

Weight Gain Associated With Use of Psychotropic Medications

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Weight gain is associated with the use of many psychotropic medications, including lithium, valproic acid, and several conventional and newer antipsychotics. Patients asked to select from among several comparable drugs often choose the one least likely to cause weight gain, even if the drug is less effective or has other troublesome adverse effects. For many patients, weight gain is so intolerable that they discontinue treatment. Patients who continue treatment are at risk for clinically significant weight gain that can progress to obesity. Even after patients stop taking the drug, weight gained during therapy may be difficult to lose. Thus, the best approach is to attempt to prevent weight gain when feasible, possibly through pretreatment dietary counseling and judicious drug selection, and to intervene as soon as weight gain becomes evident. (*J Clin Psychiatry* 1999;60[suppl 21]:16-19)

For patients with schizophrenia, bipolar disorder, clinical depression, or other mental illness, psychotropic drugs can be an effective means of relieving symptoms and improving the overall quality of life. However, a prime drawback to the use of many psychotropic medications is their potential for causing significant weight gain. Although the problem often receives little attention, weight gain associated with drug use is quite common. Nearly 25% of all cases of obesity are drug related.¹

From clinical experience, we know that many patients taking psychotropic medications gain enough weight to adversely affect their health and that losing this weight, even after the psychotropic drug is discontinued, can be difficult. Being able to predict which patients will gain the most weight and knowing which drugs cause the greatest weight gain are valuable skills for patient management. Yet, clinical data may provide little help in these areas. One problem is that there is no standard definition of clinically significant weight gain. (The U.S. Food and Drug Administration defines significant weight gain as an increase of 7% or more of body weight, but this definition has not been universally adopted.) Some investigators report changes in raw weight only, which has clinical meaning only in relation to the size of the patient.² Change in body mass index and percentage increase in body weight

are more useful measures of weight gain,² provided these measures are compared with baseline values (which is not always the case in many studies).

Results of clinical trials of psychotropic drugs published in manufacturer's prescribing information typically report minimal weight gain in a low percentage of patients. However, these data are usually derived from short-term studies, of no more than 6 to 8 weeks' duration. These results are not helpful because treatment is seldom of such brief duration. Researchers also may not take into account the effect of prior treatment. Patients who gain weight with a previous drug may reach a plateau and thus gain little additional weight when they are started with a different psychotropic medication. As a result, the effect of the newer medication on weight may be underestimated.

Further confounding the study of weight gain and psychotropic drugs is the effect of various patient variables. Age, sex, and diagnosis can all affect drug-related changes in weight. For example, patients with bipolar disorder who are treated with lithium gain considerably more weight than do those with unipolar disorder also treated with lithium. Similarly, patients with bipolar disorder treated with antipsychotics may gain more weight than do those with schizophrenia who are taking these drugs.

ANTIDEPRESSANTS

For the past 35 years, researchers have been reporting excessive weight gain with the use of tricyclic antidepressants,³ a class that includes amitriptyline, imipramine, nortriptyline, and doxepin. Recent reviews, however, suggest that weight gain associated with this class of drugs may be overestimated.² In their review of several studies, Garland et al.⁴ reported that weight change among patients taking tricyclic antidepressants varied from -0.4 kg/month to 4.1

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kg/month (−0.9 to 9 lb/mo) and was related to the dose, duration of therapy, and specific tricyclic antidepressant used (among all tricyclic antidepressants, amitriptyline and imipramine appear to cause the greatest weight gain). In some long-term studies,⁵ less weight gain than expected has been reported. However, these data include only those patients continuing long-term treatment and omit patients who may have withdrawn from the study because of weight gain.

Some patients quickly gain a considerable amount of weight, as much as 15 to 20 kg (33–44 lb) within 2 to 6 months after starting treatment.³ Yet, some patients may actually lose weight when taking a tricyclic antidepressant that causes weight gain in others.³ Even though the potential for weight gain appears to vary among the different drugs in this class, depressed patients do worry about weight gain and often discontinue treatment because of it. In one study, 48% of patients stopped taking their tricyclic antidepressant because of an increase in body weight.³

Monoamine oxidase inhibitors are also reported to cause weight gain, but usually to a similar or lesser extent than tricyclic antidepressants.^{2,3} However, the newer selective monoamine oxidase inhibitors, which include moclobemide, brofaromine, and cimoxatone, do not appear to affect body weight.² In one comparative study, patients treated with a tricyclic antidepressant gained an average of 1.7 kg (3.7 lb) over 7 weeks, while no changes in weight were observed in patients given moclobemide.⁶

Selective serotonin reuptake inhibitors (SSRIs) reportedly are associated with a decrease in appetite and an increase in the basal metabolic rate.³ Consequently, acute treatment with these drugs has not been shown to increase body weight and may induce significant weight loss in some patients.² In one study comparing the SSRI zimeldine with 3 tricyclic antidepressants,⁷ patients taking a tricyclic antidepressant gained weight, while 69% of patients treated with zimeldine maintained their baseline weight and 23% lost between 1.4 to 2.7 kg (3.1 to 5.9 lb). However, this study was only 4 weeks long and short-term trials may underestimate the long-term effects of a medication on weight. During the acute phase of treatment, SSRIs are often associated with weight loss. However, during maintenance treatment with SSRIs, patients tend to gain weight. In our clinic, between 25% to 33% of patients taking SSRIs for 12 weeks or longer gain a substantial amount of weight. Weight loss does not occur with all SSRIs; paroxetine, for example, often increases appetite soon after treatment is started and may be more likely than other drugs in this class to induce weight gain.⁸

LITHIUM

One third to two thirds of patients treated with lithium gain weight.² An average weight gain of 10 kg (22 lb) over 6 to 10 years has been reported,⁴ but some patients experience impressive weight gain.⁹ Approximately 25% of pa-

tients treated with lithium gain enough weight to be considered obese.¹⁰ Lithium-induced weight gain is a dose-dependent phenomenon, with increases in weight less likely at plasma lithium concentrations of less than 0.8 mmol/L. However, because these low plasma concentrations are suboptimal, dose reduction may not be an option for preventing weight gain in patients taking lithium.²

Not surprisingly, weight gain is among the leading reasons patients discontinue taking lithium, even if they are responding well to the drug. In one study of 1594 patients enrolled in a health maintenance organization, nearly all patients had discontinued lithium use within 5.5 years.¹¹ Most patients stopped taking the drug early in treatment; the median time for continuous use was 10.8 weeks. Weight gain is more common among patients who are already overweight and may be more common in women than men.^{2,3}

Various mechanisms have been proposed to explain how lithium promotes weight gain, including increased appetite, altered carbohydrate and fat metabolism, lithium-induced hypothyroidism,¹² increased fluid intake, and endocrinologic changes.² However, none of these mechanisms have held up under study; the data are often variable and inconsistent.² What is more clear, though, is that lithium probably has an independent pharmacologic effect on body weight that is unrelated to its effects on the underlying disorder.²

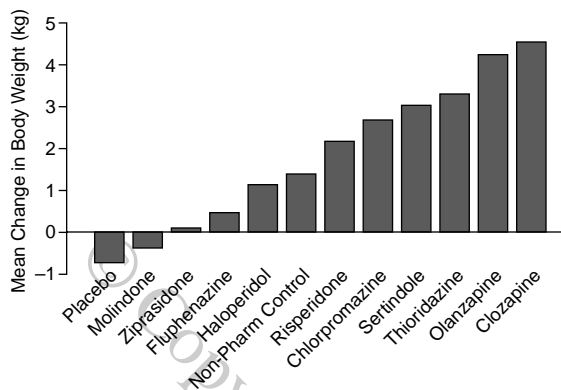
MOOD STABILIZERS (ANTICONVULSANTS)

The anticonvulsants valproic acid (sodium valproate), carbamazepine, gabapentin, lamotrigine, vigabatrin, and topiramate are often prescribed to stabilize the mood of patients with bipolar disorder. With the exception of topiramate, weight gain has been reported with each of these drugs.

Among valproate responders in my (G.S.S.) practice, weight gain is the most common reason patients discontinue treatment. Recent reports find between 8% and 59% of patients gain between 8 to 14 kg (17.6 to 30.8 lb) when taking valproate,² and some patients gain as much as 15 to 20 kg (33 to 44 lb).³ In one of the few double-blind, controlled studies of valproic acid for maintenance treatment of bipolar disorder, Bowden et al.¹³ reported that a gain of more than 7% of body weight occurred in 4% of patients receiving placebo, 16% of those given lithium, and 23% of those treated with divalproex. Dinesen et al.¹⁴ found that weight gain varied considerably among individual patients and appears to have no relationship to the patient's sex, pretreatment body weight, or valproate dose.

Weight gain with valproic acid is associated with the duration of treatment.¹³ The percentage of patients who gain weight when valproic acid is used as monotherapy or added to other medications increases considerably after 20 months.^{13–15} Men are at greater risk for weight gain with valproic acid than are women.¹⁵ Women, however, who be-

Figure 1. Estimated Mean Weight Gain at 10 Weeks for Selected Antipsychotic Drugs^a



^aAdapted from Allison et al.²⁰

come obese while taking valproic acid may be at increased risk for hyperandrogenism. The reported incidence of hyperandrogenism is quite high among women with epilepsy taking valproic acid, but is not evident in clinical populations treated for bipolar disorder.¹⁶

Reports of weight gain with carbamazepine are conflicting, with some studies reporting weight gain comparable to that seen with valproic acid and others reporting that it is less severe and less likely to occur.^{2,3} Gabapentin and vigabatrin have both been associated with weight gain. In one long-term study of vigabatrin,¹⁷ 48% of patients gained 3% to 33% of their initial body weight. Yet in a study using similar drug doses, only 6% of patients taking vigabatrin gained weight (mean gain = 10% of initial body weight).¹⁸ Results in both studies may have been affected by the by other concurrently administered drugs. Weight gain does not appear to be a problem with lamotrigine.

Clinical reports indicate that topiramate promotes weight loss and, when added to an existing treatment regimen, may lessen weight gain associated with other drugs. The possibility of weight loss is an attractive feature of this drug for many patients.

ANTIPSYCHOTICS

No generalizations can be made about weight gain associated with the use of antipsychotic drugs (this topic is reviewed in detail by Ganguli¹⁹ in this issue). Even among individual drug classes, such as the newer atypical antipsychotics, the potential for weight gain varies substantially owing to the varying affinity of these drugs for different neurotransmitter receptors.

As shown in Figure 1, clozapine and olanzapine, 2 newer antipsychotics that have similar receptor binding profiles, cause the greatest mean weight gain over a 10-week period.²⁰ Ackerman and Nolan² note that clozapine has frequently been implicated in some of the largest

weight gains attributed to use of antipsychotic agents. Retrospective studies have reported increases from baseline body weight of 9% to 11% in patients taking clozapine for up to 6 months.² In one study of patients treated with 500 to 600 mg of clozapine for up to 90 months, almost half of the patients gained 20% or more of their pretreatment weight.²¹ Similar results were seen in a randomized, double-blind trial comparing clozapine with haloperidol. In this study,²² patients treated with clozapine for 10 weeks gained an average of 7% of their baseline body weight while those given haloperidol gained only 1% of their pretreatment weight. Among the patients who elected to continue clozapine therapy after the study ended, 58% gained at least 10% of their baseline body weight and 21% gained more than 20% of their baseline weight.

The potential for weight gain with other newer antipsychotics (risperidone, sertindole, quetiapine, and ziprasidone) is less than that with clozapine and olanzapine. In analyzing data from patients treated with olanzapine or risperidone at our clinic, we (C. Guille, G. S. Sachs, S. M. Ghaemi, unpublished data, 1999) found significant differences in weight gain among patients treated for 12 weeks or longer. In patients receiving olanzapine, the mean weight gain was 10.7 kg (23.5 lb) after a mean duration of treatment of 33 to 36 weeks. In the risperidone group, the mean weight gain was 1.7 kg (3.7 lb) and the duration of treatment was considerably longer (mean = 112 weeks) ($p < .05$).

Among the conventional neuroleptics, the potential for weight gain is greatest with thioridazine and chlorpromazine (weight gain associated with chlorpromazine may be dose dependent).²³ Haloperidol, however, is less likely than many newer antipsychotics and most conventional neuroleptics to increase body weight.³

Molindone is the only antipsychotic consistently shown not to increase weight,²⁴ and small studies have reported loss of weight with this drug.³ In one study of 9 patients with schizophrenia, patients lost a mean of 7.6 kg (16.7 lb) after 3 months of treatment with molindone.²⁵ In a well-controlled trial, Dufresne et al.²⁶ confirmed that molindone was associated with weight loss. Some evidence suggests that loxapine may also be associated with loss of weight.²

TREATMENT CONSIDERATIONS

For some patients, weight gain is an inevitable consequence of psychotropic drug therapy, and we should not gloss over this fact. Before patients begin treatment, they should be informed of all possible adverse effects, including the potential for clinically significant weight gain. Clinicians who avoid this topic for fear that patients will refuse treatment do their patients a disservice and may compromise their alliance with these patients.

In my practice, I (G.S.S.) routinely present patients with data showing the various risks associated with a particular drug before they start treatment. The chart shown in

Table 1. Potential Risk of Adverse Effects of First-Line Antidepressants^a

Antidepressant	Sedation	Anti-cholinergic Effects	Hypotension	Sexual Dysfunction	Seizure Risk	Weight Gain
Bupropion	-/+	-	-	-	0.1%	-
Desipramine	-/++	++	+	+	...	+
Fluvoxamine	++	-	-	++	0.2%	-
Fluoxetine	-/+	-	-	+++	0.2%	-
Nefazodone	++	+	+	-	...	-
Nortriptyline	++	+	+	++	...	++
Paroxetine	-/++	-	-	+++	0.1%	+++
Sertraline	-/+	-	-	++	...	-

^aSymbols: - = none/infrequent, + = common, ++ = frequent, +++ = very frequent.

Table 1, which summarizes the principal adverse effects of first-line antidepressants, is an example of the type of information provided for patients to review at the time of medication selection. My experience has been that data on weight gain receive a disproportionate amount of attention, and patients will often choose no treatment at all over the possibility of gaining weight. Patients should be informed that the clinician is sensitive to the potential of treatment-emergent weight gain. It can be pointed out that the problem is relevant only when the treatment is effective. Assurance can be given that weight gain does not occur in all patients, and that if weight gain does occur, the patient will determine whether the benefit exceeds the burden of increased weight.

When clinically significant weight gain does occur, several management options are available. These options include decreasing the drug dose, switching to another drug, and implementing a weight loss program. Dietary advice given to patients before they start treatment might also prevent significant weight gain.^{12,27}

Weight gain is an adverse effect of many psychotropic drugs and a common reason for treatment noncompliance. Yet when patients are doing well with a medication, clinicians may become complacent, overlooking or not carefully monitoring increases in weight until a patient has become severely overweight or obese. Given the considerable health risks associated with obesity (and with weight gain itself), we cannot ignore the problem of weight gain in our patients. The best course of action is to be honest with patients about the potential for weight gain before starting treatment, closely monitor changes in weight once they begin treatment, and intervene before clinically significant weight gain occurs.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), desipramine (Norpramin and others), divalproex (Depakote), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), loxapine (Loxitane), molindone (Moban), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), sertraline

(Zoloft), thioridazine (Mellaril and others), topiramate (Topamax), valproic acid (Depakene and others), vigabatrin (Sabril).

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