Review of the Safety of Second-Generation Antipsychotics: Are They Really "Atypically" Safe for Youth and Adults?

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ABSTRACT

Objective: There is general consensus that second-generation antipsychotics are at least as effective as and more tolerable than first-generation antipsychotics. We address questions of safety and tolerability in both the short-term and long-term use of these medications by reviewing the existing literature in youth and adults.

Data Sources: A MEDLINE search was conducted via PubMed using the following keywords (in various combinations): *typical antipsychotics, atypical antipsychotics, children, adolescents, side effects, weight gain, diabetes, metformin, metabolic syndrome,* and *CATIE*. Only English-language articles published from 2000–2010 were included. The bibliographies of papers identified through MEDLINE searches were also reviewed.

Results: Six adult studies were analyzed in detail. A summary of the data suggests that there may be a lower association of weight gain and diabetes with ziprasidone, aripiprazole, and haloperidol, while olanzapine, clozapine, quetiapine, and risperidone appear to be more highly associated. There may be less difference than originally thought concerning frequency of extrapyramidal side effects among these medications. All of these antipsychotics, including perphenazine, are similarly efficacious in treating psychosis, with the exception of clozapine, which demonstrates significantly more effectiveness. Although the studies on youth tend to be small (few subjects with large age ranges of 4 to 19 years) and short term in comparison to the adult studies, the data reviewed from 5 studies suggest that, in youth, olanzapine may be associated with the greatest weight gain, extrapyramidal side effects and metabolic changes are quite prevalent, and the antipsychotics studied seem to be similarly effective.

Conclusions: Considering effectiveness, safety, and tolerability, this literature review suggests that in adults there may be a lower association of weight gain and diabetes with ziprasidone, aripiprazole, and haloperidol as compared with olanzapine, clozapine, quetiapine, and risperidone. Youth may be particularly sensitive to weight gain, especially with olanzapine, as well as extrapyramidal side effects and metabolic changes. The literature suggests similar effectiveness among the antipsychotics, perhaps with the exception of clozapine having greater effectiveness, at least in adults.

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The general consensus in mental health as well as primary care settings is that second-generation antipsychotics (SGAs) are at least as effective as and more tolerable than first-generation antipsychotics (FGAs). The FGAs were effective, but the extrapyramidal side effects (EPS) were often intolerable, leading to the development of SGAs, which appear to have less risk for these effects (although this notion has been challenged in recent years).[1] For this reason, SGAs are being prescribed widely, and considered first-line, for various indications.

Particularly in child and adolescent populations, there has been an exponential increase in prescribing SGAs since they became available. In outpatient settings, Olfson et al[2] noted a 6-fold increase between 1993 and 2002. However, growing evidence suggests an association between SGAs and a worsening in metabolic parameters. Here, we review the literature on side effects associated with FGAs and SGAs, particularly in children who may be especially sensitive to both EPS and metabolic changes.[3]

Historical Overview

We refer to antipsychotic medications in this article as either *first-generation antipsychotics* or *second-generation antipsychotics*. This differentiation is based more on the timeline of when they were released into medical practice rather than on a truly scientific basis. FGAs are classified according to their chemical structure (phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, and dihydroindolones), while SGAs are classified according to their pharmacologic properties.

Chlorpromazine, the first antipsychotic discovered, was originally developed as a surgical anesthetic. The discovery of psychoactive effects of chlorpromazine in 1952 led to greatly reduced use of physical restraint, seclusion, and sedation in the management of agitated patients. However, this use of "chemical restraint" has been criticized. Some have found it to be mismanaged by health care workers for the convenience of the staff rather than the benefit of the patient. We are unaware of any comparative studies looking at physical versus chemical restraint.

FGAs were originally called *neuroleptics* (from the Latin "to grasp the neuron") because EPS were thought to be essential for their therapeutic efficacy, and they improved outcome by about 50% compared to the "pre-neuroleptic" era. FGAs have also been called "typical" (after SGAs were called "atypical"), "conventional," and "classical." These terms appear to be referring only to an era in psychiatry and the general acceptance these medications had before the SGAs were developed.

SGAs have been called "atypical" primarily because of the low propensity to induce EPS. Clozapine, discovered in the 1950s and introduced into clinical practice in the 1970s, but not approved by the US Food and Drug Administration (FDA) until 1989, was the first to be recognized as "atypical." Clozapine was associated with serious side effects (agranulocytosis, myocarditis/cardiomyopathy, seizures) and required weekly blood monitoring, and thus researchers sought novel

Clinical Points

- Treatment effectiveness may be similar among all antipsychotics for various indications in youth and adults.
- Youth appear to be especially sensitive to both metabolic and extrapyramidal side effects.
- There may be a lower association of metabolic changes with certain antipsychotics, which should be carefully considered as the prevalence of obesity increases in the United States.

compounds with similar effectiveness without the toxicity or inconvenience factor. Similar antipsychotics were therefore developed and became available in the early 1990s.[4]

Review of Pharmacology

It is important to briefly review how antipsychotics are thought to work at a molecular level. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences, and the intended effects of antipsychotics are a result of blocking the D_2 receptors in this pathway. Dopaminergic innervations in the brain also include mesocortical, tuberoinfundibular, and nigrostriatal pathways. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects of antipsychotics. Specifically, it is thought that acute EPS are caused by excessive dopamine antagonism in the nigrostriatal pathway. Tardive dyskinesia is believed to be caused by denervation supersensitivity of nigrostriatal dopamine receptors, which produces up-regulation of their density (as evidenced by increased volume of the caudate nucleus). FGAs are not particularly selective and block dopamine receptors in all of the pathways. *Potency* refers to the ability of the drug to bind to dopamine receptors, and FGAs were commonly classified on a spectrum of low to high potency. SGAs have a similar blocking effect on D_2 receptors (although aripiprazole is a partial agonist and sometimes considered a "third-generation" antipsychotic). Some also block or partially block serotonin receptors (particularly 5-$HT_{2A,}$ 5-HT_{2C}, and 5-HT_{1A} receptors), ranging from risperidone, which acts overwhelmingly on serotonin receptors, to amisulpride, which has no serotonergic activity.

Focus on Side Effects

Intolerable EPS in FGAs were the main reason for developing the newer SGAs. These side effects include dystonias, parkinsonism, akathisia, and tardive dyskinesia. EPS, in general, appear to be less common with SGAs (although EPS may occur more frequently with risperidone when there is a rapid titration or elevated final dose), but there is concern about associated weight gain, obesity, hyperlipidemia, impaired glucose tolerance, and diabetes mellitus. Obesity and weight gain themselves have been associated with hypertension, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some types of cancer (endometrial, breast, prostate, and colon).[5]

Recently, questions have been raised regarding the long-term metabolic costs of prescribing SGAs. There may be a trade-off between more short-term tolerability of SGAs and the potential long-term morbidity and mortality due to metabolic-associated diseases.[6] In addition, there are emerging findings indicating that youth are especially vulnerable to antipsychotic medication–induced weight gain, and abnormal childhood weight and metabolic status adversely affect adult cardiovascular outcomes via continuation of these risk factors.[7]

METHOD

A MEDLINE search was conducted via PubMed using the following keywords (in various combinations): *typical antipsychotics, atypical antipsychotics, children, adolescents, side effects, weight gain, diabetes, metformin, metabolic syndrome,* and *CATIE.* Only English-language articles published from 2000–2010 were included. The bibliographies of articles identified through MEDLINE searches were also reviewed.

RESULTS

Given the paucity of studies in children and adolescents comparing side effects in FGAs and SGAs, we initially present the more extensive literature in adults. Six studies in adults are analyzed in detail, and 5 studies of children and adolescents are then analyzed.

Review of the Adult Literature

Table 1 summarizes the studies conducted in adults.

In 2009, Parsons et al[8] looked specifically at weight effects associated with antipsychotics. They mention that most of the previous studies assessing weight change are less than 6 months in duration. In their analyses, they pooled short- and long-term randomized controlled trials to create a large integrated analysis dataset from several countries. Overall, ziprasidone-treated and haloperidol-treated subjects experienced the lowest clinically significant weight gain in comparison to those treated with risperidone and olanzapine. This study was industry-supported but was consistent with findings from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which also will be reviewed.

In 2009, also using a large, integrated database, Baker et al[9] were able to suggest a low association with diabetes mellitus, hyperglycemia, increased blood glucose, diabetic ketoacidosis, and non–insulin-dependent diabetes mellitus for aripiprazole, haloperidol, and ziprasidone and more frequent diabetes-related adverse events for olanzapine, clozapine, quetiapine, and risperidone. It is interesting that haloperidol is often the FGA chosen in these studies over other FGAs. Our assumption is that it is chosen due to its being more frequently prescribed compared to the other FGAs.

Table 1. Summary of Adult Studies Comparing Side Effects in First-Generation Antipsychotics (FGAs) and Second-Generation Antipsychotics (SGAs)

Study	Journal	Type of Study	Findings
Parsons et al,[8] 2009	*Schizophrenia Research*	Analysis of a large integrated dataset of short-term (N = 1,742, 4–12 wk) and long-term (N = 1,649, > 6 mo) randomized controlled trials looking at weight effects	Ziprasidone and haloperidol were associated with significantly lower weight gain in both short- and long-term studies compared to risperidone and olanzapine
Baker et al,[9] 2009	*Psychopharmacology Bulletin*	Analysis of a large integrated database (US Food and Drug Administration Adverse Event Database) looking at association with diabetes-related adverse events	Low association with diabetes for aripiprazole, haloperidol, and ziprasidone. Higher association with olanzapine, clozapine, quetiapine, and risperidone
Miller et al,[1] 2008	*British Journal of Psychiatry*	Analysis of CATIE data for comparison of incidence of EPS between antipsychotics	No consistent, substantial, or statistically significant difference in incidence of EPS between any SGA and perphenazine (although more subjects dropped out due to EPS) or between SGAs
Jones et al,[14] 2006	*Archives of General Psychiatry*	Multisite, randomized trial (N = 227) comparing quality of life outcome measures in SGAs vs FGAs (CUtLASS)	No disadvantage in terms of quality of life, symptoms, or associated costs of care across 1 y with FGAs rather than SGAs in schizophrenic patients whose medication had been changed
Lieberman et al,[11] 2005	*New England Journal of Medicine*	Large (N = 1,493), randomized, multisite (57) trial looking at effectiveness via rates of discontinuation between antipsychotics (CATIE)	Olanzapine was most effective in terms of discontinuation rate (but associated with most weight gain). Perphenazine was similarly efficacious to the SGAs. Clozapine was significantly more effective than all others
Sernyak et al,[10] 2002	*American Journal of Psychiatry*	Analysis of a large data set (N = 38,632) from the VA comparing FGA and SGA association with diabetes	Patients receiving SGAs found to be 9% more likely to have diabetes when controlled for age effects (all groups had high rates of diabetes, however)

Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, CUtLASS = Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, EPS = extrapyramidal side effects, VA = Department of Veterans Affairs.

In 2002, Sernyak et al[10] analyzed data from another large data set over 4 months in patients in the Veterans Affairs system who were receiving either FGAs or SGAs. When the effects of age were controlled, patients who received SGAs were 9% more likely to have diabetes than those who received FGAs, although all of the treated groups had very high rates overall. It is well known that patients with schizophrenia, regardless of treatment, have a higher rate of diabetes than the general population. It is important to note that the results are indicative of differential effects of SGAs in their propensity to cause diabetes-related adverse events (but do not determine causality or relative risk).[9]

CATIE is one of the largest and most-analyzed studies in psychiatry over the last half decade. Published in 2005,[11] it included a large adult sample that was randomly (and double-blindly) assigned to receive olanzapine, perphenazine, quetiapine, or risperidone (and ziprasidone was included after it was approved by the FDA during phase 2 of the study, along with clozapine, which was open-label) for up to 18 months. However, 74% of patients discontinued the study medication before 18 months. The primary outcome measure was discontinuation for any cause. In phase 1, olanzapine was the most effective in terms of rates of discontinuation; however, it was also associated with the greatest weight gain and increases in measures of glucose and lipid metabolism. Perphenazine, an FGA, was found to be similarly efficacious to the SGAs. In phase 2, clozapine was significantly more effective than other SGAs and perphenazine for patients who had switched from a different antipsychotic in phase 1. This trial was unique in its large sample size and "real-world" conditions, meaning patients were not excluded if they had stable comorbid psychiatric and/or substance-use disorders upon enrollment. The study was independent from industry sponsorship. There are several limitations and criticisms, however. First, clozapine treatment was open label (a necessity due to complexities involving weekly blood draws). Second, perphenazine was the only FGA used for comparison (chosen because of its lower potency and decreased risk for EPS). Third, dosing was unusually low for quetiapine, ziprasidone, and risperidone while high for olanzapine and perphenazine, which may have accounted for the better outcomes for the olanzapine group and EPS intolerability for the perphenazine group. Also, one cannot conclude with certainty that the primary outcome of discontinuation is due solely to the drug interventions and not to other aspects of care.[12] In phase 3, patients who had discontinued antipsychotic treatment in phases 1 and 2 selected 1 of 9 antipsychotic regimens in consultation with their study physician. Weight loss was seen in patients who selected ziprasidone and aripiprazole (although patients who selected aripiprazole had the greatest increases in blood glucose levels).[13] There is concern for potential bias due to the open-label approach in this phase, although, again, it reflects more "real-world" conditions.

In 2008, Miller et al[1] performed an analysis of the CATIE data and found that the incidence rates for dystonia, parkinsonism, akathisia, and tardive dyskinesia as determined by continuous rating scale measures showed no statistically significant differences between any SGA and perphenazine, or between any pair of SGAs. They report that their

Table 2. Summary of Child and Adolescent Studies Comparing Side Effects in First-Generation Antipsychotics (FGAs) and Second-Generation Antipsychotics (SGAs)

Study	Journal	Type of Study	Findings
Correll et al,[7] 2009	*Journal of the American Medical Association*	Large (N = 272), nonrandomized, multisite, controlled, 12-week trial examining cardiometabolic risk of SGAs in treatment-naive youth (aged 4–19 y) (SATIETY)	Aripiprazole, olanzapine, quetiapine, and risperidone were all associated with rapid and significant increases in body composition, but metabolic changes were less uniform. Actual metabolic syndrome and diabetes rarely developed
Sikich et al,[16] 2008	*American Journal of Psychiatry*	Small (N = 119), 8-week, randomized trial comparing efficacy and safety of olanzapine and risperidone with molindone in treatment of early-onset schizophrenia and schizoaffective disorder (TEOSS)	No significant difference in response rates (molindone: 50%, olanzapine: 34%, risperidone: 46%). Olanzapine and risperidone associated with significantly greater weight gain (random assignment to olanzapine was discontinued). Molindone group had more self-reported akathisia
Fleischhaker et al,[17] 2008	*Journal of Neural Transmission*	Small (N = 33), nonrandomized trial looking at weight and BMI for patients treated with clozapine, olanzapine, and risperidone over 45 wk	All groups experienced significant weight gain. Risperidone group reached weight gain plateau at 25–29 wk
Wonodi et al,[18] 2007	*Movement Disorders*	Small (N = 118), nonrandomized trial with healthy control group (35 subjects) looking at tardive dyskinesia in children receiving antipsychotics	Nine percent exhibited tardive dyskinesia (11 of 118, including 5 of 81 receiving SGAs only) over more than 2 y
Sikich et al,[3] 2004	*Neuropsychopharmacology*	Small (N = 50), 8-week, double-blind, randomized controlled trial comparing acute antipsychotic effect size and side effect propensity of risperidone and olanzapine to haloperidol in youth (aged 8–19 y)	Risperidone, olanzapine, and haloperidol were similarly effective; however, EPS were significant in all groups, as was weight gain

Abbreviations: BMI = body mass index, EPS = extrapyramidal side effects, SATIETY = Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth, TEOSS = Treatment of Early-Onset Schizophrenia Spectrum Disorders.

findings were consistent with a recent large meta-analysis of 31 randomized controlled trials. They also comment on studies that have shown a lower incidence of EPS in patients receiving SGAs; however, they point out that haloperidol (a high-potency FGA) was used as the comparator at relatively high doses in those studies.

The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) in 2006[14] studied patients from community psychiatric services in the English National Health Service. This noncommercially funded randomized controlled trial compared FGAs to SGAs for patients with schizophrenia and related disorders switching treatment at baseline by looking at Quality of Life Scale scores, symptoms, adverse effects, participant satisfaction, and costs of care as outcome measures over 1 year. The authors concluded that there is no disadvantage in terms of quality of life, symptoms, or associated costs of care with FGAs rather than SGAs in patients whose medication is being changed because of intolerance or inadequate response. Although the patients were being treated with a wide variety of antipsychotic medications, some were prescribed depot injections, making comparisons difficult due to possible differences in compliance.[15]

It is important to comment here on some general limitations in these adult studies. Little, if anything, is mentioned of comorbid conditions and treatments that may have impacted symptomatology and even primary outcome measures (eg, concomitant medications that may cause changes in blood antipsychotic levels). There is no mention of family history of diabetes, obesity, or other metabolic problems—therefore, these were quite likely not controlled for. Finally, there are no comments on the increase in rates of obesity and diabetes in Western society and what impact that may have.

Review of the Child and Adolescent Literature

Table 2 summarizes the studies in children and adolescents.

In 2004, Sikich et al[3] examined the acute antipsychotic effect size and side effect propensity of risperidone and olanzapine in comparison to haloperidol in youth with positive psychotic symptoms. They concluded that risperidone and olanzapine reduce psychotic symptoms to at least as great an extent as haloperidol; however, moderate doses of risperidone and olanzapine may be associated with side effects in youth that are more prevalent and severe than those reported in psychotic adults. More than half of patients experienced at least mild to moderate EPS (and required low-dose benztropine to manage), which is consistent with earlier studies suggesting that youth are particularly sensitive to EPS. EPS were significantly more frequent and severe in the haloperidol group, however. Most of the youth gained considerable weight (average of 7.1 kg with olanzapine; 4.9 kg with risperidone; 3.5 kg with haloperidol). The study is limited by its small sample size and variations in age and developmental status. Adjunctive medications were also permitted.

In 2009, the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study[7] examined the cardiometabolic risk of SGAs in treatment-naive youth, the largest study of changes in weight and metabolic parameters in treatment-naive youth to date. Patients had mood spectrum disorders (47.8%), schizophrenia spectrum disorders (30.1%), and disruptive or aggressive spectrum disorders (22.1%). Fifteen patients who refused treatment or were nonadherent served as a comparison group. After a median of 10.8 weeks, aripiprazole, olanzapine, quetiapine, and risperidone were

each associated with rapid and significant increases in body composition, whereas metabolic changes were less uniform. Average weight gain was 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone, and 4.4 kg with aripiprazole compared to 0.2 kg in the comparison group. Olanzapine and quetiapine were associated with increases in total cholesterol, triglycerides, non–high-density lipoprotein (HDL) cholesterol, and ratio of triglycerides to HDL cholesterol. With risperidone, triglyceride levels increased significantly. With aripiprazole and in the comparison group, no significant metabolic changes were detected. With quetiapine, there were modestly higher incidence rates of hyperglycemia and the metabolic syndrome (which can include central obesity, reduced HDL cholesterol, raised blood pressure, fasting glucose, and triglycerides, depending on which definition is used), while with olanzapine there were higher incidence rates. Changes in body composition parameters were not dose-dependent in the aripiprazole, olanzapine, or quetiapine groups but were significant with risperidone at doses greater than 1.5 mg/d. There also were greater increases in total cholesterol and non-HDL cholesterol if patients were treated with greater than 1.5 mg/d of risperidone or 10 mg/d of olanzapine. Lipid abnormalities predominated over glucose abnormalities after short-term exposure (triglycerides and ratio of triglycerides to HDL cholesterol may be more sensitive than glucose and insulin for the early identification of worsening insulin resistance), but the metabolic syndrome and diabetes rarely developed. Interestingly, pubertal status was unrelated to metabolic changes in any antipsychotic medication group. However, this was a short-term study with a nonrandomized design and flexible dosing that allowed comedications and had a small comparison group consisting of patients who refused to be included or were nonadherent to treatment. Unfortunately, the authors do not comment on whether or not any of their findings were diagnosis-specific. It is unclear whether children with psychotic disorders are more prone to cardiometabolic effects than children with bipolar disorder or pervasive developmental disorder who are taking one of these antipsychotics. It is also important to note that risperidone was the only drug tested that had a sufficient number of subjects to permit a real test of a dose effect. Since a dose effect was indeed found with risperidone, this suggests that dose effect may be an important issue and should be further explored.

In the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study in 2008,[16] the efficacy and safety of 2 SGAs (olanzapine and risperidone) were compared with those of an FGA (molindone plus prophylactic benztropine treatment) in the treatment of early-onset schizophrenia and schizoaffective disorder. No significant differences were found among treatment groups in response rates or magnitude of symptom reduction. Youth treated with olanzapine gained an average of 6.1 kg, and those treated with risperidone gained 3.6 kg. Those treated with molindone did not have any body mass changes, but they did have more self-reports of akathisia. The olanzapine group also showed increases relative to the other groups in total cholesterol, low-density lipoprotein cholesterol, and insulin levels. Of note, random assignment to olanzapine was discontinued due to interim data showing a greater increase in weight without greater evidence of efficacy. This was a short-term study with a small sample size and no comparison group. The decision to provide prophylactic benztropine treatment with molindone may have minimized differences in EPS.

In a 2008 European study, Fleischhaker et al[17] evaluated youth for long-term weight gain associated with clozapine, olanzapine, and risperidone. The weight and body mass index of initially hospitalized patients treated with these SGAs were prospectively monitored for 45 weeks. Weight gain was alarmingly high, with an average gain of 16.2 kg with olanzapine, 9.5 kg with clozapine, and 7.2 kg with risperidone. At 25 to 29 weeks, the weight gain with risperidone reached a plateau, but not with the olanzapine and clozapine groups. This was a small sample size, and most patients were exposed to previous treatment, especially in the clozapine group.

In 2007, Wonodi et al[18] looked at tardive dyskinesia in children treated with SGAs. Eleven of 118 youth (9%) exhibited tardive dyskinesia (including 5 of 81 receiving SGAs only) compared to 0 of 80 in the antipsychotic-naive group, and the risk seemed to increase with duration of treatment. The sample size was small, but there was a healthy comparison group. Comedications were allowed in this study, however.

Finally, we would like to draw attention to 2 articles published in 2008[19] and 2009[20] in the *Journal of the Canadian Academy of Child and Adolescent Psychiatry* that reviewed the literature on ziprasidone and aripiprazole, 2 of the newer SGAs. The first of these reviews[19] found 2 prospective, randomized trials and 5 open-label prospective studies for ziprasidone in children and adolescents. Ziprasidone appears to have a low potential for EPS and is associated with less weight gain (in one study it was similar to placebo, and in another the ziprasidone group lost weight).

In the second review,[20] 4 prospective randomized controlled trials and 9 open-label prospective studies were found for aripiprazole. The incidence of EPS was notable in most studies (incidence range, 8%–28%), although the authors noted that these reactions still did not appear as frequently or to the same degree of severity as with high-potency FGAs. In all 4 randomized controlled trials, there was no significant increase in body mass index. In 1 open-label study, weight gain appeared to be associated with higher dose and longer treatment duration. In a contrasting study, some patients lost significant weight when switched from another SGA to aripiprazole. In the few studies that looked specifically at metabolic parameters, there were no significant changes.

DISCUSSION

Our review suggests that SGAs are at least as effective as FGAs and that side effect profiles differ between and within

each class. Safety and tolerability may depend on one's perspective. We are particularly concerned about long-term outcomes of patients taking SGAs for years—common for those with primary psychotic disorders. There is relatively less experience with SGAs because they have been available for 2 decades or less (with clozapine being the exception).

It is important to note the limitations of this review, in particular those related to the methods in which this review was conducted. First and foremost, only English-language articles were included, and so we quite likely have missed a large portion of relevant data from around the world. In using a MEDLINE search via PubMed, we attempted to use keywords (and in various combinations) that we felt would best reflect the questions pertaining to safety, tolerability, and effectiveness of antipsychotics. However, there may have been other keywords and combinations that we could have used to retrieve even more literature relevant to our subject. We also recognize that since this review was conducted, new data have quite likely surfaced that may strengthen or challenge our findings or perhaps have raised new questions.

Many of the studies in this review are short-term, have small sample sizes, and/or are not randomized controlled trials. This is especially true of the child and adolescent studies, which included two 8-week trials, one 12-week trial, a 45-week trial (with N = 33 and nonrandomized), and a 2-year study looking at tardive dyskinesia. The length of the trials may be especially important as there is evidence to suggest that continued improvement with antipsychotic treatment can be delayed for many months.

This review suggests that SGAs in general, with differences between specific medications, are more associated with weight gain and metabolic-associated problems and FGAs are more associated with EPS (although in some studies excessive doses of the comparator FGA has been used, perhaps increasing frequency or severity of EPS). Effects such as weight gain or increases in blood glucose, triglycerides, and cholesterol may not be subjectively intolerable, at least not in the short term, compared to dystonias, parkinsonism, akathisia, and tardive dyskinesia. EPS, whether short-term or long-term, can be distressing, stigmatizing, and debilitating (even life-threatening in the case of laryngeal dyskinesia). It is difficult to weigh these against morbidity and mortality as a result of obesity, hyperlipidemia, impaired glucose tolerance, and diabetes mellitus, which can lead to or contribute to coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some types of cancer. In addition, children and adolescents may be particularly vulnerable to both EPS and metabolic changes with all antipsychotic medications.[3]

Unfortunately, to our knowledge the current literature does not comment on whether this vulnerability is present in all youth aged 18 or 19 years and under or prepubertal children versus adolescents, or if specific diagnoses make any difference. Another important consideration is that obesity has been increasingly cited as a major health issue in recent decades for all ages. To our knowledge, no studies have addressed the question of whether the observed weight gain is a direct result of this growing trend in obesity in society, or the medications themselves, or a combination of the two. We believe these to be important areas for further exploration.

We also question the validity of grouping the antipsychotics into 2 types. This is a gross oversimplification in FGAs, a group that includes antipsychotics of different potencies, which greatly affects side effect profiles. SGAs are arguably more heterogeneous, with varying affinities for dopamine, serotonin, and other receptors, resulting in varying mechanisms of action and side effect profiles and making comparison difficult.

It is also important to consider the underlying mechanisms for individual patients developing metabolic changes or EPS while on antipsychotics. It is well known that there are remarkable interindividual differences of antipsychotic-induced weight gain, even some patients showing no change. It is generally accepted that genetic factors play an important role.[13]

The underlying causes of lipid abnormalities and abnormalities in glucose metabolism, however, are unclear. One possible mechanism may be increased insulin resistance as a result of antipsychotic-induced weight gain. In the general population, the association between weight gain and both hyperlipidemia and risk of diabetes is well established. A direct effect of antipsychotics on insulin secretion has not been excluded either.[9,21] Some studies also have suggested a relationship between serotonergic antagonism in SGAs and a reduction in insulin sensitivity. However, many reports show that hyperglycemia tends to occur within 6 weeks after the beginning of treatment with an SGA, and most new-onset cases are reversible upon discontinuation of the SGA, suggesting an independent drug-related mechanism. Also, the prevalence of type II diabetes in drug-naive patients with schizophrenia is estimated to be 3 times higher than in the general population, suggesting a genetic predisposition.[21]

Differences among individuals also exist in the likelihood of developing tardive dyskinesia. It has been suggested that such differences may be due to genetic polymorphisms that code for D_2 receptor binding site affinity or to prior exposure to environmental toxins.[22]

CONCLUSIONS

It is clear that there are more large-scale, randomized controlled trials done in adults as compared to youth, which tend to be small and short-term studies. In this review, 6 adult studies were analyzed in detail. A summary of the data suggests that there may be a lower association of weight gain and diabetes with ziprasidone, aripiprazole, and haloperidol, as compared to olanzapine, clozapine, quetiapine, and risperidone (which has also demonstrated some dose-dependent effects). Also, there may be less difference than originally thought concerning frequency of EPS among these medications. All of these antipsychotics, including perphenazine, are similarly efficacious in treating psychosis, with the exception of clozapine demonstrating significantly more effectiveness.

Although the studies on youth tend to have fewer subjects (and large age ranges of 4–19 years) and are short-term in comparison to the adult studies, the data reviewed from 5 studies suggest that, in youth, olanzapine may be associated with the greatest weight gain, EPS and metabolic changes are quite prevalent, and the antipsychotics studied seem to be similarly effective for their various indications in these studies.

It is difficult to definitively compare the long-term safety of SGAs and FGAs. In general, trends suggest that EPS are more frequent and severe in FGAs, particularly in the higher potency drugs. By comparison, metabolic disturbances appear to be more frequent in SGAs, but perhaps less so with ziprasidone and aripiprazole (including in youth; however, there is a paucity of data).

It is known that some patients respond to one antipsychotic medication and not to another, even from the same class.[23] There is quite likely a multifactorial explanation for this preferential response to one drug over another, and perhaps in the not-too-distant future, genetic technology will help us identify patients who will respond best (and with limited adverse effects) to a specific antipsychotic.

It is important for clinicians to be aware of all that is currently available, and being developed, to treat psychiatric disorders and to not simply dismiss older medications as inferior. With any case, all clinical decisions should be made after considering the individual patient's presentation, history, and family history; the clinician's medical knowledge of and comfort level with specific disorders and evidence-based treatment options; and patient and family preferences. Regardless of treatment decisions, however, adverse events and side effects must always be monitored and properly addressed.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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