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A review of the effect of atypical antipsychotics on weight

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Abstract

Controlled research trials have shown that atypical antipsychotics have important advantages over standard antipsychotics, including a broader spectrum of efficacy and improved tolerability profile, particularly with regard to neurological adverse events such as extrapyramidal symptoms (EPS). Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and other adverse health effects. The mechanisms involved in antipsychotic drug-related weight gain are as yet uncertain, although serotoninergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity.

Keywords: Atypical antipsychotics; Schizophrenia; Weight gain; Long-term therapy

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Contents

1. Introduction

Atypical antipsychotics are an important advance in the treatment of schizophrenia and other psychoses, and have become widely used as first-line pharmacotherapy for psychosis. One of the main advantages of the atypical antipsychotics over standard antipsychotics is their broad spectrum of efficacy. Unlike the older conventional antipsychotics, atypical antipsychotics are effective in the treatment of all schizophrenia domains (positive, negative, affective, and cognitive symptoms) (Javitt, 1999; Purdon et al., 2001). Conventional antipsychotics (e.g. haloperidol, chlorpromazine) do not always fully resolve positive symptoms, have little effect on negative symptoms, and may worsen cognitive symptoms in some patients (Spohn and Strauss, 1989; Purdon et al., 2001).

As with all drugs, efficacy must be accompanied by a tolerable side-effect profile to optimize clinical effectiveness. Extrapyramidal symptoms (EPS) are a major problem with conventional antipsychotics and often lead to poor compliance (Tran et al., 1997; Davies et al., 1998). Atypical antipsychotics, however, have been shown to cause less EPS than standard antipsychotics, although dose-related EPS do occur with some agents (Owens, 1994; Peuskens, 1995; Daniel et al., 1999). With the declining use of conventional antipsychotics and reduced incidence of acute EPS as well as tardive dyskinesia, other side effects of antipsychotics, such as weight gain, have become more prominent as impediments to clinical effectiveness.

Weight gain is associated with many conventional and some atypical antipsychotics (Allison et al., 1999a) and its degree is dependent on the drug and the individual patient. Weight gain occurs shortly after starting treatment but may plateau or

even decrease after 1 year. Weight gain is linked to a decreased metabolic rate, increased calorie intake, and decreased physical activity (Weinsier et al., 1998; Baptista, 1999), although it is not yet known by which precise mechanisms it is induced by atypical antipsychotics.

The consequences of excessive weight gain (obesity) associated with antipsychotic drugs are likely to include poor compliance or even discontinuation of therapy by the patients. Poor adherence almost always leads to relapse and a worsened long-term outcome (Bernstein, 1987; Fenton et al., 1997). As obesity is frequently a comorbid condition with schizophrenia (Allison et al., 1999b), schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type II diabetes (Mukherjee et al., 1996; Nasrallah, 2000). Particular consideration should therefore be given to the choice of antipsychotic drugs in this patient population with regard to weight change as a potential serious adverse health effect.

This review examines the limited evidence regarding the mechanism of weight gain with antipsychotic drugs and then focuses on the differential effects of atypical antipsychotics on weight. In the majority of the studies discussed, weight gain was assessed for each patient by calculating the difference between body mass index (BMI) at the start and end of treatment. BMI describes relative weight for height and is a widely accepted measure of weight change and classification (WHO, 1998). It is calculated as the weight in kilograms divided by the square of the height in meters. Optimal BMI is between 20 and 25, while 25–30 is regarded as 'overweight' and >30 as 'obese'.

2. Mechanisms of weight gain with atypical antipsychotics

It is generally believed that there are multiple mechanisms by which antipsychotic drugs induce weight gain but their precise nature remains unknown. Weight gain as a drug effect may be a multifactorial process, involving serotonergic, histaminergic, and/or adrenergic neurotransmission (Baptista, 1999). Atypical antipsychotics achieve their therapeutic effects by modulating the activity of these neural pathways. Weight gain as a side effect may be due to the blockade of certain receptors, e.g. 5-HT_{2c}, that modulate appetite and body weight (Stanton, 1995). The ratios between various receptor affinities may also be important. As the atypical antipsychotics vary in their receptor affinity profiles, it would be expected that they differ in their tendency to cause weight gain.

The specific interaction between antipsychotic drugs and hormones (such as insulin and leptin) that regulate appetite and obesity has yet to be fully elucidated. Melkersson et al. (2000) found that olanzapine therapy was associated with increased levels of insulin and leptin, as well as with weight gain. Leptin regulates food uptake and energy expenditure; it is synthesized by fat cells and its serum levels correlate positively with BMI (Kraus et al., 1999). An increase in serum leptin levels has been associated with olanzapine and clozapine therapy (Brömel et al., 1998; Kraus et al., 1999). This increase may be a direct effect of the antipsychotics on the feedback

mechanism for this hormone or an effect of the increased appetite, impaired satiety, and weight gain associated with the antipsychotic drugs.

3. Clozapine

Clozapine is associated with some of the largest weight gains seen with any antipsychotic drug (Stanton, 1995; Sussman and Ginsberg, 1999). Cohen et al. (1990) reported a mean weight gain of 11.2 kg for six patients taking clozapine at maximum doses of 175–600 mg/day for a mean duration of 6.5 months. Included in this group was one patient who had substantial weight gain of 31.3 kg while taking clozapine at a maximum dose of 400 mg/day for 9 months. It should be noted that a gain of >7% of the ideal body weight is considered a health risk. This amounts to about 4 kg for an average woman and 6 kg for an average man.

Leadbetter et al. (1992) reported a mean weight gain of 6.3 kg (9% increase in body weight) in 21 patients over 16 weeks of treatment. Eight (38%) patients experienced marked weight gains (>10% of their body weight). Lamberti et al. (1992) reported a mean weight gain of 7.7 kg for 36 patients receiving a mean clozapine dose of 380 mg/day over 6 months. This increase represented 11% of the patients' maximum ideal weight. Twenty-seven (75%) of the patients gained at least 4.5 kg and 15 (42%) patients gained at least 9 kg.

In a retrospective study of 82 patients treated with clozapine 500–600 mg/day for up to 90 months, Umbricht et al. (1994) found that about 50% of patients became substantially overweight (≥20%). Patients who were underweight at baseline had significantly higher percentage weight increases than those with ideal weight and those who were overweight. The cumulative incidence rates were >80% of patients for a 10% weight gain and 38% of patients for a 20% weight gain. Weight gain occurred mostly within the first year but continued into the third year.

Frankenburg et al. (1998) found significant mean increases (5.9 and 3.3 kg/m^2 in female and male patients, respectively) in BMI among 42 patients receiving clozapine over a 3-year period. The final BMI appeared to be dependent on the baseline BMI and the dose of clozapine.

Finally Reinstein et al. (1999) reported significant weight loss (mean 4.2 kg; range 0.45–18.6 kg over 10 months) with the addition of quetiapine to the treatment regimen of 65 patients who had previously been on clozapine monotherapy. Furthermore, they reported a significant improvement in glycemic control in three (20%) of 13 patients who developed diabetes during clozapine monotherapy.

4. Olanzapine

Olanzapine is associated with significant weight gain with a magnitude comparable to that produced by clozapine (Jibson and Tandon, 1998). Nemeroff (1997) reviewed the safety and efficacy data from four clinical trials in which olanzapine was compared with placebo and/or haloperidol in nearly 3000 patients. Olanzapine patients

had a dose-related increase in weight, achieving after 1 year a mean weight gain of approximately 12 kg with a high dose (12.5–17.5 mg/day), compared with a mean weight gain of 3 kg with a low dose (1 mg/day) (Fig. 1) (Nemeroff, 1997). Weight gain was greatest for patients who had a starting dose of 12.5–17.5 mg/day of olanzapine and/or were underweight (as indicated by BMI) at the start of the study.

Beasley (1997) reported that 41% of a total of 1455 patients receiving olanzapine in four combined studies experienced a clinically significant (≥7%) weight gain. The incidence of weight gain was highest (32%) among patients who were underweight at baseline and lowest (11%) among those who were overweight. Most weight gain occurred during the first 6–8 weeks of therapy and reached a plateau by the end of the first year. Further evidence of olanzapine-associated weight gain provided by Weiden et al. (1996) showed that after >6 weeks of olanzapine treatment, one-third of the patients reported weight gain as the 'most problematic' side effect. Weight gain occurred in most of the 15 patients and was regarded as a serious problem for 3/15 (20%) patients.

In addition, a study of nine patients with schizophrenia showed that 16 months of treatment with olanzapine was associated with a rise in triglyceride levels and mean weight gain of 10 kg (Sheitman et al., 1999). The rise in triglyceride levels is an important factor for some patients because of its link with an increased risk for coronary artery disease. Finally, a recent study of olanzapine with or without fluoxetine in treatment-resistant depression reported a weight gain of 6.07 kg with olanzapine alone over 8 weeks (Shelton et al., 2001). It may be that patients with mood disorders are especially susceptible to weight gain with olanzapine.

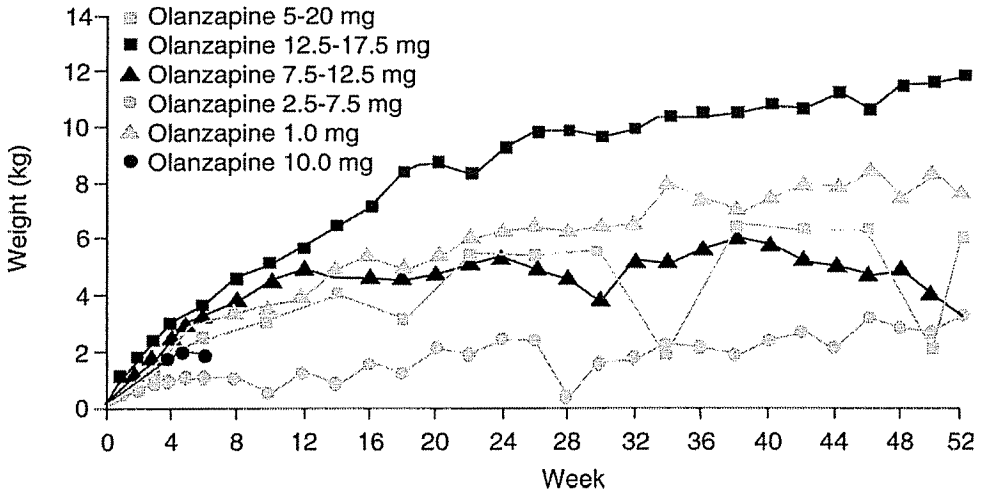


Fig. 1. Mean change in weight over time at different olanzapine dosages. Data from four different studies combined. Olanzapine dosages were as follows: Study 1—fixed at 1 and 10 mg/day; Study 2—flexible within three dose ranges (2.5–7.5, 7.5–12.5, and 12.5–17.5 mg/day); Study 3—as Study 2 with the addition of a fixed dose of 1 mg/day; and Study 4—flexible within the range 5–20 mg/day. Adapted from Nemeroff (1997). Copyright 1997, Physicians Postgraduate Press. Reprinted by permission.

5. Risperidone

Risperidone is associated with modest weight gain that is not dose related. The literature reveals consistent values for weight gain with risperidone therapy. Claus et al. (1992) reported a mean weight gain of 2 kg after 12 weeks of treatment with risperidone at a mean final dose of 12 mg/day. Owens (1994) reported mean weight gains of 1–2 kg after 8 weeks of treatment with risperidone at 2–16 mg/day.

A mean weight gain of 2.8 kg occurred after 8 weeks of treatment in 11 patients randomized to 2, 6, 10, or 16 mg/day risperidone. The change in weight from baseline was statistically significant, as was the difference in weight change between the risperidone and placebo groups. There was no significant correlation between weight gain and risperidone dose or plasma concentration (Anderson et al., 1993). Brecher and Geller (1997) reported an average weight gain of 2.6 kg among 1200 patients treated for a mean duration of 213 days (30 weeks) in long-term risperidone trials.

A recent study comparing risperidone and haloperidol over 1 year showed a mean weight gain of 2.3 kg in the risperidone group and a decrease of 0.73 kg in the haloperidol group (Csernansky et al., 2002).

6. Ziprasidone

Ziprasidone has been associated with minimal weight loss, minimal weight gain, or no effect on weight. A pooled analysis of four short-term (4–6 week) studies showed the proportion of patients who experienced weight gain exceeding 7% body weight was significantly greater in those treated with ziprasidone (dose range 10–200 mg/day) compared with placebo (10 versus 4%) (Geodon (ziprasidone HCl) Prescribing Information, 2001). The same analysis indicated that the overall incidence of anorexia adverse events with ziprasidone was low (2 versus 1% placebo) but was reported to be dose related.

In a randomized, placebo-controlled, double-blind study, Arato et al. (1999) assessed ziprasidone in 219 chronic schizophrenia patients for 1 year, at three dose levels (40, 80, and 160 mg/day). Patients in this study were carefully monitored, being either in hospital or in sheltered accommodation with continuous medical or nursing supervision. Ziprasidone was not associated with weight gain but it remains to be established whether these results will replicate in patients managed in an unsupervised outpatient setting.

In a head-to-head, double-blind, 6-week, randomized trial, ziprasidone was associated with a small increase in weight (n = 116, 0.93 kg, 0.24 kg/m^2) that was significantly lower than with olanzapine (n = 120, 3.57 kg, 1.17 kg/m^2) (Simpson et al., 2001). However, the incidence of gastrointestinal-related adverse events such as dyspepsia (11.8 versus 7.5%) and nausea (10.3 versus 6.0%) was higher amongst patients receiving ziprasidone than those receiving olanzapine and the extent to which this may have affected food intake and weight change is not known.

Results from various studies of these four atypical antipsychotics (clozapine, olanzapine, risperidone, and ziprasidone) were included in a meta-analysis by Allison et

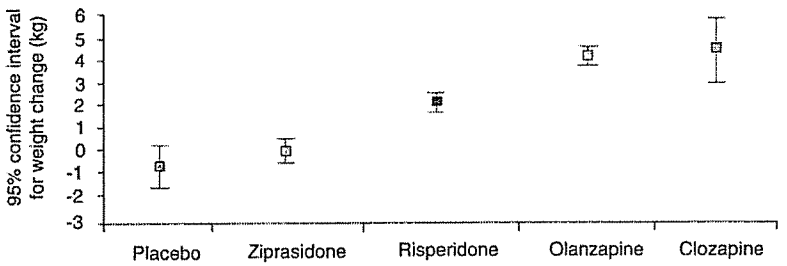


Fig. 2. Mean weight change with 95% confidence intervals after 10 weeks on standard drug doses. Adapted from Allison et al. (1999a). Copyright 1999, American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.

al. (1999a). The mean weight change was estimated after 10 weeks of treatment with antipsychotic drugs at a standard dose (Fig. 2) (Allison et al., 1999a). The results, with substantial weight gain for clozapine and olanzapine, modest weight gain for risperidone, and negligible weight gain for ziprasidone, were consistent with previous reports as described above.

7. Quetiapine

Results from several clinical trials have shown that short-term quetiapine treatment is associated with modest weight gain that is not dose related. The effects on weight are neutral when quetiapine is used as long-term monotherapy.

A total of 2216 patients who had participated in controlled, uncontrolled, and open-label extension trials were included in an analysis of weight change in long-term (12 months) quetiapine treatment (Jones et al., 2000; Rak et al., 2000). Analysis of the overall data showed a small mean weight increase of 2.08 kg (n = 778) over the first 5–6 weeks of treatment (Table 1) and no dose-related weight gain (Table 2). Over longer treatment periods, the increases from baseline showed little change (Table 1) and remained unrelated to dose (Table 2). The mean dose of quetiapine at 9–12 months was 428 mg/day. An analysis of weight change by BMI categories at baseline revealed a trend for greater weight gain in patients with low baseline

Table 1
Mean weight change from baseline in patients treated with quetiapine during controlled, uncontrolled, and open-label extension trials; data from Rak et al. (2000)

Duration of treatment	No. of patients	Mean weight change, kg (+SE)
5–6 weeks	778	2.08 (0.15)
9–10 weeks	171	2.16 (0.46)
6–9 months	556	1.85 (0.48)
9–12 months	360	2.77 (0.56)

Table 2
Mean weight change in patients receiving different quetiapine doses during controlled, uncontrolled, and open-label extension trials; adapted from Jones et al. (2000)

Dose (mg)	Mean weight change (kg)	
	5–6 weeks of treatment	9–12 months of treatment
<125	1.21	1.78
125–225	2.95	1.38
>225–450	2.13	3.83
>450–675	1.95	2.26
>675	2.05	2.13

BMIs (<23) than in patients with normal (23–27) or high (>27) baseline BMIs. Only one patient withdrew from treatment because of weight gain. It should be noted that most of the patients included in this analysis had participated in studies in which antipsychotics other than quetiapine were allowed. It is therefore difficult to attribute weight gain specifically to quetiapine or the other antipsychotics or a combination of both.

The absence of a dose-related weight gain is consistent with the results of an earlier double-blind, dose-ranging study in which 361 patients received quetiapine for up to 6 weeks and in which no apparent relationship was found between weight change and dose (Arvanitis and Miller, 1997; Jones et al., 2000). A separate analysis included patients from controlled, uncontrolled, and open-label extension trials in which quetiapine was the only antipsychotic permitted (Brecher et al., 2000; Brecher and Melvin, 2001). A total of 427 patients received a mean dose of 475 mg/day after 1 year of open-label quetiapine treatment. There was minimal weight gain over an 80-week period (Fig. 3) (Brecher et al., 2000).

Quetiapine had no overall effect on weight across the baseline BMI range. The relationship between weight change and BMI was examined in a subset of 178 patients who had received quetiapine for at least 26 weeks (mean duration of 18.6 months) at a mean final dose of 473 mg/day. Patients were categorized according to their baseline BMIs (<18.5 = underweight; 18.5 to <25 = normal weight; 25 to <30 = overweight; 30 to <35 = obese; and ≥35 = severely obese). Small numbers of patients in some of these categories resulted in wide 95% confidence intervals associated with the mean weight change from baseline. Fig. 4 shows that the 95% confidence intervals of the mean weight change from baseline included zero when all BMI groups were considered together and individually (with the exception of the severely obese) (Brecher et al., 2000). These results indicate an absence of weight effect across the BMI range with long-term quetiapine treatment except in severely obese patients, where quetiapine was associated with a statistically significant decrease in weight. The effect of quetiapine was not related to dose or gender. Fig. 5 shows weight changes by dose group, using the modal dose value for the last recorded weight (endpoint) value (Brecher et al., 2000). There were no statistically significant changes from baseline in mean weight. The 95% confidence intervals of

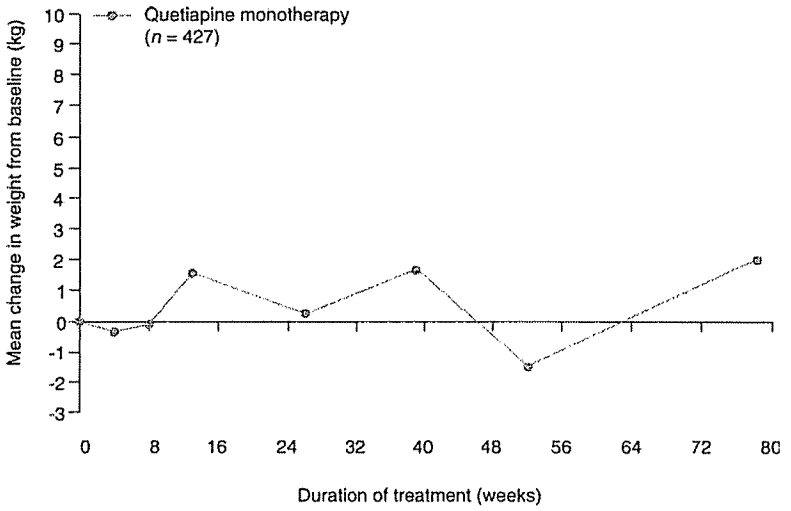


Fig. 3. Mean weight change from baseline during quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

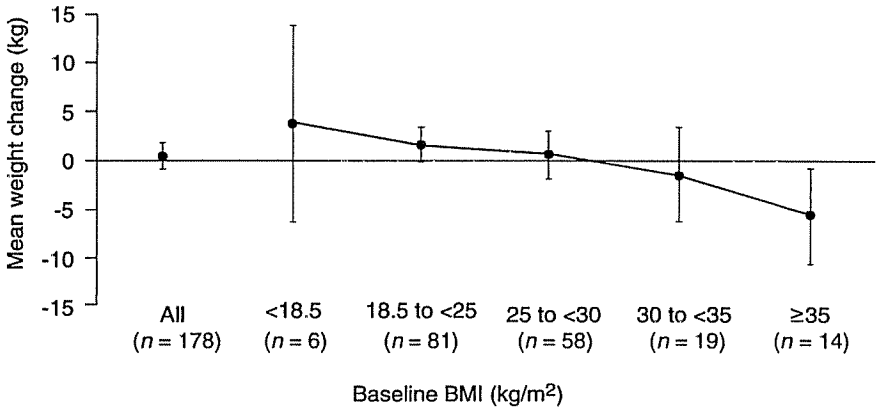
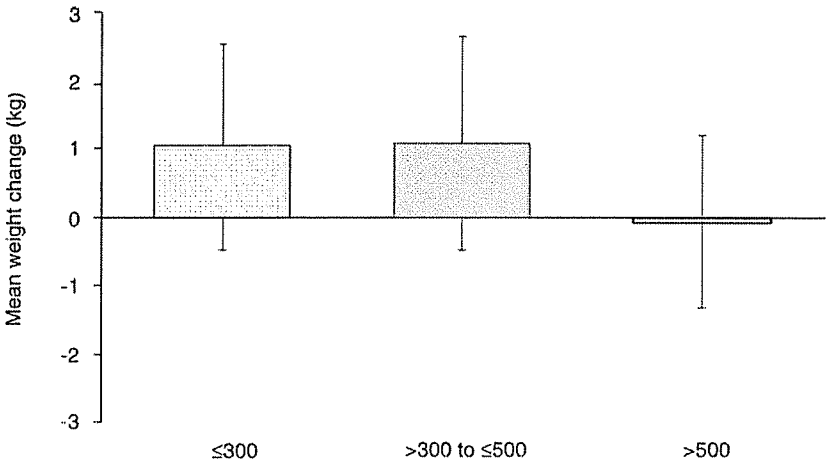


Fig. 4. Mean weight change with 95% confidence intervals from baseline to endpoint by baseline category in patients receiving quetiapine monotherapy for at least 6 months. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

the mean weight change from baseline included zero for all three dose groups, indicating that the effect of quetiapine on patient weight was neutral across the dose range. There was also no correlation between increasing dose and mean long-term weight changes.

These studies cumulatively suggest that quetipine is associated with only minimal weight changes during short-term use which are not dose related and do not increase over time. Further, given the chronic nature of maintenance antipsychotic therapy, the long-term effect of quetiapine on weight change appears to be neutral overall and potentially weight normalizing in some obese patients.



Mean duration of treatment (days)	343	407	327
No. patients	103	94	174

Fig. 5. Mean weight change with 95% confidence intervals from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

8. Discussion

Weight gain can be a serious iatrogenic health problem in patients with schizophrenia and other psychoses. It is an important side effect of antipsychotic medication and may have adverse implications for adherence with long-term antipsychotic therapy. Excessive weight gain may also lead to other adverse health effects, e.g. type II diabetes, hyperlipidemia, and cardiovascular disease. Weight gain occurs to varying extents depending on the drug.

In the atypical class of antipsychotics, clozapine and olanzapine are associated with the most significant weight gain. Risperidone is associated with modest weight changes that are not dose related. Ziprasidone has a relatively low risk of weight gain during short-term treatment and no overall weight gain during long-term treatment in patients under continuous clinical supervision.

Quetiapine is associated with modest short-term weight changes that do not increase over time and are not dose related. The overall effect of quetiapine on weight in long-term treatment is neutral, with some weight loss in severely obese patients. Quetiapine has favorable efficacy and tolerability profiles, which have resulted in high levels of patient satisfaction and the normalization of eating habits

in 73% of the study population (Hellewell et al., 1999). Hence, the available data suggest that quetiapine has a favorable benefit:risk profile. Taking into account both the minimal weight change and placebo-level EPS across the full dose range, quetiapine should be considered as a first-choice antipsychotic in the long-term treatment of schizophrenia.

While high BMI and obesity are well-known risk factors for diabetes and are associated with insulin resistance, more recently some of the atypical antipsychotics have themselves been linked to impaired glucose metabolism and diabetes mellitus (see supplement Sussman, 2001, for review of this area). Because patients with psychosis (schizophrenia and mania) have an increased risk for comorbid diabetes even before antipsychotic pharmacotherapy is initiated (Mukherjee et al., 1996; Cassidy et al., 1999), it can be difficult to determine a causal link between atypical antipsychotic-induced diabetes, antipsychotic exacerbation of pre-existing diabetes, or the development of diabetes as a comorbidity of the psychotic disorder itself. However, while there have been no definitive well-controlled and randomized trials, there is some evidence from case reports in the literature that clozapine (Koval et al., 1994; Popli et al., 1997) and olanzapine (Wirshing et al., 1999; Goldstein et al., 1999) may impair glucose metabolism and increase the risk of diabetes in patients with schizophrenia (Henderson, 2002). Interestingly in another recent study, Newcomer et al. (2002) found that glucose levels were significantly elevated in nondiabetic schizophrenia patients treated with clozapine and olanzapine but not in those treated with risperidone or typical agents.

In conclusion, the differential weight gain of various atypicals should be considered in the selection of a first-line antipsychotic, given the potentially serious health effects of obesity. However, other adverse events such as dose-dependent EPS (Jibson and Tandon, 1998), hyperprolactinemia-induced sexual dysfunction (Turrone et al., 2002), and cardiac conduction effects (Glassman and Bigger, 2001) should also be taken into consideration in the selection of a first-line atypical antipsychotic. By minimizing adverse effects, patient adherence to long-term treatment of psychotic disorders is substantially increased.

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