate is indicated for epilepsy, but its therapeutic potential in a number of other disorders, including migraine prevention, bipolar disorder, binge eating, painful diabetic neuropathy, and obesity, is under investigation. Weight change with topiramate has been assessed in several small published trials.

Potter et al.[36] reported sustained weight loss with 12-month topiramate therapy in a small, single-center, dose-titration study of 16 patients. In that study, the weight loss was greatest between 3 and 6 months, peaked at 9 months, and was sustained over the course of the study. Topiramate titration rate, initial body weight, and use of concomitant antiepileptic drugs were not predictors of weight loss. Recently, Smith et al.[37] reported that topiramate significantly reduced body weight ($p < .01$) and lowered food intake in patients with epilepsy. The investigators evaluated weight, body composition, food intake, thyroid hormone levels, fecal fat excretion, oral glucose tolerance test results, and glucose, insulin, lipid, and leptin levels. When weight loss data for the 34 patients who completed 1 year with a median dosage of 175 mg/day were examined, weight loss was most evident in obese patients: 7 of 8 patients with a BMI greater than 30 lost at least 5% of their initial body weight and the mean weight loss within this group was 11% of initial body weight. The reduction in body weight was associated with a 20% loss of body fat mass and only a 4% loss of lean body mass.[37] Blood glucose levels decreased by 16%, and insulin values decreased by 24% in obese topiramate-treated patients. Fasting triglyceride levels also declined substantially from 2.7 to 2.0 mmol/L in the obese patients.[37] Self-reported food intake was decreased, and no evidence of malabsorption was found. Weight loss with topiramate therapy has also been observed in trials for other neurologic and psychiatric conditions. In a double-blind, placebo-controlled trial on the efficacy and safety of topiramate for painful diabetic neuropathy, weight loss was one of the most common side effects.[38] In open-label studies of topiramate as add-on therapy in bipolar disorder, significant reductions in both body weight ($p < .05$) and BMI ($p \leq .002$) during therapy were reported.[39,40] As in the study by Smith et al.,[37] the degree of body weight loss was associated with initial body weight in one of these investigations.[39]

Topiramate therapy has also been associated with weight loss in patients with binge-eating disorder.[41] In an open-label study of 13 patients with binge-eating disorder as defined by DSM-IV criteria, topiramate therapy resulted in a significant mean weight loss from baseline (99.3 ± 26.4 kg [220.4 ± 58.6 lb] to 87.5 ± 20.4 kg [194.3 ± 45.3 lb]; $p = .02$). Seven of the 13 patients lost at least 5 kg (11 lb), and weight loss was related to the topiramate dose.[41]

The consistently noted weight loss associated with topiramate prompted preclinical studies to clarify its effects on energy balance. These studies have demonstrated that topiramate significantly reduced fat deposition

in animals by reducing food intake and/or stimulating energy expenditure.[42,43]

Other Antiepileptic Drugs

Carbamazepine and phenytoin have both been noted to produce weight gain, although the weight gain potential is smaller than that with either valproate or gabapentin.[44] Tiagabine, a recently approved selective GABA uptake inhibitor, appears to be weight neutral when used as add-on therapy.[44]

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

Overweight and obesity are of increasing concern in all fields of medicine because they contribute negatively to the overall health of patients and to health care costs. In many therapeutic categories, iatrogenic obesity—that associated with specific medications—contributes to reduced adherence to the medication regimen. In patients with schizophrenia, for example, weight gain is a leading cause of noncompliance, which can result in relapse and rehospitalization.

General Recommendations

Because overweight and obesity are associated with significant morbidity and mortality, it is essential to incorporate weight assessment into clinical practice. The most important and first step is to weigh all patients and monitor weight changes over the course of therapy. BMI should be calculated, or estimated from a chart. In some patients, it may be beneficial to measure waist circumference as an independent measure of health risk. The possibility of weight gain as a side effect should be discussed with patients before initiating therapy. Some patients may be amenable to beginning dietary interventions before therapy starts. To distinguish medication-induced weight gain from weight gain caused by other factors, a history of recent weight changes should be obtained prior to starting medication.

For overweight or obese patients, agents that do not promote weight gain or that are weight neutral should be considered as alternative therapeutic agents. Similarly, if normal-weight patients begin to exhibit a pattern of weight gain, switching to a medication that is not associated with weight gain or to one that promotes weight loss may be beneficial. In all cases, these decisions assume that the primary condition can be managed effectively with alternative agents and that other, possibly comorbid conditions are not exacerbated by medication changes. Table 2 presents a summary of common agents used in neurology and psychiatry grouped by their effect on body weight. Note that these are not absolute classifications and that effects may differ among individuals and according to dosage and duration of therapy. The mechanisms of weight gain associated with use of psychotropic medications, as reviewed by Malhi et al.[45] and shown in Figure 2, are complex and involve both energy intake and energy expenditure pathways.

Table 2. Drugs That May Promote Weight Gain and Therapeutic Alternatives

Drugs That May Promote Weight Gain	Drugs That Are Weight Neutral or Promote Weight Loss
Psychiatric/neurologic medications	Alternative psychiatric/neurologic medications
Antipsychotics	Antipsychotics
Olanzapine, clozapine	Ziprasidone, risperidone, quetiapine
Antidepressants	Antidepressants
SSRIs, TCAs, MAOIs	Bupropion, nefazodone
Antiepileptic drugs	Antiepileptic drugs
Gabapentin, valproate, carbamazepine	Topiramate, lamotrigine
Lithium	
Steroid hormones	Alternatives to steroid hormones
Hormonal contraceptives	Barrier methods
Corticosteroids	NSAIDs
Progestational steroids	Weight loss
Antidiabetic agents	Alternative antidiabetic agents
Insulin	Metformin
Sulfonylureas	Acarbose, miglitol
Thiazolidinediones	Orlistat, sibutramine
Antihistamines	Decongestants, inhalers
Antihypertensive agents	Alternative antihypertensive agents
α- and β-Adrenergic blockers	ACE inhibitors, calcium channel blockers
Protease inhibitors[a]	

[a]May cause weight gain, but less than the drugs they replace.
Abbreviations: ACE = angiotensin-converting enzyme, MAOI = monoamine oxidase inhibitor, NSAID = nonsteroidal anti-inflammatory drug, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

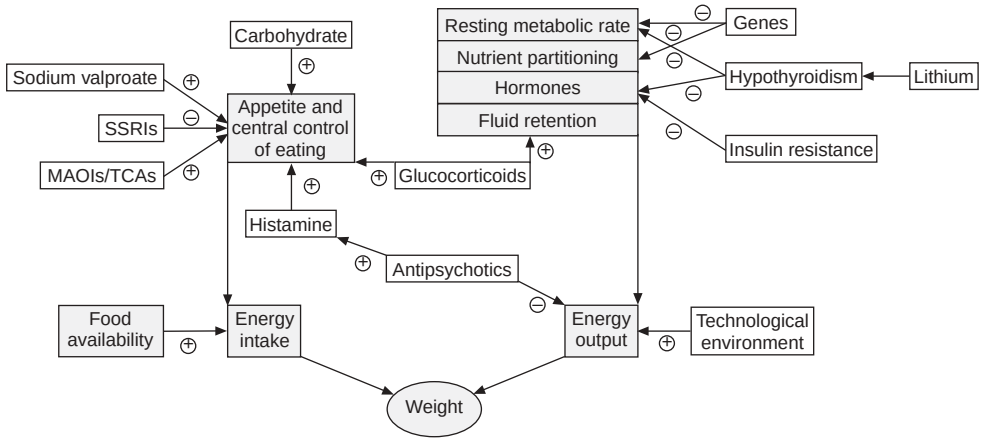
In addition to agents that act in the central nervous system, many other medications may also cause weight gain.[46] Alternatives are available in many therapeutic categories as well. It is important to determine whether other medications as well as nonpharmacologic factors, such as changes in diet and physical activity, also contribute to observed weight gain.

CONCLUSION

In summary, obesity is a known risk factor for many disorders, and modest weight loss of 5% to 10% is associated with significant health benefits. Pharmacologic treatment for many psychiatric and neurologic conditions may be associated with substantial weight gain that increases morbidity and mortality and impedes patient compliance. Thus, it is critical to weigh patients regularly, determine whether medication regimens are contributing to weight gain, and consider agents that do not promote gain or that may cause weight loss. Drug selection for each patient must be based on the patient's profile and suitability of alternative agents for that individual without sacrificing therapeutic efficacy.

Drug names: acarbose (Precose), amitriptyline (Elavil and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), citalopram (Celexa), clozapine

Figure 2. Proposed Mechanisms for Weight Gain Associated With Psychotropic Drugs[a]



[a]Reprinted with permission from Malhi et al.[45] Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Symbols: + = facilitation, – = inhibition.

(Clozaril and others), felbamate (Felbatol), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), mesoridazine (Serentil), metformin (Glucophage), miglitol (Glyset), mirtazapine (Remeron), molindone (Moban), nefazodone (Serzone), olanzapine (Zyprexa), orlistat (Xenical), paroxetine (Paxil), phenelzine (Nardil), phenytoin (Dilantin), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl and others), sertraline (Zoloft), sibutramine (Meridia), tiagabine (Gabitril), topiramate (Topamax), tranylcypromine (Parnate), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, lamotrigine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; orlistat and sibutramine for the treatment of type 2 diabetes; and topiramate for the treatment of bipolar disorder, migraine headaches, binge-eating disorder, diabetic neuropathy, and obesity.

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