

Weight Change and Atypical Antipsychotic Treatment in Patients With Schizophrenia

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Schizophrenic patients who have been prescribed atypical antipsychotics have a potential risk of gaining weight. The implications of weight gain for clinical care may differ depending on whether a patient is underweight or overweight at baseline. The exact mechanism for weight gain is not known, but several factors have been identified that can help predict which patients are at risk for gaining weight. These factors include better clinical outcome, increased appetite, and low baseline body mass index. In patients treated with olanzapine for up to 3 years, weight gain trended toward a plateau at approximately 36 weeks. Weight gain interventions, including behavioral modifications, show promise in controlling or reducing weight in patients treated with antipsychotics.

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Antipsychotic medications as a class have been temporally associated with changes in body weight,¹ an effect manifested as either weight gain or weight loss.²⁻⁴ Some patients can show large increases in body weight during drug treatment, while others show little change or even a loss in body weight. Weight gain has been cited as a major reason for treatment noncompliance,⁵ although there is evidence suggesting that some patients with the most weight gain may also have the best clinical response.⁶ These observations illustrate the complexity of changes in body weight as a response to antipsychotic medications.

The precise physiologic mechanism underlying weight gain in patients treated with antipsychotics is presently unknown, although antagonism of several neurotransmitter systems has been proposed. For example, antagonism of the serotonergic 5-HT_{2C} receptor has been shown to play a major role in increasing food consumption and leading to weight gain.⁷ It has also been demonstrated that histaminergic H₁ receptor antagonists increase food intake and weight gain in both humans and rats,⁸ an effect that may be associated with increased release of norepinephrine.⁹ Furthermore, it has been suggested that some patients experience anticholinergic adverse events such as a dry mouth, which has been attributed to a blockade of muscarinic M₁ receptors. Dry mouth may cause some pa-

tients to drink large quantities of high-caloric liquids that may lead to weight gain.¹⁰

In this article, we compare changes in body weight of schizophrenic patients during treatment with olanzapine, an atypical antipsychotic, with those observed during treatment with other atypical and typical antipsychotics. We also review factors that can help predict which patients may gain weight during antipsychotic treatment and evidence that behavioral interventions are useful in controlling weight gain during drug exposure.

METHOD AND SUBJECTS

The data were collected and analyzed from over 3000 patients evaluated after 6 weeks of olanzapine therapy with more than 400 patients evaluated after 2 years of drug treatment (many were evaluated at timepoints between 6 weeks and 2 years) (data on file, Eli Lilly and Company, Indianapolis, Ind., 2000). In addition, in some of the clinical trials, patients treated with olanzapine were compared with patients treated with haloperidol, a typical antipsychotic (1-year endpoint; N = 386, olanzapine; N = 85, haloperidol), or risperidone, an atypical antipsychotic (28-week endpoint; N = 102, olanzapine; N = 79, risperidone).

RESULTS AND DISCUSSION

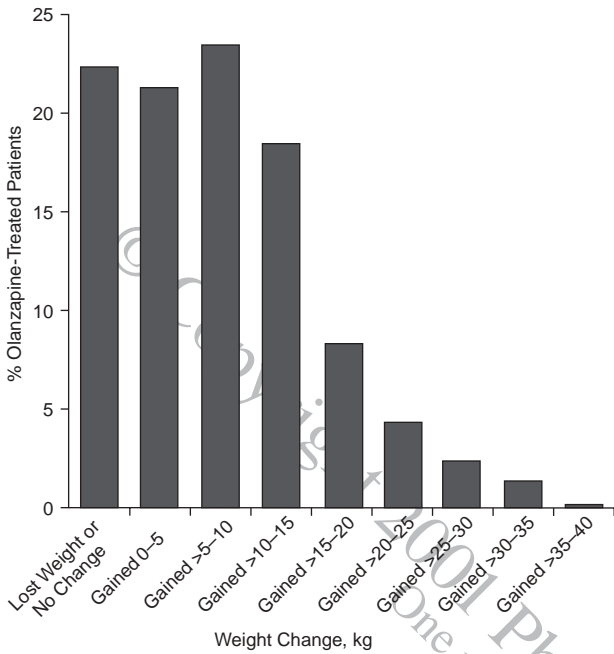
The amount of weight gained during drug treatment is variable. For example, results from the entire olanzapine database of trials sponsored by Eli Lilly and Company in which patients were treated for 2 years showed that a majority of patients (66%) gained less than 10 kg (Figure 1).¹¹ Approximately 7% of the patients gained more than 20 kg

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Figure 1. Distribution of Weight Change During Long-Term Olanzapine Treatment After 2 Years (observed cases)^a



^aData from Basson et al.¹¹

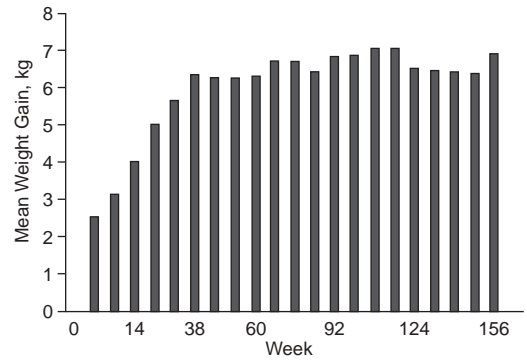
after 2 years. However, approximately 1 in 4 patients actually lost weight or gained no weight at all.

For both the clinician and the patient, it is important to know when weight gain may occur, if at all, during treatment with antipsychotic medications. For example, in patients treated with olanzapine for up to 3 years, the increase in body weight trended toward a plateau at approximately 36 weeks of drug exposure, with no significant further increases occurring on subsequent treatment, on average (Figure 2).¹²

Dose was not a significant predictor of long-term changes in weight in patients treated up to 3 years.¹² Therefore, decreasing the dose will probably not affect weight change and may negatively affect clinical response if it results in a subtherapeutic dose. Likewise, starting dose also appears not to affect weight gain. A 6-month study compared fixed doses of olanzapine (5 and 20 mg/day) with placebo in schizophrenic patients displaying prominent negative symptoms (data on file, Eli Lilly and Company, Indianapolis, Ind., 2000). The results demonstrated that weight gain was very similar between the 2 starting doses of olanzapine (Figure 3).

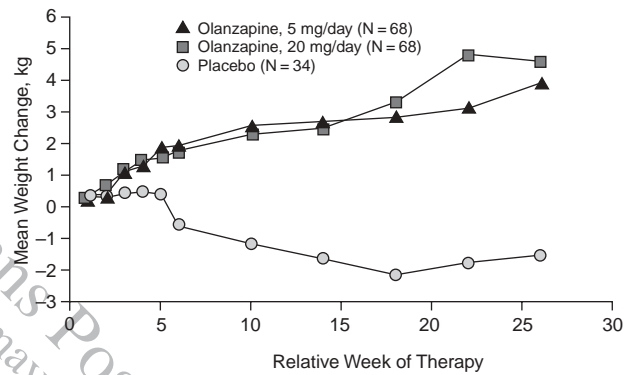
Differences have been observed in the amount of weight gained during treatment with typical and atypical antipsychotics. Comparison of weight gain following exposure to olanzapine or haloperidol revealed that 72% of olanzapine-treated patients versus 91% of haloperidol-treated patients lost weight, had no weight change, or gained less than 10 kg at 1 year, while 6% of olanzapine-

Figure 2. Weight Gain and Plateau During Long-Term Olanzapine Treatment^a



^aData from Kinon et al.¹²

Figure 3. Relationship Between Starting Dose of Olanzapine and Weight Gain^a

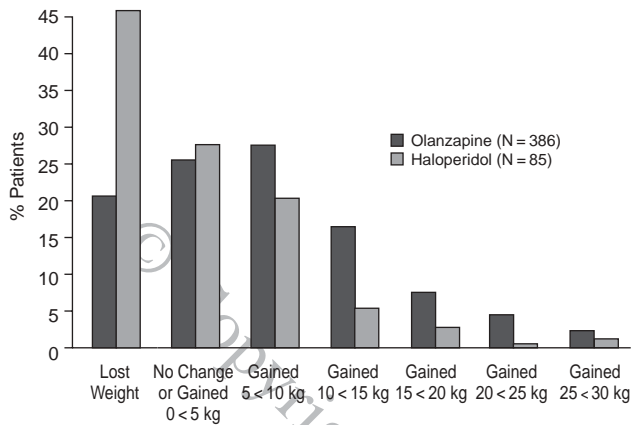


^aData on file, Eli Lilly and Company, Indianapolis, Ind., 2000.

treated patients and 1% of haloperidol-treated patients gained more than 20 kg (Figure 4) (data on file, Eli Lilly and Company, Indianapolis, Ind., 2000). Conversely, 20% of olanzapine- and 45% of haloperidol-treated patients actually lost weight. However, it is important to realize that, even though haloperidol-treated patients may experience less weight gain, patients with olanzapine, as well as other atypical antipsychotics, have a lower rate of extrapyramidal symptoms.¹³⁻¹⁷

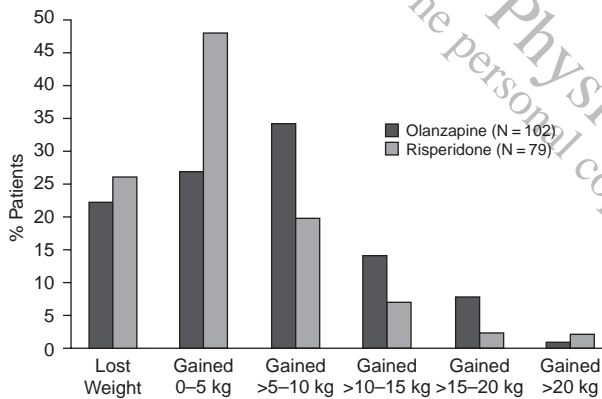
All of the currently available atypical antipsychotics have been reported to cause weight gain to varying degrees.¹⁸ One recent survey reported that clozapine-treated patients experienced the greatest amount of weight gain.¹⁹ Olanzapine-treated patients have generally experienced more weight gain than patients treated with risperidone, although the differences can be fairly small depending on the clinical trial. For example, in a study by Tran et al.,²⁰ a higher percentage of risperidone patients (88%) compared with olanzapine patients (78%) gained less than 10 kg. More olanzapine patients had weight gains greater than 10 kg (20.0%) compared with risperidone patients (8.6%).

Figure 4. Weight Change With Olanzapine Versus Haloperidol at 1 Year^a



^aData on file, Eli Lilly and Company, Indianapolis, Ind., 2000.

Figure 5. Weight Change With Olanzapine Versus Risperidone at 28 Weeks^a

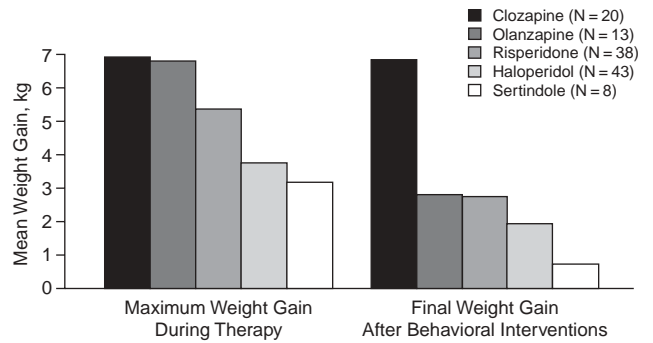


^aData from Tran et al.²⁰

About 20% and 25% of patients lost weight in the olanzapine and risperidone groups, respectively (Figure 5). At endpoint (28 weeks), the mean weight gains were 4.1 kg and 2.3 kg in the olanzapine and risperidone groups, respectively. This absolute difference of 1.8 kg over 28 weeks was statistically significant ($p = .015$), although the data were based on the last observation carried forward.

What factors can help predict whether weight gain may occur during treatment with olanzapine? One important variable appears to be the patient's baseline body mass index (BMI) prior to drug treatment. The results of a recent study¹² showed that patients with a high baseline BMI had significantly lower ($p < .002$) mean weight gains than the medium- and low-BMI patients, beginning at 13 weeks. By endpoint (3 years), the high-BMI patients had a significantly lower ($p > .001$) mean weight gain than the medium- and low-BMI patients. At endpoint the high-BMI group aver-

Figure 6. Behavioral Interventions: Weight Gain by Antipsychotic^a



^aData from Wirshing et al.¹⁸

aged a weight gain of less than 4 kg compared with about 8 kg for the low-BMI group. Because many schizophrenia patients are thin and have a low BMI, weight gain may be a benefit if it results in a BMI that is normalized.

To determine if baseline BMI has an influence on weight gain during treatment with other atypicals, a retrospective analysis compared olanzapine and risperidone from 3 randomized, double-blind studies.²⁰⁻²² The results demonstrated that patients with low BMI gain the most weight whether they are receiving olanzapine or risperidone (data on file, Eli Lilly and Company, Indianapolis, Ind., 2000). Moreover, patients who were considered overweight (BMI > 27) had the least amount of weight gain compared with normal and underweight patients in both treatment groups. Therefore, it is likely that BMI is a predictor of weight gain for patients taking atypical antipsychotics.

In a post hoc analysis by Basson et al.,¹¹ 6-week data from 2 large multicenter, double-blind clinical trials suggest that clinical response, increased appetite, and, again, baseline BMI are predictors of weight gain for patients taking olanzapine. Those patients with a better clinical response gained significantly ($p = .0075$) more weight than those with poorer responses. Increased appetite was an even better predictor. Those patients with an increased appetite gained significantly ($p = .0001$) more weight compared with patients with normal appetites. It is also interesting to note that patients prone to gain weight during treatment with other antipsychotics often have a robust clinical improvement²³⁻²⁶ and/or low baseline BMI.^{27,28}

In the same analysis,¹¹ olanzapine was compared with haloperidol or risperidone, and it was found that a better clinical outcome and low baseline BMI were indicators of weight gain for all 3 drugs. In addition, younger patients gained more weight than older patients with the atypicals, but this was not observed with haloperidol. When comparing only olanzapine with haloperidol, the predictive factor with the greatest effect on weight change was initial randomization to atypical versus conventional therapy. More-

over, predictors of weight gain for olanzapine, but not haloperidol, were increased appetite and male sex.

Can weight gain during antipsychotic drug treatment be controlled? A recent study incorporated a variety of behavioral interventions for patients who had gained considerable amounts of weight during treatment with antipsychotics (maximal weight gain between 2.5 and 8.0 kg, depending on the drug).¹⁸ A stepwise approach was taken such that patients were subject to increasingly intensive interventions (self-weighing, food diary, nutrition consultation, education, group support, exercise classes), depending on their ability to control their weight. The maximum weight gained during therapy and final weight gain after interventions are depicted for different drugs in Figure 6. Only those patients taking clozapine failed to have any response to the interventions.

A comprehensive review of antipsychotics and weight gain by Baptista²⁹ includes current and future interventions in managing this adverse event. Weight gain control may include both pharmacologic and nonpharmacologic interventions (e.g., diet, exercise). Importantly, and as noted above, weight gain in most cases is probably manageable, which should encourage the patient to begin intervention, especially if they are predicted to gain weight.^{1,18} Equally important is the goal of understanding the mechanism(s) in weight gain during antipsychotic treatment. Once the mechanism(s) are known, that knowledge should allow for additional and more precise interventions in controlling weight gain.

SUMMARY

Weight gain has been reported during treatment with nearly all the atypical antipsychotics. Over a period of 2 years, nearly half of the patients in the clinical trial database either lost weight, remained stable, or gained 5 kg or less. Treatment-emergent weight gain in patients treated with up to 3 years of olanzapine therapy trended toward a plateau after about 36 weeks of treatment. Predictors of weight gain during olanzapine treatment include good clinical response, low baseline BMI, increased appetite, and, possibly, age of less than 40 years and male sex. Daily and starting drug dose do not appear to be correlated with weight gain in olanzapine-treated patients. Finally, patients for whom weight gain is an issue should be encouraged to follow healthy diet and exercise habits.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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