Side Effects of Atypical Antipsychotics: Extrapyramidal Symptoms and the Metabolic Syndrome

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In this article we examine the two major classes of side effects with atypical antipsychotics: extrapyramidal symptoms (EPS) and the metabolic syndrome (the triad of diabetes, dyslipidemia, and hypertension, with associated obesity). We conclude that atypical antipsychotics continue to have notable risks of EPS, particularly akathisia, and that these agents also appear to increase the risk of the metabolic syndrome, though this effect seems most marked with clozapine and olanzapine. Novel conclusions based on this review are as follows: we provide a classification scheme based on low versus high D2 binding affinity (which is, to our knowledge, a new means of classifying atypical antipsychotics); we emphasize that the akathisia risk is likely equal among agents and that tardive dyskinesia is an early, and not late, risk in treatment (a common misconception); we make the methodological point that in randomized clinical trials, there is a high risk of false-negatives regarding side effects; we raise the issue of confounding bias in epidemiological studies of metabolic syndrome; and we stress the need to compare side effects in the same studies and not different studies. Future prospective observational cohort studies must target side effects and be designed to collect and analyze data on confounding factors. (HARV REV PSYCHIATRY 2006;14:152–164.)

Keywords: antipsychotic agents, diabetes mellitus, dyslipidemia, extrapyramidal symptoms, hypercholesterolemia, metabolic syndrome, obesity, side effects

Atypical antipsychotics have been widely hailed as offering equivalent or better efficacy than traditional antipsychotics while causing fewer side effects. The benefits of atypical antipsychotics have been many, but there has recently been an increased recognition of side effects such as the metabolic syndrome. Also, real-world experience suggests that extrapyramidal symptoms (EPS) are still a concern with regard to these agents. In this review, we will examine these two major classes of side effects.

Rather than being a systematic review, this article represents an effort to provide a reasonable interpretation of some of the literature on this topic, with more attention paid to randomized data (where available) than to observational studies. At the same time, we have not discounted observational data, which can be especially relevant to a discussion of side effects. While other interpretations of this large literature are possible, we provide here what we hope will be a helpful perspective on it.

In the interest of space and readability, we do not detail every relevant study. Instead, we highlight the randomized and observational studies that are best designed to achieve direct comparisons between the side effects of...
atypical antipsychotics, with attention to methodological strengths and weaknesses. In focusing on the clinical relevance of those studies, we will try to identify whether, and then how frequently, a particular agent is associated with a side effect. We provide only limited discussion of managing side effects.

A MEDLINE search was conducted with the following keywords: antipsychotic, atypical, second generation, side effects, extrapyramidal, parkinsonism, akathisia, metabolic syndrome, diabetes, weight, cholesterol, lipids. The resulting abstracts were screened by the authors. Those that involved randomized trials or direct comparisons of two or more neuroleptics were then obtained in full text for further analyses. This procedure was supplemented by hand-searching the last ten years of three major American psychiatric journals: American Journal of Psychiatry, Archives of General Psychiatry, and Journal of Clinical Psychiatry. Available data from research posters obtained by the authors at psychiatric meetings over the past decade—if not published—were also included.

NOVEL ASPECTS OF THE CURRENT REVIEW

There have been many narrative reviews of atypical antipsychotic side effects. Yet previous reviews have not paid sufficient attention to certain important topics:

1. We provide a new classification scheme for atypical antipsychotics—one based on low versus high D2 binding affinity. While this perspective has roots in traditional views regarding typical antipsychotics, it has not, to our knowledge, previously been applied to atypical antipsychotics. The scheme proves to be a useful way to classify atypical antipsychotic agents, at least in terms of EPS side effects, as described below.

2. Our review of this literature suggests that there is a likely equality of akathisia risk among atypical antipsychotic agents.

3. We emphasize that tardive dyskinesia (TD) is an early, rather than late, risk in antipsychotic treatment (a common misconception).

4. We make the important methodological point that in randomized clinical trials (RCTs), there is a high risk of false-negatives regarding side effects.

5. We emphasize the issue of confounding bias in epidemiological studies of metabolic syndrome.

6. We stress the need to compare side effects in the same studies and not different studies.

PRELIMINARY DEFINITIONS

D2 Binding Affinity Classes

In the past, traditional antipsychotics were often divided into classes based on low versus high D2 receptor binding affinity or blockade. We suggest here that it is helpful to categorize atypical antipsychotics in a similar manner (see text box)—which may be especially relevant if one is interested in EPS differences among these agents. As shown in the text box, a number of biochemical studies suggest that aripiprazole, risperidone, and ziprasidone are potent D2 blockers (though in the case of aripiprazole, this mechanism is also influenced by some D2 agonism); clozapine and quetiapine are weak D2 blockers; and olanzapine falls into an intermediate range.1–5

| Classification of Atypical Antipsychotics Based on D2 Binding Affinity (Blockade) |
|-----------------------------------------|---------------------------------|---------------------------------|
| Low affinity                            | Middle affinity                 | High affinity                   |
| Clozapine                               | Olanzapine                      | Risperidone                     |
| Quetiapine                              | Intermediate, with exception of weight gain* | Ziprasidone                    |
| Less D2 potency                         |                                | Aripiprazole                    |
| Less 5-HT2 potency                      |                                |                                |
| Less parkinsonian EPS                   |                                |                                |
| Multiple receptor blockade effects      |                                |                                |
| More weight gain*                       |                                |                                |

*Olanzapine produces more weight gain than quetiapine—which may be due to olanzapine’s greater serotonin blockade and the potential contribution of such blockade to weight gain (in addition to histamine blockade, which occurs with both agents).

Note: In general, akathisia and tardive dyskinesia do not differ among affinity groups within either traditional or atypical neuroleptic classes. Also, weight gain is most likely related to the presence or absence of other multiple-receptor blockade, not D2 blockade.
This nomenclature is not meant to suggest that there is no other way of classifying these agents, such as the rapid-dissociation model of Seeman and Kapur.6 It can be objected that a catchall concept of “D2 binding affinity” does not do justice to the complexity of the processes associated with receptor antagonism (such as dose-dependent interactions, or speed of dissociation). However, olanzapine and risperidone have high D2 occupancy at high doses, whereas quetiapine and clozapine do not, suggesting that D2 receptor blockade in itself is a clinically relevant parameter in classifying atypical antipsychotics. The clinically relevant parameter is in vivo D2 receptor occupancy, as measured by positron emission tomography, at clinically relevant doses. Based on this parameter, we believe the literature2–7 supports the classification set forth in the text box.

Our proposed classification, while useful heuristically for some side effects, such as EPS, may not be helpful in understanding others, such as metabolic syndrome or weight gain. That does not invalidate, however; the clinical utility of the D2 binding affinity concept. We are not trying to present a single mechanism that explains all antipsychotic side effects; there is no such thing. We are suggesting, instead, that there are two broad important classes of atypical antipsychotics—EPS and metabolic syndrome—and the D2 binding affinity classification scheme applies to the EPS side effects. The scheme’s utility is that it provides a biologically supported shorthand for classifying these agents and for seeing some agents as more similar than others (e.g., clozapine and olanzapine versus risperidone and ziprasidone) in terms of EPS. Otherwise, one would have no way of organizing the specific agents, and one would end up acting as if they were equally similar or dissimilar in terms of EPS, which is not the case either empirically or biologically.

**EPS and Metabolic Syndrome Defined**

Numerous definitions of EPS have been proposed over the years, whereas the concept of the metabolic syndrome is relatively new in medicine, with a formal definition only recently proposed.8 For the purposes of this review, we will use the following definitions.

EPS are defined as including parkinsonian tremor, rigidity, akathisia, dystonia, and TD. A clinical definition of metabolic syndrome could be given as the triad of diabetes, hypertension, and hypercholesterolemia, with associated abdominal obesity and dyslipidemia. There are other definitions, however; another common one is any three of the following: central obesity (waist circumference), hypertriglyceridemia, low HDL cholesterol, hypertension, and elevated fasting plasma glucose. The underlying pathophysiology of the metabolic syndrome is thought to be hyperinsulinemia and insulin resistance.9

**Randomized Versus Observational Studies**

There are some important methodological issues that relate to any discussion of side effects. One major problem is that most RCTs do not directly compare atypical neuroleptic agents. Yet, one cannot compare side effect rates in different RCTs because those studies are randomized only within each sample, not between samples.10 In other words, each sample differs in many characteristics (clinical and demographic), with the consequence that direct comparisons of EPS rates are invalid (often called “the apples and oranges error” in epidemiology)11 due to the presence of confounding bias from other factors.12

Another major problem is that RCTs often underestimate side effects for a variety of reasons. For example, since such studies are powered to assess efficacy, they may mistakenly claim the absence of a side effect because of the lack of statistical significance.13 It is sometimes claimed that EPS do not occur because their rate is “the same as” placebo, whereas the rate (if you examine the data) may actually be much higher than placebo. Although some studies are (appropriately) reporting the absolute rates (without p values), one still sees an underestimation of relative risk in the interpretations of some RCTs. For example, in a pooled report of two clinical trials of ziprasidone for schizoaffective disorder, the authors reported that “the incidence of individual adverse events was generally low in all treatment groups.”14 In one of the studies, however, four patients in each of two ziprasidone dose groups (8 of 49 patients overall, or 16.3%) experienced akathisia, versus no patients on placebo (n = 19); these data are best presented as relative risks with confidence intervals, which in the case of this study would yield a relative risk of infinity (16.3%/0%), which is large. With those sample sizes, and when comparing 16.3% versus 0%, the differences are not statistically significant (p = .15). But statistical significance is irrelevant here; a notable numerical difference exists.

Various other problems also make it difficult to identify EPS and to compare their frequency with different medications. RCTs often do not carefully measure side effects, leading to “information bias”15—a problem that is especially relevant to akathisia, which is often mistaken for agitation and can be difficult to detect. Further, due to the highly select group of subjects who qualify for, and agree to be in, RCTs, such samples often experience fewer side effects, undercutting any efforts to generalize from the results.16 That is, psychiatric research studies often exclude as potential subjects those who have risk factors for side effects, such as medical comorbidities, substance abuse, and psychiatric comorbidities. Moreover, certain groups, like minorities and children, are less likely to participate in research, yet often are more sensitive to side effects.16 Thus, RCTs generally reflect side-effect rates in middle-aged, healthy adults,
a group that is unrepresentative of much of the psychiatric population.

A classic example of the utility of observational studies in identifying side effects that were neglected by RCTs (due to lack of generalizability and information bias) is sexual dysfunction. Unfortunately, observational reports often fail to use sensitive instruments (like validated rating scales) to detect EPS. Since the main drawback of observational research is the effect of confounding variables, the use of regression models is an important analytic technique to further clarify side-effect risks.

The CATIE Study

The recent CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study (http://www.catie.unc.edu) has been a major advance. Because the study is randomized, it minimizes confounding bias, and because at least part of the study is unblinded (in Phase 2, when patients may receive an open-label trial of clozapine), generalizability to the real world of patient care is enhanced. It also directly compares multiple atypical neuroleptics, as well as the typical neuroleptic perphenazine. This type of study is ideal for assessing side effects. And since the CATIE results have the least methodological limitations of all the available studies on the side effects of neuroleptics, we make reference to the results throughout this article.

Given that the CATIE data are so informative regarding side effects, it is unfortunate that the published article utilizes \( p \) values instead of relative risks and confidence intervals to describe those side effects more accurately. For instance, due to a \( p \) value of .47 for comparisons across all the agents, the CATIE report deemphasizes the higher parkinsonism rate observed with olanzapine and risperidone compared to quetiapine—although the study was not powered for such differences. Such false-negative interpretations are difficult to justify given the authors’ statistical design, in which they attempted to use hypothesis-testing methods in the absence of clear hypotheses. Thus, in our review, we have ignored all \( p \) values from the CATIE study’s side-effect assessments and have, instead, converted data (where needed) to relative risks and confidence intervals. Further, it should be noted that since CATIE was a large \( (n = 1460) \), randomized study, confounding factors should have been minimized by randomization. However, due to the preferential nonrandomized allocation of 212 subjects with TD to the nonperphenazine groups, confounding bias regarding EPS could have been introduced. In our reading of the methods section, this confounding factor of TD status was corrected in the study’s efficacy analyses, but not in the study’s side-effect comparisons.

PART I: EXTRAPYRAMIDAL SYMPTOMS

Based on available RCTs, atypical neuroleptics have generally considered to be less likely to produce movement disorders than conventional neuroleptics. Yet recent data from the CATIE study throw this view into some doubt. Further, the occurrence of EPS varies among atypical agents, and this variation may be related to each drug’s unique pharmacology, such as striatal dopamine (D2) and serotonin 2A (5-HT2A) receptor occupancy rates.

Biochemistry of EPS

The risk of developing EPS has been shown to increase when D2 receptor occupancy reaches 70 to 80%. Additionally, some studies suggest that the occupancy of 5-HT2A receptors may mitigate EPS induced by high rates of D2 occupancy. Clozapine and quetiapine have the lowest D2 occupancy rates at therapeutic doses and appear to be associated with fewer EPS. Further, EPS rates with both clozapine and quetiapine do not appear to be dose dependent. In contrast, risperidone and olanzapine have higher striatal D2 occupancy rates and are associated with more EPS. Although risperidone and olanzapine have high 5-HT2A affinities, at higher doses they appear to induce a greater risk for EPS. These findings are consistent with animal models that support the positive relationship between D2 occupancy, EPS, and therapeutic effect.

Acute Dystonias

Dystonic reactions (acute muscle spasms, usually of the head or neck) occur shortly after initiation of drug treatment; 50% occur within 48 hours, 95% within 96 hours. Risk factors include family history of dystonia, prior dystonic reactions, recent history of cocaine or alcohol use, young age, and male gender. Acute dystonic reactions occur with atypical neuroleptics, though probably less often than with typical neuroleptics.

Parkinsonism

Medication-induced parkinsonism is characterized by rigidity, resting tremor, masked faces, generalized slowing of movements, and cogwheel rigidity. Mental abnormalities associated with parkinsonism include emotional blunting, apathy, anhedonia, and social withdrawal. Atypical antipsychotic agents have repeatedly been demonstrated to have lower rates of parkinsonism than typical neuroleptics, though absolute rates are not minimal. For instance, in one RCT, EPS emerged in 55% of patients with haloperidol but was also noted in 26% with olanzapine. Other randomized evidence suggests similar rates with risperidone but lower...
rates with quetiapine (in the 5–10% range).\textsuperscript{31} Clozapine also appears to have low parkinsonism rates.\textsuperscript{31–33}

Clinicians sometimes assume that risperidone should have more parkinsonism than olanzapine—due to the presumed higher D2 binding affinity with risperidone. But both agents have similar D2 blockade binding affinity at higher doses.\textsuperscript{2} If there is lower parkinsonism with olanzapine compared to risperidone, it might be due to the anticholinergic, instead of D2, effects of olanzapine. Empirical head-to-head studies have not demonstrated lower parkinsonism with olanzapine compared to risperidone, though some suggestion can be found in a few available studies. In one observational report, the parkinsonism rate with olanzapine was 1 out of 20 (5%), versus 4 out of 25 (16%) with risperidone.\textsuperscript{34} In another long-term comparison, with 29 patients, parkinsonism rates were the same.\textsuperscript{35} A clinical trial involving 329 patients treated with risperidone versus olanzapine for bipolar disorder also found that EPS rates were similar.\textsuperscript{36}

In the CATIE study, Simpson Angus EPS scores were abnormal in 6% of perphenazine-treated patients versus 8% of those treated with risperidone or olanzapine,\textsuperscript{18} thus conflicting with the usual view that typical neuroleptics have less parkinsonism than traditional neuroleptics. However, quetiapine had lower Simpson Angus EPS abnormal scores (4%), though not much different than perphenazine. This lack of difference can be attributed, in part, to the randomization of only persons without TD to the perphenazine group, since TD has been associated with elevated rates of EPS.\textsuperscript{37} It is also notable that EPS with perphenazine may have been more severe than with atypical neuroleptic agents, as suggested by the perphenazine group’s higher discontinuation rate due to EPS (8%, vs. 2–4% with the other agents).\textsuperscript{18} When comparing quetiapine to risperidone or olanzapine, however, the difference was notable, with 93% more parkinsonism with olanzapine or risperidone compared to quetiapine (RR = 1.93; 95% CI = 0.98, 3.81).

**Acute Dyskinesias and Tardive Dyskinesia**

Schizophrenia is associated with a spontaneous TD rate in otherwise healthy young adults of about 0.5% per year,\textsuperscript{38} in contrast to the normal population and patients with affective disorders, who do not experience spontaneous TD below age 60. After age 60, in the non–psychiatrically ill general population, spontaneous TD occurs at about 0.5% per year. These natural history factors need to be kept in mind when assessing TD risk related to neuroleptic medications.

It is crucial to note that the risk of TD is highest in the first five years of treatment with typical neuroleptics, and that the incidence of TD decreases after the first five years. Because the prevalence increases, however, clinicians sometimes confuse the issue. For instance, in a carefully conducted long-term TD study, 398 patients with psychotic disorders (mostly schizophrenia) were followed prospectively with TD rating scales every three months for eight years.\textsuperscript{39} Almost 20% of patients developed TD in the first three years of treatment. After the first three years, however, the TD rate plateaued at about 1% per year. Given that the spontaneous TD rate in schizophrenia is about 0.5% per year, the added risk due to neuroleptics is about 0.5% per year after the first three years of treatment. Thus, the incidence of TD, as shown in Figure 1, does not increase linearly, but asymptotically, over time, with the highest risk in earlier time periods.

In the elderly, one must add that the risk of TD is even higher. In the first year of treatment with a traditional neuroleptic, the risk of TD in elderly persons with schizophrenia has been shown to be 29%, and rises to about 63% after three years.\textsuperscript{40} The elderly patient has about as much TD risk in one year as a young adult faces in five years.

![FIGURE 1. Real versus presumed courses of tardive dyskinesia. Source: Ghaemi SN. Mood disorders: a practical guide. Philadelphia: Lippincott, Williams, & Wilkins, 2003 (reprinted with permission).](image-url)
It has been suggested that there are not enough long-term data on atypical agents to assess TD risk. However, based on the data provided above concerning traditional neuroleptics, one to three years of data should provide evidence on the highest risk period. For risperidone, RCT data ($n = 3298$) in the first year of treatment for schizophrenia indicated a TD incidence of 0.6% versus 2.7% with haloperidol. For olanzapine, RCT data ($n = 1192$) in the first year of treatment for schizophrenia found a TD incidence of 0.52% versus 7.45% with haloperidol ($RR = 11.86; 95\% CI = 2.30, 61.14$); the risk of TD was consequently almost 12 times higher with haloperidol than with olanzapine. TD rates with risperidone and olanzapine were equal to the spontaneous rate in schizophrenia.

Risk of TD with risperidone has also been studied in the high-risk elderly population with schizophrenia. The TD rate is about 5% with risperidone at nine months of treatment, versus about 30% with haloperidol (total $n = 122$).

Since for ethical reasons, the CATIE study preferentially excluded those with TD from being randomized to perphenazine, the comparative data from that study regarding TD with typical versus atypical neuroleptic agents is weighted in favor of perphenazine. With that caveat, in one year of follow-up, all agents had similar abnormal Abnormal Involuntary Movement Scale scores—in the 13–17% range. In the CATIE study, 212 patients (14.5% of the total sample of 1460 patients) had TD upon entry into the study. These rates thus suggest a stable frequency of TD, neither improved nor worsened, with neuroleptic treatment in the CATIE study. Post hoc analyses of the TD subgroup determined that they also had higher rates of akathisia, parkinsonism, and psychopathology. Substance abuse predicted TD, but metabolic syndrome features of diabetes or hypertension did not. These associations were adjusted in a regression model for anticholinergic use. Otherwise, since the study was randomized, confounding factors should not have had a major impact on the results.

Akathisia

Akathisia is poorly understood and difficult to diagnose, and some investigators question whether akathisia should be categorized along with other EPS since its neurobiological mechanisms are unknown. Yet akathisia occurs mainly with drugs that cause other EPS. Indeed, there are neuroanatomical hypotheses for akathisia that involve extrapyramidal areas (like the striatum) and that might justify viewing akathisia as a subtype of EPS.

Akathisia is highly associated with noncompliance and is easy to confuse with other conditions. In contrast to parkinsonian side effects, akathisia is not responsive to anticholinergic manipulations. Rather, akathisia can be improved with beta-blockers, benzodiazepines, or, most importantly, by reducing the dose. Hence, akathisia rates do not differ between neuroleptic agents with low versus high binding affinity. Further, the addition of anticholinergic drugs is usually not helpful.

Akathisia can be intermittent and has a subjective component, thus making it difficult to detect. Akathisia represents about one-half of all cases of EPS. Consequently, if akathisia is missed, half of all EPS cases can be misinterpreted as other conditions. Conservative estimates indicate that about 25% of patients treated with traditional neuroleptics develop akathisia. In about half the cases of akathisia, its onset is delayed, not occurring until after the first month of treatment, though most cases occur within three months. (There are also rare cases of extremely delayed and chronic, or “tardive,” akathisia.) Subjectively, akathisia consists of an intense feeling of dysphoria and extreme anxiety, as occurs with panic attacks. Objectively, it is associated with observed physical restlessness and an inability to sit still. This restlessness is not necessarily constant, and it can be merely intermittent, occurring for a few hours or less each day. Consequently, akathisia cannot be ruled out based on lack of observed physical restlessness during an office visit.

One of the prominent researchers on akathisia in the 1970s and 1980s, Theodore Van Putten, conducted a number of studies in which up to 10% of patients with schizophrenia experienced worsening psychosis driven by akathisia. Identifying psychosis due to akathisia was crucial since the psychotic symptoms improved with lowered antipsychotic dosing, whereas in idiopathic psychosis the dose would need to be increased.

When missed or ignored, akathisia can lead to suicidality. Patients sometimes fail to recognize that their intense dysphoria, anxiety, and restlessness may be a side effect. Instead, these symptoms are more frequently attributed to their depressive or manic syndromes, leading to demoralization and sometimes suicide.

Unlike parkinsonism, akathisia rates appear similar among atypical antipsychotics. Drugs with low binding affinity, such as clozapine and quetiapine, have the reputation of causing minimal EPS, yet a blind review using the Extrapyramidal Rating Scale found akathisia to be present in 39% of clozapine-treated patients ($n = 23$) compared to 45% of patients treated with typical neuroleptic agents ($n = 29$), with the severity of akathisia (based on the ERS) being comparable in the two groups. Similar findings were reported in another blind review of 151 patients with schizophrenia participating in a multicenter study; akathisia was as common with clozapine as with chlorpromazine, whereas parkinsonism was less common with clozapine.

One observational study that compared EPS in patients treated with clozapine ($n = 19$), risperidone ($n = 9$),
or typical neuroleptics ($n = 22$) found the prevalence of akathisia to be 10.5% with clozapine, 11.1% with risperidone, and 22.7% with typical neuroleptic agents. Parkinsonian symptoms were reported to be 0% with clozapine, 11.1% with risperidone, and 31.8% with typical neuroleptics.

Along the same lines, RCTs repeatedly report akathisia rates with olanzapine in the 14–16% range—which again, though lower than with haloperidol (35–52%), is still not insubstantial. New randomized data with aripiprazole also report an akathisia rate of 10%, compared to 18% with haloperidol.

In summary, the literature prior to the CATIE study indicates that akathisia rates tend to run in the 10–20% range with atypical neuroleptic agents, which is lower than the 20–52% with typical neuroleptics but still high enough to remain a common problem.

The CATIE study confirms the impression that akathisia is still a problem with atypical neuroleptic agents, though at lower rates than indicated by much of the above literature. In CATIE, using the Barnes Akathisia Rating Scale, abnormal scores were observed in 5% of patients treated with olanzapine or quetiapine, 7% with risperidone or perphenazine, and 9% with ziprasidone. The rates were, again, similar when comparing atypical neuroleptics and perphenazine, but we should keep in mind that preferential distribution of TD patients away from the perphenazine group would lead to an underestimation of akathisia in that group since TD is associated with akathisia. Comparing the two extreme rates, there appeared to be more akathisia with ziprasidone than with olanzapine, though the confidence intervals are wide enough, mainly due to smaller sample size with ziprasidone ($n = 185$, vs. $n = 336$ for olanzapine), to limit the precision of this estimate (RR = 1.71; 95% CI = 0.85, 3.46).

PART II: METABOLIC SYNDROME

Persons with schizophrenia are more likely than the general population to develop metabolic diseases such as dyslipidemia and type II diabetes. Relevant risk factors include poor diet, inadequate physical exercise, unhealthy lifestyles, and lack of financial, medical, and social resources.

Drugs are now also implicated in this disease process. In 2003, the U.S. Food and Drug Administration required manufacturers of atypical antipsychotics to update product labeling to include a warning about a possible link with type II diabetes.

Weight Gain

Nearly one-half of adults in the United States currently meet criteria for being overweight (body mass index [BMI], 25 to 29.9) or obese (BMI > 30). Obesity is a known risk factor for hypertension, elevated triglycerides, insulin resistance, and diabetes mellitus. As adiposity increases, particularly excess abdominal fat, so does the occurrence of metabolic abnormalities. In the Framingham Offspring Study cohort, small increments of weight gain led to significantly increased occurrence of type II diabetes. Even modest increases in BMI (1.0) show a positive linear correlation with increased mortality from cardiovascular disease.

Head-to-head comparison studies indicate that clozapine appears to induce the greatest weight increase among atypical antipsychotics, followed by olanzapine and quetiapine, in that order. A recent meta-analysis of short-term clinical trials (mostly about one month in duration) reported the mean weight gain was greatest with clozapine at 4.45 kg, followed by olanzapine at 4.15 kg, risperidone at 2.10 kg, and ziprasidone at 0.04 kg. Due to insufficient data, quetiapine was not included in the analysis.

Follow-up studies have provided more data on the extent of the problem. In one RCT of clozapine use for one year or more, 58% of patients gained at least 10% of their baseline weight. Calculations derived from the Framingham Heart Study suggest that treatment with clozapine may reduce by 416 the number of deaths due to suicide in a population of 100,000 schizophrenic patients. Additional calculations reveal, however, that approximately 492 deaths are likely to occur in the same population as a result of cardiovascular disease associated with clozapine-induced weight gain.

BMI increases of almost 10% and weight gain in excess of 10 kg have been observed after one year of olanzapine treatment at commonly prescribed doses. Furthermore, a review of four studies (3000 patients) indicated that patients treated with olanzapine experienced a mean increase of 11.79 kg with moderate doses (12.5–17.5 mg/d). Overall, 40.5% of olanzapine patients gained more than 7% of baseline weight. In their major clinical trials, risperidone and quetiapine are also associated with weight gain compared to placebo, though apparently less severe in magnitude than in the case of clozapine or olanzapine (as described above). Of all the atypical antipsychotics, aripiprazole and ziprasidone appear to have the lowest weight-gain liability.

Some studies of olanzapine and quetiapine report no weight gain at one-year follow-up. However, an important methodological issue in such studies is that the majority of patients dropped out of follow-up (often due to weight gain) before one year and thus were not included in the survival curve at end point. The follow-up data are consequently not helpful in this particular instance.

The CATIE study observed much more weight gain (BMI increase by 7% of baseline) with olanzapine—30% within the follow-up period (up to one year)—than with other agents (quetiapine, 16%; risperidone, 14%; perphenazine, 12%; ziprasidone, 7%). It is notable that the typical neuroleptic...
perphenazine was not clearly different in this analysis than risperidone or quetiapine, though ziprasidone seemed notably the lowest.

Dyslipidemia

The first comparative RCT designed to address dyslipidemia with atypical antipsychotics was a prospective, randomized, double-blind, 14-week trial of clozapine, haloperidol, olanzapine, risperidone, and haloperidol in hospitalized patients \((n = 157)\) with schizophrenia or schizoaffective disorder. At 8 weeks, cholesterol levels rose for clozapine \((14.7 \pm 30.5 \text{ mg/dl})\) and olanzapine \((12.3 \pm 28.1 \text{ mg/dl})\), but not haloperidol or risperidone \((-4.9 \pm 17.7 \text{ and } 4.2 \pm 29.7 \text{ mg/dl}, \text{ respectively})\). At 14 weeks, in completers, the increases for clozapine and olanzapine were even greater \((16.3 \pm 39.6 \text{ and } 20.1 \pm 26.8 \text{ mg/dl}, \text{ respectively})\); haloperidol remained unchanged \((-4.4 \pm 25.2 \text{ mg/dl})\) and risperidone was somewhat higher, although the small subsample \((n = 14)\) and the wide standard deviation at this point in the study \((9.2 \pm 36.7 \text{ mg/dl})\) precluded a definitive judgment. Thus, this RCT found evidence of dyslipidemia with clozapine and olanzapine, not with haloperidol, and likely not with risperidone. The unavailability of laboratory results for the complete group of randomized patients \((\text{unavailable for }46 \text{ subjects})\) is a limitation of this study, as is its small sample size for a multiple-arm study.89

Most observational studies do not pay adequate attention to confounding variables, with the consequence that the reported conclusions vary markedly. In a study of clozapine \((n = 117)\), triglyceride levels rose from 184.6 mg/dl to 273.4 mg/dl in men and from 164.9 mg/dl to 223.3 mg/dl in women.90 These results are adjusted only for age, weight, gender, daily antipsychotic dose, and concurrent medications. Similar results were found in another study comparing clozapine to typical neuroleptics, corrected only for age and gender.91

A large case control study in the United Kingdom \((n = 9226)\) similarly found a fivefold higher odds ratio of dyslipidemia with olanzapine compared to no treatment, and a threefold higher rate with olanzapine compared to typical antipsychotic treatment. No such associations were found with risperidone.92 However, the study is adjusted only for age, gender, concomitant medications, and presence of other medical illnesses \((\text{e.g., diabetes})\) associated with dyslipidemia. Other studies also suggest that olanzapine does tend to be associated with dyslipidemia.93,94

In a nonrandomized study in which 36 non-obese patients on clozapine, olanzapine, or risperidone were matched for BMI, fasting total cholesterol levels were higher with clozapine \((155.6 \pm 31.2 \text{ mg/dl})\) and olanzapine \((182.6 \pm 62.5 \text{ mg/dl})\) than risperidone \((129.1 \pm 26.7 \text{ mg/dl})\).95 HDL was somewhat higher, and LDL somewhat lower, with risperidone, but these differences were not as marked as the overall total difference. Triglyceride levels were notably higher with clozapine \((193.5 \pm 145.4 \text{ mg/dl})\) and olanzapine \((205.9 \pm 147.1 \text{ mg/dl})\) than risperidone \((73.6 \pm 17.4 \text{ mg/dl})\). This study was prospective and matched for BMI, but not corrected in statistical analysis for other important confounding factors.

All of the above nonrandomized studies suffer from only partial correction, at best, for confounding bias. They usually correct for age and gender, and sometimes for BMI, but frequently not for other important confounding factors such as diet, exercise, concomitant medications, and familial risk. Again, such confounding bias limits the validity of these studies and likely accounts for any divergent results.

Turning to quetiapine, the pivotal RCTs indicate a 17% increase in triglycerides along with an 11% increase in total cholesterol levels versus placebo.96 Head-to-head epidemiological comparisons of risperidone versus olanzapine, though limited methodologically, report less dyslipidemia with risperidone.97,98 Thus, quetiapine and risperidone appear to have some impact on dyslipidemia, though perhaps less so than clozapine and olanzapine.

To date, RCT data with ziprasidone and aripiprazole do not find evidence of dyslipidemia.54,99,100

In the CATIE study, total cholesterol was elevated most with olanzapine \((by \ 9.7 \pm 2.1 \text{ mg/dl})\) during the follow-up period \(up \text{ to one year)}\), somewhat with quetiapine \((by \ 5.3 \pm 2.1 \text{ mg/dl})\), but not with risperidone \((decreased \ by \ 2.1 \pm 1.9 \text{ mg/dl})\) or perphenazine \((minimally \ increased \ by \ 0.5 \pm 2.3 \text{ mg/dl})\), and was notably improved with ziprasidone \((decreased \ by \ 9.2 \pm 5.2 \text{ mg/dl})\).18 Triglycerides were elevated the most with olanzapine \((by \ 42.9 \pm 8.4 \text{ mg/dl})\), somewhat with quetiapine \((by \ 19.2 \pm 10.6 \text{ mg/dl})\), marginally with perphenazine \((by \ 8.3 \pm 11.5 \text{ mg/dl})\), not at all with risperidone \((decreased \ by \ 2.6 \pm 6.3 \text{ mg/dl})\), and improved with ziprasidone \((decreased \ by \ 18.1 \pm 9.4 \text{ mg/dl})\). The CATIE study thus strongly argues against the FDA's warning about dyslipidemia with atypical neuroleptics as a class. The study suggests that risk exists with olanzapine and somewhat with quetiapine, but not with risperidone. Moreover, ziprasidone may actually have a salutary effect on lipid profile.

Diabetes Mellitus

In schizophrenia, the risk of developing type II diabetes is two to three times greater than in the general population; in fact, the lifetime prevalence of type II diabetes is estimated to be at least 15% among patients with schizophrenia.101,102 A recent study of 345 hospitalized patients with bipolar disorder found the prevalence of diabetes to be 9.9%.103 Cigarette smoking, poor diet, physical inactivity, and obesity are more common among patients with schizophrenia than the general population, and all of these factors are known to increase the risk of type II
diabetes. Several documented cases of insulin and glucose resistance were noted by physicians prior to the introduction of neuroleptics. In addition, some studies have found that the prevalence of type II diabetes, impaired glucose tolerance, and insulin resistance are more common in schizophrenic patients not receiving antipsychotic treatment than in those taking such drugs.

While the above features of schizophrenia may account for some cases of type II diabetes within the population, a growing body of literature implicates the use of atypical antipsychotics, leading to a 9% increase in type II diabetes versus conventional antipsychotic agents. It remains to be determined whether side effects like weight gain lead to the increased risk, or whether there is a direct impact on insulin resistance and impaired glucose tolerance. The latter mechanism appears to be relevant. One study of schizophrenic patients treated with clozapine, olanzapine, risperidone, or a typical antipsychotic found that glucose and insulin levels were increased, independent of increased adiposity, only in patients treated with atypical antipsychotics (versus a no-treatment control group). Again, as with dyslipidemia, attention needs to be paid to potential confounding factors in interpreting any observational or epidemiological studies.

At one level, case reports provide a first line of evidence regarding the risk of diabetes with atypical antipsychotics. A study pooling the results from the U.S. Food and Drug Administration MedWatch surveillance system and other published case reports found new-onset diabetes associated with atypical antipsychotics in 242 clozapine-treated patients, 225 olanzapine-treated patients, and 78 risperidone-treated patients; the development of metabolic acidosis or ketosis in 80 clozapine patients, 100 olanzapine patients, and 26 risperidone patients; and, during hyperglycemic episodes, deaths of 25 clozapine patients, 25 olanzapine patients, and 4 risperidone patients. Another study analyzed 45 case reports of new-onset diabetes and diabetic ketoacidosis, and found that 20 were associated with clozapine, 19 with olanzapine, 3 with quetiapine, and 3 with risperidone. Noteworthy, too, is that 42% presented with diabetic ketoacidosis; 50% had no weight gain from the initiation of atypical treatment to time of event; and 59% had glucose abnormalities within the first three months of treatment, with the number increasing to 84% by six months.

In epidemiological studies, the risk of diabetes appears highest with antipsychotics having low binding affinity. In one study, the odds ratios (with confidence intervals) for comorbid diabetes in 38,632 schizophrenic patients previously diagnosed with diabetes and receiving neuroleptics was calculated to be 1.25 (1.07, 1.46) for clozapine, 1.11 (1.04, 1.18) for olanzapine, 1.31 (1.11, 1.55) for quetiapine, and 1.05 (0.98, 1.12) for risperidone. However, this study was statistically adjusted only for age and gender, and not for other, potentially important confounding factors.

The first randomized comparative study designed to assess impaired glucose tolerance, as noted above, involved 157 patients who were randomized to clozapine, haloperidol, olanzapine, or risperidone treatment—101 of whom provided blood samples. In the first 8 weeks of treatment, the fasting glucose level rose 17.1 ± 29.6 mg/dl for clozapine and 8.4 ± 17.7 mg/dl for haloperidol, but was unchanged for olanzapine and risperidone (1.9 ± 16.9 and −1.3 ± 14.9 mg/dl, respectively). In an analysis of those who completed the 14-week study, only olanzapine demonstrated elevation in plasma glucose level (14.3 ± 25.5 mg/dl). Thus, this RCT found evidence of increased risk of diabetes, at least short term, with clozapine and olanzapine, but not risperidone. Again, the unavailability of laboratory results for all randomized patients is a limitation of this study, as is its small sample size for a multiple-arm study.

In a nonrandomized study in which 36 non-obese patients on clozapine, olanzapine, or risperidone were matched for BMI, fasting plasma glucose level was higher with clozapine (97.8 ± 7.8 mg/dl) and olanzapine (95.3 ± 13.8 mg/dl) than with risperidone (88.9 ± 5.5 mg/dl) (p = 0.09). Fasting serum insulin was also higher with clozapine (11.1 ± 8.1 mg/dl) and olanzapine (10.6 ± 8.8 mg/dl) than with risperidone (4.3 ± 3.2 mg/dl) (p = 0.05). The insulin sensitivity index was lower with clozapine (3.2 ± 4.1 mg/dl) and olanzapine (4.5 ± 2.7 mg/dl) than with risperidone (0.9 ± 0.5 mg/dl) (p < 0.001). This study has the advantage of using more sensitive measures of glucose metabolism than fasting glucose levels; however, it is nonrandomized and matched only for BMI. Again, other important confounding factors—including age, concomitant medications, diet, exercise, and duration of treatment with the atypical antipsychotic agent—are not corrected in the analysis.

Laboratory studies tend to support these clinical studies. They generally find that clozapine and olanzapine, but not other atypical antipsychotics, are associated with marked increases in plasma glucose, plasma insulin levels, and insulin resistance following oral and intravenous glucose tolerance tests.

To date, RCT data with aripiprazole and ziprasidone do not find evidence of abnormal glucose metabolism compared to placebo.

In the CATIE study, blood glucose was elevated the most with olanzapine (by 15.0 ± 2.8 mg/dl), somewhat with quetiapine (by 6.8 ± 2.5 mg/dl), risperidone (by 6.7 ± 2.0 mg/dl), and perphenazine (by 5.2 ± 2.0 mg/dl), and not more than trivially with ziprasidone (by 2.3 ± 3.9 mg/dl). Hemoglobin A1C was elevated with olanzapine (by 0.41 ± 0.09 mg/dl), but not with the other agents (ranging from −0.10 to +0.08). These results again suggest that the main diabetes risks exist with olanzapine, and perhaps somewhat with quetiapine, but not with risperidone.
TABLE 1. Recommended Clinical Evaluation for Metabolic Syndrome

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or ziprasidone, both of which seem similar to perphenazine in this regard.

CLINICAL RECOMMENDATIONS

A recent consensus panel of endocrinologists, psychiatrists, and internists has made specific recommendations for assessing risk of metabolic syndrome with atypical antipsychotics (see Table 1). These consensus recommendations are consistent with our interpretation of the literature above—in particular, stronger association of metabolic syndrome with clozapine and olanzapine compared to the other agents. The CATIE data appear to suggest that quetiapine has moderate metabolic risks, that risperidone is largely free of such risks, and that ziprasidone may have some protective effect on dyslipidemia. Further, due to the direct impact of the atypical antipsychotics on insulin resistance (independent of weight gain), one must assess these effects in all potentially affected patients. And due to the risk of diabetic ketoacidosis, early attention to blood glucose levels is necessary. Ongoing monitoring of lipid profiles is also important. Given the limitations of the current literature, such monitoring makes sense for all of these agents, though special attention should be paid to clozapine and olanzapine.

SUMMARY

The initial expectation that atypical antipsychotics represented an unalloyed advance over traditional neuroleptics has been tempered with time, as continued evidence of EPS and new evidence regarding the risk of metabolic syndrome have emerged. The risk of side effects has been confused by many factors, including promotional marketing. The scientific issues of most concern—and that are not yet well recognized—are the limitations of RCTs in assessing side effects, and the impact of confounding factors in observational studies. The literature needs to be assessed with these methodological issues in mind. Future research should consist of well-designed, prospective, observational, cohort studies targeted specifically at side effects and designed to collect and analyze data on confounding factors.

REFERENCES


89. Lindemann J, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia...