Clinical Pharmacology and Medication-Associated Side Effects: A Review of Second-Generation Antipsychotics for Schizophrenia

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Abstract

Second-generation antipsychotics (SGAs) have largely replaced conventional antipsychotics as first-line therapy for the treatment of schizophrenia in the United States. While recent evidence suggests similar efficacy with low-dose conventional antipsychotics, much of the advantage favoring SGAs comes from the fact that there are less extrapyramidal side effects (EPS) at effective doses with these drugs. As a medication class, and with the exception of clozapine, the SGAs overall are very similar with regard to efficacy, yet are heterogeneous with respect to receptor binding and structure-activity as well as their side effect liabilities. This paper will review the clinical psychopharmacology of the SGAs, as well as adverse events associated with these drugs. Because certain side effects may be associated with a higher likelihood for nonadherence with treatment, more detailed data for each of the SGAs with regard to EPS, weight gain and metabolic abnormalities, and sexual dysfunction is presented.

Key Words: Second-Generation Antipsychotics, Side Effects, Weight Gain, Extrapyramidal Side Effects, Prolactin, Pharmacology

Introduction

Antipsychotic medications have long been the primary component of effective treatment for schizophrenia. Chlorpromazine was first used for the treatment of psychotic symptoms in the 1950s. This drug was initially developed for preoperative anxiety and within its first year of use was recognized as a potential treatment for psychosis (1). This medication gained rapid acceptance due to the lack of other effective treatments for psychosis. Many other medications were shortly marketed such as thioridazine, fluphenazine, haloperidol, and thiothixene. For thirty years conventional antipsychotics have been the mainstay of treatment for schizophrenia. These medications, however, all have important limitations to use: they are not effective for all patients, they have several serious adverse effects, and they have poor long-term outcomes associated with their use. In 1989, the Food and Drug Administration (FDA) approved clozapine, the first of a new class of antipsychotic medications. This class of medications, the second-generation antipsychotics (SGAs), differed primarily by producing minimal or no extrapyramidal side effects (EPS) in humans (2). Since the introduction of clozapine, six other antipsychotics have been approved (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone ER). These drugs share the propensity for causing relatively few extrapyramidal side effects at clinical doses. They are often called the atypical or novel antipsychotics, and they differ in their pharmacologic and tolerability profiles.

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Revised: May 8, 2007; Accepted: May 14, 2007

While conventional antipsychotics exert most of their receptor blockade through D2 receptors, SGAs may work through other mechanisms as well. There has been a great deal of speculation regarding the role of serotonin receptor antagonism in regard to antipsychotic effects. Many traditional antipsychotics are highly active at serotonin receptors, but this property does not distinguish the clinical effects of these drugs in a meaningful way. The serotonin hypothesis of psychosis actually predates the dopamine hypothesis, largely because of lysergic acid diethylamide (LSD), a drug with psychotomimetic properties which releases serotonin. Interest in this theory was renewed by the finding that clozapine, which has a hundred-fold selectivity for serotonin compared to dopamine receptors, is highly efficacious (3). The other SGAs also have high serotonin to dopamine binding ratios. Serotonin receptor binding may be important to these drugs' actions, possibly by stimulating dopamine activity in mesocortical pathways. Neurochemical studies suggest that serotonin projections tonically inhibit mesolimbic and nigrostriatal dopaminergic activity. Additionally, serotonin may directly inhibit dopamine release from striatal nerve terminals (4). However, a compelling theory relating dopamine and serotonin receptor affinities has not yet been articulated, and it is not clear why serotonin receptor affinity of newer antipsychotics is more important to their clinical effects than it was for older drugs.

Much of the advantage favoring SGAs comes from the fact that there is a wider separation between doses that cause EPS compared to effective doses with these drugs compared to conventional antipsychotics (2). Because of this and its potential associated benefits (i.e. better compliance), the use of these new medications increased quickly after their approvals by the FDA. By 1999, 60% of all patients with schizophrenia who received an antipsychotic in the United States were prescribed an SGA, and this proportion had increased to over 90% by 2006 (5). While the SGAs have moved into first-line therapy it is important to note that some recent studies comparing SGAs to low doses of haloperidol have failed to find differences in efficacy in both short- and long-term trials (6, 7). Others have also offered up this claim using meta-analytic techniques (8). Additionally, the largest and most comprehensive comparative trial to date, the Clinical Antipsychotic Treatment of Intervention Effectiveness (CATIE) Trial found that in over 1,400 patients randomly assigned to atypical (olanzapine, risperidone, quetiapine, ziprasidone) or perphenazine that time to discontinuation for any reason was similar for the treatments (both conventional and SGAs) with a benefit in longer medication continuation noted for olanzapine (9). However, this same study reported significantly greater adverse effects such as weight and metabolic-related effects with olanzapine.

It should be noted, however, that the SGAs as a group are very heterogeneous in regards to receptor binding and structure-activity, as well as their side effect liabilities. Each SGA will be presented below with information on clinical pharmacology and side effect profiles. Furthermore, the following sections will review some of the most serious or most commonly occurring side effects of each medication. EPS, most notably akathisia, sexual dysfunction, and weight gain are three commonly cited adverse effects possibly related to medication nonadherence (10).

Clinical Psychopharmacology and Specific Side Effects

Clozapine

Clozapine is the only drug approved and effective for the treatment of therapy-refractory schizophrenia. A great deal of interest has been generated in understanding what pharmacological properties of clozapine contribute to its superior efficacy. Clozapine has an increased ratio of D_1 to D_2 antagonism, greater D_3 and D_4 blockade, 5-HT_{2A} and 5-HT_{2C} antagonistic properties, anticholinergic and antiadrenergic properties, and increased mesolimbic specificity with relative sparing of nigrostriatal dopaminergic neurons (11).

Drowsiness/sedation (39%) and salivation (31%) are the most frequently occurring spontaneous reported side effects from clinical trials. Other frequently occurring side effects reported in trials include tachycardia (25%), dizziness (19%), and constipation (14%). Excessive sweating is unique to clozapine and has a reported incidence rate of 6%. Orthostatic hypotension is often self-limiting and occurs transiently during clozapine initiation and titration (6%) (11). There are reports of clozapine-associated cardiomyopathy and cardiorespiratory arrest (12, 13). Urinary incontinence occurs in about 1% of patients taking clozapine, but is thought to be under reported because of the embarrassing nature of the adverse effect. The risk of seizures is dose-related in patients taking clozapine. The risk of seizure occurrence is 1-2% at doses less than 300 mg/day, similar to traditional antipsychotics, and is approximately 5% at doses greater than 600 mg/day. Lastly, current estimates are that agranulocytosis will develop in approximately 0.8% of patients treated with clozapine; however, the risk decreases after the first six months (14).

Risperidone

Risperidone, a benzisoxazole derivative, was the first SGA to be marketed following the release of clozapine. This antipsychotic has high binding affinity to both 5-HT_{2A} and D_2 receptors and binds to $alpha_1$ and $alpha_2$ receptors, with very little blockade of cholinergic receptors (15).

Spontaneously reported adverse effects are reported most commonly for insomnia (26%) and agitation (22%).

Rhinitis occurs in 10% of patients, and gastrointestinal complaints such as vomiting, dyspepsia, nausea, constipation, and abdominal pain are reported to occur in about 4-7% of patients. Because of risperidone's alpha blocking activity, orthostatic hypotension may occur. Orthostasis may be associated with dizziness, tachycardia, and in some patients, syncope. Syncope occurs rarely, approximately in 0.2% of patients. Tachycardia has been reported to occur in approximately 3% of patients. Orthostatic hypotension is generally seen during the initial dose titration and is usually transient (11).

Olanzapine

Olanzapine has a pharmacological profile of activity similar to that of clozapine. In preclinical studies, olanzapine demonstrated a range of receptor affinities distinct from conventional antipsychotics and generally comparable to those of clozapine. However, in clinical trials olanzapine has not been found to be as efficacious for treatment-resistant schizophrenia as is clozapine (16). Olanzapine has greater affinity for 5-HT_{2A} than for D_2 receptors. In addition, the compound has affinity at the binding sites of D_4, D_3, 5-HT_3, 5-HT_6, H_1, alpha$_1$ adrenergic, muscarinic M_{1-5} receptors, and histamine H_1 receptors (17).

Somnolence (26%) and agitation (23%) are the most frequently reported adverse effects in clinical trials. Insomnia occurs in about 20% of patients. Anticholinergic effects such as constipation, dry mouth, and tachycardia occur in 7-9% of patients, but may be more frequent at higher doses. Hypotension is reported to occur in 5-7% of patients taking olanzapine, and tachycardia occurs in approximately 4% of patients. In placebo-controlled studies, clinically significant alanine transferase (ALT, SGPT) elevations of >3 times the upper limit of the normal range were observed in 2% of patients taking olanzapine. Also, during premarketing studies the incidence of ALT elevations was 2%, but was not associated with jaundice or other symptoms attributable to liver impairment. Transient increases may be seen, but usually normalize with olanzapine continuation (11).

Quetiapine

Structurally, quetiapine is related to clozapine and olanzapine. Quetiapine has high affinity for 5-HT_{2A} receptors and lower affinity for D_2 and D_1 receptors. This drug has some affinity for alpha$_1$, alpha$_2$, and H_1 receptors, and very little for muscarinic receptors (11).

Somnolence is one of the most commonly occurring side effects associated with quetiapine treatment (18%) and is usually transient after the first week. In clinical trials a dose-related decrease of total and free thyroxine (T4) of approximately 20% was seen in a few patients in the first two to four weeks of treatment and maintained during chronic therapy generally considered not clinically significant. Quetiapine may also cause orthostatic hypotension associated with dizziness, tachycardia, and in some patients (1%), syncope. Asymptomatic transient and reversible elevations in plasma transaminases (primarily ALT) have been reported (6%). Lastly, within manufacturer labeling, the warning for cataract development appears in bold type as required by the FDA. These cataracts appeared during chronic administration in beagles and have not been documented in humans (11).

Ziprasidone

Ziprasidone was developed within a structure-activity investigation intended to find a compound that potently blocks D_2 receptors, but that binds with even greater affinity to central 5-HT_{2A} receptors. As a result, ziprasidone has a binding affinity ratio of 11:1 for 5-HT_{2A}/D_2. Ziprasidone also binds with relatively high affinity for 5-HT_{2C}, 5-HT_{1D}, alpha$_1$ adrenergic, and D_1 receptors (18).

Somnolence has been reported to occur in clinical trials in about 14% of patients, twice that seen with placebo. Gastrointestinal complaints such as nausea, diarrhea, dyspepsia, and constipation are reported in approximately 5-10% of patients. Syncope and orthostatic hypotension occur infrequently and usually during the initial dose-titration period. Ziprasidone has the propensity to prolong the QTc interval. In placebo-controlled trials ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at 160 mg/day. Lastly, during clinical trials seizures occurred in 0.4% of patients treated with ziprasidone (11).

Aripiprazole

Aripiprazole was discovered in the early 1980s as an attempt to find an antipsychotic that would function as a potential entity with both antagonist and agonist activity to the D_2 receptor. Hence, aripiprazole is the first potent D_2 partial agonist for the treatment of schizophrenia. In a hyperdopaminergic state, aripiprazole functions as an antagonist, while under conditions of hypodopaminergic activity it functions more like an agonist. This novel mechanism has been labeled a dopamine system stabilizer. Aripiprazole also has high affinity for D_3 receptors and moderate affinity at the D_4 receptors. It is a partial agonist at 5-HT_{1A} receptors and an antagonist at 5HT_{2A} receptors. Aripiprazole has a moderate affinity for alpha$_1$ and H_1 receptors with no appreciable affinity for the M_1 receptor (19).

Insomnia occurs frequently with aripiprazole with about 24% of patients spontaneously reporting. This side effect, however, is reported to be transient and diminishes within the first week. Gastrointestinal complaints also initially occur with nausea and vomiting reported to occur in 12-14% of patients. Sedation is the only side effect noted to possibly

have a dose-relationship occurring most prominently with the 30 mg/day dose (10-15%) (11).

Paliperidone ER

Paliperidone ER is a new chemical entity of the active metabolite of risperidone, 9-hydroxy risperidone. It is a monoaminergic antagonist that exhibits both antagonism of dopamine$_2$ and serotonin$_{2A}$ receptors. It is a racemic mixture of two equally potent enantiomers. Paliperidone ER is delivered in extended release tablets using OROS® technology to deliver the psychotropic with an ascending profile over twenty-four hours. Paliperidone ER is delivered with smooth plasma concentrations with small twenty-four hour peak-to-trough fluctuations at steady state due to the OROS® technology. The gradual ascending release profile allows treatment to begin at a therapeutically effective dose without the need for initial dose titration for tolerability. Paliperidone ER undergoes limited hepatic metabolism and, therefore, is not likely to have clinically significant drug-drug interactions. It is primarily excreted renally with approximately 50% of this excretion occurring through active secretion in the renal tubule via an organic cation transport system (11). Discontinuation rates due to adverse events for all paliperidone ER doses were comparable to placebo in short-term registration trials. This was also true for the overall incidence of treatment–emergent adverse events pooled across the three premarketing studies. The pooled data from the studies shows that the incidence of tachycardia is higher for patients taking paliperidone ER (12%) compared to placebo (7%). There was no relationship noted between dose and tachycardia occurrence (20). Dose-related side effects included somnolence, orthostatic hypotension, and extrapyramidal side effects.

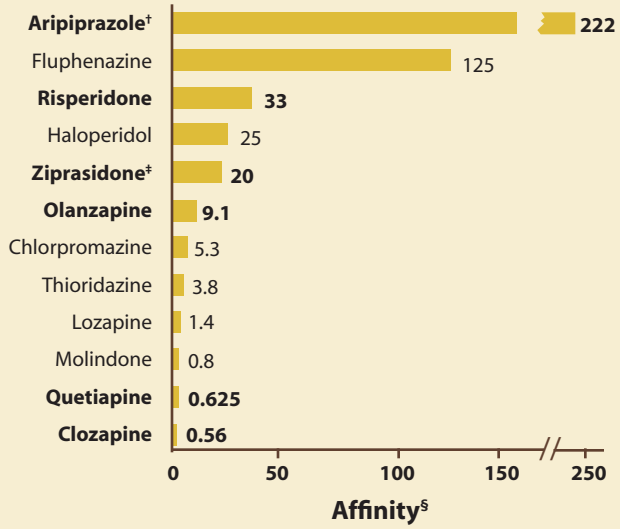
Extrapyramidal Side Effects

Extrapyramidal side effects (EPS), including akathisia, dystonia, and pseudoparkinsonism, are the major adverse effects associated with traditional antipsychotic therapy. These side effects are a result of dopamine antagonism in the nigrostriatal pathways. Akathisia is the most frequently occurring of these adverse effects. Approximately 50% of patients treated with traditional drugs will experience a subjective feeling of restlessness. Tardive dyskinesia (TD) is a movement disorder characterized by abnormal choreiform (rapid, objectively purposeless, irregular, and spontaneous movement) and athetoid (slow and irregular) movements occurring late in onset in relation to initiation of antipsychotic therapy. This adverse effect usually develops over several months and occurs after at least three months of neuroleptic treatment. The estimated average prevalence is 20% with a range of 13-36%. The incidence of new cases per treatment year with conventional antipsychotics is approximately 5% (21).

Clinically, the rates of EPS are comparable to the *in vitro* binding (Figure 1). Clozapine is associated with little to no EPS, and quetiapine has been found to have no greater rates of EPS than placebo. Olanzapine and risperidone both cause EPS less so than traditional antipsychotics, but in a dose-related fashion. Risperidone treatment is associated with parkinsonism rates similar to placebo in doses under 6 mg/day. Doses higher than 6 mg/day are associated with EPS rates of 20% or greater. Parkinsonism with olanzapine is similar to placebo with doses up to 10 mg/day. At higher doses the rates increase to 20%. Akathisia with olanzapine is significantly higher than placebo at doses greater than 10 mg/day. Rates of EPS on quetiapine are similar to placebo. Extrapyramidal side effects with paliperidone appear to be similar to risperidone. EPS as listed in the package labeling are shown in Figure 2.

Tardive dyskinesia with all the SGAs appears to occur at an incidence of less than 1%, but few long-term follow-up studies are available. A systematic review of one-year studies reported the mean risk of TD to be 0.8% in adults on SGAs compared to 5.3% on conventionals (22). Another six-month naturalistic study reported a risk of 0.9% with SGAs and 3.8% with conventional agents (23). Clozapine treatment has not been shown to cause TD. In fact, improvements in choreic and athetoid movements are seen with long-term clozapine

Figure 1 Dopamine-2 Receptor Affinities of Antipsychotics*



Second-generation antipsychotic drug names are bold faced.

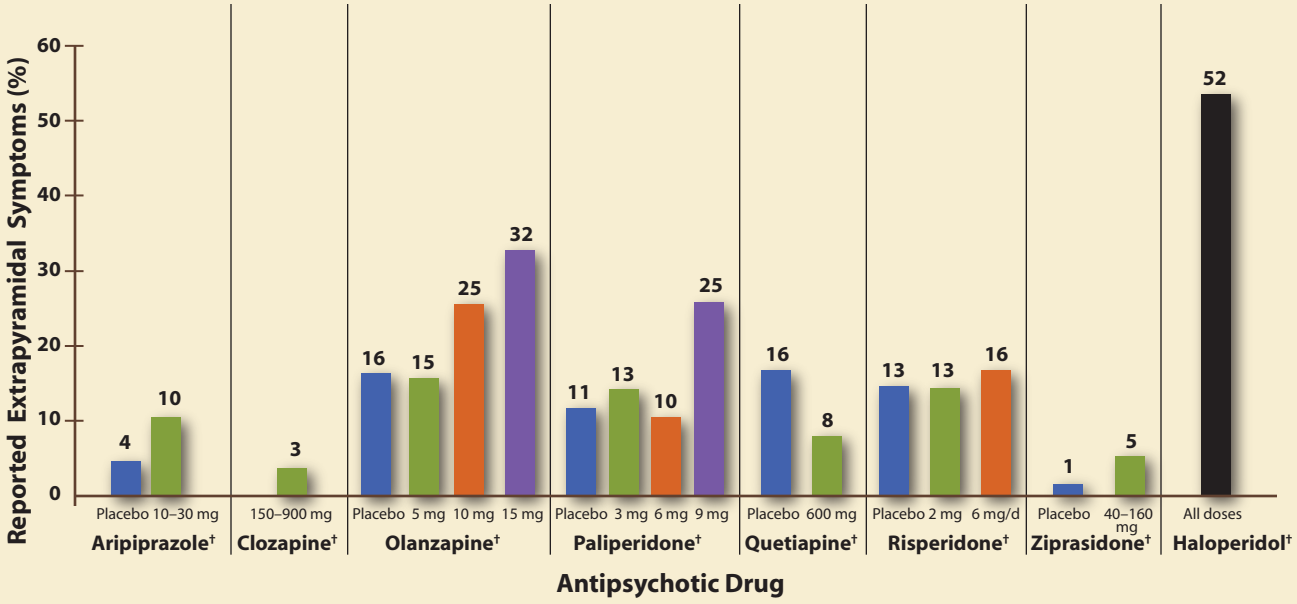
*Affinity data was compiled from Richelson E, Nelson A. Eur J Pharmacol 1984;103:197-204; Moore NA, et al. Curr Opin Invest Drugs 1993;2:281-293; Hyttel J, et al. Clin Neuropharmacol 1992;15:267-268.

†Data on file for aripiprazole: Otsuka America Pharmaceutical, Inc., Rockville, MD. Partial D2 agonist activity.

‡Adapted from Daniel DG, et al. Neuropsychopharmacology 1999;20:491-505.

§10-7 X 1/Kd where Kd = equilibrium dissociation in molarity.

Figure 2 **Incidence of Extrapyramidal Symptoms as Adverse Effects***



*In short-term, placebo-controlled trials.

†Percentages of extrapyramidal symptoms are derived from U.S. labeling and include the following terminology: acute dystonia, parkinsonism, akathisia, tardive dyskinesia, dystonic events, dykinetic events, akinesia, rigidity extrapyramidal syndrome, hypertonia, neck rigidity, and tremor.

All data from Physicians' Desk Reference, 60th edition, Medical Economics Company, Inc., Montvale, NJ (2006) with the exception of paliperidone data which is from the manufacturer's labeling.

treatment (24). Cases of discontinuation and dose reduction of clozapine, however, have reported the reemergence of preexisting TD (25, 26). Olanzapine, risperidone, ziprasidone, and quetiapine have all been implicated in a few case reports to both treat preexisting TD and cause this adverse effect (27). The incidence, however, with all of the SGAs appears to be minimal and much lower than the risk on traditional antipsychotics. Beasley et al (21) published a double-blind comparison of olanzapine and haloperidol in over 1,600 subjects for up to 2.6 years. The relative risk of TD over one year was 7.5% with haloperidol and 0.5% with olanzapine. In two long-term studies of risperidone in elderly adults the risk of spontaneous TD was less than 1% (28, 29). Evidence suggests that improvements in preexisting TD have been evident with quetiapine and aripiprazole (30-33). The risk of TD with paliperidone ER would be expected to be similar to risperidone.

Weight Gain and Metabolic Considerations

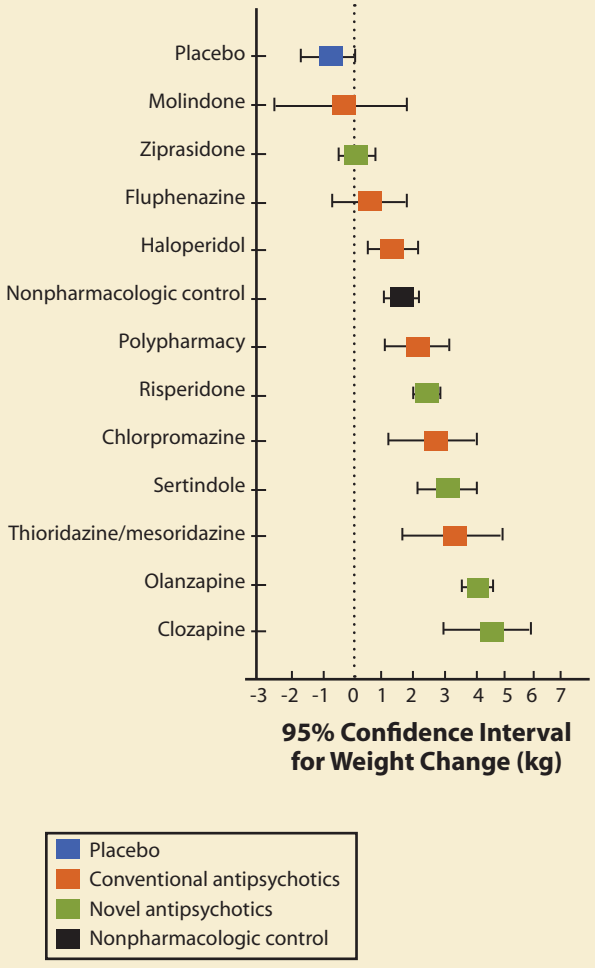
Weight Gain

In the United States, one-half of adults are currently overweight (body-mass index [BMI] >25 kg/m^2), and a fifth of the population is considered to be obese (BMI >30 kg/m^2). BMI among people with schizophrenia, however, exceeds the general population estimates. Many psychiatric patients, including those with schizophrenia, have sedentary lifestyles with little exercise, as well as potentially already being predisposed to metabolic effects associated with weight gain. Obesity in general increases the risk for a myriad of medical disorders such as hypertension, stroke, cancer, diabetes, and atherosclerosis. People with schizophrenia exhibit high relative rates of smoking and drug abuse and have several medical disorders that also compound the high rates of morbidity and mortality seen in this population (34).

Many short-term studies describe weight gain among people taking various antipsychotic drugs. The most comprehensive report to date is a meta-analysis of over eighty studies. Weight gain is highly variable among antipsychotics; however, two SGAs, olanzapine and clozapine, clearly appear to be associated with the highest degree of weight gain in short-term trials (4-4.5 kg over 10 weeks) (35) (Figure 3). Additionally, the percentage of patients with a >7% increase in body weight from baseline in pivotal trials is shown in Table 1.

Several reports describe the effects of long-term clozapine treatment on body weight. For example, Hummer et al (36) reported that after one year of clozapine treatment 36% of subjects gained more than 10% of their initial body weight with the average being about 3.5 kg. Significant weight gain also is widely known to occur with olanzapine treatment. Olanzapine weight gains at doses of 12.5-17.5 mg/day have

Figure 3 **Meta-Analysis of Antipsychotics and Weight Gain: Estimate at 10 Weeks**



Adapted from Allison DB, et al. A J Psychiatry 1999;156:1686-1696.

Table 1 **Percentage of Patients with a >7% Increase in Body Weight**

	Increase w/Drug	Increase w/Placebo
Aripiprazole	8%	3%
Paliperidone	8%	5%
Ziprasidone	10%	4%
Risperidone	18%	9%
Quetiapine	25%	4%
Olanzapine	29%	3%

been found to average 12 kg after one year of use (37). Kinon et al (38) reported mean weight gains after 1.05 years of 6.3 kg. This number is most likely conservative as it was reported in an intent to treat design. Weight gain with olanzapine appears to peak after 40 weeks of treatment and may be greater than gains associated with clozapine treatment (39). Weight gain with risperidone appears to plateau early on and remain at about 2-3 kg at one year (40). Studies on long-term quetiapine, ziprasidone, and aripiprazole treatment have reported weight gains of approximately 0.5-2 kg over at least one year (41-43). Most data implies that weight gain is generally not dose-dependent with the SGAs and that subjects with low BMIs may gain the most weight.

In the CATIE trial, average weight changes in the eighteen months ranged from -2.0 lbs. to over 9 lbs., demonstrating a highly variable rate among antipsychotics over longer treatment. Table 2 shows weight data from the CATIE trial. Olanzapine was associated with significantly greater weight gain as compared to other agents (8).

Glucose Dysregulation

Metabolic disturbances, particularly impaired glucose metabolism, were first described in psychotic subjects prior to the introduction of antipsychotic medications. The risk for type 2 diabetes mellitus (DM) is also known to be higher in schizophrenia subjects than in the general population. In addition, antipsychotic medications are associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis. Possible consequences of DM include retinopathy, cataracts, infection, neuropathy, kidney failure, and circulatory disorders. Abdominal or central adiposity may contribute to glucose dysregulation (44).

Some of the SGAs have been linked to hyperglycemia, DM, and diabetic ketoacidosis. A recent review of seventeen pharmacoepidemiologic studies reported that the majority of studies found that olanzapine is associated with a significantly increased risk of new-onset diabetes as compared to untreated schizophrenia, as well as other SGA treatments (45). While the majority of cases of DM occur in people who were overweight prior to treatment, studies have shown that diabetes may occur in the absence of weight gain. Diabetic ketoacidosis (DKA) has been a presenting symptom in at least ten reported cases during clozapine treatment and in at least five case reports of olanzapine treatment (46).

Direct prospective comparative studies are difficult to undertake, and data is lacking as it may take years for a prediabetic person to actually show overt signs of diabetes and for actual increases in fasting glucose to increase. During the CATIE trial, there were no significant differences in fasting serum glucose changes among antipsychotic treatments (olanzapine 13.7±2.5 mg/dl; quetiapine 7.5±2.5 mg/dl;

Table 2 Weight Changes from the CATIE Trial

	Olanzapine N=336	Quetiapine N=337	Risperidone N=341	Perphenazine N=261	Ziprasidone N=185
Weight gain >7%	30%	16%	14%	12%	7%
Mean weight change (lbs)	9.4	1.1	0.8	-2.0	-1.6
Lbs per month	2.0	0.5	0.4	-0.2	-0.3

risperidone 6.6±2.5 mg/dl; ziprasidone 2.9±3.4 mg/dl; perphenazine 5.4±2.8 mg/dl) (8). However, the change in glycosylated hemoglobin was four to ten times greater with olanzapine as compared to the other antipsychotic medications.

Hyperlipidemia

Increases in plasma lipid levels have been noted with the phenothiazines, but negligible effects on lipids have occurred with the higher potency drugs such as haloperidol. Early on, clozapine was noted to have a profound increase on serum triglycerides as well as small increases in total cholesterol levels (47). Henderson et al (48) found that over sixty months mean triglyceride levels increased from 175 mg/dl to approximately 400 mg/dl. They also noted a slight but nonsignificant increase in serum cholesterol levels. Studies have also suggested that olanzapine use is associated with the development of hyperlipidemia. A report by Sheitman et al (49) suggested that olanzapine treatment may result in marked increases in triglyceride levels for some subjects. Another cohort study of twenty-five inpatients treated with olanzapine for twelve weeks showed a mean increase of 60 mg/dl in fasting triglycerides (50). In a recent study using the U.K.-based General Practice Research Database, the prescription of olanzapine was associated with a statistically significant four-fold increase in the odds of those developing hyperlipidemias compared to those not prescribed antipsychotics. No significant increase was noted for risperidone in the sample of approximately 20,000 (51). High triglyceride levels have been reported with quetiapine (52, 53). Risperidone, ziprasidone, and aripiprazole appear to have neutral effects on triglycerides and total cholesterol levels, and some switch studies have noted improvements in lipids when switching to these agents from other treatments known to elevate lipids (54, 55). As evidenced by the CATIE trial and others, increases in total cholesterol and triglycerides are most evident with olanzapine and quetiapine (8). Clozapine is also known to significantly elevate cholesterol and triglycerides. Less is known about the effects of antipsychotics on lipid fractions; however, some data suggests increases in LDL with these medications as well.

Prolactin-Related Adverse Effects/ Sexual Dysfunction

Sexual functioning has received little attention and recognition as being an important aspect of patient care for those suffering from severe mental disorders such as schizophrenia. Sexual dysfunction has been implicated as one of the major factors contributing to noncompliance with antipsychotic medications (56). A recent survey identified that the area of "personal relationships" was one of the treatment areas with the most unmet needs noted by people with schizophrenia (57). It is known that approximately 50% of patients have reported dysfunction in the area of sexuality during treatment with conventional antipsychotic treatment (58). It is likely that a better focus on sexuality and preventing sexual dysfunction in schizophrenia would be a major benefit for improving treatment.

Sexual dysfunction during antipsychotic therapy can be attributed to several mechanisms including excessive sedation, weight gain, EPS, or receptor antagonism such as cholinergic and calcium channel blockade (59). The evidence, however, for elevated prolactin contributing to sexual dysfunction is convincing. Hyperprolactinemia is known to cause hypogonadism and decrease testosterone levels (60). Prolactin itself appears to have a direct effect on sexual activity, as high prolactin levels have been associated with sexual dysfunction, and normalization of prolactin levels with bromocriptine has been shown to restore sexual functioning (58).

Only a handful of articles exists, other than case reports, that discuss sexual functioning with the use of SGAs. Largely, clinical trials have omitted systematically rating sexual function and have relied upon spontaneous reporting of sexual side effects, thus potentially leading to underestimation of true occurrences (61). One recent study comparing risperidone, olanzapine, quetiapine, and haloperidol is the largest study to date to measure sexual dysfunction and reproductive side effects. This study reported rates of sexual dysfunction between 35-43% for risperidone, olanzapine, and haloperidol. Rates of sexual dysfunction on quetiapine were 18%. Also, reproductive side effects were similar for haloperidol and olanzapine (6-7%), while lower with quetiapine (3%) and higher with risperidone (12%) (62).

Clozapine has a low propensity to block dopamine in the tuberoinfundibular pathway and has a negligible effect on plasma prolactin levels (63). Sexual function during clozapine treatment has been comparatively better than treatment with conventional antipsychotics (64). Of all the SGAs, risperidone has the highest propensity to elevate plasma prolactin levels and does so in a dose-related fashion (65). A recent retrospective chart review reported a significantly higher proportion of sexual dysfunction with risperidone as compared to haloperidol and clozapine (66), and other prospective comparative studies have found higher rates of both with sexual dysfunction and reproductive side effects with risperidone as compared to olanzapine, quetiapine, and haloperidol (62). Olanzapine causes transient elevations in plasma prolactin levels. During treatment in adults prolactin levels remain slightly elevated in about one-third of patients (61). Elevation of prolactin appears to be a dose-related phenomenon (67). Quetiapine has negligible effects on the elevation of prolactin. In all of the large trials of quetiapine, prolactin levels were reported to decrease from baseline to endpoint during quetiapine treatment, and no differences were noted between quetiapine and placebo (68). Few reports of sexual dysfunction or hormonal problems have been reported. Very little data is available pertaining to either plasma prolactin levels or sexual functioning with ziprasidone. It appears that slight elevations may occur with ziprasidone (41). Serum prolactin levels during treatment trials with aripiprazole have been found to decrease from baseline across all dose ranges, and sexual dysfunction and hormonal disturbances have not been reported (42). Prolactin elevations with paliperidone are similar to risperidone. However, only plasma levels of paliperidone significantly correlate with plasma levels, and it is believed that paliperidone may contribute more to the increased serum prolactin as compared to the parent compound, risperidone (69, 70). Lastly, recent evidence suggests that elevated prolactin levels with antipsychotic treatment may lead to an increased risk of osteoporosis and bone fracture. This may be secondary to hypogonadism from prolactin-elevating drugs. Studies have shown an increased risk with risperidone and haloperidol (71, 72).

Conclusions

Second-generation antipsychotics are all effective in clinical doses that cause markedly fewer extrapyramidal side effects (EPS) than conventional antipsychotics. This is the trait that most clearly distinguishes these two drugs "types." Extrapyramidal side effects are common and serious side effects that are generally associated with the use of conventional antipsychotic drugs. In addition to the discomfort and distress caused to patients, EPS may contribute to poor compliance and ultimately poor treatment outcome. The results of clinical trials with the new generation of atypical antipsychotics suggest that they are associated with a reduction in both early- and late-occurring EPS. All of the new-generation agents produce substantially fewer EPS and reduce the need for antiparkinsonian medications, which are also associated with marked problems of their own. Data from long-term studies suggests that new-generation antipsychotics are also associated with a reduced risk of tardive dyskinesia. This differential effect of these drugs is the most compelling reason for their first-line use and may explain much of the differential efficacy seen with these drugs, with the likely exception of clozapine.

The tendency of most of the SGAs to induce weight gain to a larger extent than that of conventional antipsychotics has renewed the interest in weight problems of patients with schizophrenia. Drug-induced weight gain has been identified as a major risk factor for cardiovascular disease and various medical disorders that might be responsible for some of the increased morbidity and mortality rates in this disorder. Also, it has a major impact on adherence. Patients treated with these drugs should be informed of their risks, be offered dietary advice, and regular exercise and behavior modification programs. Physicians must be aware of the problem of weight gain and metabolic-associated side effects with schizophrenia treatment, and select SGAs carefully in patients at high risk for weight gain. The ADA has published guidelines to monitor for weight and metabolic side effects (Table 3) (73). Additionally, the Mount Sinai conference guidelines for monitoring for serious side effects are listed in Table 4 (74).

While the seven SGAs listed above are medications representing significant advances in treatment and outcomes of people with schizophrenia, we are in need of understanding the underlying pathophysiology of schizophrenia and discovering novel drug targets. As we work to more accurately identify people who are vulnerable to psychosis and to understand brain regions associated with this illness, we should also work to more effectively integrate current treatment options with active psychosocial and rehabilitative programming in an attempt to provide beneficial treatment for the people we see today. People who suffer from schizophrenia today will benefit from optimized medication therapy. These benefits include marked improvements in functioning and quality of life. The pharmacotherapy of schizophrenia has evolved from a relatively simple strategy involving a very homogenous class of medications with a high ratio of behavioral toxicity to beneficial effects to a more complex group of drugs with improved efficacy. There is, however, no magic bullet or a correct therapy for all patients. As we continue to use the SGAs available and await new treatments, clinicians should now attempt to optimize therapy for each patient in a highly individualized way.

Table 3 Monitoring Protocol for Patients on Second-Generation Antipsychotics (73)

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/Family History*	X					X	
Weight	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Plasma Lipids	X			X			X

*Obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease

Table 4 Recommended Monitoring Frequency for Particular Safety Concerns by Antipsychotic (74)

	TD	EPS	BP/Pulse	Weight	Glucose*	Cholesterol/ Triglycerides*	Prolactin/ Sexual Side Effects	EKG
FGAs	B, q6M	B, q visit as long as a problem, then q1Y	q1Y	B, 3M, q1Y	B, if weight gain >7% body weight, then q1Y	B, if weight gain >7% body weight, then q1Y	B, q visit first 3M until stable, q1Y	Only if on thioridiazine or mesoridazine, B, q1Y
Clozapine†	B, q1Y	B, q1Y	q visit until stable	q visit for 6M, then q3M	Same as above	Same as above	Same as above	NA
Olanzapine	B, q1Y	B, q visit as long as a problem, then q1Y	B, q1Y	Same as above	Same as above	Same as above	Same as above	NA
Risperidone	B, q1Y	Same as above	B, q1Y	Same as above	Same as above	Same as above	Same as above	NA
Quetiapine	B, q1Y	B, q1Y	q visit until stable	Same as above	Same as above	Same as above	Same as above	NA
Ziprasidone	B, q1Y	B, q visit as long as a problem, then q1Y	B, q1Y	B, 3M, q1Y	Same as above	Same as above	Same as above	B, q1Y
Aripiprazole‡	B, q1Y	Same as above	B, q1Y	B, 3M, q1Y	Same as above	Same as above	Same as above	NA
Paliperidone‡	B, q1Y	Same as above	B, q1Y	q visit for 6M, then q3M	Same as above	Same as above	Same as above	NA

B=baseline, BP=blood pressure, EKG=electrocardiogram, EPS=extrapyramidal side effects, FGA=first generation antipsychotic, M=months, NA=not applicable, q=repetition interval, TD=tardive dyskinesia, Y=year

* If a fasting specimen was not collected and the value is abnormal, a fasting specimen should be obtained. Since the guidelines were published it has been noted that glucose and lipid changes may occur independent of weight. Thus, more frequent monitoring should be performed. A baseline and 12 weeks should be obtained with some experts recommending every 3-6 months (75).

† Patients receiving clozapine should have their white blood count monitored. Current requirements mandate weekly white blood count monitoring for 6 months, every other week for 6 months, and once monthly after one year.

‡ Not included in the Mount Sinai published recommendations.

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