

Review of Atypical Antipsychotics and Weight Gain

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Prescribing an antipsychotic for a patient with schizophrenia requires a risk-benefit analysis. Weight gain has become an issue recently as a result of reports that 2 of the atypical antipsychotic agents, clozapine and olanzapine, are associated with a higher risk than other drugs of causing excessive weight gain. Some degree of weight gain may occur with any atypical antipsychotic agent, particularly early in treatment. A more important consideration is the long-term effects of the atypical antipsychotic on body weight, since many of the patients in this population require chronic therapy. This is important because weight gain is an adverse effect that is associated with noncompliance and medical problems. In this article, I review recent reports about the weight effects of different atypical antipsychotic drugs. To provide accurate understanding of the effects of atypical antipsychotic agents, data analyses should include both short-term and long-term findings, the relationship of changes in body weight to pretreatment body mass index (BMI), relationship to dose, both intent-to-treat and complete analyses, and presentation of both mean and median changes in weight. It is also important to know whether the studies have been done in an inpatient or outpatient setting, since patients who are institutionalized may be less likely to exhibit increases in body weight. Such complete information and multidimensional analysis would minimize obfuscation about the true nature of a drug's impact on body weight.

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All atypical antipsychotic agents are comparable in efficacy. Thus, drug selection primarily involves a clinical risk-benefit analysis. For example, the most common safety concerns associated with antipsychotics are tardive dyskinesia, impairment of cardiac conduction, and endocrine abnormalities such as hyperglycemia and hyperprolactinemia. Weight gain has become an issue recently as a result of reports that 2 of the atypical antipsychotic agents, clozapine and olanzapine, are associated with a higher risk than other drugs of causing excessive weight gain.¹⁻⁴ In this article, I review recent reports about the weight effects of different atypical antipsychotic drugs and discuss the importance of how data are collected and analyzed in understanding the true nature of these weight effects.

All antipsychotics produce some weight gain, but there are differences among the various antipsychotics. For example, a meta-analysis was performed recently to estimate the weight change after 10 weeks of treatment at a standard dose of different antipsychotics.¹ The results indicate

that the largest increases occurred with clozapine and olanzapine (Figure 1).

Weight gain is an adverse effect that is associated with noncompliance and medical problems. For example, obesity is a well-documented threat to health and longevity because of its association with hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and some types of cancer.⁵⁻⁸

Using data from the Framingham Heart Study's public use data set, it is possible to estimate the consequences of antipsychotic-induced weight gain on both health and mortality rate.⁹ For example, the use of clozapine associated with a 10-kg (22-lb) weight increase would prevent 492 suicide deaths per 100,000 patients with schizophrenia over a 10-year period. However, there would be an estimated additional 416 deaths due to the antipsychotic-induced weight gain. This analysis suggests that the magnitude of weight gain induced by many antipsychotic agents may have important deleterious effects on mortality and health.

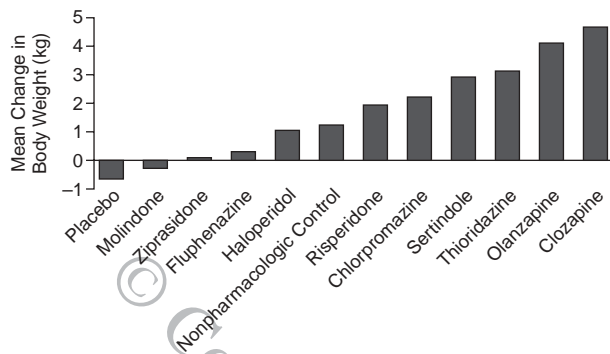
When an antipsychotic is prescribed, patient compliance is also a consideration. The European umbrella support group charity, European Federation of Associations of Families of Mentally Ill People (EUFAMI), conducted a survey to assess patients' satisfaction with antipsychotic medication and how effectively their condition is managed.¹⁰ A total of 441 patients were surveyed from the United Kingdom, Italy, Spain, and Germany. Of the respondents, 91% reported that they had suffered treatment

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Figure 1. Estimated Mean Weight Gain at 10 Weeks^a



^aData from Allison et al.¹

side effects; 60% of those patients suffered from weight gain. Of this 60% of patients, over half (54%) reported that they considered weight gain to be the most difficult side effect to cope with. Although the degree of weight gain experienced with various antipsychotics may vary according to which drug is used, weight gain may cause patients to discontinue their medication and thus may ultimately lead to relapse.¹¹

RECENT REPORTS OF ATYPICAL ANTIPSYCHOTICS AND WEIGHT GAIN

Clozapine

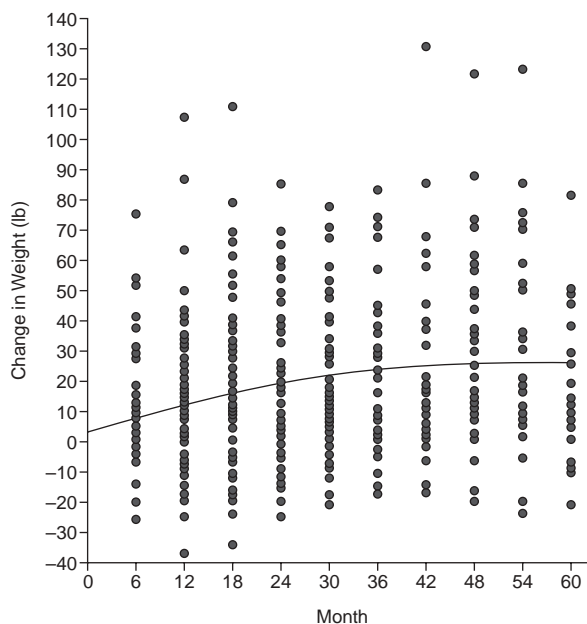
The first of the atypical antipsychotics, clozapine, has been associated with numerous reports of weight gain. A 5-year naturalistic study of clozapine¹² has confirmed this propensity of clozapine to cause weight gain. Records of 82 outpatients with schizophrenia or schizoaffective disorder were examined at 6-month intervals. Patients experienced significant weight gain that continued until approximately month 46 from initiation of treatment with clozapine (Figure 2).

Another study examined 93 treatment-resistant patients with schizophrenia who were weighed monthly for 4 months during clozapine treatment.¹³ Patients gained an average of 2.4 kg (5.3 lb) in body weight; however, individual body weight changes ranged from -17.5 kg to +12.9 kg (-38.6 to +28.4 lb). Furthermore, patients with lower initial body mass index (BMI) demonstrated greater weight gain.

Risperidone

Since its introduction in the United States in 1994, risperidone has been widely prescribed for the treatment of schizophrenia. Cohen et al.¹⁴ conducted a retrospective chart review on records of 50 adult patients with mental retardation treated with risperidone while residing at a rehabilitation center. Thirty-nine patients had adequate data for analysis. Thirty-seven of the 39 patients gained weight,

Figure 2. Change in Weight From Baseline During a 60-Month Study in 82 Patients Receiving Clozapine^a

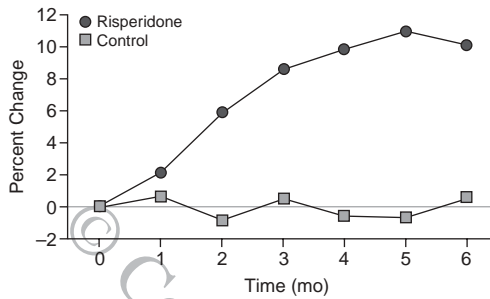


^aReprinted with permission from Henderson et al.¹² The solid curve shows the quadratic fit to all available data.

with a mean increase of 8.3 kg (18.8 lb) over 2 years. Twenty of the 37 patients were subsequently calorie-restricted, and 3 of the 20 calorie-restricted patients lost weight at a rate of 0.2 lb per month (0.1 kg/month). The rest of the patients continued to gain weight at a rate of 0.8 lb (0.4 kg) per month during another 2 years of treatment. The amount of weight gain was not dose related. The investigators concluded that, in this study, weight gain was associated with risperidone therapy in adults with mental retardation, and that this weight gain was not necessarily reversed with calorie restriction.

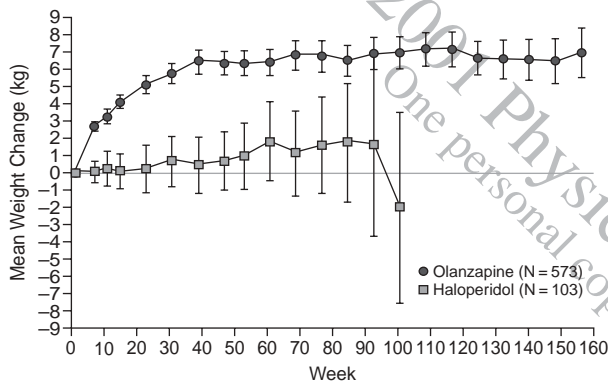
A retrospective chart review¹⁵ evaluated age- and gender-adjusted weight changes linked to risperidone by comparing 37 child and adolescent inpatients treated with risperidone for 6 consecutive months with 33 psychiatric inpatients with no atypical antipsychotic exposure. Children and adolescents treated with risperidone experienced significant weight gain from baseline by 6 months ($p < .001$). Weight gain was first evident within 2 months of starting treatment, and mean weight increased at an average rate of 1.2 kg (2.6 lb) per month (Figure 3). No plateau in weight gain was reached during the 6 months of observation. Furthermore, there was a substantial risk in the patients of a greater than 7% increase from baseline weight (odds ratio = 3.5, 95% confidence interval [CI] = 1.8 to 6.6, $p < .001$). For example, 6 months of exposure to risperidone was associated with clinically significant weight gain in 78% of children and adolescents (as opposed to 24% of those in the control group,

Figure 3. Mean Percentage Change From Baseline Weight in Children and Adolescents Treated With Risperidone (N = 37) and Those Treated With Typical Antipsychotics (N = 33)^a



^aReprinted with permission from Martin et al.¹⁵

Figure 4. Mean Change in Body Weight (kg) of Patients Treated With Olanzapine (N = 573) or Haloperidol (N = 103) From Baseline Out to 3 Years (observed cases)^a



^aReprinted with permission from Kinon et al.¹⁸

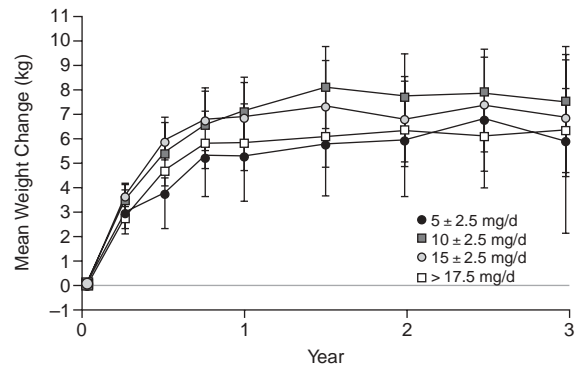
$p < .001$). Risperidone dosage and concomitant medication use were not associated with increased risk of weight gain.

In an open-label study¹⁶ of 26 inpatients (children and adolescents, aged 10–18 years) with mixed diagnoses and aggressive behavior, risperidone was given in daily dosages ranging from 0.5 to 4 mg for 2 to 12 months. Two patients (8%) had marked weight gain in the first 8 weeks of treatment. The authors concluded that weight gain and sedation could be troublesome side effects of treatment with risperidone.

Olanzapine

Since the introduction of olanzapine in the United States in 1996, more reports implicating the drug as a cause of weight gain and glucose dysregulation have appeared recently than for other new antipsychotic drugs. For example, in a prospective, naturalistic study¹⁷ of 2967 outpatients with schizophrenia, 2128 patients were treated with olanzapine as monotherapy or combined with other drugs (olanzapine group), and 821 patients were treated

Figure 5. Mean Change in Body Weight (kg) by Mean Olanzapine Dose (mg/day) of Olanzapine-Treated Patients Observed 39 Weeks or More^a



^aReprinted with permission from Kinon et al.¹⁸ No significant differences were observed between mean daily dose categories over the entire study period.

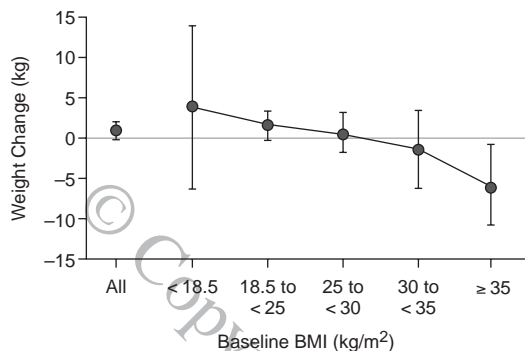
with other antipsychotic drugs as monotherapy or combined with other drugs (control group). Somnolence and weight gain were significantly more frequent in the olanzapine group compared with the control group.

Kinon et al.¹⁸ conducted a retrospective analysis of 573 patients receiving olanzapine and 103 patients receiving haloperidol for 39 weeks or more from a study of 1996 patients randomly assigned 2:1 to either olanzapine, 5 to 20 mg/day, or haloperidol, 5 to 20 mg/day. The last-observation-carried-forward (LOCF) mean weight change of 6.26 kg (13.8 lb) for olanzapine-treated patients was significantly higher than that for haloperidol-treated patients who had a mean weight gain of 0.69 kg (1.5 lb) after 1.15 years. Mean weight gain for olanzapine-treated patients observed for a median of 2.54 years showed a trend toward a plateau after the first 39 weeks (Figure 4). The investigators concluded that higher baseline BMI was predictive of a lower long-term weight gain and that dose was not a significant predictor of greater long-term weight changes (Figure 5).

An open-label, multicenter study¹⁹ enrolled 159 patients with schizophrenia, 156 of whom were included in the analysis. The most commonly reported treatment-emergent symptoms, occurring at a frequency of 10% or more, were insomnia, weight increase, excitement, sleepiness, anxiety, malaise, and dull headaches.

Another recent study of olanzapine, this time for the treatment of acute bipolar mania, was double-blind and parallel-group in design.²⁰ One hundred fifteen patients with DSM-IV diagnosis of bipolar disorder, manic or mixed, were randomly assigned to receive olanzapine, 5 to 20 mg/day (N = 55), or placebo (N = 60) for 4 weeks. Olanzapine-treated patients had a significantly greater mean weight gain than placebo-treated patients (2.1 ± 2.8 vs. 0.45 ± 2.3 kg [4.6 ± 6.2 vs. 1.0 ± 5.1 lb], respectively).

Figure 6. Mean Change in Weight and Associated 95% CI From Baseline to Endpoint by Baseline Body Mass Index (BMI) Category in Patients Treated With Quetiapine Monotherapy for at Least 6 Months^a



^aReprinted with permission from Brecher et al.²⁵ N = 178; mean treatment duration = 18.6 months; mean daily dose = 473 mg.

A study conducted by Melkersson et al.²¹ analyzed 14 patients with DSM-IV–diagnosed schizophrenia who were treated with olanzapine. Twelve of the 14 patients reported weight gain between 1 and 10 kg (2.2 and 22.0 lb) during a median treatment period of 5 months (data were not available for the other 2 patients). Furthermore, 3 patients were subsequently diagnosed with diabetes mellitus. The investigators concluded that, in this study, olanzapine treatment was associated with weight gain and elevated levels of insulin, leptin, blood lipids, and insulin resistance.

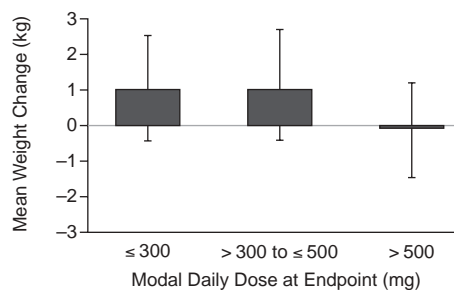
An open-label study²² analyzed 14 adult patients with Tourette’s syndrome who were treated with olanzapine for 6 weeks. Two patients (14%) reported weight gain of 3 to 5 kg (6.6 to 11.0 lb) and increased appetite.

In a 3-month, open-label trial of adjunctive olanzapine,²³ 23 patients with obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors were taking 5 mg/day of olanzapine. The most common adverse effects were mild-to-moderate weight gain and sedation. Similarly, a case study of 3 acutely manic prepubertal children,²⁴ diagnosed with bipolar disorder and treated with olanzapine in addition to existing mood stabilizer, reported adverse effects that included sedation and weight gain.

Quetiapine

Minimal short-term weight gain (2.16 kg [4.76 lb] over 10 weeks) has been reported with quetiapine, and long-term analyses of weight change have shown that quetiapine has a favorable weight profile.²⁵ Long-term weight data were analyzed from 427 patients with schizophrenia who received quetiapine monotherapy in controlled and open-label extension studies.²⁵ Quetiapine was flexibly dosed up to 800 mg/day, and the mean dosage was 473 mg/day. The mean duration of the open-label extension was 18.6

Figure 7. Dose-Related Effect of Long-Term Treatment With Quetiapine on Weight^a



Mean Duration of Treatment (days)	343	407	327
Number of Patients	103	94	174

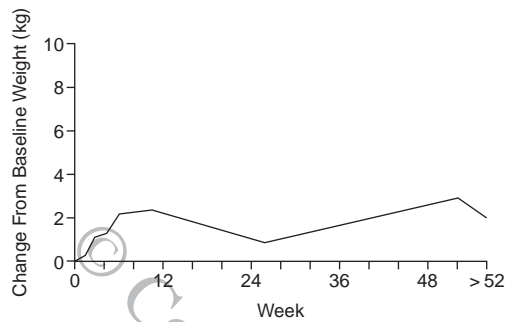
^aReprinted with permission from Brecher et al.²⁵ Mean change in weight and associated 95% CI from baseline to endpoint (final recorded weight measurement) by modal daily dose at endpoint in patients receiving quetiapine monotherapy.

months. Patients were stratified into 5 categories according to their BMI at baseline: underweight (BMI < 18.5 kg/m²), normal weight (BMI = 18.5 to < 25 kg/m²), overweight (BMI = 25 to < 30 kg/m²), obese (BMI = 30 to < 35 kg/m²), and severely obese (BMI ≥ 35 kg/m²).

This analysis showed that there was a favorable overall effect on weight across the BMI spectrum (Figure 6).²⁵ Long-term quetiapine monotherapy had a minimal effect on weight change across all categories (95% CI included 0) except for the most severely obese group (BMI ≥ 35 kg/m²) in whom the mean weight decreased. Quetiapine appeared to have a “normalizing” effect, with a tendency toward favorable shifts in body weight in underweight (BMI < 18.5 kg/m²) and severely obese (BMI ≥ 35 kg/m²) patients. The mean overall weight change in patients who had completed at least 6 months of quetiapine monotherapy was 0.41 kg (0.90 lb). The effect of quetiapine dose on weight was investigated by comparing the weight at baseline and at endpoint for each of 3 dosage groups. Figure 7 shows that there was no effect of quetiapine on weight at any dose and that there was no correlation between increasing doses and mean long-term weight changes. During the total duration of exposure to quetiapine, only 1 patient withdrew because of weight gain.

Jones et al.²⁶ collected data from 2216 patients from phase 2 and 3 controlled, uncontrolled, and open-label extension studies of quetiapine. Within specified time intervals, weights were summarized using an LOCF approach. Mean weight gain at 5 to 6 weeks was similar to that observed at < 3 months, 3 to 6 months, and > 6 months, indicating that any acute weight gain did not appear to predict long-term increases (Figure 8). The investigators concluded that long-term therapy with quetiapine induced a minimal mean increase in weight that is less than that reported for clozapine and olanzapine.

Figure 8. Mean Change in Weight From Baseline During Quetiapine Treatment (N = 2216)^a



^aData from Jones et al.²⁶

Treatment with quetiapine does not appear to warrant the medical concerns about weight gain associated with some of the other atypical antipsychotics.²⁵ In fact, adjunctive therapy with quetiapine appears to have beneficial effects in patients experiencing weight gain with clozapine.²⁷ The addition of quetiapine for 65 patients who had experienced a 6.5-kg (14.3-lb) mean increase in weight during 6 months of clozapine monotherapy produced a mean weight loss of 4.2 kg (9.3 lb) during the subsequent 10 months.²⁷ Glycemic control was also significantly improved by quetiapine, with eventual normalization of elevated glycosylated hemoglobin in the 13 patients (20%) who had developed type 2 diabetes while receiving clozapine monotherapy.

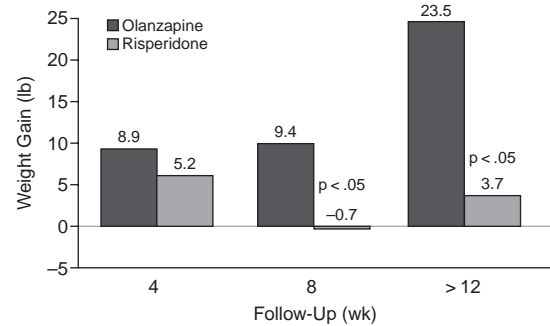
Ziprasidone

The newest of the atypical antipsychotics, ziprasidone, has demonstrated a low incidence of weight gain in short-term clinical trials.²⁸ Two recently presented study results tend to support these early findings.

Three double-blind studies that were either placebo-controlled or versus haloperidol were examined for long-term efficacy, safety, and tolerability.²⁹ One study was for 28 weeks in 301 outpatients with stable, chronic, or subchronic schizophrenia; another was for 40 weeks in 599 outpatients with stable, chronic, or subchronic schizophrenia; and the third study was for 52 weeks in 278 chronically ill, stable inpatients. In the 40-week study, clinically significant weight gain (> 7%) was less common in ziprasidone-treated than in haloperidol-treated patients. Furthermore, in the 52-week inpatient study, compared with placebo, treatment with ziprasidone was not associated with weight gain. The author concluded that long-term therapy with ziprasidone was well tolerated with an effect on weight similar to placebo. There are no published 52-week data among outpatients.

In another study, changes in body weight were assessed following a switch to ziprasidone from other antipsychotics.³⁰ The information came from three 6-week, ran-

Figure 9. Weight Gain in Bipolar Patients Receiving Atypical Antipsychotics^a



^aReprinted with permission from Guille et al.³¹

domized, open-label trials evaluating outcome in stable patients with schizophrenia following a switch from conventional antipsychotics (N = 93), olanzapine (N = 88), and risperidone (N = 41). Patients were randomly assigned in each trial to 1 of 3 dosing schedules and received ziprasidone, 40 to 160 mg/day. BMI was calculated for all patients. A significant improvement in total cholesterol and triglycerides was noted for patients switched from olanzapine and risperidone ($p < .05$). For patients switched from olanzapine, a significant reduction in weight (mean change = -1.71 kg [-3.77 lb]) and BMI was observed ($p < .05$). A decrease in weight in patients switched from olanzapine is consistent with other findings suggesting a weight-neutral profile for ziprasidone.

COMPARATIVE STUDIES OF DIFFERENT ATYPICAL ANTIPSYCHOTICS

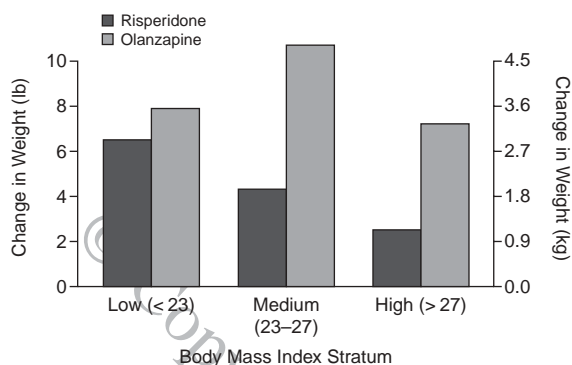
Clozapine vs. Risperidone vs. Olanzapine

A retrospective study³¹ was conducted of 50 patients with DSM-IV bipolar disorder type I who had received adjunctive treatment with risperidone, olanzapine, or clozapine, along with standard mood stabilizers. The magnitude of the weight gain was significantly larger in patients treated with olanzapine than patients treated with risperidone at time periods of 8 weeks or more (Figure 9). Patients treated with clozapine experienced weight gain of a similar magnitude as those receiving olanzapine. The authors also suggested that mood-stabilizing drugs, like lithium or divalproex sodium, might potentiate the weight-gain effects of atypical antipsychotics.

Risperidone vs. Olanzapine

A double-blind study³² of 377 patients with schizophrenia or schizoaffective disorder who were randomly assigned to risperidone (2–6 mg/day) or to olanzapine (5–20 mg/day) for 8 weeks found an increase in body weight of > 7% in 27% of olanzapine-treated and 12% of risperidone-treated patients. This is consistent with other reports of roughly

Figure 10. Changes in Body Weight at Week 8 in Participants Treated With Risperidone or Olanzapine by Body Mass Index Stratum at Baseline^a



Risperidone	N = 23	43	71
Olanzapine	N = 23	43	59

^aReprinted with permission from Conley and Mahmoud.³²

double the incidence of clinically significant weight gain with olanzapine versus risperidone. Figure 10 shows the changes in body weight at week 8 in patients stratified by BMI at baseline.

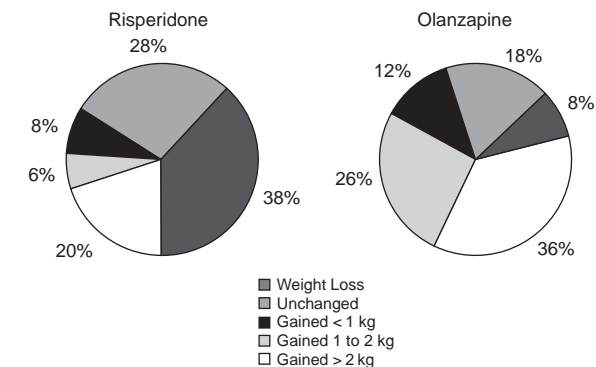
A retrospective chart review of 2 cohorts of patients with schizophrenia who had newly started treatment with either risperidone or olanzapine was undertaken.³³ One hundred patients were reviewed—50 in each treatment group. After 4 months of treatment, body weight and BMI were assessed. Risperidone-treated patients showed no significant change in mean body weight or BMI; however, olanzapine-treated patients showed a significant increase in both mean body weight and BMI ($p < .001$). Thus, treatment with olanzapine was associated with a mean weight gain of about 2 kg (4.4 lb) from baseline, whereas treatment with risperidone was associated with no mean weight change. Figure 11 shows a comparison of weight gained or lost in patients treated with risperidone or olanzapine.

Meyer³⁴ performed a retrospective comparison at 1 year of patients at Oregon State Hospital who received treatment with olanzapine (N = 175) or risperidone (N = 155) during July–August 1999. Patients were included if data were available within 3 months prior to drug initiation and at 1 year of treatment. The changes from baseline were +17.5 lb and +2.55 kg/m² for olanzapine (N = 47) versus +10.7 lb and +1.55 kg/m² for risperidone (N = 47) for body weight and BMI, respectively. All values were significantly different from baseline ($p < .001$), and the differences between olanzapine and risperidone were not statistically significant.

Quetiapine vs. Risperidone vs. Olanzapine

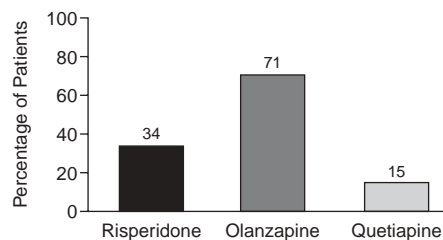
A retrospective chart review³⁵ analyzed data from patients treated in an outpatient mental health clinic serving children and adolescents. There were 97 patients: 75 pa-

Figure 11. Comparison of Weight Gained or Lost in Patients Treated With Risperidone or Olanzapine^a



^aReprinted with permission from Ganguli et al.³³

Figure 12. Percentage of Patients (treated with risperidone, olanzapine, or quetiapine) With Significant Weight Gain (≥ 10 lb) at 3 Months^a



^aData from Grcevich et al.³⁵

tients treated with risperidone, 25 with quetiapine, and 16 with olanzapine. Substantial weight gain was defined as a weight gain ≥ 4.5 kg (≥ 10 lb) during the first 3 months of treatment. The mean duration of treatment was 408.3 days with risperidone, 176.8 days with olanzapine, and 119.8 days with quetiapine. The mean maximum daily dosage of each medication was 2.6 mg with risperidone, 13.3 mg with olanzapine, and 210.3 mg with quetiapine. The percentage of patients with significant weight gain at 3 months was 34%, 71%, and 15% for risperidone, olanzapine, and quetiapine, respectively (Figure 12). Mean weight gain at 3 months was the following: risperidone, 8.6 lb (3.9 kg); olanzapine, 14.6 lb (6.6 kg); quetiapine, 7.2 lb (3.3 kg). Thus, the mean weight gain at 3 months was highest for patients treated with olanzapine, and patients treated with quetiapine experienced the lowest percentage of significant weight gain at 3 months.

Ziprasidone vs. Olanzapine

A 6-week double-blind study³⁶ of 269 inpatients with acute schizophrenia or schizoaffective disorder randomly assigned patients to ziprasidone (40–80 mg twice daily) or olanzapine (5–15 mg daily). There were no differences in efficacy measures, but patients receiving olanzapine

had significantly greater mean weight gain ($p < .0001$) and median increases in total cholesterol ($p = .0001$), low-density lipoprotein cholesterol ($p < .0004$), triglycerides ($p = .0027$), and measures of insulin resistance ($p < .0001$).

In a 6-week, multicenter, randomized, double-blind trial,³⁷ inpatients with schizophrenia who required treatment for acute exacerbation of symptoms were randomly assigned to ziprasidone ($N = 43$) and olanzapine ($N = 46$). The median body weight after treatment was significantly increased from baseline values in olanzapine-treated patients (+3.0 kg [+6.6 lb]), but was decreased in ziprasidone-treated patients (-0.6 kg [-1.4 lb]); this difference was statistically significant ($p = .0001$).

CONCLUSION

Atypical antipsychotics have different propensities for producing weight gain. During long-term treatment, clozapine and olanzapine produce the most weight gain. Quetiapine and ziprasidone produce the least weight gain. Risperidone produces intermediate weight gain. Some populations of patients, such as children and adolescents, mentally retarded adults, and patients with bipolar disorder, may be more vulnerable to weight gain, but this has not been systematically studied. Gender differences in drug effects on weight have also not been studied.

Switching to an atypical antipsychotic with fewer propensities for producing weight gain may be the most efficient way to deal with antipsychotic-induced weight gain. Other countermeasures for weight gain have been discussed and reported. These include the addition of topiramate³⁸ or histamine (H_2) antagonists such as nizatidine.³⁹ However, the evidence supporting these recommendations is limited, and the success rate seems overstated in clinical practice.

Ziprasidone has been shown in short-term clinical trials to have a low propensity to cause weight gain; however, the antipsychotic has not yet been used extensively in the clinical setting. Its long-term effects on body weight are thus not known, but the drug will probably not be associated with substantial weight gain. At the moment, quetiapine is the only atypical antipsychotic with both extensive clinical and published acute and long-term outpatient and inpatient data that show a lack of significant weight gain and glucose dysregulation.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluphenazine (Prolixin), haloperidol (Haldol and others), molindone (Moban), nizatidine (Axid), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, nizatidine and topiramate are not approved by the U.S. Food and Drug Administration for drug-induced weight loss.

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