Antipsychotic-Associated Weight Gain and Clinical Outcome Parameters

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Weight gain has been observed with many of the antipsychotics, including the atypical antipsychotics. The assessment of whether, and to what degree, a drug causes changes in body weight is not straightforward, since clinical studies performed during a drug development program are not designed to measure changes in body weight. Even when weight change data are obtained from adverse event data or from part of the vital signs measured during a study, assessment is not standardized. Nevertheless, evidence points to the fact that weight gain with the atypical antipsychotics is becoming an increasing problem. This review examines whether antipsychotic-associated weight gain, when it occurs, is associated with clinical outcome parameters.

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Shortly after the conventional antipsychotic drugs were introduced in the 1950s, marked increases in body weight were observed and reported among patients taking these agents. Since then, it has been increasingly recognized that many antipsychotic drugs are associated with weight gain. In fact, excessive weight gain has been reported in up to 50% of patients receiving chronic antipsychotic treatment.[1]

Today, it is recognized that weight gain has a number of unfavorable consequences. In the general population, excessive weight gain and obesity are associated with increased morbidity from coronary heart disease, diabetes, hypertension, gallbladder disease, and some forms of cancer.[2] In patients with schizophrenia, drug-induced weight gain is a common cause of noncompliance with and discontinuation of antipsychotic treatment, which may result in relapse of the illness.[3–6] The consequences of weight gain on health, morbidity, and noncompliance with drug treatment are discussed in further detail by Kurzthaler and Fleischhacker[7] in this supplement.

Among the conventional antipsychotics, weight-gain liability appears to be greatest with low-potency antipsychotics, such as thioridazine and chlorpromazine.[5,8] Reported weight gain ranges were between 1.54 kg and 4.08 kg over 12 weeks,[9,10] reaching a plateau after 1 to 2 years of treatment.[8]

The introduction of the atypical antipsychotics has revolutionized the treatment of schizophrenia. Broad symptom control, combined with more favorable tolerability profiles than those achieved with the conventional antipsychotics, has resulted in improved benefit/risk ratios and better outcomes for patients with schizophrenia.[11] However, in contrast to aspects of tolerability, such as extrapyramidal symptoms (EPS), the atypical antipsychotics do not appear to be superior to the conventional antipsychotics in terms of weight gain.[12] Consideration is generally given to patients' views and attitudes to treatment since distress caused by side effects may have an impact on patient well-being.[13] The degree to which an antipsychotic drug causes weight gain may therefore have an increasing role to play in treatment decisions.

This review examines whether antipsychotic-associated weight gain, when it occurs, is associated with clinical outcome parameters.

IS WEIGHT GAIN ASSOCIATED WITH ALL ANTIPSYCHOTICS?

Assessment of Weight Changes in Clinical Studies

The assessment of whether, and to what degree, a drug causes changes in body weight is not a straightforward process, since clinical studies performed during a drug development program are not designed to measure changes in body weight. Weight-change data are obtained in 1 of 2 ways: weight is either assessed in a subjective manner by the spontaneous identification and reporting of adverse events, or it is measured objectively as one aspect of the

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vital signs that are evaluated in the study. Evaluation of weight change is further complicated by the manner in which weight is assessed in clinical trials, since assessment has not been standardized.

Presentation of changes in weight varies considerably, from changes in actual weight and body mass index (BMI) to percentage increases or decreases in body weight. In addition, there is no standard definition of clinically significant weight gain. Although the U.S. Food and Drug Administration defines clinically significant weight gain as an increase of ≥ 7% of baseline body weight, this definition has not been universally adopted.[14]

Weight Gain Reported With Antipsychotics

Meta-analyses, chart reviews, clinical trial data, and experience with the atypical antipsychotics support the notion that some patients gain weight markedly during treatment.[15–17]

In addition to the comprehensive meta-analysis by Allison and colleagues[17] that addressed weight gain with antipsychotics (see also Allison and Casey[18] in this supplement), corresponding data were obtained in 2 retrospective analyses.[15,16] The first was a retrospective chart review,[15] performed to evaluate the effects of clozapine (N = 29), risperidone (N = 15), zotepine (N = 19), sulpiride (N = 8), and a number of conventional antipsychotics (N = 49) on weight gain. Charts were evaluated for all patients admitted to the study center with a DSM-III-R diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder over a 4-year period. The study included all patients who were treated for longer than 2 weeks with any of the drugs. Data analysis showed that weight gain with the atypical antipsychotics in this study was statistically significantly greater than with the conventional antipsychotics (p = .01). The mean weight gain with clozapine was 3.1 kg; risperidone, 1.5 kg; sulpiride, 1.9 kg; and zotepine, 4.3 kg. The mean weight gain with the conventional antipsychotics, comprising butyrophenones, phenothiazines, and piperidines, was 0 to 0.5 kg.

A second retrospective analysis[16] examined the relative weight gain–inducing effects of clozapine, risperidone, olanzapine, and sertindole compared with haloperidol. A total of 122 clinical records from patients with a DSM-III-R diagnosis of schizophrenia were reviewed for maximal weight gain, final weight, and time to achieve maximal weight. Data analysis was performed controlling for age, treatment duration, and initial weight. For all measures, statistically significant differences were observed between the groups of patients treated with clozapine, risperidone, olanzapine, sertindole, and haloperidol. Clozapine- and olanzapine-treated patients had the highest mean maximal weight gain compared with the other groups: clozapine, 7.5 ± 6.0 kg; olanzapine, 8.0 ± 6.0 kg; risperidone, 4.1 ± 3.4 kg; haloperidol, 3.5 ± 4.1 kg; sertindole, 2.5 ± 3.3 kg. The time course was distinct among treatment groups. Risperidone- and sertindole-treated patients reached a plateau after a relatively short time (circa 10 weeks), whereas olanzapine- and clozapine-treated patients continued to gain weight over a longer period (circa 20 weeks) before weight stabilized.

Clozapine. In both open-label and double-blind, randomized, short-term and long-term studies, clozapine has been associated with weight gain.

Short-term studies have ranged from 8 to 16 weeks. Leadbetter et al.,[19] in an open-label study over 16 weeks, demonstrated that 67% of clozapine-treated patients experienced "marked-to-moderate" weight gain. In a 10-week comparative study[20] with haloperidol, the clozapine-treated patients had a 7% increase in body weight over baseline. In an 8-week comparative study[21] with risperidone, clozapine-treated patients demonstrated a statistically significant increase in mean body weight of 2.7 kg from baseline (p = .01). Risperidone-treated patients had a 1.1-kg increase in mean body weight (not statistically significant).[21]

Significant weight gain early in the course of clozapine treatment was reported by Hummer et al.,[22] who compared clozapine with haloperidol over 12 weeks. The mean weight gain was 3.49 kg in clozapine-treated patients and 1.49 kg in haloperidol-treated patients. At 1 year, 36% of patients treated with clozapine had gained ≥ 10% of their initial body weight, with most of the weight gain occurring within the first 12 weeks of treatment.

Similar findings have been reported in long-term studies. In a retrospective chart review,[23] clozapine-treated patients gained a substantial amount of weight over a 6-month period (mean = 7.66 kg). In another retrospective chart review, Umbricht et al.[24] found that weight gain in clozapine-treated patients was greatest during the first 12 months but continued at a slower rate for at least 36 months.

Olanzapine. Olanzapine has been associated with weight increase in both short- and long-term studies, irrespective of dose.

Two placebo-controlled, short-term studies, 1 in patients with acute exacerbation of schizophrenia[25] and 1 in patients with bipolar disorder,[26] have shown increases in mean weight from baseline of 2.2 kg over 6 weeks and 1.65 kg over 3 weeks, respectively. A short-term comparative trial with haloperidol over 6 weeks[27] demonstrated that patients treated with olanzapine had a mean increase in weight of 1.88 kg from baseline. Olanzapine, at a mean ± SD dose of 15 ± 2.5 mg/day, was associated with a mean ± SD weight gain of 3.5 ± 3.9 kg over 6 weeks.[28]

In the longer term, patients treated with olanzapine over 28 weeks had a statistically significant increase in mean weight from baseline (p < .001).[29] Nemeroff[30] reported an 11.79-kg increase in body weight after 1 year of olanzapine treatment, and in a 4- to 6-month study, Ganguli et al.[31] showed that olanzapine-treated patients had a mean ± SD

weight increase from baseline of 2.2 ± 3.4 kg ($p < .001$). In addition, the efficacy of olanzapine, 5 mg and 20 mg, was compared with amisulpride, 150 mg, and placebo over 6 months.[32] Mean weight gain was significantly more frequent in the 5-mg and 20-mg olanzapine groups (24.3% and 20.0%, respectively) than in the 150-mg amisulpride (8.6%) and placebo groups (5.7%). Over the 6-month period, mean weight gain with olanzapine, 5 mg, was 2.56 ± 5.88 kg; with olanzapine, 20 mg, mean weight gain was 2.31 ± 5.53 kg; and with amisulpride, 150 mg, mean weight gain was 0.21 ± 5.99 kg.[31]

Risperidone. Changes in weight have been observed in risperidone-treated patients during short- and long-term comparative studies with the conventional antipsychotics haloperidol and perphenazine.

Peuskens et al.[33] conducted a fixed-dose, double-blind, comparative study with risperidone and haloperidol over 8 weeks in 1362 patients with chronic schizophrenia. Weight significantly increased with risperidone at all doses used in this trial. Mean increase in weight from baseline varied from 0.3 kg in the 1-mg/day risperidone group to 1.6 kg in the 8-mg/day risperidone group.[32] The weight increases in the 8-mg, 12-mg, and 16-mg risperidone groups were significantly higher than in the haloperidol group. The degree of weight gain with haloperidol was not reported.[32]

In another 8-week study,[34] statistically significant increases in body weight were reported in risperidone-treated patients. Increases occurred in 39% of the 55 patients treated with risperidone. In addition, a case report[35] has been published that describes 2 patients whose weight increased by 17.28 kg after 15 weeks and 17.05 kg after 12 weeks of risperidone treatment.

A long-term, flexible-dose, comparative study with risperidone and haloperidol[36] reported a mean increase in weight of 2.27 kg in risperidone-treated patients, which was significantly different from a mean decrease in weight of 0.74 kg in haloperidol-treated patients over 52 weeks ($p < .001$).

Quetiapine. Only short-term data are available for quetiapine. Currently, no long-term studies have included measurement of body weight.

In a 6-week, placebo-controlled study,[37] patients treated with quetiapine had a mean increase in weight of 2 kg compared with an increase of 0.1 kg in placebo-treated patients. In another study,[38] quetiapine-treated patients gained an average of 5.5 kg over 6 weeks in comparison with placebo-treated patients, who gained an average of 0.5 kg. The study sample comprised 636 patients, and 25% of quetiapine-treated patients demonstrated an increase in body weight of ≥ 7% from baseline.[38]

In another 6-week study,[39] patients with an acute exacerbation of chronic or subacute chronic schizophrenia received fixed doses of quetiapine (75, 150, 300, 600, or 750 mg/day) or fixed-dose haloperidol (12 mg/day). Patients treated with quetiapine had mean increases in weight ranging from 0.9 to 2.9 kg over the 6-week study. Finally, Peuskens[40] reported a 6-week study in which 27% of quetiapine-treated patients and 18% of chlorpromazine-treated patients gained weight. Weight gain for quetiapine-treated patients at final observation was 1.8 kg, which was similar to that reported in chlorpromazine-treated patients (1.3 kg).

Zotepine. Wetterling and Müßigbrodt[41] evaluated the weight of consecutively admitted hospital patients with schizophrenia who were treated with atypical antipsychotics for more than 2 weeks (N = 110). Mean weight gain for zotepine-treated patients was 3.6 kg in comparison with 1.3 kg for those receiving other atypical antipsychotics.[41] In a retrospective chart review of antipsychotics, zotepine, together with clozapine, produced the highest increases in body weight.[15]

Ziprasidone. Data on changes in body weight with ziprasidone, a new antipsychotic in the late stages of clinical development, are available from short-term, long-term, and "switch" studies. These data suggest that ziprasidone has a weight-neutral profile.

A double-blind, placebo-controlled study[42] evaluated the efficacy and safety of ziprasidone in 139 patients with acute exacerbation of schizophrenia or schizoaffective disorder. Patients were randomly assigned to ziprasidone, 40 mg/day or 120 mg/day, or placebo over 28 days. The only observed change in body weight was a median increase of 1 kg in the 40-mg/day ziprasidone group.

In a 6-week, placebo-controlled study,[43] patients treated with ziprasidone, 80 mg/day, showed a median increase in weight of 1 kg. Neither the patients receiving ziprasidone, 160 mg/day, nor those receiving placebo showed any weight gain. A 28-week study[44] produced similar results, with negligible changes in body weight.

Studies have investigated the efficacy and safety of switching to ziprasidone following unsuccessful treatment either with conventional antipsychotics or with olanzapine or risperidone because of inadequate efficacy or poor tolerability.[45–47] Changes in body weight during ziprasidone treatment were recorded in each study. Following treatment with conventional antipsychotics, patients switched to 6 weeks of ziprasidone treatment showed no changes in body weight.[45] In both the olanzapine-to-ziprasidone switch study[46] and the risperidone-to-ziprasidone switch study,[47] patients lost weight over the 6-week treatment period with ziprasidone. Further details are provided in the Clinical Implications of Weight Gain section of this article.

A long-term study with ziprasidone also supports these findings. Arato et al.[48] conducted a prospective, randomized, double-blind, parallel-group study that investigated the efficacy and safety of 3 fixed doses of ziprasidone in the treatment of chronic schizophrenia over 1 year. Previous treatment with antipsychotics or anticholinergics was

withdrawn before patients were randomly assigned to double-blind medication. In all treatment groups, there was a small median reduction in body weight from baseline to endpoint between 2.65 and 3.27 kg. Changes in weight in the ziprasidone-treated groups were indistinguishable from those of placebo-treated patients, in whom weight loss was 3.77 kg.[48]

Direct comparisons of the atypical antipsychotics. There are very few studies incorporating body weight data that have directly compared weight changes associated with one atypical antipsychotic with those of another atypical antipsychotic. Tran et al.[29] showed that olanzapine-treated patients had a statistically significantly greater increase in body weight than risperidone-treated patients over 28 weeks ($p = .015$). In another olanzapine-risperidone comparative study,[49] changes in body weight were not measured. However, Sachs and Guille[14] analyzed data from patients treated for 12 weeks or longer with olanzapine or risperidone and found that olanzapine-treated patients had a statistically significantly greater weight gain than risperidone-treated patients ($p < .05$). In olanzapine-treated patients, the mean weight gain was 10.7 kg after a mean treatment duration of 33 to 36 weeks. In risperidone-treated patients, the mean weight gain was 1.7 kg, and the duration of treatment was 112 weeks ($p < .05$).[14]

Individual study details and results have been tabulated for each atypical antipsychotic and presented in Appendix 1. The degree to which antipsychotics induce weight gain appears to vary from drug to drug. It is possible that the differential effects of antipsychotics on body weight may be a result of their individual receptor-binding profiles, which are unique for each atypical antipsychotic.[51] This is discussed in greater detail by Casey and Zorn[52] in this supplement.

IS WEIGHT GAIN ASSOCIATED WITH ANY CLINICAL PARAMETERS?

Treatment-Related Factors

Length of treatment. To determine whether there is a distinct time course over which weight gain occurs, it is necessary to observe weight changes over long periods of time.

Wirshing et al.[16] observed that clozapine- and olanzapine-treated patients gained weight over a prolonged period of time (circa 20 weeks). This was in contrast to risperidone- and sertindole-treated patients, who had a more limited period of weight gain: patients reached a weight plateau after a comparatively short initial period of about 10 weeks.

Wetterling and Müßigbrodt[15] noted that in general the maximal increase in weight with the atypical antipsychotics occurred in the first few weeks of treatment. With the exception of clozapine, the maximal increase of weight occurred in the first 3 to 5 weeks of treatment.

With clozapine, maximal weight gain appears to take longer.[15] Hummer et al.[22] observed the greatest weight gain during the first 12 weeks of clozapine treatment, although patients continued to gain weight over the course of the 1-year study. Leadbetter et al.[19] noted that weight gain with clozapine was particularly evident during the second half of a 16-week trial. Umbricht et al.[24] demonstrated that weight gain with clozapine was greatest during the first 6 to 12 months, then continued at a slower rate over the next 36 months when weight stabilized.

Weight gain with olanzapine tends to occur within a shorter time frame. Weight gain has occurred over 3 weeks in short-term studies and over 6 weeks.[26,27] In addition, a retrospective study noted that a small number of olanzapine-treated patients were considered obese (defined by a BMI of 28 in men and a BMI of 27 in women) by the end of the 4-month treatment period (mean duration of treatment = 115.5 ± 19.1 days).[31]

Weight gain with risperidone is apparent during both short-term (8 weeks) and longer-term (52 weeks) studies.[33,34,36] No definitive conclusions may be drawn with quetiapine because of the lack of long-term data; however, quetiapine has been associated with weight gain during short-term 6-week trials.[38–40]

In contrast, ziprasidone appears to have a weight-neutral effect, which has been consistently demonstrated during short- and long-term studies (Figures 1 and 2).[42,43,48,53,54]

Dose of antipsychotic. Evidence is inconclusive as to whether a link exists between weight gain and the dose of antipsychotic (conventional or atypical).[16] The relationship between dose of antipsychotic and the degree of weight gain is complex because, in clinical practice, dosage is related to the type and severity of illness.[1,15,55,57]

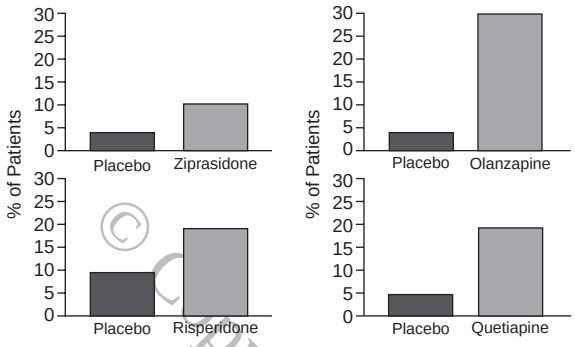
A positive correlation has been shown between the extent of weight gain and the dose of the conventional antipsychotic chlorpromazine.[55,57] However, few data demonstrate a dose-response relationship with other antipsychotics.

An inverse relationship has been demonstrated by Jalenques et al.[58] They showed that patients with schizophrenia who displayed a significant increase in body weight during clozapine treatment had received lower doses of clozapine than those who had lost weight.

However, a positive dose-response relationship with weight gain has been reported with the atypical antipsychotic olanzapine. Doses between 1 and 20 mg/day were administered in a 1796-patient multicenter study.[1] A positive relationship was reported between the dose of olanzapine taken and the magnitude of the increase in body weight. Nemeroff[30] analyzed the optimal dosing of olanzapine by the investigation of efficacy and dose-response relationships from 4 double-blind, randomized trials. He concluded that weight gain with olanzapine was dose related.

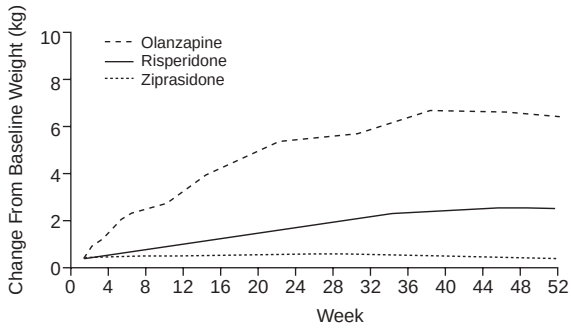
In a double-blind study that investigated the safety, efficacy, and optimal dose of risperidone in the treatment

Figure 1. Novel Antipsychotics With a Greater Than 7% Increase Over Baseline Weight in Short-Term, Placebo-Controlled Trials[a]



[a]Data from references 42, 43, 48, and 53.

Figure 2. Mean Change From Baseline Weight With Olanzapine, Risperidone, and Ziprasidone[a]



[a]Data from references 42, 43, 48, and 54, and data on file, Pfizer Inc. Only timepoints representing more than 400 patients are plotted for olanzapine.

of patients with schizophrenia, Marder and Meibach[50] reported a statistically significant positive correlation with weight gain and the dose of risperidone (2, 6, 10, 16 mg/day; $p < .05$).

Arvanitis et al.[39] concluded that weight gain with quetiapine was not dose related. In addition, Wetterling and Müßigbrodt[15] found no correlation between dose of antipsychotic and weight gain with either the atypical antipsychotics zotepine, clozapine, or risperidone or the conventional antipsychotics.

Different from other atypical antipsychotics, ziprasidone appears to be weight neutral across its recommended dose range (80–160 mg/day).[42,43]

Clinical response. It has been suggested that there is a relationship between the clinical efficacy of an antipsychotic and the degree of weight gain that results.[15,19,58,59] However, some studies have failed to demonstrate such a relationship.[20,22,24,39] Kalucy[56] concluded that although some weight gain (or restoration to pre-illness weight) may be expected when a patient recovers from a severe mental disorder, the excessive weight gain observed in up to 40% of subjects taking antipsychotics is not an indication of clinical improvement.

Patient-related factors. A number of patient-related variables may complicate the evaluation of whether, and to what extent, a drug may affect body weight. These factors are considered in detail by Kurzthaler and Fleischhacker[7] in this supplement.

Age and gender. Age and gender can affect drug-related changes in weight.[14] Weight naturally increases with age, and in the general population, obesity is more prevalent in women than in men. These factors further confound the interpretation of body weight data during treatment with antipsychotics.[1,16]

Hummer et al.[22] demonstrated that changes in weight with clozapine were consistent between male and female patients. This finding was supported by Tollefson et al.[27] with olanzapine. With respect to age, it has been suggested that weight gain with antipsychotic treatment correlates in a positive manner.[15]

Cigarette smoking. In comparison with the general population, individuals with schizophrenia have an increased prevalence of smoking.[60] Smoking may influence a patient's liability for weight gain since it is well established in the general population that people who smoke cigarettes tend to gain less weight than those who do not smoke.[61]

Baseline BMI. It has been suggested that patients with a low BMI at baseline are likely to gain more weight than patients with a higher BMI at baseline, and some data support this theory.[24,27]

Umbricht et al.[24] demonstrated with clozapine that there was a correlation between being underweight at baseline and gaining the maximum amount of weight. Tollefson et al.[27] stated that BMI was a relevant predictor of weight gain with olanzapine. Nemeroff[30] noted that weight increase with olanzapine was greatest for patients who had a starting dose of 15 mg/day and/or were underweight, as indicated by the BMI, at the start of the study.

Wetterling and Müßigbrodt[15] reported a positive correlation between weight gain with conventional and atypical antipsychotics and baseline BMI. However, no correlation between baseline BMI and weight gain was demonstrated in a retrospective analysis of clinical records from clozapine-, olanzapine-, risperidone-, sertindole-, and haloperidol-treated patients.[16]

Environment. Body weight measurements are often obtained from inpatient studies in which patients are sedentary. In this situation, patients may be less active than normal, are provided with regular meals, and are less able to control their intake of food because it is provided for them by hospital staff. Patients in this type of environment may be more liable to gain weight.[15]

Appetite. A number of studies have demonstrated that conventional antipsychotic treatment is associated with

an increase in appetite.[5] However, the exact nature of this increase in appetite is not as clear as it is with the antidepressants, where "carbohydrate craving" has been reported.[62]

CLINICAL IMPLICATIONS OF WEIGHT GAIN

Psychological Consequences

There are a number of psychological consequences to weight gain. Weight gain is distressing to most patients who experience it, and therefore it may impact on well-being.[13,14] In addition, patients who are already suffering the stigma associated with mental illness may be further stigmatized and discriminated against in daily life as a result of being overweight.[63]

Weight gain may also adversely affect compliance with treatment.[13] In a 51-patient study,[64] weight gain was rated by the patients as the most distressing of 27 adverse effects listed and the most likely to contribute to poor compliance in the future. This finding has implications for long-term outcomes because compliance with treatment is one of the factors that determine the degree of success of antipsychotic treatment.[65] Patients who fail to take their medications as directed have a poorer long-term outcome, suffer more frequent and more severe relapses, and make more demands upon their families and rehabilitation services.[64]

Implications for Management of Antipsychotic-Induced Weight Gain

Several management options are available that may help to minimize the potential for weight gain during treatment with antipsychotics.[14] These options include choosing, or switching to, an antipsychotic that has a lower liability for inducing weight gain. Polypharmacy should be avoided.[62] Dietary advice may be considered where appropriate,[67,68] as may the implementation of a weight loss program.[14] A number of studies have shown the potential benefit of switching from one antipsychotic to another in patients who require a change in drug treatment owing to inadequate efficacy or unacceptable side effects. For example, Weiden et al.[45] noted that body weight change was negligible following treatment switch from conventional antipsychotics to ziprasidone. Daniel et al.[46] demonstrated that after switching patients from olanzapine to 6 weeks of ziprasidone treatment, 40 to 160 mg/day, there was a statistically significant reduction in mean ± SD body weight from 91.3 ± 18.1 kg at baseline to 89.7 kg ± 8.4 at last visit ($p < .01$) (last observation carried forward for all patients). Similar results were reported following a switch to ziprasidone from risperidone.[47] Mean body weight at the start of switching to ziprasidone treatment was 83.5 ± 4.0 kg. After 6 weeks of treatment with ziprasidone, 40 to 160 mg/day, mean body weight had decreased to 82.6 kg ± 13.6 kg.

CONCLUSION

Weight gain during treatment with the majority of the atypical antipsychotics, particularly with clozapine and olanzapine, is a serious health problem. This observation is further supported by data from double-blind, randomized studies showing that weight gain with the atypical antipsychotics is greater than that associated with the conventional antipsychotics.[17,19,23] Clinically significant weight gain of ≥ 7% has been demonstrated during short- and long-term treatment with the atypical antipsychotics clozapine, olanzapine, risperidone, and quetiapine. The limited data with amisulpride and zotepine suggest that both compounds may also show weight gain.[15,32]

Short- and long-term studies with ziprasidone, a novel antipsychotic in the late stages of clinical development, suggests that ziprasidone has a weight-neutral profile. Furthermore, preliminary evidence from switch studies suggests that ziprasidone may reduce weight in patients previously treated with other antipsychotics.[45–47] However, since no direct comparisons have yet been published between ziprasidone and the other atypical antipsychotics, the available evidence should be interpreted with caution.

Currently available evidence suggests that when weight gain occurs with the atypical antipsychotics, it occurs irrespective of dose within the recommended dose range and does not appear to correlate with efficacy of antipsychotic treatment. Evidence does not support the strategy of dose reduction to minimize the degree of weight gain, nor does it support the view that weight gain is a predictor of clinical response with the atypical antipsychotics clozapine, olanzapine, risperidone, and sertindole.[16,24]

The impact that weight gain has on patient well-being, health status, compliance with treatment, and, ultimately, the degree of success of pharmacologic treatment of schizophrenia means that a drug's weight gain liability is an important aspect of its tolerability and acceptability profile. In everyday clinical practice, patients showing a positive initial response to an atypical antipsychotic will usually continue treatment with the same drug. It should be noted that not all patients would gain weight; many will benefit from effective treatment without experiencing this distressing side effect. However, in many patients, continued treatment may lead to a substantial increase in body weight.

Thus, when considering treatment options and management strategies for an individual patient, the weight gain liability of an antipsychotic should be taken into account.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal).

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Appendix 1. Changes in Body Weight Reported With Atypical Antipsychotics

Reference	Dose of Study Antipsychotic	Comparator (dose)	Placebo?	Patient Population	Design	Duration	Results
Clozapine							
Bustillo et al (1996)[20]	Mean ± SD dose at 10 wk = 410.5 ± 45.8 mg/d	Haloperidol (mean ± SD dose at 10 wk = 24.8 ± 5.5 mg/d)	No	Outpatients with schizophrenia (N = 39)	Double-blind, randomized, parallel group Doses fixed during the last 4 weeks Following completion of 10-wk study, clozapine given open label for 1 year (N = 33)	10 wk	Clozapine group gained 7% ± 5% over baseline, i.e., 5.3 ± 3.17 kg Haloperidol group gained 1% ± 4% over baseline, i.e., 0.68 ± 2.72 kg Statistically significant difference between the groups ($p < .001$) At 1 year of open-label treatment, 58% of clozapine group gained ≥ 10%; 21% of group gained ≥ 20%
Umbricht et al (1994)[24]	500–600 mg/d	None	No	Patients with chronic schizophrenia (N = 82)	Retrospective chart review Dose titration over 3–5 wk	12 wk (N = 73) and 90 mo (N = 68)	Mean weight increase at wk 4: 4.4% ± 5.4%; wk 8: 8.0% ± 7.6%; wk 12: 9.0% ± 7.5% Over 90 mo, cumulative proportion of patients becoming 10%, 20%, 30%, and 40% overweight was 86%, 54%, 23%, and 13%, respectively
Hummer et al (1995)[22]	Mean ± SD dose = 240.6 ± 138.4 mg/d	Haloperidol	No	Patients with treatment-resistant or treatment-intolerant schizophrenia (N = 81)	Prospective naturalistic study	12 wk, with long-term follow-up for as long as patients remained on clozapine treatment	Over 12 wk, 35.7% of clozapine group gained ≥ 10% of their initial body weight Clozapine group gained 3.5 ± 4.6 kg Haloperidol group gained 1.5 ± 1.8 kg
Lamberti et al (1992)[23]	Mean ± SD dose = 380 ± 135 mg/d	None	No	Inpatients with chronic schizophrenia (N = 36)	Retrospective chart review	6 mo	Clozapine group gained a mean of 7.66 ± 4.94 kg ($p < .0001$) over 6 mo 75% of patients gained ≥ 4.53 kg 4.7% of patients gained ≥ 9.07 kg
Leadbetter et al (1992)[19]	Not available	None	No	Inpatients with treatment-resistant schizophrenia or schizoaffective disorder (N = 21)	Open-label dose-titration study	16 wk	Mean weight gain = 8.9% over baseline (6.3 kg) At 16 wk, 38% had ≥ 10% increase in weight At 16 wk, 29% had ≥ 5%–10% weight gain
Bandolfi et al (1998)[21]	Mean dose = 291.2 mg/d	Risperidone (mean dose = 6.4 mg/d)	No	Treatment-resistant patients with chronic schizophrenia (N = 86)	Double-blind, randomized, controlled, multicenter, flexible dose	8 wk	Clozapine group gained a mean of 2.7 kg ($p = .01$); risperidone group gained 1.1 kg (NS)

(continued)

Appendix 1. Changes in Body Weight Reported With Atypical Antipsychotics (cont.)

Reference	Dose of Study Antipsychotic	Comparator (dose)	Placebo?	Patient Population	Design	Duration	Results
Olanzapine							
Tollefson et al (1997)[27]	Mean ± SD modal dose = 13.2 ± 5.8 mg/d	Haloperidol (mean ± SD modal dose = 11.8 ± 5.6 mg/d)	No	Patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (N = 1996)	Double-blind, randomized, multicenter, flexible dose	6 wk	Olanzapine group mean weight gain of 1.88 ± 3.54 kg Haloperidol group mean weight gain of 0.02 ± 2.79 kg ($p < .001$)
Tran et al (1997)[29]	Mean ± SD modal dose = 17.2 ± 3.6 mg/d	Risperidone (mean ± SD modal dose = 7.2 ± 2.7 mg/d)	No	Patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (N = 339)	Double-blind, randomized, parallel group, multicenter, flexible dose	28 wk	Within-group increase in mean weight was statistically significant ($p < .001$) Olanzapine group gained 4.1 ± 5.9 kg Risperidone group gained 2.3 ± 4.8 kg Between groups, difference was statistically significant ($p = .015$)
Tohen et al (1999)[26]	Mean ± SD modal dose = 14.9 ± 5 mg/d	None	Yes	Patients with bipolar disorder, manic or mixed episode (N = 139)	Double-blind, randomized, placebo controlled, parallel group, flexible dose	3 wk	Olanzapine group gained 1.65 ± 2.54 kg Placebo group lost 0.44 ± 2.35 kg ($p < .001$)
Beasley et al (1996)[28]	5 ± 2.5 mg/d, 10 ± 2.5 mg/d, 15 ± 2.5 mg/d	Haloperidol (15 ± 5 mg/d)	Yes	Patients with acute exacerbation of schizophrenia (N = 335)	Double-blind, randomized	6 wk plus 46-wk double-blind extension	Olanzapine high-dose group had mean weight gain of 3.5 ± 3.9 kg
Beasley et al (1996)[25]	1 mg/d, 10 mg/d	None	Yes	Patients with acute exacerbation of schizophrenia (N = 152)	Double-blind, randomized, placebo controlled, fixed dose	6 wk	For the olanzapine 10-mg group, mean weight gain of 2.2 ± 4 kg For the placebo group, mean weight loss of 0.4 ± 3.1 kg
Risperidone							
Høyberg et al (1993)[34]	5–15 mg/d; mean daily dose = 8.5 mg	Perphenazine (16–48 mg/d; mean daily dose = 28 mg)	No	Patients with acute exacerbation of chronic schizophrenia (N = 107)	Double-blind, randomized, parallel group, multicenter	8 wk	39% of risperidone group gained weight 20% of perphenazine group gained weight
Peuskens et al (1995)[33]	Fixed doses: 1, 4, 8, 12, 16 mg/d	Haloperidol (10 mg/d)	No	Patients with chronic schizophrenia (N = 1362)	Double-blind, randomized, parallel group, multicenter, fixed dose	8 wk	Significant weight gain in all risperidone groups Mean increase varied: 0.3 kg in risperidone 1-mg group, 1.6 kg in risperidone 8-mg group Weight gain in 8-, 12-, and 16-mg risperidone groups was significantly greater than that for haloperidol group
Marder and Meibach (1994)[50]	Fixed doses: 2, 6, 10, 16 mg	Haloperidol (20 mg)	Yes	Patients with schizophrenia (N = 388)	Double-blind, randomized, parallel group, fixed dose	8 wk	Weight gain correlated to risperidone dose ($p < .05$)
Csernansky and Okamoto (1999)[36]	Mean ± SD modal dose = 4.88 ± 1.89 mg	Haloperidol mean ± SD modal dose = 11.72 ± 4.96 mg)	No	Outpatients with schizophrenia and schizoaffective disorder (N = 365)	Double-blind, randomized, multicenter, flexible dose	52 wk	Risperidone group: mean ± SE weight gain = 2.27 ± 0.63 kg Haloperidol group: mean ± SE weight loss = 0.74 ± 0.54 kg ($p < .001$)
Ganguli et al (1998)[31]	Not available	Olanzapine	No	Patients with schizophrenia (N = 100)	Two patient cohorts who had received olanzapine or risperidone for ≥ 4 months Baseline weight determined from medical notes	4–6 mo	Olanzapine group gained 2.22 ± 3.4 kg ($p < .001$) Risperidone group showed no change

(continued)

Appendix 1. Changes in Body Weight Reported With Atypical Antipsychotics (cont.)

Reference	Dose of Study Antipsychotic	Comparator (dose)	Placebo?	Patient Population	Design	Duration	Results
Quetiapine							
Arvanitis et al (1997)[39]	75, 150, 300, 600, 750 mg/d	Haloperidol (12 mg/d)	Yes	Patients with acute exacerbation of chronic or subchronic schizophrenia (N = 361)	Double-blind, randomized, placebo controlled, multicenter, fixed dose	6 wk	Quetiapine group had mean weight gain of 0.9, 2.9, 2, 2.6, and 2.3 kg in low- to high-dose groups Haloperidol group had mean weight gain of 0.3 kg Placebo group lost 0.8 kg Weight increases ≥ 7% in proportion of quetiapine-treated patients: 11%, 17%, 10%, 16%, and 13%; haloperidol-treated patients: 4%; placebo-treated patients: 6%
Peuskens (1997)[40]	Up to 750 mg/d; mean daily dose = 407 mg	Chlorpromazine (up to 750 mg/d; mean daily dose = 384 mg)	No	Inpatients with acute exacerbation of subchronic/ chronic schizophrenia/ schizophreniform disorder (N = 201)	Double-blind, randomized, parallel group, multicenter Dose titrated according to clinical response and tolerance	6 wk	≥ 7% Weight increase in 27% of quetiapine group and 18% of chlorpromazine group Quetiapine group had mean weight gain of 1.8 kg Chlorpromazine group had mean weight gain of 1.3 kg
Small et al (1997)[37]	≤ 750 mg/d (mean daily dose = 360 mg); ≤ 250 mg/d (mean daily dose = 209 mg)	None	Yes	Inpatients with acute exacerbation of chronic or subchronic schizophrenia (N = 286)	Double-blind, randomized, placebo controlled, parallel group, multicenter	6 wk	Quetiapine group had mean weight gain of 2 kg Placebo group had mean weight gain of 0.1 kg
Borison et al (1996)[38]	75–750 mg/d (mean daily dose = 307 mg); range, 58–526 mg	None	Yes	Inpatients with acute exacerbation of chronic or subchronic schizophrenia (N = 636)	Double-blind, randomized, placebo controlled, parallel group, multicenter, dose titration	6 wk	25% of quetiapine patients had clinically significant weight gain (≥ 7%) compared with 4% of placebo patients Quetiapine group had mean weight gain of 5.5 kg Placebo group had mean weight gain of 0.5 kg
Zotepine							
Wetterling and Müßigbrodt (1996)[41]	Not available	None	No	Inpatients with schizophrenia, schizoaffective disorder, delusional disorder (N = 110)	Retrospective chart review of consecutively admitted cases	≥ 2 wk	Zotepine group had mean weight gain of 3.6 kg Group of patients receiving other atypical antipsychotics had mean weight gain of 1.3 kg
Ziprasidone							
Arato et al (1997)[48]	40, 80, 160 mg bid	None	Yes	Patients with chronic schizophrenia (N = 294)	Double-blind, randomized, parallel group, multicenter, fixed dose	52 wk	Ziprasidone group had weight loss of 2.65–3.27 kg Placebo group had weight loss of 3.77 kg Changes in median body weight with ziprasidone indistinguishable from placebo
Keck et al (1998)[42]	40 mg/d, 120 mg/d	None	Yes	Patients with acute exacerbation of schizophrenia or schizoaffective disorder (N = 139)	Double-blind, randomized, placebo controlled, parallel group, multicenter, fixed dose	28 d	No evidence of meaningful change in body weight Only observed change was a median increase of 1 kg in 40-mg/day ziprasidone group
Daniel et al (1999)[43]	80 mg/d, 160 mg/d	None	Yes	Patients with acute exacerbation of schizophrenia or schizoaffective disorder (N = 302)	Double-blind, randomized, placebo controlled, parallel group, multicenter, fixed dose	6 wk	80-mg ziprasidone group had median increase of 1 kg; 160-mg ziprasidone group had no change Placebo group had no change

(continued)

Appendix 1. Changes in Body Weight Reported With Atypical Antipsychotics (cont.)

Reference	Dose of Study Antipsychotic	Comparator (dose)	Placebo?	Patient Population	Design	Duration	Results
Ziprasidone cont.							
Hirsch and Power (1999)[44]	80–160 mg/d; modal dose = 80 mg/d	Haloperidol (5–15 mg/d; modal dose = 5 mg/d)	No	Outpatients with stable chronic or subchronic schizophrenia (N = 301)	Double-blind, randomized, flexible dose	28 wk	Negligible changes in body weight with both drugs
Weiden et al (1999)[45]	40–160 mg/d	Switch from conventional antipsychotics	No	Outpatients with schizophrenia who required switch (N = 68)	Double-blinded rater Switch study due to lack of efficacy or unacceptable side effects with conventional antipsychotics	6 wk	Following switch to ziprasidone, changes in body weight were negligible
Daniel et al (1999)[46]	40–160 mg/d; mean daily dose = 100 mg/d	Switch from olanzapine	No	Stable outpatients with schizophrenia or schizoaffective disorder who required switch (N = 58)	Open-label, parallel-group, multicenter switch study due to lack of efficacy or unacceptable side effects with olanzapine Flexible dose	6 wk	Following switch to ziprasidone, mean ± SD body weight decreased from 91.3 ± 18.1 kg at baseline (last observation carried forward) to 89.7 ± 18.4 kg ($p < .001$)
Simpson et al (1999)[47]	Mean daily dose = 100 mg	Switch from risperidone	No	Stable outpatients with schizophrenia or schizoaffective disorder (N = 23)	Blinded-rater, parallel-group, multicenter switch study due to lack of efficacy or unacceptable side effects with risperidone Flexible dose	6 wk	Following switch to ziprasidone, mean ± SD body weight decreased from baseline (83.5 ± 14.0 kg) to endpoint (82.6 ± 13.6 kg)