Are Weight Gain and Metabolic Side Effects of Atypical Antipsychotics Dose Dependent? A Literature Review

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Background: Numerous publications have provided evidence for clinically important metabolic adverse effects of antipsychotics, but there is no systematic evaluation as to whether weight gain and other metabolic changes are dose dependent.

Objective: This review of the available literature aimed to explore a possible relationship between dosage of second-generation antipsychotics (SGAs) and the degree of metabolic side effects.

Data Sources: A literature review was conducted in 3 steps: (1) Articles published between 1975 and 2004 were identified on the basis of the bibliography of an extensive review of the metabolic effects of SGAs. (2) Articles published between 2004 and 2008 were identified by a PubMed search with the keywords *weight gain*, *metabolic*, *glucose*, *insulin*, and *lipid* AND *dose* combined with *amisulpride*, *aripiprazole*, *clozapine*, *quetiapine*, *risperidone*, *sertindole*, and *ziprasidone*. (3) A hand search was conducted based on the bibliography of the identified articles.

Study Selection and Data Extraction: All studies that provided information on metabolic side-effects in different dose ranges were selected. Data extraction was carried out independently by 2 observers.

Data Synthesis: Preliminary evidence suggests a dose-response relationship between clozapine and olanzapine serum concentrations and metabolic outcomes, although the association between administered daily dose and metabolic outcomes is not clear. Data are controversial with regard to risperidone, and no study has as yet assessed risperidone serum concentrations in association with metabolic outcomes. For the other SGAs, there was little evidence to suggest a dose-response relationship, although, in these agents also, no assessment of serum concentrations was conducted.

Conclusions: The finding that metabolic complications may be associated with clozapine and olanzapine plasma concentrations provides further evidence for a causal contribution to the metabolic disturbances observed with these agents. Further well-designed, prospective studies investigating a possible association between SGA serum concentrations and metabolic outcomes are needed.

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Second-generation antipsychotics (SGAs) are an effective treatment for patients with schizophrenia and have a reduced risk of extrapyramidal side effects compared to first-generation antipsychotics.[1–7] However, there is substantial evidence that certain SGAs are associated with clinically significant weight gain, increased risk for insulin resistance, hyperglycemia, type 2 diabetes mellitus, and dyslipidemia compared with first-generation antipsychotics.[8–11]

Weight gain, which is considered to be a risk factor for type 2 diabetes mellitus and cardiovascular disease, is one of the most widely studied adverse effects of SGAs. Findings in the literature consistently showed that individual SGAs differ in their liability to induce weight gain or other metabolic effects.[8,10–12] Generally, olanzapine and clozapine were found to be associated with the highest risk of clinically significant weight gain, followed by quetiapine, risperidone, and sertindole. Amisulpride, ziprasidone, and aripiprazole have the lowest risk for clinically significant weight gain.[8,10,11,13–19] These differences are mirrored in the individual SGA receptor binding affinity.[20,21] Besides the affinity for dopamine D_2 receptors, SGAs have varying affinity for histamine, serotonin (5-HT), glutamate, α-adrenergic, and muscarinic receptors. Kroeze et al.[21] analyzed the relationship between SGA receptor-binding profiles and side effects and found that the affinity to the H_1 histamine receptor was the most robust predictor of an SGA potential to induce weight gain. This finding was supported by others[20,22,23] and is in line with several animal models in the literature. For example, the observed effect of SGAs on a hypothalamic

enzyme (adenosine monophosphate [AMP]-kinase), which is involved in potentially orexigenic processes, was abolished in H_1 knockout mice.[23] Furthermore, an association was also found between the binding affinity for 5-HT_{1A}, 5-HT_{2C}, α-adrenergic, and D_2 receptors and the drug's propensity to induce weight gain.[22]

The risk for dyslipidemia and type 2 diabetes mellitus are less-studied metabolic side effects. However, there is growing evidence that clozapine and olanzapine are associated with elevated risk for dyslipidemia, hyperglycemia, and type 2 diabetes mellitus, while published data are more controversial regarding the risk with risperidone and quetiapine.[11,18,24] Ziprasidone, amisulpride, and aripiprazole do not seem to affect blood glucose regulation or have a negative effect on serum lipid levels.[8,13–15,19] Based on the few published studies on the effect of sertindole on serum glucose or lipids, sertindole seems to carry a low risk for hyperglycemia, while there was no clinically significant effect of sertindole on lipid levels observed.[7,25,26] The different potential of SGAs to induce hyperglycemia and type 2 diabetes was also connected to certain receptor binding affinities, such as affinity for 5-HT_{2C}, H_1, and M_3 muscarinic receptors.[20,22,27–29] Animal models also support these findings, as, for example, 5-HT_{2C} knockout mice develop insulin resistance and impaired glucose tolerance in addition to experiencing severe weight gain.[30] In a canine model, Ader et al.[31] reported that olanzapine not only caused weight gain, increased adiposity, and insulin resistance in dogs, but also blocked β-cell compensation.

Although there is growing evidence that the SGA receptor-binding affinity determines in part its potential to cause metabolic side effects, the underlying mechanisms are incompletely understood.[21] Genetic factors further complicate the understanding of these mechanisms. For example, among treatment-naive patients, a specific variant of the 5-HT_{2C} receptor gene seems to be protective against olanzapine-induced weight gain, compared to the wild-type polymorphism.[20,32,33]

Although there is a wealth of evidence on the existence and clinical importance of metabolic adverse effects of SGAs, there is less information on whether there may be a relationship with the dose. It is plausible to hypothesize that the degree of receptor occupancy (i.e., dose) is an important determinant for the induction of metabolic side effects. This review of the available literature aims to explore a possible relationship between SGA-induced metabolic effects and dose.

METHOD

A literature search for relevant articles was carried out in 3 steps. First, articles published between 1975 and 2004 were identified on the basis of the bibliography of an extensive review of metabolic effects of SGAs.[11] Second, articles published between 2004 and 2008 were identified by a PubMed search with the keywords: *weight gain*, *metabolic*, *glucose*, *insulin*, *lipid* AND *dose* combined with *amisulpride*, *aripiprazole*, *clozapine*, *quetiapine*, *risperidone*, *sertindole* and *ziprasidone*. Third, a hand search was conducted based on the bibliography of the identified articles. From the identified articles, all studies that provided information on metabolic side effects in different dose ranges were selected. Data extraction, from the selected studies, was carried out independently by 2 observers.

RESULTS

Sixty relevant articles were identified, 15 reviews and 45 original papers, posters, or oral presentations at conferences.

The majority of information about a possible relationship between dose of a specific antipsychotic agent and metabolic outcomes is derived from large, controlled clinical trials and retrospective data analysis of these studies. Additional data were found in clinical or observational studies—generally with relatively small sample sizes—controlled or uncontrolled for another agent or placebo.

We summarize the results on possible dose-dependent effects of each individual SGA agent in separate sections.

Clozapine

Clozapine is considered to have the highest potential for weight gain, hyperglycemia, type 2 diabetes, and dyslipidemia.[8,17,19,24]

Six studies assessed a possible association between clozapine dose and metabolic outcomes (Table 1). Three of these studies suggested the possibility that metabolic effects of clozapine are dose related.[34–36] One study reported no relationship between dose and new-onset diabetes mellitus in a 5-year naturalistic study,[37] and another study reported no dose effect on weight gain in a small naturalistic sample.[38] One small study reported an inverse association between daily dose of clozapine and weight gain, more specifically that significantly more weight gain was observed in responders to lower doses of clozapine (mean = 220 mg/day vs. 608 mg/day).[39] However, at baseline, low-dose responders had a lower weight, and both groups reached similar weights at endpoint of the study (21 months).

Melkersson et al.[40] and Melkersson and Dahl[41] used a different approach, namely investigating the association between serum clozapine levels and, among others, serum insulin, glucose, and triglyceride levels. There are great differences between subjects in plasma concentrations of clozapine even when given equal doses, mainly because of large interindividual pharmacokinetic variations.[42] Clozapine is metabolized in the liver, and specific enzymes (e.g., CYP1A2 and CYP2D6 from the cytochrome P450 enzyme family) are considered to be responsible for its metabolism. The activity of these enzymes is influenced by genetic and environmental factors resulting in the aforementioned

Table 1. Studies Investigating Whether Metabolic Effects of Clozapine Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
De Leon et al[34a]	Double-blind, randomized, 3 phase (nonresponders in the first phase could go on to second phase, nonresponders of the second phase could go on to the third phase)	50	16–48 wk (each phase 16 wk)	Multiple fixed dosages: 100 mg/d 300 mg/d 600 mg/d	Mean weight gain by the end of 15th wk: Total sample: 2.8 ± 4.9 kg 100 mg/d: 1.3 ± 4.7 kg 300 mg/d: 2.6 ± 4.9 kg[b] 600 mg/d: 4.4 ± 5.1 kg[b]
Frankenburg et al[35a]	Open-label follow-up, uncontrolled	42	1 y	NR	Mean ± SD BMI baseline: Female: 23.2 ± 6.3 Male: 26.4 ± 3.7 Mean ± SD BMI endpoint: Female: 29.1 ± 5.5 Male: 29.7 ± 5.1
Henderson et al[37]	Naturalistic follow-up study, uncontrolled	82	5 y	NR	36.6% of the subjects developed diabetes mellitus, unrelated to dose
Hummer et al[38]	Naturalistic follow-up study, haloperidol as control condition	82	≈ 6 y	Mean ± SD = 240.6 ± 57 mg/d	Clinically relevant weight gain (> 10% from baseline) was found in 35.7% of the patients, unrelated to dose (data NR)
Jalenques et al[39]	Open-label	15	21 mo	Mean = 220 mg/d (low-dose group) and 608 mg/d (high-dose group)	Weight gain in both groups, but significantly more weight gain in responders to low dose (mean: 12.5 kg) versus patients requiring higher dose over time (mean: 5 kg) (responders to low dose, however, had 5 kg lower weight at baseline)
Lu et al[36]	Prospective, randomized, open-label	68	12 wk	Monotherapy < 600 mg/d clozapine at endpoint: mean ± SD = 307.4 ± 120.8 mg/d; combined at endpoint: mean ± SD = 130.1 ± 56.3 mg/d[c] + fluvoxamine	Only in monotherapy group: significantly increased weight, BMI, and glucose, triglyceride, and cholesterol levels; dependent of serum norclozapine level

[a]Based on multiple regression analysis, weight gain or BMI was dose related.
[b]Significantly higher than 0.
[c]Significant difference between treatment groups ($p < .05$).
Abbreviations: BMI = body mass index, NR = not reported.
Symbol: ≈ = approximately.

interindividual differences in clozapine metabolism.[42,43] In the first study of Melkersson et al.,[40] it was found that insulin levels were positively associated with serum clozapine concentration but not with daily clozapine dose. In the second study, serum clozapine concentration was associated with hyperinsulinemia and hypertriglyceridemia, again independent of daily dose.[41]

Olanzapine

Olanzapine is considered to have a high potential for causing weight gain and a high risk for causing hyperglycemia, type 2 diabetes, and dyslipidemia, perhaps even similar in magnitude to that of clozapine.[8,11,12,17–19,24] This fact recently led to a label change required by the U.S. Food and Drug Administration.[13] Mean weight gain over a 1-year period was reported to be greater than 6 kg, based on pooled data of clinical trials with multiple doses of olanzapine assessed.[17]

Eleven articles were found in which data on the relationship between daily dose of olanzapine and metabolic effects were reported. The vast majority of these studies did not find dose-dependent metabolic effects (Table 2).[44–48] There are 2 studies that found dose-dependent weight gain during treatment with olanzapine.[49,50] The first (n = 431) was a short-term, double-blind, controlled, randomized clinical trial. However, doses ranged from 1 mg (as placebo) to 2.5 mg–17.5 mg, with the majority of these doses below the recommended therapeutic range.[49] This limitation was previously noted by others.[11,17]

The second study was a recent study by Kinon et al.[50] This study was a short-term, multicenter, randomized, double-blind, parallel fixed-dose study including 599 patients in 3 randomized treatment groups receiving 10 mg, 20 mg, or 40 mg daily doses of olanzapine. A significant dose-related change in mean weight gain was found with significant difference between the 10-mg and the 40-mg groups, although differences compared to the 20-mg group were not significant. However, this finding is complicated by the fact that the authors did not find a correlation between olanzapine plasma concentration and weight gain.[51] In addition, baseline antipsychotic use also impacted the dose response, since, for patients who were not taking an

Table 2. Studies Investigating Whether Metabolic Effects of Olanzapine Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
Beasley et al[49]	Double-blind RCT	431	6 wk	1 mg 5 ± 2.5 mg 10 ± 2.5 mg 15 ± 2.5 mg	Data NR: "weight gain was associated with increasing olanzapine dose"
Kinon et al[50]	Multicenter, double-blind RCT	599	8 wk	10 mg 20 mg 40 mg	Significant dose response (p = .003); mean change (kg) to endpoint (SD): 10 mg = −1.9 (3.5), significant difference from 40 mg (p = .002); 20 mg = −2.3 (4.2); 40 mg = −3.0 (4.0)
Jones et al[46]	Retrospective analysis of Eli Lilly data	> 3000 > 400	6 wk to 2 y	NR	Data NR; dose was not a significant predictor of long-term changes in weight (based on Kinon et al[51])
Kinon et al[51]	Retrospective analysis of a double-blind RCT	573	39 wk to 3 y	5–20 mg	Dose was not found to be significantly predictive of changes in weight (p > .183)
Lindenmayer et al[52]	Open-label, crossover	45	14 wk	20–40 mg	Significant effect on weight gain by the mean dose in the last week of treatment (F = 6.3, df = 1,42; p < .01) and by olanzapine doses over 20 mg/d (F = 3.9, df = 1,42; p < .05)
Melkersson et al[41]	Cross-sectional, comparison of clozapine and olanzapine	16 (34 all)	Mean duration of treatment before analysis: 1.2 y (range, 0.5–5.5 y)	7.5–20 mg	Serum insulin and triglyceride levels were correlated to the ratio of serum olanzapine and N-methyl-olanzapine concentrations, whereas serum fasting glucose was inversely correlated to serum concentration of N-methyl-olanzapine; insulin: r = 0.63, p = .008; glucose: r = −0.54, p = .03; triglycerides: r = 0.51, p = .04
Hennen et al[45]	Double-blind RCT + extended open-label phase	113 bipolar I	3 wk + 1 y	NR	Data NR; BMI increase was not related to dose
Lee et al[48]	Case-control study comparing olanzapine and risperidone, with retrospective analysis of case records	28 pairs Chinese population	Mean ± SD duration of treatment before analysis: 103.5 ± 47.4 d	Mean ± SD dose: 12.4 ± 6.7 mg	Data NR; mean daily dose had no effect on weight gain
Dunayevich et al[44]	Retrospective analysis of 4 double-blind RCTs	615	6 to 26 wk	5 mg 10 mg 15 mg 20 mg	Weight gain was significantly greater in patients of the 15-mg group than in the 5-mg (all subjects and 26-wk completers only: both p = .02) and 10-mg (all: p = .01; 26-wk completers: p = .05) groups; 20-mg group did not differ significantly from any other treatment group
Perry et al[53]	Retrospective analysis	39	6 wk	NR	> 20.6 ng/mL serum olanzapine concentration was associated with clinically significant weight gain (> 7% BMI change) even after controlling for confounders (OR = 10.1, 95% CI = 1.3 to 75, p = .024); dose, after controlling for confounders, did not relate to weight change (OR = 3.0, 95% CI = 0.6 to 14.5, p = .1644)
Mitchell et al[54]	Double-blind, randomized	37	30 d	A: 20 mg for 20 d B: 30 mg for 10 d and 40 mg for 10 d C: 40 mg for 20 d	A: 17%; B: 27%; and C: 14% of the subjects gained weight; these cases did not follow a dose-dependent pattern

Abbreviations: BMI = body mass index, NR = not reported, RCT = randomized controlled trial.

Table 3. Studies Investigating Whether Metabolic Effects of Risperidone Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
Marder and Meibach[56]	Double-blind RCT	233 (340 all)	8 wk	2 mg, 6 mg, 10 mg, and 16 mg fixed doses	Weight gain was associated with dose of risperidone ($p < .05$)
Peuskens[57]	Double-blind RCT	1362	8 wk	1 mg, 4 mg, 8 mg, 10 mg, and 12 mg fixed doses	Mean weight increase between 0.3 kg (1 mg) and 1.6 kg (8 mg); 8 mg, 10 mg, and 12 mg groups had significantly higher weight increase than haloperidol group (data NR)
Kelly et al[61]	Retrospective analysis	70[a]	6 mo	0.5–10 mg	No correlation between dose and weight gain ($r = 0.296$, $p = .2332$)
Buitelaar[59]	Open-label	26[a]	1 y	0.5–4 mg	8% of patients gained 8–10 kg; correlation between dose and weight gain reported
Cohen et al[62]	Retrospective chart review	37 patients with mental retardation	2 y	4–6 mg	Mean weight gain: 8.3 kg; no correlation between dose and weight gain was reported
Hellings et al[60]	Controlled	11[a]	1 y	1–3 mg	Mean weight gain in children: 8.2 kg; in adolescents: 8.4 kg; no correlation between dose and weight gain was reported
Csernansky et al[63]	Double-blind, prospective	177[b]	364 d	Mean ± SD = 4.9 ± 1.9 mg	Mean weight gain: 2.3 kg; no correlation between dose and weight gain was reported (data NR)
Fleischhacker et al[64]	Open-label	615[c]	1 y	25mg, 50mg, and 75 mg depot	Mean weight gain: 25 mg: 1.7 kg 50 mg: 2.6 kg 75 mg: 1.9 kg
Lane et al[58]	Prospective, open-label	146 subjects from China and Taiwan	6 wk	Mean ± SD = 4.3 ± 1.4 mg	On the basis of multiple linear regression analysis, dose was a predictor for weight gain (1-mg increment: estimated coefficient = 0.0839; standard error = 0.0344; $P = .0148$)
Lee et al[48]	Retrospective analysis of case reports, comparison between olanzapine and risperidone	28 pairs Chinese population	Mean ± SD duration of treatment before analysis: 93.2 ± 50.6 wk	Mean ± SD = 4.5 ± 2.8 mg	Mean ± SD weight gain: 2.74 ± 8.09 kg; no correlation between dose and weight gain was reported (data NR)

[a]Children and/or adolescents.
[b]44.1% Dropout from the risperidone group due to reason other than relapse.
[c]65% Completed the study.
Abbreviations: NR = not reported, RCT = randomized controlled trial.

SGA before study entrance, no significant dose and weight gain relationship was found. Furthermore, no significant difference was found between the dose groups in the percentage of patients with clinically significant (≥ 7%) weight gain. Taking into consideration the short-term aspect of the study, the authors suggested that higher-than-standard doses of olanzapine may be associated with greater weight gain compared to standard doses.[50] No statistically significant dose-response relationship was found with respect to fasting glucose, triglycerides, or cholesterol.[50]

An open-label, uncontrolled switch study of 45 treatment-refractory patients found that patients who received less than 20 mg/day gained significantly more weight than those who received higher doses.[52]

Three studies also investigated whether metabolic effects were associated with olanzapine plasma concentration, or its metabolite, N-methyl-olanzapine. Melkersson and Dahl[41] observed a correlation between the ratio of serum olanzapine and N-methyl-olanzapine concentrations and serum insulin and triglyceride levels, whereas an inverse correlation between N-methyl-olanzapine concentration and serum fasting glucose was found, suggesting that the N-methyl-olanzapine could have a counter-acting effect on olanzapine-associated metabolic changes. Furthermore, no association was found between olanzapine daily dose and its serum concentration. Perry et al.[53] reported an association of plasma olanzapine concentration with amount of weight gained, which was independent from the daily olanzapine dose. The third study investigated the short-term pharmacokinetics and tolerability of high doses of olanzapine (20–40 mg) on a relatively small sample of patients. This study found that clinically significant weight gain did not follow a dose-dependent pattern when using high doses of olanzapine.[54] The magnitude of weight gain (approximately 3 kg across all doses over the duration of the study) was similar to that observed with approved doses of olanzapine. Additionally, no cases of dose-dependent, olanzapine-induced impaired glucose tolerance were found. Although this study did not conduct a systematic analysis on whether any association existed between serum concentrations of

Table 4. Studies Investigating Whether Metabolic Effects of Quetiapine Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
Small et al[69]	Double-blind RCT	268	6 wk	High dose > 750 mg Low dose < 250 mg	25% of patients in high-dose group and 16% of patients in low-dose group gained clinically significant weight (> 7% from baseline)
Arvanitis and Miller[2]	Double-blind RCT	361	6 wk	75–750 mg multiple fixed doses	Mean (SD) weight gain, kg: 75 mg: 0.09 (1.98) 150 mg: 2.9 (6.38) 300 mg: 2.0 (4.4) 600 mg: 2.6 (5.1) 750 mg: 2.3 (5.1)
Jones et al[66]	Critical retrospective analysis	NR	1 y	> 675 mg	Mean weight gain: 2.13 kg; no correlation between dose and weight gain reported
Rak et al[67]	Critical retrospective analysis	360	1 y	Mean: 428 mg	Mean weight gain: 2.77 kg; no correlation between dose and weight gain reported
Brecher et al[65]	Open-label extension phase of controlled and uncontrolled trial	178	80 wk	> 475 mg	Mean weight gain: 0.41 kg; no correlation between dose and weight gain reported
Brecher et al[68]	Retrospective analysis	352	52 wk	< 200 mg 200–399 mg 400–599 mg ≥ 600mg	No clear dose relationship; mean/median weight gain, kg: < 200 mg: 1.54/0.95 200–399 mg: 4.08/3.40 400–599 mg: 1.89/2.00 ≥ 600 mg: 3.57/3.34

Abbreviations: NR = not reported, RCT = randomized controlled trial.

olanzapine and weight gain or glucose tolerance, the authors reported great interindividual differences in plasma concentrations when applying the same dosage, but at the same time plasma concentration levels followed a dose-proportional pattern with increasing dosage.[54]

Risperidone

Risperidone is associated with a moderate level of weight gain, hyperglycemia, and type 2 diabetes mellitus, and a low risk for dyslipidemia.[24] Pooled data of clinical trials with multiple doses of risperidone indicated a mean weight gain of 2 to 3 kg over a 1-year period.[11,17] Data are inconclusive on whether metabolic changes induced by risperidone are dose-related. Eleven articles were identified in this literature search. One of them was a case report on a 32-year-old, drug-naive, female patient with dose-related excessive weight gain (20% of baseline body mass index [BMI]) and dyslipidemia during 6 weeks of treatment with risperidone.[55] Five of the studies also suggested a possible dose-response relationship to metabolic complications (Table 3). An early, large, double-blind, controlled randomized study comparing placebo and haloperidol to fixed doses of risperidone found that weight gain was associated with daily dose.[56] A similar study using fixed doses of risperidone reported a mean weight increase varying between 0.3 kg (with dose of 1 mg/day) and 1.6 kg (with 8 mg/day).[57] However, this study did not systematically report data of weight gain in all dose groups separately nor did it formally assess a possible significant association between dose and weight gain. A similar short-term (6-week) study including subjects from China and Taiwan and evaluating directly the possible predictors of risperidone-induced weight gain, found a significant association between weight gain and dose of risperidone.[58] Two further studies suggested dose-dependent weight gain during treatment with risperidone; however, both of these studies were conducted with children and/or adolescents, making it difficult to compare the results to those obtained in adults.[59,60] In contrast, 1 study with adolescents did not find a relationship between risperidone dose and weight gain.[61]

Two retrospective analyses including a relatively small number of subjects[48,62] and 2 prospective studies with a large sample,[63,64] the latter (Fleishhacker et al.[64]) investigating the long-acting injectable formulation of risperidone, reported no correlation between daily dose of risperidone and weight gain (Table 3).

Quetiapine

Quetiapine is considered to have moderate risk, comparably similar to that of risperidone, for clinically significant weight gain, type 2 diabetes mellitus, and dyslipidemia.[8,17,24] According to Newcomer and Haupt,[17] mean weight gain over a 1-year period is about 2 to 3kg, when pooling data of clinical trials with multiple doses of quetiapine.

There are 6 studies investigating whether the metabolic effects of quetiapine are dose related (Table 4). A double-blind placebo-controlled clinical trial (n = 361),[2,17] an open-label extension phase of controlled and uncontrolled clinical trials (n = 178),[65] and 2 critical analyses of previous studies[66,67] found no association between the daily dose of quetiapine and clinically significant weight gain. At the same time, a retrospective analysis of long-term data on 352 subjects[68]—working with observed cases, unlike most of the other studies in this field that used last-observation-

Table 5. Studies Investigating Whether Metabolic Effects of Ziprasidone Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
Keck et al[72]	Double-blind RCT	139	4 wk	40 mg 120 mg	Weight gain observed in 40 mg group only (median: 1 kg)
Daniel et al[71]	Double-blind RCT	210 (302 all)	6 wk	80 mg 160 mg	Median weight gain: 80 mg: 1 kg 160 mg: 0 kg (indistinguishable from placebo)
Arato et al[1]	Double-blind RCT	210	1 y	40 mg 80 mg 160 mg	Weight reduction was observed: 40 mg: −2.7 kg 80 mg: −3.2 kg 160 mg: −2.9 kg

Abbreviation: RCT = randomized controlled trial.

carried-forward method—showed a descriptive, but not statistically significant, pattern of weight gain in different dose ranges at 52 weeks of treatment. Specifically, the < 200-mg group and the 400- to 599-mg group had a similar degree of mean and median weight gain (mean = 1.54 kg, median = 0.95 kg for the < 200-mg group; mean = 1.89 kg, median = 2.00 kg for the 400- to 599-mg group), while the 200- to 399-mg and 400- to 599-mg groups had greater, but also very similar, weight gain (mean/median = 4.08 kg/3.40 kg and 3.57 kg/3.34 kg, respectively).[68] Patients with a lower BMI at baseline gained the most weight, and at endpoint, 37% of patients had a > 7% change of weight.

Only 1 short-term study (n = 268) reported a significant difference in weight gain (16% vs. 25%) when using < 250 mg/day or > 750 mg/day of quetiapine, respectively,[67–69] but a dose lower than 250 mg/day may be considered to be below the therapeutic range typically recommended for psychotic disorders.[70]

Ziprasidone

On the basis of the few articles published on the metabolic effects of ziprasidone, this SGA shows little or no effect on serum lipid levels and blood glucose.[18,24] The relative risk for weight gain during treatment with ziprasidone is considered to be low compared to other SGAs.[8,11,17,24] According to Newcomer and Haupt,[17] mean weight gain over a 1-year period is about 1 kg based on clinical trials data with multiple doses of ziprasidone.[11,17] However, ziprasidone was also found to cause significant weight loss over 1 year in 1 study.[1]

There are only 3 studies reporting on whether weight or other observed metabolic changes are associated with the daily dose of ziprasidone (Table 5). None of these studies found evidence for such an association.[1,71,72]

Aripiprazole

Only a limited number of publications are available on the metabolic effects of aripiprazole, a recently introduced SGA. On the basis of these reports, aripiprazole showed limited or no effect on serum lipid levels and blood glucose regulation.[18,24] Weight gain could be detected, although the relative risk of weight gain compared to the other SGAs is low, similar to that of ziprasidone.[18,24] Mean weight gain over a 1-year period is about 1 kg when pooling data of clinical trials with multiple doses of aripiprazole.[17]

A short-term (4-week) double-blind, controlled (risperidone and placebo) study including 404 patients reports an incidence of clinically significant weight gain of 9% and 13% at daily doses of 30 mg and 20 mg of aripiprazole, respectively.[16,73] A retrospective analysis of 5 short-term, placebo-controlled clinical trials[5] showed that weight changes associated with aripiprazole appear not to be dose dependent.[11,16–19,24]

Amisulpride

Amisulpride is an SGA that has been used widely in several European countries since 1986. However, there are very few data available on its metabolic effects. Recent reviews concluded that amisulpride is associated with minimal weight change, ranging between 0.2 to 1.4 kg over varying treatment durations.[19,74] There is only 1 study available examining dose dependency of weight gain during treatment with amisulpride, a retrospective analysis of 11 prospective randomized studies including 1392 patients with a daily dose range of amisulpride of 50 to 1200 mg.[75] This analysis found no correlation between dose and the degree of weight gain (p = .7). Exclusion from the analysis of all patients who received less than 400 mg of amisulpride did not change the results to any substantial degree.[16,74,75]

Sertindole

Sertindole has recently been reintroduced in Europe. Studies have been focused mainly on investigating cardiac adverse effects, and there are fewer data in the literature on the metabolic effects of sertindole. Sertindole is generally considered to have moderate effect on weight gain (approximately 2–4.5 kg), similar to that of risperidone.[7,76] Based on the few published data available on the effect of sertindole on serum glucose or lipids, there seems to be a low risk for hyperglycemia, while there was no clinically significant effect found on lipid levels.[7,25,26]

Except for 4 studies providing descriptive information on weight gain by different doses, there is no systematic analysis published on possible dose-related metabolic effects of sertindole (Table 6).[77–80] These 4 studies did not analyze whether weight gain was dose related.[77–81]

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Table 6. Studies Investigating Whether Metabolic Effects of Sertindole Are Dose Related

Study	Design	Sample Size	Duration	Dosage	Relevant Results
Zborowski et al[79]	RCT	461	8 wk	20 mg 24 mg	Weight gain: 20 mg: +3.4 kg 24 mg: +3.1 kg
Van Kammen et al[78]	RCT	205	40 d	8 mg, 12 mg, 10 mg, 20 mg	No weight gain data by dose
Hale et al[77]	RCT	617	8 wk	8 mg, 16 mg, 20 mg, 24 mg	Weight gain: 8 mg: +1.3 kg 16 mg: +1.8 kg 20 mg: +1.3 kg 24 mg: +1.9 kg
Zimbroff et al[80]	RCT	497	8 wk	12 mg, 20 mg, 24 mg	Weight gain, all doses: +2.2 kg to +3.3 kg

Abbreviation: RCT = randomized controlled trial.

CONCLUSION

On the basis of the literature reviewed, it can be concluded that the possible relationship between SGA-induced metabolic changes and dose is not adequately studied. There are only a limited number of studies investigating the topic specifically. Studies investigating the possible relationship between dose and metabolic effects of SGAs in large samples, taking into consideration possible confounding effects such as baseline BMI, previously or currently administered medications, and certain genetic factors (e.g., 5-HT_2 receptor polymorphism), are lacking.

The available data suggest that individual SGAs are different with regard to whether dose is associated with their metabolic effect, as well as to their potential to induce such metabolic effects.

Aripiprazole, amisulpride, quetiapine, sertindole, and ziprasidone seem to have no dose-related metabolic effects.

Results of the studies investigating whether clozapine-induced metabolic effects are related to daily dose are mixed, and the interpretation of the results is hampered by several methodological limitations of these studies, especially small sample sizes, uncontrolled design, and concomitant use of other psychoactive drugs. Because doses varied considerably across studies, it is difficult to compare the results. For clozapine, however, there appears to be an association between weight gain and/or metabolic changes and its daily dose and/or plasma concentration. The evidence is stronger for a correlation between certain metabolic changes and the serum clozapine concentration, which in turn is not related to the daily dose of clozapine. These metabolic changes dependent on serum clozapine concentration were confirmed in a recent study and were shown to be influenced by CYP1A2 polymorphisms.[42]

Olanzapine, an SGA similar to clozapine with regard to its chemical structure, also appears to have serum concentration–dependent metabolic effects. This association is complicated by a metabolite (N-methyl-olanzapine) that may have a counteracting effect on metabolic changes. Again, as seen in the case of clozapine, daily dose of olanzapine appears not to be related to serum concentrations. The finding that metabolic complications may well be associated with clozapine and olanzapine plasma concentrations in a dose-response fashion provides further evidence for a causal contribution to metabolic disturbances of these agents.

Risperidone has the most controversial data. The reviewed literature shows that risperidone-induced weight gain could be dose related to some extent, although data are contradictory. Many of the studies reviewed have several methodological problems, such as relatively small sample size, uncontrolled design, retrospective chart reviews with incomplete reporting of data, and, most importantly, no study assessed serum concentrations of risperidone and its metabolites. Until data on a possible association between biologic risperidone availability in terms of serum concentration and metabolic outcomes are available, no firm conclusions can be drawn with regard to possible dose-related metabolic complications. It must be noted, however, that within the therapeutic dose range, the expected weight gain is moderate, and a possible dose dependency varies within a relatively narrow range.

A possible underlying pharmacologic mechanism for the observed serum plasma concentration/dose-dependent metabolic effect of these drugs (clozapine and olanzapine) may be situated in the fact that these SGAs have strong affinity for the H_1-histamine, muscarinic, and α-adrenergic receptors. This property is strongly suggested to be in connection with their metabolic effects, and also with their sedative effects. It is plausible that with elevating plasma concentration, the saturation of these receptors increases, resulting in increasing metabolic effects on one hand, and decreasing caloric expenditure due to their sedating effects on the other.[82,83]

The assumptions of this review have to be judged in light of some limitations. First, we did not use meta-analytic techniques; this is a descriptive literature review. Second, we did not assess the original (unpublished) clinical trial data, but our review relied on published data available from PubMed and through a hand search based on the references of identified, related articles.

In conclusion, limited data are available on a possible dose-response relationship between SGAs and metabolic complications. Preliminary evidence suggests a dose-response relationship between clozapine and olanzapine

serum concentrations and metabolic outcomes, but not between administered daily dose and metabolic outcomes. Data are controversial with regard to risperidone, and no study has as yet assessed risperidone serum concentrations in association with metabolic outcomes. For the other SGAs, there was little evidence to suggest a dose-response relationship, although no assessment of serum concentrations was conducted in these agents either.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

REFERENCES

1. Arato M, O'Connor R, Meltzer HY. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol.* 2002;17(5):207–215.
2. Arvanitis LA, Miller BG and the The Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997;42(4):233–246.
3. Fitton A, Heel RC. Clozapine: a review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs.* 1990;40(5):722–747.
4. Fulton B, Goa KL. Olanzapine: a review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drugs.* 1997;53(2):281–298.
5. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res.* 2003;61(2–3):123–136.
6. Mortimer A, Martin S, Loo H, et al. A double-blind, randomized comparative trial of amisulpride versus olanzapine for 6 months in the treatment of schizophrenia. *Int Clin Psychopharmacol.* 2004;19(2):63–69.
7. Perquin L, Steinert T. A review of the efficacy, tolerability and safety of sertindole in clinical trials. *CNS Drugs.* 2004;18(suppl 2):19–30.
8. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999;156(11):1686–1696.
9. Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. *J Clin Psychiatry.* 2008;69(4):514–519.
10. Haddad P. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol.* 2005;19(6 suppl):16–27.
11. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs.* 2005;19(suppl 1):1–93.
12. Citrome L. The effectiveness criterion: balancing efficacy against the risks of weight gain. *J Clin Psychiatry.* 2007;68(suppl 12):12–17.
13. American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinology (AACE), North American Association for the Study of Diabetes. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27(2):596–601.
14. De Hert M, van Eyck D, De Nayer A. Metabolic abnormalities associated with second-generation antipsychotics: fact or fiction? Development of guidelines for screening and monitoring. *Int Clin Psychopharmacol.* 2006;21(suppl 2):S11–S15.
15. De Nayer A, De Hert M, Scheen A, et al. Belgian consensus on metabolic problems associated with atypical antipsychotics [conference report]. *Int J Psych Clin Pract*. 2005;9(2):130–137
16. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. *Drug Saf.* 2006;29(4):303–319.
17. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry.* 2006;51(8):480–491.
18. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry.* 2007;68(suppl 4):8–13.
19. Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. *CNS Drugs.* 2001;15(7):537–551.
20. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry.* 2008;13(1):27–35.
21. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology.* 2003;28(3):519–526.
22. Matsui-Sakata A, Ohtani H, Sawada Y. Receptor occupancy–based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. *Drug Metab Pharmacokinet* 2005;(5):366–378
23. Kim SF, Huang AS, Snowman AM, et al. Antipsychotic drug-induced weight gain mediated by histamine H_1 receptor–linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA.* 2007;104(9):3456–3459.
24. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs.* 2007;21(11):911–936.
25. Lindstrom E, Levander S. Sertindole: efficacy and safety in schizophrenia. *Expert Opin Pharmacother.* 2006;7(13):1825–1834.
26. Murdoch D, Keating GM. Sertindole: A review of its use in schizophrenia. *CNS Drugs.* 2006;20(3):233–255.
27. Silvestre JS, Prous J. Research on adverse drug events, pt 1: muscarinic M_3 receptor binding–affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find Exp Clin Pharmacol.* 2005;27(5):289–304.
28. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new-onset diabetes. *Biol Psychiatry.* 1998;44(8):778–783.
29. Gilles M, Wilke A, Kopf D, et al. Antagonism of the serotonin (5-HT)-2 receptor and insulin sensitivity: implications for atypical antipsychotics. *Psychosom Med.* 2005;67(5):748–751.
30. Nonogaki K, Strack AM, Dallman MF, et al. Leptin-independent hyperphagia and type 2 diabetes in mice with mutated serotonin $5\text{-}HT_{2C}$ receptor gene. *Nat Med.* 1998;4(10):1152–1156.
31. Ader M, Kim SP, Catalano KJ, et al. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes.* 2005;54(3):862–871.
32. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a $5\text{-}HT_{2C}$ receptor gene polymorphism. *Lancet.* 2002;359(9323):2086–2087.
33. Templeman LA, Reynolds GP, Arranz B, et al. Polymorphisms of the $5\text{-}HT_{2C}$ receptor and leptin genes are associated with antipsychotic drug–induced weight gain in Caucasian subjects with a first-episode psychosis. *Pharmacogenet Genomics.* 2005;15(4):195–200.
34. de Leon J, Diaz FJ, Josiassen RC, et al. Weight gain during a double-blind multidosage clozapine study. *J Clin Psychopharmacol.* 2007;27(1):22–27.
35. Frankenburg FR, Zanarini MC, Kando J, et al. Clozapine and body mass change. *Biol Psychiatry.* 1998;43(7):520–524.
36. Lu M-L, Lane H-Y, Lin S-K, et al. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. *J Clin Psychiatry.* 2004;65(6):766–771.
37. Henderson DC, Nguyen DD, Copeland PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry.* 2005;66(9):1116–1121.
38. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. *Eur Neuropsychopharmacol.* 1995;5(4)437–440.
39. Jalenques I, Tauveron I, Albuissian E., et al. Weight gain and clozapine [in French]. *Encephale.* 1996;22(Spec No 3):77–79
40. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 1999;60(11):783–791.
41. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. *Psychopharmacology (Berl).* 2003;170(2):157–166.
42. Melkersson KI, Scordo MG, Gunes A, et al. Impact of CYP1A2 and CYP2D6 polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients. *J Clin Psychiatry.* 2007;68(5):697–704.
43. Buur-Rasmussen B, Brosen K. Cytochrome P450 and therapeutic drug

monitoring with respect to clozapine. *Eur Neuropsychopharmacol.* 1999;9(6):453–459.
44. Dunayevich E, Sethuraman G, Wei H, et al. Olanzapine dose and weight gain. Presented at the 8th World Congress of Biological Psychiatry; Jun 28–Jul 3, 2005; Vienna, Austria.
45. Hennen J, Perlis RH, Sachs G, et al. Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry.* 2004;65(12):1679–1687.
46. Jones B, Basson BR, Walker DJ, et al. Weight change and atypical antipsychotic treatment in patients with schizophrenia. *J Clin Psychiatry.* 2001;62(suppl 2):41–44.
47. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry.* 2001;62(2):92–100.
48. Lee E, Leung C-M, Wong E. Atypical antipsychotics and weight gain in Chinese patients: a comparison of olanzapine and risperidone. *J Clin Psychiatry.* 2004;65(6):864–866.
49. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol.* 1997;7(2):125–137.
50. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder. A randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol.* 2008;28(4):392–400.
51. Kinon BJ, Volavka J, Bergstorm J, et al. Steady state concentrations after standard and higher dose of oral olanzapine in acutely ill patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *Neuropsychopharmacology*. 2006;31:S115.
52. Lindenmayer J-P, Czobor P, Volavka J, et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *J Clin Psychiatry.* 2002;63(10):931–935.
53. Perry PJ, Argo TR, Carnahan RM, et al. The association of weight gain and olanzapine plasma concentrations. *J Clin Psychopharmacol.* 2005;25(3):250–254.
54. Mitchell M, Riesenberg R, Bari MA, et al. A double-blind, randomized trial to evaluate the pharmacokinetics and tolerability of 30 or 40 mg/d oral olanzapine relative to 20 mg/d oral olanzapine in stable psychiatric subjects. *Clin Ther.* 2006;28(6):881–892.
55. Sahoo S, Mishra B, Akhtar S. Dose-dependent acute excessive weight gain and metabolic changes in a drug-naive patient on risperidone are reversible with discontinuation: a case report. *Br J Clin Pharmacol.* 2007;64(5):715–716.
56. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry.* 1994;151(6):825–835.
57. Peuskens J, on behalf of the Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry.* 1995;166(6):712–726.
58. Lane H-Y, Chang Y-C, Cheng Y-C, et al. Effects of patient demographics, risperidone dosage, and clinical outcome on body weight in acutely exacerbated schizophrenia. *J Clin Psychiatry.* 2003;64(3):316–320.
59. Buitelaar JK. Open-label treatment with risperidone of 26 psychiatrically hospitalized children and adolescents with mixed diagnoses and aggressive behavior. *J Child Adolesc Psychopharmacol.* 2000;10(1):19–26.
60. Hellings JA, Zarcone JR, Crandall K, et al. Weight gain in a controlled study of risperidone in children, adolescents, and adults with mental retardation and autism. *J Child Adolesc Psychopharmacol.* 2001;11(3)229–238.
61. Kelly DL, Conley RR, Love RC, et al. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. *J Child Adolesc Psychopharmacol.* 1998;8(3):151–159.
62. Cohen S, Glazewski R, Khan S, et al. Weight gain with risperidone among patients with mental retardation: effect of calorie restriction. *J Clin Psychiatry.* 2001;62(2):114–116.
63. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med.* 2002;346(1):16–22.
64. Fleischhacker WW, Eerdekens M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry.* 2003;64(10):1250–1257.
65. Brecher M, Rak IW, Melvin K, et al. The long-term effect of quetiapine (Seroquel) monotherapy on weight in patients with schizophrenia. *Int J Psychiatry Clin Pract.* 2000;4(4):287-291.
66. Jones A, Rak IW, Raniwalla J. Weight changes in patients treated with quetiapine. Poster presented at the 153rd Annual Meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill.
67. Rak IW, Jones AM, Raniwalla J, et al. Weight changes in patients treated with Seroquel (quetiapine) [abstract]. *Schizophr Res.* 2000;41(1):206.
68. Brecher M, Leong RW, Stening G, et al. Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry.* 2007;68(4):597–603.
69. Small JG, Hirsch SR, Arvanitis LA, et al, and the Seroquel Study Group. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry.* 1997;54(6):549–557.
70. Kinon BJ, Ahl J, Stauffer VL, et al. Dose response and atypical antipsychotics in schizophrenia. *CNS Drugs.* 2004;18(9):597–616.
71. Daniel DG, Zimbroff DL, Potkin SG, et al, and the Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial.*Neuropsychopharmacology.* 1999;20(5): 491–505.
72. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl).* 1998;140(2):173–184.
73. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry.* 2003;60(7):681–690.
74. Tschoner A, Engl J, Laimer M, et al. Metabolic side effects of antipsychotic medication. *Int J Clin Pract.* 2007;61(8):1356–1370.
75. Leucht S, Wagenpfeil S, Hamann J, et al. Amisulpride is an "atypical" antipsychotic associated with low weight gain. *Psychopharmacology (Berl).* 2004;173(1–2):112–115.
76. Kasper S. Sertindole: safety and tolerability profile. *Int J Psych Clin Pract.* 2002;6(suppl 1):S27–S32.
77. Hale A, van der Burght M, Friberg HH, et al. Dose ranging study comparing 4 doses of sertindole and 1 dose of haloperidol in schizophrenic patients [abstract]. *Eur Neuropsychopharmacol.* 1996;6(suppl 1):61.
78. van Kammen DP, McEvoy JP, Targum SD, et al. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology (Berl).* 1996;124(1–2):168–175.
79. Zborowski J, Schmitz P, Staser J, et al. Efficacy and safety of sertindole in a trial of schizophrenic patients. Poster presented at the 15th Annual Convention of Scientific Programs, Biological Psychiatry, Society of Biological Psychiatry; May 20, 1995; Miami, Fla.
80. Zimbroff DL, Kane JM, Tamminga CA, et al, and the Sertindole Study Group. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *Am J Psychiatry.* 1997;154(6):782–791.
81. Hale AS. A review of the safety and tolerability of sertindole. *Int Clin Psychopharmacol.* 1998;13(suppl 3):S65–S70.
82. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Saf.* 2001;24(1):59–73.
83. Elman I, Borsook D, Lucas SE. Food intake and reward mechanisms in patients with schizophrenia: implications for metabolic disturbances and treatment with second-generation antipsychotic agents. *Neuropsychopharmacology.* 2006;31(10):2091–2120.

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