Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE STUDY OF OBESITY

Antipsychotic medications are an important component in the medical management of many psychotic conditions. With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol).

Because of the close associations between obesity, diabetes, and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between the SGAs and the development of these major CVD risk factors. To gain a better understanding of this relationship, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference 19–21 November 2003 on the subject of antipsychotic drugs and diabetes. An eight-member panel heard presentations from 14 experts drawn from the areas of psychiatry, obesity, and diabetes. Presentations were also made by a representative from the U.S. Food and Drug Administration (FDA) and by representatives from the AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer pharmaceutical companies. In addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed, English language clinical studies published in this area, as well as additional articles from animal studies; other papers and abstracts were reviewed at the conference.

With this information, the panel developed a consensus position on the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, prediabetes, and type 2 diabetes in the populations in which the SGAs are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipedemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipedemia, and diabetes?

1. WHAT IS THE CURRENT USE OF ANTIPSYCHOTIC DRUGS?

— Antipsychotic medications (Table 1) are the mainstay of treatment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced ~50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence.

The effort to find more effective medications with fewer and less-severe side effects led to the development of the SGAs, often referred to as the "atypical antipsychotics." SGAs have fewer or no extrapyramidal side effects at clinically effective doses. Many of these newer medications are also more effective than the older agents at treating the negative, cognitive, and affective symptoms of psychotic illnesses.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles. One of them, clozapine, is clearly the most effective antipsychotic. However, clozapine is only indicated after other medications have failed or in patients at high risk for suicidal behavior, largely because it can cause agranulocystosis.

In general, SGAs are better tolerated and more effective than the FGAs. Aside from clozapine, they have become the first-line agents for their indicated use and

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Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FDA, Food and Drug Administration; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

Table 1—*Antipsychotic medications*

	Generic name	Trade name	Year approved
Commonly used FGAs	Chlorpromazine	Thorazine	—
	Perphenazine	Trilafon	—
	Trifluoperazine	Stelazine	—
	Thiothixene	Navane	—
	Haloperidol	Haldol	—
	Fluphenazine	Prolixin	—
SGAs	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

are increasingly being used off-label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, dementia, psychotic depression, autism, and developmental disorders and, to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and posttraumatic stress disorder. These psychiatric conditions are common and often require lifelong treatment. In the U.S., the prevalence of schizophrenia and related conditions is ~ 1%, the prevalence of bipolar disorders is ~ 2%, and the prevalence of major depression is ~ 8%. The SGAs are therefore widely used medications, and their use has important public health ramifications.

2. WHAT IS THE PREVALENCE OF OBESITY, PRE-DIABETES, AND TYPE 2 DIABETES IN THE POPULATIONS IN WHICH THE SGAs ARE USED?

— It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment. Most of the available data are derived from studies of individuals with schizophrenia, and even in this condition, the evidence is very limited. Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is ~1.5–2.0 times higher than in the general population. Many characteristics of people with schizophrenia, such as sedentary behavior, may contribute to the apparently higher prevalence of metabolic abnormalities. However, none of these studies controlled for all of the major diabetes risk factors. For example, BMI and family history of diabetes were rarely determined, nor were the control populations appropriately matched for these and other variables. Thus, it is unclear whether psychiatric conditions per se, independent of other known diabetes risk factors, account for the increased prevalence.

There are limited data evaluating the metabolic profile and diabetes risk of drug-naïve subjects with schizophrenia. In a small cohort of adults with schizophrenia untreated with medications, visceral fat content (which is correlated with insulin resistance) was threefold higher than in age- and BMI-matched control subjects. In another study, the same investigators found that drug-naïve patients presenting with their first episode of schizophrenia had an increased prevalence of impaired fasting glucose, were more insulin resistant, and had higher plasma levels of glucose, insulin, and cortisol than did matched control subjects.

Overall, the limited amount of epidemiological data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself versus its treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk factor characterization are necessary in order to resolve this issue.

3. WHAT IS THE RELATIONSHIP BETWEEN THE USE OF THESE DRUGS AND THE INCIDENCE OF OBESITY OR DIABETES?

— Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including DKA. Subsequent drug surveillance and retrospective database analyses suggest there is an association between specific SGAs and both diabetes and obesity. This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. High rates of smoking and physical inactivity may also contribute to the excess mortality. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern.

Although there are significant shortcomings in many of the studies examining the relationships between the SGAs and obesity or diabetes, clear-cut trends can be identified.

Obesity

There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. There is, however, considerable variability in weight gain among the various SGAs (Table 2). At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from ~0.5 to 5.0 kg. Limited data suggest that in humans, most of the weight gained

Table 2—*SGA's and metabolic abnormalities*

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

is fat. Data derived from a canine model indicated that certain SGAs increase total visceral fat mass and intrahepatic lipid content.

The mechanism(s) responsible for weight gain associated with SGA therapy are unknown. Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both. Even a small, chronic imbalance between energy intake and expenditure can lead to large changes in body weight over time. For example, ingestion of ~500 kcal/day more than is expended can account for the largest average weight gain reported with SGA therapy (4.5 kg at 10 weeks). This amount of daily increase in energy intake represents the calories in a normal-size candy bar plus a soda or in an ice cream dessert. Hunger and satiety may be altered in people taking SGAs because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine-H1 receptors. All of these receptors have been implicated in the control of body weight.

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β-cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Diabetes

Numerous case reports have documented the onset or exacerbation of diabetes, including the occurrence of hyperglycemic crises, following initiation of therapy with many of the SGAs.

Several of these events occurred within a few weeks of initiating drug treatment. In some, but not all cases, hyperglycemia promptly resolved after the medication was discontinued. Several reports documented recurrent hyperglycemia after another challenge with the same drug. Additional cases of diabetes or hyperglycemia have been reported through MedWatch into the FDA's Adverse Event Reporting System.

Large retrospective cohort studies have been reported that estimate the prevalence of diabetes in patients using SGAs. These reports relied on a variety of methods for determining the diagnosis of diabetes, such as ICD-9 codes and data on prescriptions for diabetes medications. In addition, several cross-sectional studies of patients taking different SGAs, "switch studies" of patients changed from one medication to another, and one prospective randomized controlled trial evaluating SGA therapy on parameters of insulin sensitivity and glycemic control have been conducted. Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs. The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not. The two most recently approved SGAs, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes (Table 2).

One possible mechanism for hyperglycemia is impairment of insulin action (i.e., insulin resistance). Drug-induced insulin resistance may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues. Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with FGAs, even after adjusting for body weight. To date, studies in humans have not shown adverse effects of any antipsychotic medication on β-cell function, but this issue has not been adequately studied in individuals with psychiatric illnesses.

Dyslipidemia

An additional related consequence of SGA use is their effect on serum lipids. Although the data are limited, the available evidence suggests that changes in serum lipids are concordant with changes in body weight. Clozapine and olanzapine, which produce the greatest weight gain, are associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids (Table 2).

Risk-benefit assessment

Despite the adverse effects cited above, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity, diabetes, and dyslipidemia have considerable clinical implications in this patient population and should also influence drug choice.

Even for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. For example, clozapine has unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior. Since treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.

4. GIVEN THE ABOVE RISKS, HOW SHOULD PATIENTS BE MONITORED FOR THE DEVELOPMENT OF SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES, AND HOW SHOULD THEY BE TREATED IF DIABETES DEVELOPS?—

Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring. Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference. These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic

Table 3—*Monitoring protocol for patients on SGAs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

complications for which these patients are at increased risk.

Baseline monitoring

The panel recommends that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include

- Personal and family history of obesity diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height (so that BMI can be calculated)
- Waist circumference (at the level of the umbilicus)
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

These assessments can determine if the patient is overweight (BMI 25.0–29.9) or obese (BMI ≥30), has pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If any of these conditions are identified, appropriate treatment should be initiated. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

The panel recommends that nutrition and physical activity counseling be provided for all patients who are overweight or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or program with expertise in weight management may also be appropriate.

Health professionals, patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as DKA (Table 4). The latter is a life-threatening condition and always requires immediate treatment. Patients, family members, and caregivers also need to know that treatment with some SGAs may be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidemia. For patients with, or at higher risk for, diabetes and in those treated with other medications that may increase these risks (e.g., valproate, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain and glucose intolerance (Table 2). Potential for weight gain should also be considered in the choice of other psychiatric and nonpsychiatric medications.

Table 4—*DKA clinical presentation*

Rapid onset of:
- Polyuria, polydipsia
- Weight loss
- Nausea, vomiting
- Dehydration
- Rapid respiration
- Clouding of sensorium, even coma

Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits (Table 3). If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated.

Although limited data are available in children and adolescents regarding the risks of diabetes when SGAs are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes (Table 2). All patients with diabetes should be referred to an American Diabetes Association–recognized diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes is recommended. These patients should carry diabetes identification.

Immediate care or consultation is required for patients with symptomatic or severe hyperglycemia (glucose values ≥300 mg/dl), symptomatic hypoglycemia, or glucose levels ≤60 mg/dl, even in the absence of symptoms. The presence of

symptoms of DKA (Table 4), requires immediate evaluation and treatment.

Blood pressure, lipid, and glycemic goals of therapy for people with diabetes apply equally to those who also have psychiatric disorders. However, all goals need to be individualized. The benefits and risks of different therapeutic agents used in the treatment of diabetes and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

5. WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN THESE DRUGS AND SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES?

— Evidence for weight gain and abnormalities of glucose and lipid metabolism in patients taking SGAs is in part derived from case-control studies, pharmacovigilance (e.g., through MedWatch), and database reviews. Many of these studies suffer from their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. Comparison studies among SGAs are also limited by relatively short periods of study, by failure to control for a possible treatment sequence bias in "switchover" studies, and by not always using clinically equivalent dosages of the medications.

Trials with SGAs should be randomized and controlled, preferably using drug-naïve subjects. Weight gain and measures of glucose and lipid metabolism should be thoroughly evaluated. Study subjects should be well-characterized in terms of their baseline risk factors for diabetes, obesity, and lipid disorders and their degree of baseline impairment in insulin sensitivity and β-cell function. The duration of exposure to the various SGAs should be carefully controlled. Future research studies should focus on the following:

- Baseline body composition in untreated patients with psychiatric disorders and changes that occur during treatment with SGAs need to be better characterized. This would include measures of fat versus fat-free mass and visceral and subcutaneous adipose stores, using valid methods to measure body fat (e.g., magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry).
- The contribution of altered neuroendocrine function (e.g., hypothalmic-pituitary-adrenal axis activation) to alterations in body composition and abnormalities in glucose and lipid metabolism needs further study to distinguish the acute effects of stress from the underlying disease process.
- Studies are needed that examine glucose and lipid metabolism as they relate to alterations in insulin sensitivity in peripheral and hepatic tissues (e.g., euglycemic-hyperinsulinemic clamp with labeled glucose infusions), alterations in β-cell function (hyperglycemic clamp or frequently sampled intravenous glucose tolerance test), and alterations in lipid metabolism (using tracer infusions).
- Large prospective studies should be conducted to identify baseline and early treatment factors that predict the later occurrence of abnormalities in body weight and composition and disorders of glucose and lipid metabolism during treatment with these drugs.
- Additional studies are needed to identify whether there are baseline characteristics that predict acute, life-threatening complications (e.g., DKA, pancreatitis).
- Additional data are needed to determine whether the risks of therapy are increased in certain ethnic groups (e.g., African Americans).
- Studies determining the effect of SGAs in various psychiatric disorders are needed to clarify the disease-related risk for the development of weight gain and metabolic disturbances.
- Alterations in energy intake and expenditure as contributors to weight gain in the psychiatric population and how these processes are altered by treatment with SGAs should be studied.
- Studies are needed to determine whether the disorders of body weight and glucose and lipid metabolism are due to central nervous system or peripheral tissue actions of the SGAs. Valuable information on the direct effects of SGAs on different body tissue compartments might be obtained from studies in appropriate animal models.
- Studies of the genetic markers that are associated with, and may be causally related to, the metabolic disturbances occurring in treated patients with psychiatric disorders (e.g., 5-$HT_{2C,}$ histamine-H1 receptor alleles) are needed.

SUMMARY — The SGAs are of great benefit to a wide variety of people with psychiatric disorders. As with all drugs, SGAs are associated with undesirable side effects. One constellation of adverse effects is an increased risk for obesity, diabetes, and dyslipidemia. The etiology of the increased risk for metabolic abnormalities is uncertain, but their prevalence seems correlated to an increase in body weight often seen in patients taking an SGA. Direct drug effects on β-cell function and insulin action could also be involved, since there is insufficient information to rule out this possibility. In the general population, being overweight or obese also carries a much higher risk of diabetes and dyslipidemia.

These three adverse conditions are closely linked, and their prevalence appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.

The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications.

APPENDIX

Consensus panel

Eugene Barrett, MD, PhD, Chair; Lawrence Blonde, MD, Stephen Clement, MD, John Davis, MD, John Devlin, MD, John Kane, MD, Samuel Klein, MD, William Torrey, MD.

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Presenters at the conference

David Allison, PhD, Richard Bergman, PhD, John Buse, MD, PhD, Patrizia Cavazzoni, MD, Fred Fiedorek, MD, Rohan Ganguli, MD, Andrew Greenspan, MD, David Kendall, MD, Ron Leonge, MD, Antony Loebel, MD, Patrick Lustman, PhD, Herbert Meltzer, MD, John Newcomer, MD, Judy Racoosin, MD, Bryan Roth, MD, Michael Sernyak, MD, Jogin Thakore, MB, Donna Wirshing, MD, William Wirshing, MD.

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Article

A Randomized, Double-Blind, Placebo-Controlled Trial of Quetiapine in the Treatment of Bipolar I or II Depression

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Objective: There is a major unmet need for effective options in the treatment of bipolar depression.

Method: Five hundred forty-two outpatients with bipolar I (N=360) or II (N=182) disorder experiencing a major depressive episode (DSM-IV) were randomly assigned to 8 weeks of quetiapine (600 or 300 mg/day) or placebo. The primary efficacy measure was mean change from baseline to week 8 in the Montgomery-Åsberg Depression Rating Scale total score. Additional efficacy assessments included the Hamilton Depression Rating Scale, Clinical Global Impression of severity and improvement, Hamilton Anxiety Rating Scale, Pittsburgh Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire.

Results: Quetiapine at either dose demonstrated statistically significant improvement in Montgomery-Åsberg Depression Rating Scale total scores compared with placebo from week 1 onward. The proportions of patients meeting response criteria (≥50% Montgomery-Åsberg Depression Rating Scale score improvement) at the final assessment in the groups taking 600 and 300 mg/day of quetiapine were 58.2% and 57.6%, respectively, versus 36.1% for placebo. The proportions of patients meeting remission criteria (Montgomery-Åsberg Depression Rating Scale ≤12) were 52.9% in the groups taking 600 and 300 mg/day of quetiapine versus 28.4% for placebo. Quetiapine at 600 and 300 mg/day significantly improved 9 of 10 and 8 of 10 Montgomery-Åsberg Depression Rating Scale items, respectively, compared to placebo, including the core symptoms of depression. Treatment-emergent mania rates were low and similar for the quetiapine and placebo groups (3.2% and 3.9%, respectively).

Conclusions: Quetiapine monotherapy is efficacious and well tolerated for the treatment of bipolar depression.

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Depressive episodes in bipolar I and II disorder are an important source of morbidity and mortality. While symptomatic, patients with bipolar I disorder experience depressive symptoms for about threefold longer than manic symptoms, and the recovery time is considerably longer for depressive than manic episodes (1–4). Symptomatic patients with bipolar II disorder spend almost 40 times longer depressed than hypomanic patients (5). Bipolar depression is associated with high rates of disability (6) and an increased risk of suicide, which occurs in 10% to 20% of patients with bipolar disorder (7).

Although multiple agents, including several atypical antipsychotics, have demonstrated efficacy in the treatment of the manic phase of bipolar I disorder (8), the acute treatment of bipolar depression has not been as well studied (9). Lithium and lamotrigine are recommended as initial treatments for acute bipolar I depression (10, 11). However, the response of bipolar depression to lithium is often incomplete in a substantial proportion of patients (12), and the efficacy of lamotrigine in the treatment of acute bipolar I depression has only been demonstrated in one adequately powered placebo-controlled trial (13).

More recently, the atypical antipsychotic olanzapine was found to be superior to placebo in the treatment of acute bipolar I depression as monotherapy when data were pooled from two 8-week trials (14). Fixed doses of olanzapine in combination with the antidepressant fluoxetine were administered to small groups of patients in these studies and were found to be both superior to placebo and superior to olanzapine monotherapy.

Quetiapine is efficacious in the treatment of acute bipolar mania, both as monotherapy and in combination with other mood stabilizers (15, 16). Preliminary evidence for the efficacy of quetiapine in the treatment of depressive symptoms in a variety of psychotic and mood disorders (including bipolar disorder, rapid-cycling bipolar disorder, and adolescent mania) has been reported in several randomized or open-label studies (17–24).

Based on the need for new treatment options for bipolar depression, the effectiveness of atypical antipsychotics in acute mania, and the emerging evidence for their use in bipolar depression, we evaluated the efficacy and safety of quetiapine compared with placebo in the treatment of depressive episodes in patients with bipolar I or bipolar II disorder.

Method

This double-blind, randomized, fixed-dose, placebo-controlled, parallel-group monotherapy study of quetiapine versus placebo was conducted at 39 centers in the United States between September 2002 and October 2003. After a washout period of at least five half-lives of any prior psychotropic medications, subjects were treated for 8 weeks to evaluate the efficacy, safety, and tolerability of 600 and 300 mg/day of quetiapine and placebo in the treatment of depressive episodes in adult patients with bipolar I or II disorder.

The study was approved by institutional review boards for each site and performed in accordance with the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before participation.

Patient Population

Outpatients ages 18 to 65 years who met DSM-IV criteria for bipolar I or II disorder and were experiencing a major depressive episode were eligible for inclusion in the study. The diagnosis was confirmed with the Structured Clinical Interview for DSM-IV. The patients were required to have a Hamilton Depression Rating Scale 17-item score ≥20 (25), a Hamilton depression scale item 1 score ≥2, and a Young Mania Rating Scale (26) score ≤12 at both the screening and randomization visits. Inclusion criteria were based on the Hamilton depression scale rather than the primary efficacy measure (the Montgomery-Åsberg Depression Rating Scale [27]).

Patients were excluded from the study if they were diagnosed with an axis I disorder other than bipolar disorder that was the primary focus of treatment within 6 months before the screening, if the current episode of depression exceeded 12 months or was less than 4 weeks in duration, or if they had a history of nonresponse to an adequate (6-week) trial of more than two classes of antidepressants during the current episode. Additional exclusion criteria included a diagnosis of substance dependence (DSM-IV) or substance use (except for nicotine) within 12 months before the screening or a clinically significant medical illness. Patients who posed a current serious suicidal or homicidal risk were also excluded. Patients were not permitted to take benzodiazepines during the washout period, and only limited use was permitted during the first 3 weeks after random assignment.

Random assignment was achieved in a non-center-specific manner with an interactive voice-response central randomization service. Random assignment was stratified according to bipolar type (I or II) to ensure a relative balance in the total number of patients among groups (1:1:1). The patients were randomly assigned to one of three groups: quetiapine, 600 mg/day; quetiapine, 300 mg/day; or placebo.

Study Medication

Quetiapine (600 mg/day or 300 mg/day) or placebo was administered orally, in a single dose, once a day at bedtime. Quetiapine was initiated at 50 mg/day and administered to achieve a target dose of 300 mg/day by day 4 or 600 mg/day by week 1. All packaging of treatments was identical, with placebo and active tablets identical in appearance and number.

Prior and Concomitant Medication

Nonpsychotropic medication, including over-the-counter medications taken before entry into the study could be continued. Zolpidem tartrate (5–10 mg/day at bedtime for insomnia) and lorazepam (1–3 mg/day for severe anxiety) were permitted at the discretion of the investigator and only during the first 3 weeks of treatment but were withheld for 8 hours before psychiatric assessments were conducted. The use of all other psychotropic drugs was prohibited during the study.

Efficacy Evaluations

Clinical assessments were conducted at baseline and weekly from weeks 1 to 8. The primary efficacy variable was the mean change in the Montgomery-Åsberg Depression Rating Scale total score from baseline to week 8 (27).

Additional efficacy evaluations included a change from baseline to each assessment on the Montgomery-Åsberg Depression Rating Scale, the proportion of patients who achieved a protocol-defined response (≥50% reduction from baseline score on the Montgomery-Åsberg Depression Rating Scale), the time to response, the proportion of patients who achieved remission (Montgomery-Åsberg Depression Rating Scale score ≤12), the time to remission, as well as a Montgomery-Åsberg Depression Rating Scale item analysis. The change from baseline to each assessment on the Hamilton depression scale, the Clinical Global Impression (CGI) (28) severity of illness score, and the CGI improvement score were also assessed.

The effect of quetiapine on anxiety symptoms was assessed with the Hamilton Anxiety Rating Scale (29). Mean change from baseline to each assessment and at week 8 in the Hamilton anxiety scale total score was determined.

Quality of sleep was assessed with the Pittsburgh Sleep Quality Index, which measures several dimensions of sleep, including quality, latency, duration, efficiency, use of medication, and daytime dysfunction (30).

The 16-item short form of the Quality of Life Enjoyment and Satisfaction Questionnaire was used to measure satisfaction with various areas of daily functioning, such as social relationships, living/housing, physical health, medication, and global satisfaction (31). The Pittsburgh Sleep Quality Index and the Quality of Life Enjoyment and Satisfaction Questionnaire were administered at baseline and at weeks 4 and 8.

Safety and Tolerability Evaluations

Safety and tolerability were evaluated by assessing the incidence and severity of adverse events, as well as withdrawals because of adverse events. Extrapyramidal symptoms were assessed with the Simpson-Angus Rating Scale (32), and akathisia was assessed with the Barnes Rating Scale for Drug-Induced Akathisia (33) at random assignment and at week 8. Measurements of vital signs, including weight and fasting serum glucose levels, were obtained at each study visit. Twelve-lead ECGs, clinical chemistry, and hematology assessments were performed at the screening and at week 8.

The incidence of treatment-emergent mania was evaluated by comparing the percentage of patients in each group who had a total Young Mania Rating Scale score of ≥16 on any two consecutive visits or at the final assessment, or an adverse event of mania or hypomania.

Statistical Analyses

Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients who took at least one dose of study medication and had at least one postbaseline efficacy assessment. A last-observation-carried-forward analysis was used to impute missing data for patients who withdrew during the study. All statistical tests were two-tailed. The primary analysis of change from baseline to final assessment in the Montgomery-Åsberg Depression Rating Scale total scores tested the superiority of each dose of quetiapine in the intent-to-treat group (patients with bipolar I or bipolar II disorder) with an analysis of covariance (ANCOVA) with the baseline Montgomery-Åsberg Depression Rating Scale as the covariate and included treatment and diagnosis strata as fixed ef-

TABLE 1. Baseline Demographic Characteristics of Screened Outpatients With Bipolar I or II Disorder Who Experienced a Major Depressive Episode

	Patients Who Did Not Pass Screening (N=296)		Patients Who Were Randomly Assigned to Treatment (N=539)[a]	
Characteristic	N	%	N	%
Female sex	168	56.8	308	57.1
Caucasian race	227	76.7	438	81.3
Age (years)				
18–39	163	55.1	318	59.0
40–59	122	41.2	310	39.0
≥60	10	3.4	5	0.9

[a] Safety population that excluded three patients who did not receive any dose of study medication.

fects in the model, with adjustment for multiple comparisons. Effect size (improvement of quetiapine over placebo divided by pooled standard deviation) was determined with a mixed-model repeated-measures analysis.

Differences in response rates between treatment and placebo groups and in patients with and without rapid cycling were assessed with a Cochran-Mantel-Haenszel chi-square test across diagnostic strata. Hamilton depression scale, CGI severity and improvement, Young Mania Rating Scale, Hamilton anxiety scale, Pittsburgh Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire scores were tested with ANCOVAs. All secondary analyses were conducted at the nominal significance level of 0.05, with no adjustment for multiple comparisons.

Sample sizes were determined to provide 85% power to detect a difference of 3.6 points on the Montgomery-Åsberg Depression Rating Scale with two-tailed pairwise comparisons between treatment groups and placebo at an alpha level of 0.025 in the intent-to-treat population (patients with bipolar I or bipolar II disorder).

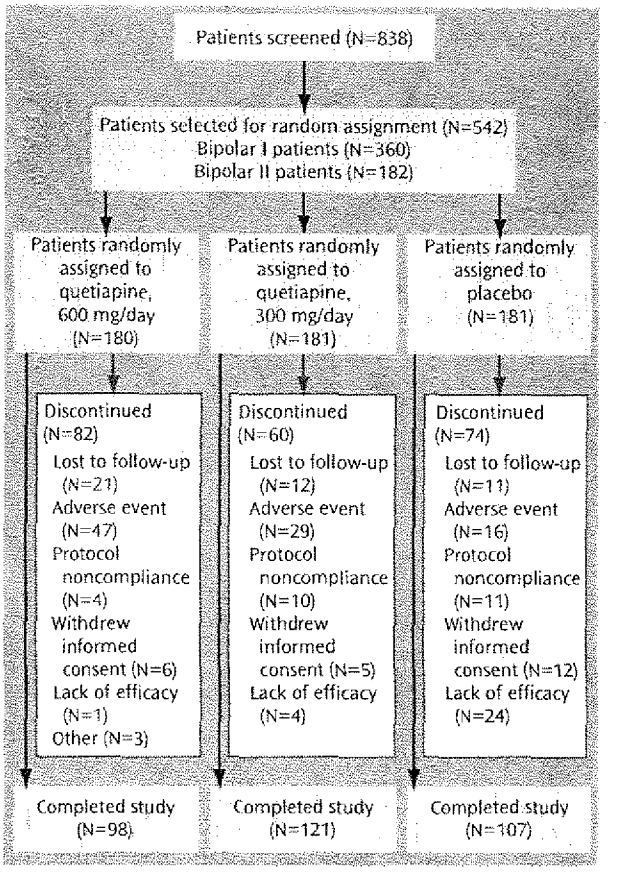
Exploratory analyses were carried out on the bipolar I and II subgroups whose group size was not predetermined to provide power for significance testing. Exploratory analyses were limited to descriptions of the mean changes in primary outcome measure across the three treatment groups, and effect size determinations for the groups taking 600 and 300 mg/day of quetiapine. The repeated measures mixed-effects model included terms for treatment, bipolar diagnosis, treatment-by-bipolar diagnosis, baseline Montgomery-Åsberg Depression Rating Scale total score, visit (week), and treatment-by-visit effects. Several covariance structures were examined, including autoregressive, banded Toeplitz, compound symmetry, and unstructured. The best-fitting covariance structure, the banded Toeplitz, was determined with the Bayesian information criterion.

Results

Patients and Disposition

A total of 838 patients were screened, and 542 patients with bipolar I (N=360) or bipolar II (N=182) disorder were randomly assigned to receive quetiapine, 600 mg/day (N=180); quetiapine, 300 mg/day (N=181); or placebo (N=181). There were no significant differences between the baseline characteristics of patients who did not pass the screening compared with those who were randomly assigned (Table 1). The most common reason for the screening failure was failure to meet eligibility criteria. Figure 1 illustrates the disposition of patients during the study. Of the 542 randomly assigned patients, 539 received at least

FIGURE 1. Disposition of Outpatients with Bipolar I or II Disorder Who Experienced a Major Depressive Episode



one dose of study medication and were included in the safety population. Of these, 511 had at least one postbaseline assessment and were analyzed for efficacy in the intent-to-treat population.

There were no statistically significant differences between treatment groups with respect to any demographic and baseline disease characteristic (Table 2). The mean age was approximately 37 years, and 58.2% of the patients were women. Mean Montgomery-Åsberg Depression Rating Scale scores at baseline were consistent with moderate to severe depression (34).

There were no statistically significant differences between the quetiapine groups and placebo in the proportion of the patients who completed the study: 54% in the 600 mg/day quetiapine group, 67% in the 300 mg/day quetiapine group, and 59% in the placebo group. The most common reasons for withdrawal were related to adverse events in the quetiapine groups (26.1% and 16.0%) and lack of efficacy in the placebo group (13.3%).

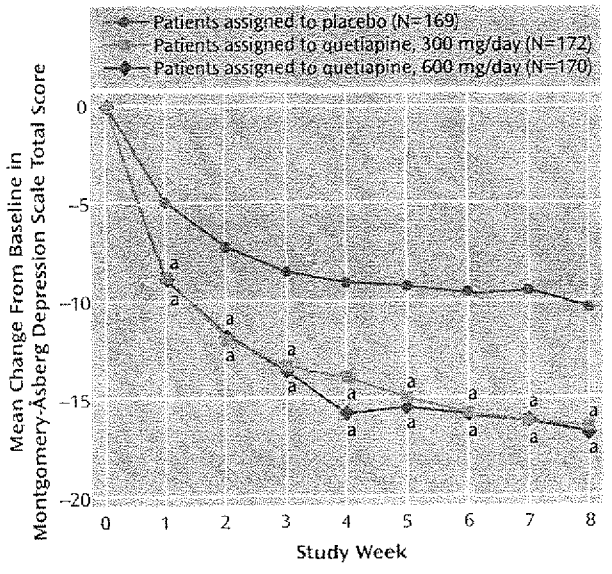
The use of lorazepam and zolpidem (permitted during the first 3 weeks of the study) was generally low across groups. Lorazepam use during the study was 5.6% and 9.5% in the 600 and 300 mg/day quetiapine groups, respectively, compared with 8.3% in the placebo group.

TABLE 2. Baseline Demographic and Clinical Characteristics of Outpatients With Bipolar I or II Disorder Who Experienced a Major Depressive Episode[a]

Characteristic	Patients Taking Quetiapine 600 mg/day (N=170)		Patients Taking Quetiapine 300 mg/day (N=172)		Patients Taking Placebo (N=169)	
	N	%	N	%	N	%
Sex						
Male	71	41.8	79	45.9	64	37.9
Female	99	58.2	93	54.1	105	62.1
Race						
Caucasian	144	84.7	141	82.0	129	76.3
Black	18	10.6	23	13.4	26	15.4
Hispanic	5	2.9	7	4.1	9	5.3
Other	3	1.8	1	0.6	5	2.9
DSM-IV diagnosis						
Bipolar I disorder	114	67.1	116	67.4	112	66.3
Bipolar II disorder	56	32.9	56	32.6	57	33.7
DSM-IV rapid cycling	31	18.2	42	24.4	35	20.7
	Mean	SD	Mean	SD	Mean	SD
Age (years)	37.3	11.4	36.6	11.2	38.3	11.1
Baseline scores						
Montgomery-Åsberg Depression Rating Scale	30.3	5.3	30.4	5.0	30.6	5.3
Hamilton Depression Rating Scale	24.7	3.5	24.5	3.0	24.6	3.3
Hamilton Anxiety Rating Scale	18.7	7.3	18.6	7.3	18.9	7.3

[a] Intent-to-treat analysis.

FIGURE 2. Least-Squares Mean Change From Baseline in Montgomery-Åsberg Depression Rating Scale Total Score at Each Assessment of Outpatients With Bipolar I or II Disorder Who Experienced a Major Depressive Episode[a]



[a] Intent-to-treat, last-observation-carried-forward analyses. Improvement in Montgomery-Åsberg Depression Rating Scale total score with both doses of quetiapine (600 mg/day and 300 mg/day) was significantly greater than placebo at every assessment (p<0.001).

Zolpidem use during the study was 6.7% and 4.5% in the 600 and 300 mg/day quetiapine groups, respectively, compared with 8.3% in the placebo group.

Efficacy

Montgomery-Åsberg Depression Rating Scale. Mean baseline Montgomery-Åsberg Depression Rating Scale scores were 30.3 (SD=5.3), 30.4 (SD=5.0), and 30.6 (SD=5.3) in the 600 mg/day, 300 mg/day, and placebo groups, respectively. Quetiapine at a dose of either 600 or 300 mg/day demonstrated significantly greater mean improvement in Montgomery-Åsberg Depression Rating Scale total scores compared with placebo as early as week 1 and at all time points that followed in the intent-to-treat group of patients with bipolar I or II depression (p<0.001 for both quetiapine doses versus placebo) (Figure 2). The mean change in Montgomery-Åsberg Depression Rating Scale total score from baseline to last assessment was −16.73 in the 600 mg/day group and −16.39 in the 300 mg/day group, compared with −10.26 in the placebo group (p<0.001 for both quetiapine doses versus placebo) (Table 3, Figure 2). The effect sizes were 0.81 for 600 mg/day and 0.67 for 300 mg/day of quetiapine.

Approximately 58% of the patients treated with either dose of quetiapine were responders at the final assessment, and both doses resulted in significantly higher response rates than placebo (36.1%) (p<0.001). Notably, the percentage of patients meeting response criteria with 600 mg/day of quetiapine was significantly higher as early as week 1 (24.3%) versus placebo (10.7%) (p<0.001). In the group taking 300 mg/day of quetiapine, a significantly higher response rate (37.2%) versus placebo (19.5%) was apparent by week 2 (p<0.001). The median time to response was significantly shorter for both 600 mg/day (22 days) and 300 mg/day (22 days) of quetiapine compared with placebo (36 days) (log-rank χ^2=33.1, df=2, p<0.001).

The percentage of patients meeting remission criteria at the final assessment was 52.9% in both the groups taking 600 and 300 mg/day of quetiapine, significantly higher than the placebo rate of 28.4% in each group (p<0.001). The median time to remission was significantly shorter for

TABLE 3. Baseline and Mean Change in Efficacy Measures at the Last Assessment of Outpatients With Bipolar I or II Disorder Who Experienced a Major Depressive Episode[a]

Measure and Treatment	Baseline Score		Change in Score at Last Assessment	Analysis (comparison with placebo)	
	Mean	SD		ANCOVA (df=1)[b]	p
Montgomery-Åsberg Depression Rating Scale					
600 mg/day of quetiapine	30.3	5.3	−16.73	−6.47 (1.12)	<0.001
300 mg/day of quetiapine	30.4	5.0	−16.39	−6.13 (1.12)	<0.001
Placebo	30.6	5.3	−10.26		
Hamilton Depression Scale					
600 mg/day of quetiapine	24.7	3.5	−13.84	−5.29 (0.81)	<0.001
300 mg/day of quetiapine	24.5	3.0	−13.38	−4.84 (0.80)	<0.001
Placebo	24.6	3.3	−8.54		
Hamilton Depression Scale item 1					
600 mg/day of quetiapine	2.9	0.5	−1.68	−0.57 (0.12)	<0.001
300 mg/day of quetiapine	2.9	0.5	−1.65	−0.54 (0.12)	<0.001
Placebo	2.9	0.4	−1.11		
Clinical Global Impression scale					
Improvement					
600 mg/day of quetiapine	4.5	0.6	2.37	−0.60 (0.14)	<0.001
300 mg/day of quetiapine	4.4	0.5	2.27	−0.71 (0.14)	<0.001
Placebo	4.4	0.6	2.97		
Severity					
600 mg/day of quetiapine	4.5	0.6	−1.66	−0.72 (0.14)	<0.001
300 mg/day of quetiapine	4.4	0.5	−1.63	−0.68 (0.14)	<0.001
Placebo	4.4	0.6	−0.95		
Hamilton Anxiety Rating Scale					
600 mg/day of quetiapine	18.7	7.3	−8.75	−3.20 (0.76)	<0.001
300 mg/day of quetiapine	18.6	7.3	−8.64	−3.10 (0.76)	<0.001
Placebo	18.9	7.3	−5.54		
Pittsburgh Sleep Quality Index					
600 mg/day of quetiapine	11.6	4.2	−5.46	−2.52 (0.43)	<0.001
300 mg/day of quetiapine	11.4	3.8	−5.16	−2.22 (0.44)	<0.001
Placebo	11.7	3.8	−2.94		
Quality of Life Enjoyment and Satisfaction Questionnaire					
600 mg/day of quetiapine	34.1	8.2	11.71	5.27 (1.14)	<0.001
300 mg/day of quetiapine	36.1	7.9	10.77	4.33 (1.15)	<0.001
Placebo	34.2	7.4	6.44		

[a] Intent-to-treat, last-observation-carried-forward analyses.
[b] Test, treatment contrast within the framework of the ANCOVA, estimated difference (standard error).

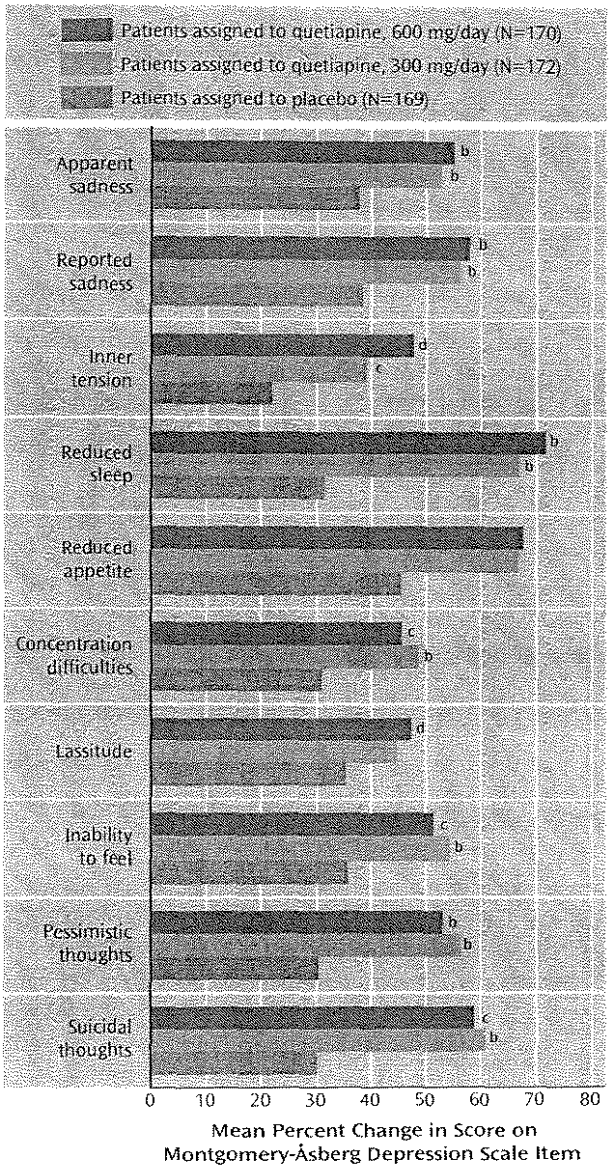
both 600 mg/day (27 days) and 300 mg/day (29 days) of quetiapine compared with placebo (65 days) (log-rank χ^2= 32.8, df=2, p<0.001).

Nine out of 10 Montgomery-Åsberg Depression Rating Scale items were significantly improved from baseline compared with placebo in the 600 mg/day quetiapine group, as were eight items in the 300 mg/day quetiapine group (p<0.05) (Figure 3). With both doses of quetiapine, these items included the core mood symptoms of apparent sadness, reported sadness, inability to feel, pessimistic thoughts, and suicidal thoughts. The core mood symptoms of apparent sadness, reported sadness, and pessimistic thoughts were significantly improved in both quetiapine groups as early as week 1 compared with placebo (p<0.05). An inability to feel and suicidal thoughts were also significantly improved by week 1 in the group taking 600 mg/day of quetiapine compared with placebo (p<0.05). Both doses of quetiapine were more effective than placebo in reducing suicidal thoughts at the final assessment (p≤0.001); the reductions with quetiapine were approximately twice that of placebo.

In the bipolar I subgroup of patients, the mean change in Montgomery-Åsberg Depression Rating Scale total score from baseline to last assessment was −18.05 in the group taking 600 mg/day group of quetiapine and −16.91 in the 300 mg/day group, compared with −9.24 in the placebo group (p<0.001 for both quetiapine doses versus placebo). The effect size in the bipolar I subgroup was 1.09 for those assigned to 600 mg/day and 0.91 for those taking 300 mg/day of quetiapine. In the subgroup of patients with bipolar II disorder, the mean change in Montgomery-Åsberg Depression Rating Scale total score from baseline to last assessment was smaller than in bipolar I patients. Although the change in Montgomery-Åsberg Depression Rating Scale total score from baseline in the patients with bipolar II disorder was statistically superior to placebo at most assessments, it did not reach statistical significance at the final assessment: −14.06 in the group taking 600 mg/day of quetiapine and −14.78 in the group taking 300 mg/day compared with −12.35 in the placebo group. The effect size in the bipolar II subgroup was 0.39 in the 600 mg/day group and 0.28 in the 300 mg/day group.

Significant improvement in Montgomery-Åsberg Depression Rating Scale total scores compared with placebo at the final assessment occurred with quetiapine treatment regardless of the presence of rapid cycling in the intent-to-treat group (patients with bipolar I or II disorder). The mean change in Montgomery-Åsberg Depression Rat-

FIGURE 3. Mean Percent Change From Baseline in Individual Montgomery-Åsberg Depression Rating Scale Items for Outpatients with Bipolar I or II Disorder Experiencing a Major Depressive Episode[a]



[a] Intent-to-treat, last-observation-carried-forward analyses. Nine of 10 and 8 of 10 Montgomery-Åsberg Depression Rating Scale items (including the core mood symptoms of depression [item 1: apparent sadness; item 2: reported sadness; item 8: inability to feel; item 9: pessimistic thoughts; item 10: suicidal thoughts]) were significantly improved from baseline compared to placebo in the groups taking 600 mg/day and 300 mg/day of quetiapine, respectively ($p<0.05$). Apparent sadness, reported sadness, and pessimistic thoughts were significantly improved in both quetiapine groups as early as week 1 compared with placebo ($p<0.05$). Both doses of quetiapine were approximately twice as effective as placebo in reducing suicidal thoughts at the final assessment ($p\leq0.01$).
[b] $p<0.001$ versus placebo.
[c] $p<0.01$.
[d] $p<0.05$.

ing Scale total score at week 8 in the patients with rapid cycling was –17.7 in the 600 mg/day quetiapine group and –18.6 in the 300 mg/day quetiapine group versus –9.9 in the placebo group ($p<0.01$ for both quetiapine doses versus placebo). The mean change in Montgomery-Åsberg Depression Rating Scale total score at week 8 in the patients without rapid cycling was –16.6 in the 600 mg/day group and –15.7 in the 300 mg/day group versus –10.3 in the placebo group ($p<0.001$ for both quetiapine doses versus placebo). A more detailed analysis of patients with and without rapid cycling in this study will be described in a separate report.

In order to explore the role of somnolence or sedation on efficacy, the mean change from baseline in Montgomery-Åsberg Depression Rating Scale total scores in the patients with and without these adverse events were compared. The number of patients in the intent-to-treat group with reported somnolence/sedation was 195 (57%) for the quetiapine groups combined and 24 (14%) for the placebo group. The mean change in the Montgomery-Åsberg Depression Rating Scale total score at week 8 in the patients with somnolence/sedation (either bipolar I or II disorder) was –18.8 in the pooled quetiapine groups (600 or 300 mg/day) versus –18.9 in the placebo group. In the patients without somnolence/sedation, the mean change in the Montgomery-Åsberg Depression Rating Scale total score was –19.3 and –11.7 for in the pooled quetiapine and placebo groups, respectively. The placebo group response was higher in the patients reporting somnolence/sedation, but the results with quetiapine were similar in the patients with or without somnolence/sedation.

Hamilton depression scale. Mean baseline Hamilton depression scale scores were 24.7 (SD=3.5), 24.5 (SD=3.0), and 24.6 (SD=3.3) in the 600 mg/day, 300 mg/day, and placebo groups, respectively (Table 2). Quetiapine at a dose of either 600 or 300 mg/day demonstrated significantly greater mean improvements in Hamilton depression scale total scores compared to placebo as early as week 1 and at all time points that followed in the patients with bipolar I or II depression ($p<0.001$). The mean change from baseline in Hamilton depression scale scores at week 8 was –13.84, –13.38, and –8.54 in the 600 mg/day, 300 mg/day, and placebo groups, respectively ($p<0.001$ for both quetiapine doses versus placebo). At the end of the study, the effect sizes for the group of patients with bipolar I or II disorder with the Hamilton depression scale was 0.93 for 600 mg/day and 0.74 for 300 mg/day of quetiapine.

Significant improvement in the Hamilton depression scale item 1 (depressed mood) was as early as week 1 ($p=0.003$) for both quetiapine doses and continued to be statistically superior to placebo at all time points.

Clinical Global Impression. Quetiapine-treated patients experienced a statistically significant improvement ($p<0.001$) on the CGI severity scale as early as week 1 that was sustained to the end of the study for both quetiapine doses versus placebo. At the final assessment, a larger percentage of patients were rated as "normal, not at all ill," or

TABLE 4. Incidence and Withdrawals Because of Adverse Events Occurring in at Least 10% of the Patients in Any Group of Outpatients with Bipolar I or II Disorder Who Experienced a Major Depressive Episode

	Patients Taking 600 mg/day of Quetiapine (N=180)				Patients Taking 300 mg/day of Quetiapine (N=179)				Patients Taking Placebo (N=180)			
	Incidence		Leading to Withdrawal		Incidence		Leading to Withdrawal		Incidence		Leading to Withdrawal	
Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%
Dry mouth	73	40.6[a]	2	1.1[a]	79	44.1[a]	0	0.0	14	7.8	0	0.0
Sedation	58	32.2[a]	17	9.4[a]	53	29.6[a]	10	5.6[a]	11	6.1	0	0.0
Somnolence	44	24.4[a]	5	2.8[a]	49	27.4[a]	7	3.9[a]	15	8.3	0	0.0
Dizziness	41	22.8[a]	6	3.3[a]	30	16.8[a]	1	0.6[a]	15	8.3	0	0.0
Fatigue	21	11.7	1	0.6	16	8.9	0	0.0	13	7.2	0	0.0
Constipation	20	11.1[a]	1	0.6[a]	21	11.7[a]	0	0.0	8	4.4	0	0.0
Headache	18	10.0	1	0.6[a]	22	12.3	0	0.0	36	20.0	0	0.0
Nausea	6	8.9	0	0.0	14	7.8	3	1.7	23	12.8	0	0.0
Upper respiratory tract infection not otherwise specified	13	7.2	0	0.0	9	5.0	0	0.0	18	10.0	0	0.0

[a] Significantly higher than placebo ($p<0.05$).

"borderline ill" in the 600 mg/day (42.4%) and 300 mg/day quetiapine groups (38.1%) compared with the placebo group (23.7%).

A larger percentage of patients was also rated as "much" or "very much" improved on the CGI improvement scale in the 600 mg/day (55.9%) and 300 mg/day quetiapine groups (64.0%) compared with the placebo group (34.3%) at the final assessment.

Anxiety symptoms. Mean baseline Hamilton anxiety scale scores were 18.7 (SD=7.3), 18.7 (SD=7.3), and 18.9 (SD=7.3) in the 600 mg/day, 300 mg/day, and placebo groups, respectively (Table 2). By the study end, the mean Hamilton anxiety scale total score had decreased by –8.75 in the 600 mg/day group, –8.64 in the 300 mg/day group, and –5.54 in the placebo group ($p<0.001$ for both quetiapine doses versus placebo). A significant improvement in the Hamilton anxiety scale total scores as early as week 1 ($p<0.05$) was maintained to the last assessment ($p<0.001$ for both quetiapine doses versus placebo). Individual items of the Hamilton anxiety scale that most differentiated quetiapine-treated patients from those who received placebo included anxious mood, depressed mood, insomnia, genitourinary symptoms, and tension. A more detailed analysis of the results of the effect of quetiapine on anxiety measures in this study has been presented in a separate report (35).

Quality of sleep. The quality of sleep improved significantly among those treated with either dose of quetiapine compared with placebo. The mean improvement in Pittsburgh Sleep Quality Index scores from baseline in patients treated with 600 mg/day (–5.46) and 300 mg/day (–5.16) of quetiapine was significantly greater with both doses ($p<0.001$) than with placebo (–2.94).

Quality of life. Quetiapine-treated patients also experienced statistically significant improvements in quality of life during the study, as determined by the change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire total scores. Mean Quality of Life Enjoyment and Satisfaction Questionnaire total scores improved by 11.71 by the last assessment among patients treated with 600 mg/day of quetiapine and by 10.77 among those treated with 300 mg/day of quetiapine, compared with 6.44 in the placebo group ($p<0.001$ for both quetiapine doses versus placebo).

Safety and Tolerability

Adverse events. Common adverse events (whether or not considered treatment related) occurred in ≥10% of patients, and withdrawals due to common adverse events are shown in Table 4. The overall rate of study discontinuation due to adverse events was 26.1% (N=47) in the 600 mg/day group, 16.0% (N=29) in the 300 mg/day group, and 8.8% (N=16) in the placebo group (Figure 1). There were no significant differences in the rates of serious adverse events across treatment groups, and none was treatment related: 5.0% (N=9) in the 600 mg/day group and 3.4% (N=6) in the 300 mg/day group compared with 8.9% (N=16) in the placebo group. Two patients attempted suicide (one in each of the active treatment groups), but no suicides or deaths occurred during the study.

The rate of discontinuation due to adverse events in the subgroup of patients with bipolar I disorder was 23.3% (N=28) in the 600 mg/day group, 13.1% (N=16) in the 300 mg/day group, and 11.9% (N=14) in the placebo group. The incidence of serious adverse events in the subgroup of patients with bipolar I disorder was 5.0% (N=6) in the 600 mg/day group, 4.2% (N=5) in the 300 mg/day group, and 11.9% (N=14) in the placebo group.

In the subgroup of patients with bipolar II disorder, the rate of discontinuation due to adverse events was 31.7% (N=19) in the 600 mg/day group, 22.0% (N=13) in the 300 mg/day group, and 3.2% (N=2) in the placebo group. The incidence of serious adverse events in the subgroup of patients with bipolar II disorder was 5.0% (N=3) in the 600 mg/day group, 1.7% (N=1) in the 300 mg/day group, and 3.2% (N=2) in the placebo group.

The incidence of treatment-emergent mania was low and not significantly different from placebo at either quetiapine dose: 2.2% with 600 mg/day of quetiapine (Cochran-Mantel-Haenszel, odds ratio=0.57, 95% confidence interval (CI)=0.17–1.91, p=0.35), 3.9% with 300 mg/day of quetiapine (Cochran-Mantel-Haenszel, odds ratio=0.97, 95% CI=0.35–2.68, p=0.95), and 3.9% with placebo.

The mean Simpson-Angus Rating Scale total score decreased in all three groups from baseline to the final assessment by –0.1, –0.2, and –0.3 in the 600 mg/day and 300 mg/day quetiapine groups and the placebo groups, respectively. There was no statistically significant difference in the number of patients with an increase from baseline in Simpson-Angus Rating Scale scores between either of the quetiapine groups and placebo: 15% (logistic regression=0.66, df=3, p<0.08), 9% (logistic regression=0.06, df=3, p=0.89), and 9% in the 600 mg/day and 300 mg/day quetiapine and placebo groups, respectively.

At the last assessment, mean Barnes Rating Scale for Drug-Induced Akathisia scores were low and similar in all groups: 0.3 in the 600 mg/day group, 0.2 in the 300 mg/day group, and 0.1 in the placebo group. There was no statistically significant difference in the number of patients with an increase from baseline in Barnes Rating Scale for Drug-Induced Akathisia score between either of the quetiapine groups and placebo: 12% (logistic regression=0.39, df=3, p=0.31), 9% (logistic regression=0.06, df=3, p=0.89), and 9% in the 600 mg/day and 300 mg/day quetiapine and placebo groups, respectively.

Adverse events considered extrapyramidal symptoms were present in 8.9% of the 600 mg/day group, 6.7% of the 300 mg/day group, and 2.2% of the placebo group; discontinuation rates for extrapyramidal symptoms were 2.8%, 1.1%, and 0.6%, respectively.

Laboratory Results and Vital Signs

No clinically relevant differences between groups were seen in the mean change from baseline for any vital signs, ECGs, hematology, or clinical chemistry parameters.

Patients treated with 600 mg/day of quetiapine experienced a mean weight gain of 1.6 kg by the final assessment compared with 1.0 kg in the 300 mg/kg group and 0.2 kg in the placebo group. At the final assessment, 16 patients (9.0%) treated with 600 mg/day of quetiapine, 15 patients (8.5%) treated with 300 mg/day of quetiapine, and three patients (1.7%) who received placebo had a weight gain of ≥7% of their baseline measurement. No patients withdrew from the study because of weight gain.

Mean fasting serum glucose levels at baseline were 86 (SD=12), 87 (SD=13), and 87 (SD=15) mg/dl in the 600 mg/day and 300 mg/day of quetiapine and placebo groups, respectively. By the final assessment, the mean change in fasting serum glucose was 6 mg/dl (SD=17), 3 mg/dl (SD=13), and 4 mg/dl (SD=26) in the 600 mg/day and 300 mg/day of quetiapine and placebo groups, respectively.

Discussion

To our knowledge, this is the first randomized, parallel-group, placebo-controlled trial to evaluate the efficacy of quetiapine in bipolar depression. It may also be the first published large-scale, controlled study to assess the efficacy of any pharmacological treatment in a group of patients with bipolar I or II depression, and one of few studies to examine an antidepressant effect in patients with rapid cycling.

Quetiapine monotherapy has significant antidepressant efficacy in a group of patients with bipolar I or II depression based on the primary efficacy analysis (mean change in Montgomery-Åsberg Depression Rating Scale total score from baseline to last assessment). The magnitude of the clinical improvement was substantial and evident from the first assessment (week 1) and at each visit thereafter. The rates of response and remission and the time to response and remission were significantly improved in the quetiapine groups compared with placebo. Compared with placebo, evidence of early and sustained efficacy was observed consistently with both doses of quetiapine and in all secondary efficacy analyses from week 1 onward.

In the Montgomery-Åsberg Depression Rating Scale item analysis, both doses of quetiapine produced a significant and early improvement in all of the core mood symptoms of depression, including objective and reported sadness, anhedonia, and pessimistic thoughts. Notably, both doses of quetiapine were approximately twice as effective as placebo in reducing suicidal ideation. These findings provide support for the conclusion that quetiapine has specific antidepressant properties.

In this study, significant antidepressant efficacy was demonstrated for quetiapine dosed once a day in the evening. This has important clinical relevance because once-daily dosing has been associated with enhanced medication adherence (36). Dosing at bedtime may also offer a means of improving tolerability, particularly regarding somnolence or sedation that are sometimes seen with quetiapine and may help treat the sleep disturbance that often accompanies bipolar depression.

Both doses of quetiapine were associated with improvements in quality of sleep and quality of life and were effective in patients with a recent history of rapid-cycling bipolar disorder. Exploratory analyses suggest that the clinical effect of both doses of quetiapine was greater in patients with bipolar I disorder than those with bipolar II disorder.

The most common side effects of quetiapine included dry mouth, sedation, somnolence, dizziness, and constipation. The most common side effects leading to withdrawal from the study were sedation and somnolence, with most discontinuations occurring within the first week. Of importance, changes in weight observed in all three groups were relatively small and did not result in withdrawal from the study. Quetiapine treatment was not associated with treatment-emergent mania. The long-term safety of quetiapine

is being explored in ongoing bipolar disorder maintenance studies. However, data from patients with schizophrenia does not suggest that unexpected adverse effects during long-term treatment should be expected (37).

Several aspects of the design of this study were innovative. First, the inclusion of patients with bipolar II disorder into a large-scale study of acute bipolar depression was novel and enhanced the generalizability of the findings, particularly since there is a higher incidence of bipolar II disorder than bipolar I disorder. The inclusion of patients with rapid cycling was also innovative and enhanced the generalizability of the findings to this difficult-to-treat subgroup. Second, rather than focusing solely on depressive symptoms, this study included sleep quality and health-related quality-of-life measures. Sleep-quality assessments (both patient- and bed-partner-rated) indicated improvements in functioning in addition to symptom severity, including several dimensions of sleep quality and daytime dysfunction. The quality-of-life scale provided novel information regarding the effect of quetiapine on social relationships, living/housing arrangements, physical health, satisfaction with medication, and global satisfaction. Improvements in these measures provide evidence for improved function and overall quality of life in addition to reduction in the symptoms of the illness.

Moreover, the inclusion of analyses that quantify the magnitude of the clinical effect through effect size determinations gives clinicians useful information. Knowing if a significant difference is caused by a small clinical effect (<0.4), a moderately sized clinical effect (0.40–0.79), or a large clinical effect (>0.79) has the potential of helping the clinician make decisions on how to use a new medication (38). The effect sizes reported in the bipolar I depression study by Tohen et al. (14) were 0.32 with olanzapine monotherapy and 0.68 with olanzapine-fluoxetine combination therapy compared with 1.09 in the bipolar I subgroup with 600 mg/day of quetiapine in this study.

This study had several limitations. First, the number of enrolled patients with bipolar II disorder was not sufficient to draw firm conclusions regarding efficacy in this subgroup. For this reason, post hoc analyses conducted in the bipolar II subgroup included effect size determinations, which are less affected by sample size than significance testing. Second, moderate rates of sedation or somnolence were observed in both quetiapine groups, which might have compromised the integrity of the double-blind design. If this were a significant factor in the assessment of efficacy, the reduction in Montgomery-Åsberg Depression Rating Scale total score in patients experiencing sedation or somnolence would have been greater than those in patients not experiencing these adverse events. However, this was not the case, and the improvements observed on the Montgomery-Åsberg Depression Rating Scale were comparable in patients with or without sedation or somnolence. Third, although the study indicated that the two doses used—chosen because of their efficacy in bipolar mania and other disorders—were effective, guidance on the best dosing for most patients or subgroups of patients should be assessed in future studies.

In conclusion, this large, randomized, double-blind, placebo-controlled study provides the first pivotal data demonstrating that quetiapine monotherapy is efficacious and well tolerated for the acute treatment of bipolar depression in a group of patients with bipolar I or II disorder.

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Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1

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Abstract

Background: Recent literature documents a stronger association between nonfasting triglycerides (TG) and cardiovascular risk compared to fasting TG. Given concerns over antipsychotic effects on serum TG, this analysis explored changes in nonfasting TG in phase 1 of the CATIE Schizophrenia Trial.
Methods: Change in nonfasting TG, adjusted for baseline value, was compared between antipsychotic treatment groups using subjects with nonfasting laboratory assessments at baseline and 3 months.
Results: Among the 246 subjects there were significant treatment differences in 3-month change from baseline ($p=0.009$). The greatest

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increases in median and adjusted mean nonfasting TG levels were seen among those randomized to quetiapine (mean+54.7 mg/dl, median+26 mg/dl) and olanzapine (mean+23.4 mg/dl, median+26.5 mg/dl), while ziprasidone was neutral (mean+0.0 mg/dl, median+8 mg/dl), and decreases were seen with risperidone (mean −18.4 mg/dl, median −6.5 mg/dl) and perphenazine (mean −1.3 mg/dl, median −22 mg/dl). Pairwise comparisons indicated a significant between-group difference for perphenazine vs. olanzapine ($p=0.002$) and a trend for perphenazine vs. quetiapine ($p=0.006$).

Conclusions: This analysis provides further evidence for differential antipsychotic metabolic liabilities, and confirms signals for the effects of olanzapine and quetiapine on serum TG seen in earlier CATIE analyses. Future consensus recommendations will clarify the role of nonfasting TG monitoring in routine clinical practice.

Keywords: Antipsychotic; Schizophrenia; Cardiovascular risk; Lipids; Triglycerides; Nonfasting

1. Introduction

Fasting triglyceride (TG) values are a marker of insulin resistance, and moderate elevations are associated with increased cardiovascular (CV) risk independent of high density lipoprotein cholesterol levels (Jeppesen et al., 1998). However, there is evidence to indicate that atherosclerosis may be a postprandial phenomenon in which atherogenic remnant lipoproteins (chylomicrons and very low-density lipoproteins) play a critical role (Eberly et al., 2003). These triglyceride-rich particles are smaller than other lipid components, and more readily penetrate arterial intimal cells. Individuals are in a nonfasting state most of the day with respect to serum TG, since fat tolerance testing notes that TG levels peak 4 h after an oral fat load, and return to basal values only after 8–10 h (Nordestgaard et al., 2007).

Data from the Copenhagen study ($n=13,981$, mean follow-up 26 years), indicate a significant linear correlation between nonfasting TG values and directly measured remnant lipoproteins (Nordestgaard et al., 2007), providing the impetus to examine the association between nonfasting TG and CV risk. Over the course of the study follow-up, there was a significant relationship between nonfasting TG levels in men and women and risk of major CV-related events including ischemic heart disease, myocardial infarction (MI), and mortality (Nordestgaard et al., 2007). Compared to those with nonfasting TG<1 mmol/l (88.5 mg/dl), women and men with levels of 2–2.99 mmol/L (177.0–264.6 mg/dl) had adjusted hazard ratios for MI of 2.5 and 1.6 respectively. The superiority of nonfasting TG over fasting TG is seen in prospective data from the Women's Health Study ($n=26,509$, median follow-up 11.4 years) (Bansal et al., 2007). While there was no relationship between increasing tertiles of fasting TG values and risk of CV events in fully adjusted models, nonfasting TG tertiles were significantly associated with CV risk, with TG levels measured 2–4 h postprandially showing the strongest association.

Schizophrenia patients are a high-risk group for CV mortality, with lifestyle factors and treatment playing additive roles (Goff et al., 2005; Newcomer and Hennekens, 2007). Given the differential impact of antipsychotics on fasting TG (Meyer et al., 2008) and random serum TG levels (Lieberman et al., 2005) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial phase 1, the *a priori* hypothesis for this analysis is that there would be significant between-drug differences for nonfasting TG changes.

2. Methods

The recruitment criteria for the CATIE Schizophrenia Trial and enrollment methods have been previously described (Lieberman et al., 2005). CATIE subjects were asked to present in a fasting state for laboratory evaluations, but there was a significant range recorded for time since last meal. Only subjects who ate <8 h prior to phlebotomy at the baseline and 3-month assessment were used for this analysis. The 3-month time point was chosen to maximize subject retention, while providing a physiologically meaningful time frame to assess the impact of antipsychotic treatment. Due to the skewness of the nonfasting TG data, treatment groups were compared with a nonparametric test, rank analysis of covariance (Koch et al., 1982). Multiple factors were examined to assess the influence on outcome (age, gender, race/ethnicity, smoking status, baseline antipsychotic medication, baseline nonfasting TG), and treatment group comparisons were adjusted for those factors that were statistically significant ($p<0.05$). A supportive unadjusted Kruskal–Wallis rank test was also performed. In both analyses, if the overall 4 *df* test for treatment group was significant at 0.05, then the 10 between-drug comparisons were evaluated using a Bonferroni correction, yielding an alpha of $0.05/10=0.005$. Due to the relatively conservative nature of this correction, *p*-values between 0.005 and 0.01 are also identified for the reader's

Table 1
Demographic comparison of CATIE subjects with nonfasting triglyceride levels at both baseline and 3-month assessments vs. other subjects with baseline and 3-month data

Parameter	Nonfasting TG	Other subjects	*p*
Age	43.0±10.7 (*n*=246)	40.4±11.0 (*n*=687)	0.001
Gender (% male)	73.6% (*n*=246)	74.1% (*n*=687)	NS
Race (% White)	55.7% (*n*=246)	63.1% (*n*=686)	0.040
Ethnicity (% Hispanic)	9.4% (*n*=246)	12.5% (*n*=687)	NS
Years since first antipsychotic treatment	16.2±11.6 (*n*=236)	13.9±10.7 (*n*=663)	0.006
Baseline DM diagnosis	12.6% (*n*=246)	13.5% (*n*=687)	NS
Smoker	55.0% (*n*=242)	59.4% (*n*=667)	NS
Body Mass Index (kg/m^2)	30.3±6.6 (*n*=246)	29.9±7.3 (*n*=677)	NS
Baseline TG (mg/dl)	216.9±162.7 (*n*=246)	200.5±166.8 (*n*=645)	NS

Table entries are mean±SD, or %.
p-values for comparison of means are from a *t*-test; those for comparison of proportions are from a chi-square test with 1 *df*.
NS=not significant ($p \geq 0.05$).

discretion. All metabolic laboratory measures were performed at the Quintiles central laboratory.

3. Results

Demographic comparison between subjects with nonfasting TG at both time points (*n*=246) and other subjects with baseline and 3-month data (*n*=687) showed similar distributions by gender, ethnicity, body mass index, diabetes mellitus and smoking prevalence, but the nonfasting TG cohort was older by 2.6 years, with 2.3 years longer drug exposure, and had fewer white subjects (Table 1). At study entry, 28.1% of the 246 subjects were on no antipsychotic, 19.1% on olanzapine, 4.9% on quetiapine, 19.5% on risperidone, 17.5% on other antipsychotics, and 11.0% on antipsychotic combinations. The distribution of median nonfasting TG is comparable to general population studies (Nordestgaard et al., 2007), and shows serum values peaking 2–4 h from last meal, with the numerically highest peak seen in subjects reporting last meal 2–3 h prior to laboratory determination (Fig. 1).

Among the demographic factors examined, only baseline nonfasting TG values were significantly associated with 3-month changes in this variable, and this was utilized in adjusted analyses. Table 2 presents median, and baseline-adjusted mean 3-month nonfasting TG changes, although all statistical testing is nonparametric (rank transformation) due to the skewness of the data. The greatest increases in median and adjusted mean nonfasting TG levels were seen among those randomized to quetiapine (mean+54.7 mg/dl, median+26 mg/dl) and olanzapine (mean+23.4 mg/dl, median+26.5 mg/dl), while ziprasidone was neutral (mean+0.0 mg/dl, median+8 mg/dl), and decreases were seen in subjects exposed to risperidone (mean −18.4 mg/dl, median −6.5 mg/dl) and perphenazine (mean −1.3 mg/dl, median −22 mg/dl). Adjustment for baseline nonfasting TG values with a ranked ANCOVA revealed overall significant treatment differences ($p=0.009$), with a

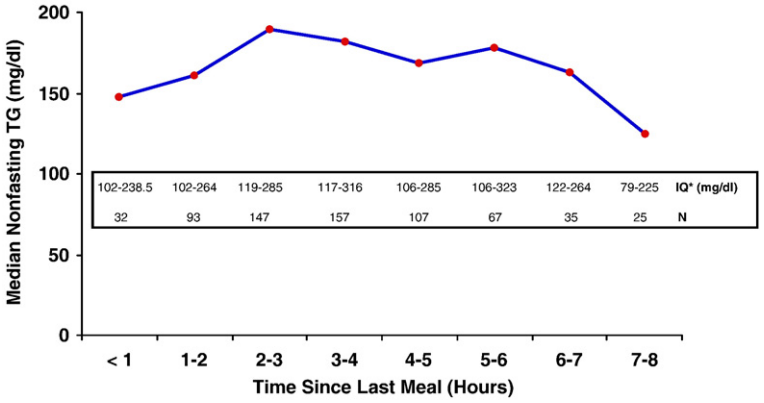

Fig. 1. Median baseline nonfasting triglyceride (TG) values by time since last meal. *IQ = interquartile range 25th–75th percentile.

Table 2
3-month changes from baseline in nonfasting triglycerides (mg/dl) by treatment group

		Observed		Adjusted[a]
	N	Median (interquartile range)	Mean±SD	Least squares mean±SE
Olanzapine	62	26.5 (−20 to 80)	33.1±159.1	23.4±22.8
Perphenazine	39	−22 (−81 to 24)	−3.7±243.8	−1.3±28.6
Quetiapine	59	26 (−34 to 96)	36.0±264.0	54.7±23.5
Risperidone	56	−6.5 (−52 to 38)	−7.9±85.3	−18.4±24.0
Ziprasidone	30	8 (−48 to 58)	0.4±145.0	0.0±32.7
Overall treatment difference		0.016[b]		0.009[c]

[a] Model adjusted for baseline triglycerides. Age, gender, race, ethnicity, baseline antipsychotic medication and smoking were allowed to enter the model but were not significant. The interaction between baseline triglycerides and treatment was also explored and was not significant.
[b] Unadjusted comparisons using the Kruskal–Wallis rank test revealed overall significant treatment differences ($p=0.016$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. perphenazine ($p=0.002$).
[c] Rank ANCOVA adjusting for baseline triglycerides revealed overall significant treatment differences ($p=0.009$). Individual pairwise comparisons revealed a significant difference for perphenazine vs. olanzapine ($p=0.002$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.006$).

significant between-group difference for perphenazine vs. olanzapine ($p=0.002$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.006$). A supportive unadjusted analysis was similar: $p=0.016$ overall, $p=0.002$ for perphenazine vs. olanzapine, and $p=0.012$ for perphenazine vs. quetiapine.

For phase 1, there was a distinct possibility that subjects could be randomized to the same medication taken at study baseline, and be unlikely to experience significant changes in outcome measures compared to those who switched medications. Among the 246 subjects, there were 37 nonswitchers (13 olanzapine, 14 risperidone, 8 quetiapine, 2 other), so the data were reexamined after excluding these subjects (Table 3). In this analysis, the between-drug treatment differences at 3 months became more pronounced ($p=0.001$, adjusted for baseline). The pairwise comparisons now revealed significant differences for olanzapine vs. perphenazine ($p<0.001$), olanzapine vs. risperidone ($p=0.002$), and quetiapine vs. perphenazine ($p=0.003$). Unadjusted results were similar (overall $p=0.001$). Due to the small number of nonswitchers, and the unbalanced composition (predominantly olanzapine and risperidone at baseline), comparisons of switchers vs. nonswitchers were not performed.

4. Discussion

Presented here are the first data to examine the impact of antipsychotic therapy specifically in subjects with

Table 3
3-month changes from baseline in nonfasting triglycerides (mg/dl) by treatment group excluding nonswitchers

		Observed		Adjusted[a]
	N	Median (interquartile range)	Mean±SD	Least squares mean±SE
Olanzapine	49	30 (−4 to 87)	64.3±137.3	61.5±24.0
Perphenazine	39	−22 (−81 to 24)	−3.7±243.8	−2.4±26.7
Quetiapine	51	27 (−32 to 96)	57.5±179.6	59.8±23.5
Risperidone	42	−10.5 (−76 to 31)	−12.2±79.8	−13.1±25.7
Ziprasidone	28	8 (−64 to 56)	−2.0±149.6	−1.8±31.5
Overall treatment difference		0.001[b]		0.001[c]

[a]Model adjusted for baseline triglycerides. Age, gender, race, ethnicity, baseline antipsychotic medication and smoking were allowed to enter the model but were not significant. The interaction between baseline triglycerides and treatment was also explored and was not significant.
[b]Unadjusted comparisons using the Kruskal–Wallis rank test revealed overall significant treatment differences ($p=0.001$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. both perphenazine ($p<0.001$) and risperidone ($p=0.001$). The change in nonfasting TG was also numerically different for perphenazine vs. quetiapine, although not statistically significant with the Bonferroni correction ($p=0.008$).
[c]Rank ANCOVA adjusting for baseline triglycerides revealed overall significant treatment differences ($p=0.001$). Individual pairwise comparisons revealed a significant difference for olanzapine vs. both perphenazine ($p<0.001$) and risperidone ($p=0.002$), and quetiapine vs. perphenazine ($p=0.003$).

nonfasting serum TG values. The concept that postprandial hyperlipidemia best reflects the role of triglyceride-rich particles in atherogenesis is quite new, and has only recently been born out by large, long-term clinical trials (Eberly et al., 2003; Bansal et al., 2007; Nordestgaard et al., 2007). Most studies of antipsychotic lipid effects have focused on fasting TG values (Meyer and Koro, 2004), and rightfully so, due to the association between fasting TG and the metabolic syndrome (McEvoy et al., 2005) or directly measured insulin sensitivity (McLaughlin et al., 2003).

Olanzapine treatment has been associated with deleterious impact on lipid profiles (Meyer and Koro, 2004), but recent findings from a large first-episode trial (McEvoy et al., 2007) and CATIE phase 1 raised concerns that, at dosages used to treat schizophrenia, quetiapine is also associated with significant increases in random TG (Lieberman et al., 2005; Correll, 2007) and fasting TG (McEvoy et al., 2007; Meyer et al., 2008). With the stringent Bonferroni correction, the quetiapine vs. perphenazine comparison ($p=0.006$) did not meet the required 0.005 level of significance, but the numerical change in nonfasting TG seen in the adjusted analysis (+54.7 mg/dl), and the significant result when nonswitchers were excluded (quetiapine vs. perphenazine $p=0.003$), suggests that quetiapine has a lipid profile distinct from risperidone (−18.4 mg/dl) in a manner not appreciated several years ago, when the American Diabetes Association/American Psychiatric Association consensus paper on antipsychotic metabolic effects found these agents comparable on the basis of the available data (American Diabetes Association, 2004). That ziprasidone, risperidone and perphenazine treatment did not significantly increase nonfasting TG was expected, although it is surprising that ziprasidone in particular did not decrease nonfasting TG.

One limitation of this study is that the small sample size of each drug arm precludes stratification by time since last meal, age, gender or race. These effects can be managed with controlled prospective studies using fat tolerance testing or other means to examine lipid metabolism. The findings from the recent large clinical trials (Nordestgaard et al., 2007; Bansal et al., 2007) demonstrate a robust association between nonfasting TG and CV risk. Whether nonfasting TG will replace fasting TG measurements, or used in addition to fasting TG to provide added information on CV risk, and the optimal time since last meal to obtain this result, awaits consensus recommendations. Nonetheless, this study provides confirmation of the differential metabolic impact of atypical antipsychotics, and the need for clinicians to routinely monitor parameters associated with metabolic risk.

Role of funding source

The CATIE Trials were supported by National Institute of Mental health (NIMH) grant #N01MH90001. The NIMH and study principal investigators are responsible for the design and conduct of the trial, and the primary analyses. There is no industry involvement in these activities.

Contributors

Drs. McEvoy, Stroup and Lieberman are the CATIE principal investigators and were involved in the study design and creation of the protocol, and oversaw data collection, with input and support from co-investigator Drs. S. Davis and M. Swartz, and collaborators Drs. Hsiao and Goff. Dr. V. Davis performed the statistical analyses. Drs. Meyer, V. Davis, Goff, McEvoy, Nasrallah, S. Davis and Daumit were involved in the interpretation of findings and outline of the manuscript. Dr. Meyer wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Jonathan M. Meyer, M.D.: Dr. Meyer reports having received research support from Bristol-Myers Squibb and Pfizer, Inc., and has received speaking or advising fees from Bristol-Myers Squibb, Janssen Pharmaceutica, Organon, Pfizer, Inc., Vanda, and Wyeth.

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Incidence of diabetes in a general practice population: a database cohort study on the relationship with haloperidol, olanzapine, risperidone or quetiapine exposure

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The present study aimed to estimate the incidence of diabetes in general practice patients who were treated with haloperidol, olanzapine, risperidone or quetiapine monotherapy and in subjects who were not exposed to antipsychotics. The design was a retrospective, up to 2 years, cohort study, with age-, sex- and length of observation-matching between subjects who were exposed and not exposed to antipsychotic drugs. Data were taken from the Health Search database, which contains information from 550 Italian general practitioners. Participants comprised 2071 subjects taking haloperidol, 266 taking olanzapine, 567 taking risperidone and 109 taking quetiapine, in addition to 6026 age- and sex-matched subjects who were not using antipsychotic drugs during the period of observation. Inclusion was limited to initially non-diabetic and antipsychotic drug-free individuals. The main outcome measure was the incidence of drug-treated diabetes. After age and sex correction by Cox regression analysis, the four groups treated with antipsychotics significantly differed from untreated subjects in hazard ratios for diabetes. The ratios for the haloperidol, olanzapine, risperidone and quetiapine groups were 12.4 (95% confidence interval 6.3–24.5), 20.4 (6.9–60.3), 18.7 (8.2–42.8) and 33.7 (9.2–123.6), respectively, with no significant differences when compared to each other. *Int Clin Psychopharmacol* **20:33–37 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Early evidence indicating that antipsychotic drugs may represent a risk factor for diabetes recognizes old routes, when the typical but not the atypical antipsychotics were available (Thonnard-Neumann, 1956; Jori and Bianchetti, 1966). Nevertheless, this problem has become the subject of serious concern only at the turn of the millennium, following the publication of case reports linking atypical antipsychotics to new onset diabetes (Lindenmayer and Patel, 1999; Ober *et al.*, 1999; Rigalleau *et al.*, 2000; Bonanno *et al.*, 2001).

Subsequently, some large-scale studies, mostly based on prescription data and on already existing databases, have confirmed that schizophrenic patients taking atypical antipsychotics show unusually high rates of diabetes (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Kornegay *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Sernyak *et al.*, 2002; Buse *et al.*, 2003).

However, these studies do not lead to any firm conclusions about possible drug- and/or class-specific contributions to the diabetogenic potential associated with the intake of antipsychotics. Indeed, head-to-head comparisons between atypical antipsychotics have produced conflicting results and the typical antipsychotics have been less systematically studied (Caro *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003).

In addition, the published reports available show a lack of a direct estimate of diabetes incidence in the general population (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Kornegay *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002), selection of patients without a previous antipsychotic drug-free period (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002), recruitment of patients exposed to antipsychotic polipharmacotherapy (Caro *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003) and the use of prevalence rather than incidence rates of diabetes (Sernyak *et al.*, 2002).

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In an attempt to overcome some of these limitations, we evaluated retrospectively, by means of a general practitioners database, the incidence of diabetes among patients who had started haloperidol, olanzapine, risperidone or quetiapine monotherapy. Age- and sex-matched individuals who were non-diabetic at study entry, and who were not prescribed antipsychotic drugs during the observational period, were also selected to control for the incidence of diabetes in the general population.

Methods

Study population

The study included subjects from the Health Search Database, a computerized system set-up in the mid-1990 s to collect data taken from the daily clinical activity of general practitioners (GP). Currently, the database contains information from 550 GPs from all over Italy with a total of approximately 800 000 patients (i.e. 1.5% of the Italian population). After extensive training on software use, GPs store data in real time and send them to a central server based in Florence, where a GPs association (the Società Italiana dei Medici di Medicina Generale) processes data for research purposes. To ensure quality, every 3 months, all the information collected in the database undergoes extensive monitoring with a scheduled feedback from administrators to users. A unique identification number links all data to an individual patient who remains anonymous and no identifying details are available. Each patient provided a written informed consent to allow processing of data taken by the GPs.

The Health Search Database has demonstrated a good concurrent validity in estimating the prevalence of diabetes mellitus in a subsample of 432 747 subjects compared to an independent population estimate (Cricelli *et al.*, 2003).

Cohorts

The cohort at risk included all non-diabetic patients who started haloperidol, olanzapine, risperidone or quetiapine in monotherapy and who were followed-up for a maximum of 2 consecutive years, provided that they had experienced an antipsychotic drug-free period from their last visit to study entry. The period under scrutiny started on 1 January 1996 and ended on 31 March 2002. Emergence of diabetes, co-therapies with other antipsychotic drugs, death or loss of the patient to follow-up for any reason were identified as the causes of truncated observations. New onset diabetes was defined as the prescription of any anti-diabetic drug after the entry visit.

In turn, the unexposed cohort was randomly selected from the database according to a list that included only those individuals who were non-diabetic and antipsychotic-free at study entry and who were not prescribed antipsychotics during the follow-up. Two rigorously age- and sex-matched subjects were extracted for each patient treated with an antipsychotic drug.

Each subject was evaluated for new onset diabetes during the same period of observation as the linked, exposed patient.

Sex, age, the length of the observational period, the interval between entry visit and the onset of diabetes, and the number of prescriptions of antipsychotics for exposed individuals comprised the study variables.

Statistical analysis

First order associations were analysed by the chi-square test or univariate analysis of variance, when appropriate. Cox regression model was applied to evaluate the hazard ratios for diabetes onset and the independent effect of age, sex and treatment on risk estimates. Linear contrasts were used to test for differences between exposed and unexposed subjects and among treatments. Power analysis was used to estimate the sample sizes needed to achieve statistical significance ($\alpha = 0.05$, $1 - \beta = 0.80$) in the comparison of different antipsychotics, taking the detected diabetes rates as reference.

All statistics were performed with the SPSS package (version 10.1) (SPSS Inc., Chicago, Illinois, USA).

Results

The haloperidol, olanzapine, risperidone and quetiapine groups included 2071, 266, 567 and 109 patients, respectively. According to the 1–2 sampling rate, the unexposed group comprised 6026 individuals.

The four treatment groups differed in age, sex and treatment variables but not in sex distribution (Table 1). The raw incidence of diabetes (per 1000 person-years) in patients taking haloperidol, olanzapine, risperidone and quetiapine was 19.6, 22.8, 24.9 and 52.7, respectively. The incidence in unexposed subjects was 1.5 (Table 2). After age and sex correction with Cox analysis, each of the four groups of patients treated with an antipsychotic drug had a hazard ratio for new-onset diabetes that was higher compared to that of the unexposed group ($P < 0.001$) (Table 3). The ratios estimated for haloperidol, olanzapine, risperidone and quetiapine were not significantly different when compared to each other.

Among all individuals who were treated with antipsychotics, patients with and without diabetes had a similar number of prescriptions, 4.4 versus 3.4 (Student's *t*-test 1.4, P = NS). Furthermore, the time needed for the onset of diabetes from the beginning of the antipsychotic therapy overlapped (248.1, 236.6, 299.5 and 275.3 days) in the groups treated with haloperidol, olanzapine,

Table 1 Sociodemographic and clinical features of patients taking olanzapine, risperidone, quetiapine or haloperidol

Variable	Olanzapine ($n=266$)	Risperidone ($n=567$)	Quetiapine ($n=109$)	Haloperidol ($n=2071$)	*P*-value
Age (mean ± SD)	52.6 ± 20.4	58.3 ± 23.3	65.0 ± 21.3	66.5 ± 21.0	$F=47.5$, $P<0.001$ (3 d.f.)[a]
Sex (%)					
Males	49.2	43.9	37.6	40.7	Chi-square 8.9, $P=0.03$ (3 d.f.)
Females	50.8	56.1	62.4	59.3	
Total prescriptions (mean ± SD)[d]	3.5 ± 3.7	2.5 ± 3.1	3.9 ± 5.0	3.7 ± 6.0	$F=7.2$, $P<0.001$ (3 d.f.)[b]
Follow-up days (mean ± SD)[e]	301.7 ± 221.8	335.9 ± 238.6	190.7 ± 135.2	430.7 ± 262.8	$F=60.5$, $P<0.001$ (3 d.f.)[c]

[a]In the post-hoc analysis, significant differences ($P<0.05$) in the pairs: haloperidol/olanzapine, haloperidol/risperidone, olanzapine/risperidone, olanzapine/quetiapine and risperidone/quetiapine.
[b]In the post-hoc analysis, significant differences ($P<0.05$) in the pairs: olanzapine/risperidone, risperidone/quetiapine and haloperidol/risperidone.
[c]In the post-hoc analysis, significant differences ($P<0.05$) in the pairs: haloperidol/olanzapine, haloperidol/quetiapine, haloperidol/risperidone, olanzapine/quetiapine and risperidone/quetiapine.
[d]Prescriptions were included only if given directly by general practitioners.
[e]If longer, truncated at 2 years.

Table 2 Raw incidence of diabetes in subjects taking haloperidol, olanzapine, risperidone or quetiapine and unexposed subjects

Treatment	Year of follow-up	Number entering the interval	Censored subjects	Population at risk	Incident diabetes	Cumulated days of observation[a]	Incidence/ 1000 person-years
Haloperidol	First	2071	843	1649.5	33	892 001	19.6
	Second	1195	532	929	15		
Olanzapine	First	266	166	183	4	80 240	22.8
	Second	96	74	59	1		
Risperidone	First	567	338	398	9	190 430	24.9
	Second	220	131	154.5	4		
Quetiapine	First	109	97	60.5	3	20 787	52.7
	Second	9	9	4.5	–		
Unexposed subjects	First	6026	2912	4570	8	2 406 446	1.5
	Second	3106	1570	2321	2		

[a]Estimated on the overall observation time (first and second years); follow-ups longer than 2 years were truncated at 2 years.

Table 3 Hazard ratios[a] for diabetes in the four treatment groups

Treatment[b]	Ratio	95% confidence interval	*P*-value
Olanzapine	20.35	6.86–60.33	<0.001
Risperidone	18.71	8.18–42.81	<0.001
Quetiapine	33.68	9.18–123.55	<0.001
Haloperidol	12.40	6.27–24.52	<0.001

[a]Cox proportional hazard regression analysis after correction for Age (ratio 1.03; 95% confidence interval 1.01–1.04; $P<0.001$) and Sex (ratio of females 1.04; 95% confidence interval 0.66–1.65; $P=0.87$).
[b]Unexposed subjects = reference group.

Table 4 Power analysis estimates of sample sizes needed to reach a significant difference between treatment groups in observed diabetes incidence

Drugs compared	No. of subjects
Risperidone versus haloperidol	25 702
Olanzapine versus haloperidol	67 237
Quetiapine versus haloperidol	1063
Risperidone versus olanzapine	175 150
Risperidone versus quetiapine	1609
Olanzapine versus quetiapine	1356

risperidone and quetiapine, respectively ($F = 0.23$, $P = \text{NS}$).

According to power analysis, the number of patients required to differentiate the risk of diabetes between the four groups treated with an antipsychotic ranged between 1063 and 175 150, where the lowest figure is for comparisons involving quetiapine, and with values increasing progressively for comparisons between risperidone and haloperidol, olanzapine and haloperidol, and risperidone and olanzapine, respectively (Table 4).

Discussion

Two key-points best summarize the results of the multiple comparisons performed. The first is that, after an antipsychotic drug-free interval, the groups treated with haloperidol, olanzapine, risperidone or quetiapine monotherapy shared a higher risk for new-onset diabetes compared to untreated subjects. The second is that the hazard ratios computed for the four treatments were not significantly separated.

Our study design was based on cohort selection (exposed versus unexposed), and not on a simpler case–control design (diabetes versus no diabetes), to ensure estimation of the incidence of the disorder within a given time frame and to compare our results with recent studies (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003) that have selected cohorts in the same way.

The inclusion of a rigorously age- and sex-matched group of untreated subjects and the selection of patients exposed to only one antipsychotic after a drug-free period

were major strong points in our study compared to most published studies.

To our knowledge, this is the first study explicitly evaluating diabetes incidence in patients treated with quetiapine: this original contribution provides added value to the study despite the relatively small size of the quetiapine sample.

The lack of information concerning life-styles, comorbidities and other variables known to facilitate the onset of diabetes represents a weak point of our study because we were unable to analyse the contribution of these risk factors. However, the very high degree of significance in all the comparisons opposing exposed and unexposed subjects, together with similar diabetes rates found in haloperidol, olanzapine, risperidone and quetiapine groups, suggests a high probability of a truly generalized phenomenon, with a reduced risk of type I errors and other spurious second-order associations.

A possible dose-dependent effect of antipsychotic drugs on the risk of new onset diabetes cannot be ruled out because doses were not recorded. However, any possible dose effect would have dampened, rather than inflated, the increased incidence of diabetes in our patients treated with antipsychotics because GPs often underdose antipsychotics (Raschetti *et al.*, 1993).

Because of the lack of information on diagnoses, it was not possible to establish to what extent different psychiatric disorders can affect the risk of diabetes. This might be the case for schizophrenia (Ryan *et al.*, 2003). However, a strong effect of second-order associations mediated by schizophrenia is unlikely in our sample of GP patients: a wide diagnostic heterogeneity is to be expected in the four treatment groups because GPs frequently prescribe antipsychotics to control the symptoms of many clinical conditions outside the spectrum of schizophrenia (Hohmann, 1989).

Numerical, but not significant, differences in the hazard ratios for diabetes onset among groups of patients treated with different antipsychotics must be interpreted with caution because the lack of balance in sample sizes may have caused false negatives. Nevertheless, power analysis, based on our incidence rates, shows that several thousand patients would be needed to achieve statistical significance in head-to-head comparisons between haloperidol, olanzapine and risperidone groups. Even if the differences between the three treatments are real, these should have questionable clinical relevance. The case of quetiapine is partially different. Relatively few patients were treated with this drug and power analysis indicates that significance in the comparisons with the other antipsychotics can be provided by relatively small samples. Therefore, any conclusion should be postponed. In the meantime, the quetiapine-associated risk for diabetes should be regarded as being equal to that of haloperidol, olanzapine and risperidone.

Our results substantially agree with those obtained in recent studies investigating the incidence of diabetes with novel antipsychotics. Regarding olanzapine and risperidone, rates of 17.0 and 16.0/1000, respectively, were reported by Caro *et al.* (2002); 25.3 and 33.3/1000, respectively, were reported by Lee *et al.* (2002); and 42.0 and 21.0/1000 (within the 8–12 months follow-up group), respectively, were reported by Gianfrancesco *et al.* (2002). The studies of Koro *et al.* (2002) and Kornegay *et al.* (2002) were based on a case–control design, so that 1-year prevalence rates could not be estimated.

Only Buse *et al.* (2003) have reported higher incidence rates for olanzapine and risperidone (58 and 79/1000). However, the same authors also reported a diabetes incidence in unexposed subjects (15.7/1000) that clearly exceeded the rates commonly observed in general population samples: 1.0–1.5/1000 in Njolstad *et al.* (1998); 0.15/1000 (type I) and 2.7/1000 (type II diabetes) in Berger *et al.* (1999); 3.7/1000 in Burke *et al.* (2002); and 2.2/1000 in the Duch study of Ubink-Veltmaat *et al.* (2003) involving the database of 61 general practitioners. The rate of 1.5/1000 found in our study is very similar to these reports.

A series of suggestions appears justified for clinical practice. The main emerging recommendation is that clinicians and patients who need antipsychotic drugs should be updated on diabetes risk during treatment with these compounds. Clear, non-dramatizing information about possible hyperglycaemia-related adverse events inserted in the product labelling of antipsychotic drugs might represent the most direct and convenient operative way. The lack of clinically relevant drug- or class-specific effects on diabetes risk highlights the need for a generalized warning for both typical and atypical antipsychotics. At least two other considerations point in this direction. One is that the estimate of the risk for new onset diabetes is likely to be more conservative for haloperidol than for olanzapine, risperidone and quetiapine because the typical antipsychotics are generally associated with a relatively poorer treatment adherence (Barnes and McPhillips, 1998). The second is that, among the typicals, haloperidol most likely has one of the most benign diabetogenic profiles because abnormal glucose metabolism has been more often associated with low potency antipsychotics (Gianfrancesco *et al.*, 2002).

Given the lack of robust evidence favouring some antipsychotics over others, clinicians should also focus on early identification of first-line candidates for diabetes

to prevent this adverse event. For early detection, physicians should carry out a careful, periodically revised, assessment of diabetes vulnerability factors and test glucose metabolism in at-risk patients (ADA *et al.*, 2004). For prevention, once it is accepted that antipsychotic drugs are needed for psychotic patients and that psychoeducational intervention reduces diabetes incidence in non-psychiatric populations (Knowler *et al.*, 2002), strong psychoeducational programmes should be tailored to the special needs of patients exposed to antipsychotics to ensure the promotion of appropriate healthy behaviour.

For research purposes, the separation of specific and non-specific antipsychotic drug effects on diabetes risk merits priority. The ideal study should not only include all the most widely prescribed antipsychotics, but also emphasize the strongest diabetes risk factors and putative diagnosis-related effects. However, an exhaustive collection of data on predisposing variables is largely beyond the reach of even the best database, and the need to start with antipsychotics as soon as possible precludes the recruitment of large samples of drug-free psychotic patients. Therefore, prospective studies recording the most relevant risk factors, controlling psychiatric diagnoses and involving enough centres to give adequate statistical power, represent the most desirable strategy.

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Original Contribution

Diabetes Risk Associated with Use of Olanzapine, Quetiapine, and Risperidone in Veterans Health Administration Patients with Schizophrenia

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To evaluate risk of new-onset type 2 diabetes associated with use of selected antipsychotic agents, the authors conducted a new-user cohort study in a national sample of US Veterans Health Administration patients with schizophrenia (and no preexisting diabetes). The authors studied 15,767 patients who initiated use of olanzapine, risperidone, quetiapine, or haloperidol in 1999–2001 after at least 3 months with no antipsychotic prescriptions. Patients were followed for just over 1 year. New-onset diabetes was identified through diagnostic codes and prescriptions for diabetes medication. In Cox proportional hazards regression adjusting for potential confounders, with patients initiating haloperidol use designated the reference group, diabetes risk was increased equally with new use of olanzapine (hazard ratio (HR) = 1.64, 95% confidence interval (CI): 1.22, 2.19), risperidone (HR = 1.60, 95% CI: 1.19, 2.14), or quetiapine (HR = 1.67, 95% CI: 1.01, 2.76). Diabetes risks were higher in patients under age 50 years. When data were reanalyzed with prevalent-user cohorts and matched case-control designs, results were similar, with slightly less elevated risk estimates. Assuming that the observed associations are causal, approximately one third of new cases of diabetes may be attributed to use of olanzapine, risperidone, and quetiapine in patients taking these medications. Prescribers should be mindful of diabetes risks when treating patients with schizophrenia.

antipsychotic agents; case-control studies; cohort studies; diabetes mellitus; pharmacoepidemiology; schizophrenia; veterans

Abbreviation: VHA, Veterans Health Administration.

The introduction of a new generation of antipsychotic drugs has been heralded as an important advance in the treatment of schizophrenia. The ''atypical'' or second-generation antipsychotic agents (e.g., olanzapine) are at least as effective as older drugs (e.g., haloperidol) in treating schizophrenia but are less likely to cause extrapyramidal side effects and tardive dyskinesia (1–11). However, some of the newer drugs have been associated with metabolic disturbances,

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including weight gain (12–17), hyperlipidemia (18–20), hyperglycemia, and new-onset diabetes mellitus (18, 21–25).

Evidence for a possible link between use of second-generation antipsychotic agents and diabetes has come from case reports (26–46), case-control studies (47), and cohort studies of ongoing users (23, 25, 48, 49). While most studies have reported an association, the magnitude of the risk and the differences in risk among agents in this class have varied between studies. This inconsistency is probably related to differences in the patient populations studied, reference groups, definitions of diabetes, exposure definitions, and control for potential confounding. Furthermore, most of the studies failed to restrict the exposure to new users or to persons using single agents, so confounding related to discontinuation or switching of medication may have biased the results (50).

We conducted a study to determine the risk of new-onset type 2 diabetes in relation to newly initiated use of single-agent antipsychotic medications among Veterans Health Administration (VHA) patients with schizophrenia. We attempted to improve exposure definition, reduce selection bias, adjust for multiple confounders, and minimize the influence of previous antipsychotic agents on the observed outcome. To facilitate comparisons with previous studies and to illustrate the impact of design choices on results of observational studies, we also describe the results obtained in a prevalent-user cohort analysis and a matched case-control analysis.

MATERIALS AND METHODS

Data sources

In this study, we used electronic data available for all VHA patients nationally (51). This includes information on all VHA medical encounters (outpatient, inpatient, and long-term-care) obtained from the Austin Automation Center, VHA outpatient and inpatient prescription data from the Pharmacy Benefits Management Strategic Healthcare Group, and death records from the Beneficiary Identification Records Locator Subsystem, a registry of all veterans who applied for VHA death benefits that is supplemented by data from Social Security records. This study was approved by the institutional review boards of the University of Illinois at Chicago and the Hines Veterans Health Administration (Hines, Illinois).

Sample selection

We identified VHA patients with schizophrenia and constructed a series of new-user cohorts of patients who began receiving antipsychotic medication after 12 or more weeks without an antipsychotic prescription. Schizophrenia patients were identified on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes for schizophrenia (295.xx) in records of inpatient stays or outpatient visits on at least two separate days from October 1, 1996, through September 30, 2001. Study subjects were restricted to those who had filled at least one prescription for an antipsychotic drug from January 1, 1999, through September 30, 2001. To study new users only, we further excluded those patients who had been prescribed antipsychotic medication during the first 12 weeks of collection of national prescription data, from October 1, 1998, through December 31, 1998. To study new-onset diabetes only, we also excluded patients who had any sign of diabetes prior to their first exposure to antipsychotic agents (a diabetes diagnostic code (250.xx) going back to October 1, 1996, or a prescription for a diabetes medication going back to October 1, 1998). We also excluded all patients whose first contact with the VHA system (based on the presence of any prescription, procedure, or diagnostic record in inpatient or outpatient data) was fewer than 12 weeks prior to their first antipsychotic drug exposure. In this way, we could be reasonably sure that patients were using the VHA on an ongoing basis and were unlikely to be receiving antipsychotic agents from other sources.

Definition of diabetes

Patients were considered to have new-onset diabetes if they were given diabetes diagnostic codes (250.xx) on at least two separate days or if they filled a prescription for an antidiabetic drug (insulin, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, or meglitinides). This definition has been shown to be reliable and valid in the VHA system (52). The date of diabetes was defined as the earliest sign of diabetes (the first diagnosis or prescription) for a subsequently confirmed case.

Analysis

Analyses were conducted using SAS, version 8.2 (53). Four new-user cohorts were constructed consisting of schizophrenic patients newly initiating use of one of three selected second-generation antipsychotic medications (olanzapine, quetiapine, or risperidone) or haloperidol, the most commonly used conventional antipsychotic agent. There were insufficient numbers of new users of clozapine, ziprasidone, and aripiprazole for these persons to be included in the new-user cohort analysis.

Cohort samples were characterized and compared in terms of demographic factors and other study variables. Cox proportional hazards regression was used to estimate hazard ratios with 95 percent confidence intervals for new-onset diabetes developing over the course of follow-up (54). Observation began on the day a patient received his or her first prescription for an antipsychotic agent (after January 1, 1999) and continued until the first occurrence of diabetes, death, initiation of use of a second antipsychotic agent, or last contact with the VHA system prior to September 30, 2001. The proportional hazards assumption was confirmed using ''log-log'' plots (55).

Multivariate regression models were constructed to adjust for potential confounders, including sex, age, race/ethnicity, marital status, exposure to other medications that may cause diabetes (beta-blockers, thiazide diuretics, lithium, phenytoin, corticosteroids) (56), and number of basic or comprehensive metabolic panels that included glucose testing performed during follow-up. The last factor was included to adjust for potential bias related to intensity of screening

for diabetes that may have varied among patients using different antipsychotic medications.

In this analysis, we present hazards for initiating use of each second-generation antipsychotic medication, with persons initiating haloperidol as the reference category. To facilitate comparison with other studies, we also present some results of parallel analyses that used patients initiating any conventional antipsychotic agent (chlorpromazine, etc.) as the reference group.

This is a study of patients on single-agent antipsychotic drug therapy, since we censored patients when they switched to another antipsychotic drug. It is possible that some patients may have been switched from one drug to another after showing signs of glucose dysregulation. If such patients developed diabetes after switching medications, our initial analysis would have missed these cases when perhaps they should have been attributed to the preswitch drug. To examine this possibility, we reran our analyses including in the models any cases of diabetes that were diagnosed 30, 60, or 90 days after switching medications.

Hazard ratios for the various second-generation antipsychotic agents were compared and differences were evaluated using the Wald test (the TEST statement in PROC PHREG in SAS). Effect modification by age and other factors was evaluated using interaction terms in the overall models and conducting separate analyses in each stratum of age. Linear trends in hazard ratios by age were evaluated using an ordinal term. Estimates of attributable risk percentage were calculated using hazard ratios obtained from proportional hazards modeling (57).

Additional analyses: prevalent-user cohorts and case-control designs

We conducted two additional analyses. In the first, we implemented a prevalent-user cohort design, which was identical to that for the new-user cohorts except that we did not exclude patients who had been exposed to antipsychotic agents during the prior 12-week period. These cohorts were larger and consisted mostly of schizophrenia patients on continuing antipsychotic drug therapy. Observation began with the first antipsychotic prescription, regardless of prior prescriptions, and continued as in the new-user cohort design, with proportional hazards regression being employed in the analysis.

In the second additional analysis, we conducted a matched case-control analysis nested in the prevalent-user cohorts. Among persons initiating use of antipsychotic agents, new-onset cases of diabetes were matched on sex, age (±5 years), and location of VHA care with up to six controls who showed no evidence of diabetes over the course of the study. Medication exposures prior to diabetes diagnosis in the case and during the same time period for matched controls were examined, without restriction to newly initiated use. Patients in the case-control study had to have been taking one and only one antipsychotic medication during the retrospective exposure period. Because there is little consensus on the timing of the putative effects of antipsychotic agents on diabetes risk, we used three different retrospective exposure periods: 12, 24, and 52 weeks prior to the development of diabetes in the case. Conditional logistic regression was used in the analysis to compute odds ratios and 95 percent confidence intervals for each of the second-generation antipsychotic medications, with haloperidol as the reference category (58). These models included terms for covariates identical to those entered in the proportional hazards regression models utilized in the new-user cohort design as described above, except for sex, since it was used in matching.

In conducting these additional analyses, we found sufficient numbers of patients prescribed clozapine to evaluate diabetes risk associated with this second-generation antipsychotic agent. Findings from parallel prevalent-user cohort and case-control analyses of this medication using similar methods are presented separately.

RESULTS

We observed 15,767 patients in the four cohorts of antipsychotic initiators studied (table 1). Patients in these cohorts were broadly similar in terms of age, sex, race/ethnicity, marital status, use of other potentially diabetogenic medications, and number of diabetes screening tests. There were slightly more women and fewer racial minority patients among the quetiapine users, and more never-married and African-American patients among those prescribed haloperidol. Otherwise, frequency distributions varied by no more than a few percentage points across the four cohorts. Average length of follow-up was also similar (just over 1 year), except for quetiapine, which was only approved for use during the study. The annual incidence (unadjusted) of new-onset diabetes over the course of follow-up ranged from 2.0 per 100 person-years of exposure in users of haloperidol to 3.6 per 100 person-years in quetiapine users.

Table 2 gives the hazard ratios and 95 percent confidence intervals for initiation of olanzapine, risperidone, and quetiapine, with patients initiating haloperidol used as the reference group. For all three second-generation antipsychotic agents, the hazard ratio was 1.6–1.7, and adjustment for potential confounders had little effect on the estimates. There were no significant differences in effects among the three second-generation antipsychotic agents. When 30, 60, or 90 days were added to follow-up in patients switching to another antipsychotic agent, the results were similar but with slightly narrower confidence intervals. There appeared to be effect modification by age, with generally higher odds ratios being seen in younger patients, at least for olanzapine and risperidone ($p = 0.05$ and $p = 0.03$, respectively, in tests of homogeneity of hazards between persons aged $\geq$50 years and $<$50 years). Estimates of attributable risk percentage were 33.3 percent, 32.0 percent, and 35.0 percent for olanzapine, risperidone, and quetiapine, respectively.

Table 3 summarizes results from the new-user cohort design in comparison with those from the two additional analyses implementing prevalent-user cohort and case-control designs. The more expanded sample of patients studied in these analyses (see table 4) was compared with patients in the new-user cohort design; except for a slightly smaller percentage of racial minority patients, there were no differences

TABLE 1. Characteristics of four cohorts of new users of antipsychotic medication ($n = 15,767$) among US veterans with schizophrenia, 1999–2001

Variable	Antipsychotic agent			
	Olanzapine ($n = 5,981$)	Risperidone ($n = 5,901$)	Quetiapine ($n = 877$)	Haloperidol ($n = 3,008$)
Mean age (years)	50.3 (11.2)*	51.1 (12.2)	50.6 (11.7)	52.0 (12.1)
Sex (%)				
Male	94.1	93.2	91.7	95.1
Female	5.9	6.8	8.3	4.9
Race/ethnicity (%)				
White	48.4	47.7	58.3	44.0
African-American	28. 8	30.8	21.2	39.4
Hispanic	6.8	4.8	4.1	5.4
Other	0.8	0.6	0.6	0.6
Unknown	15.2	16.2	15.8	10.6
Marital status (%)				
Married	22.3	22.4	21.3	16.9
Never married	40.5	40.0	39.2	46.5
Divorced, separated	32.6	32.1	33.7	30.0
Widowed	2.8	4.0	3.8	3.4
Unknown	1.8	1.4	1.9	2.1
Use of medications potentially inducing diabetes (%)				
Beta-blockers/thiazide diuretics	16.0	16.5	17.8	14.8
Lithium	5.9	5.2	5.9	5.1
Corticosteroids	1.6	1.5	0.8	1.8
Phenytoin	1.9	2.0	1.4	2.2
No. of metabolic panels per patient	0.18 (0.74)	0.18 (0.73)	0.15 (0.64)	0.19 (0.83)
Mean duration of follow-up (days)	367.4 (299.6)	371.6 (300.5)	244.3 (246.8)	364.5 (325.7)
Mean time to event (days)	240.8 (196.1)	267.3 (228.9)	214.1 (175.3)	304.1 (260.8)
No. of new cases of diabetes diagnosed during study period	200	193	21	60
Diabetes incidence per 100 person-years of exposure	3.3	3.2	3.6	2.0

* Numbers in parentheses, standard deviation.

of more than a few percentage points in the distributions of demographic factors, other medications, or laboratory tests. Except for quetiapine in the prevalent-user cohorts, the relative risk of diabetes was increased with use of all three second-generation antipsychotic agents, regardless of design. Estimates ranged from 1.2 to 1.8. In the prevalent-user cohorts, risk was elevated for both olanzapine and risperidone, but risk associated with olanzapine was significantly greater than that associated with risperidone ($p = 0.02$). Otherwise, there were no significant differences in diabetes-related risks for the three medications in any of the analyses.

When the reference group was changed from patients exposed to haloperidol to patients exposed to any conventional antipsychotic agent, the pattern of results was essentially unchanged, with somewhat lower estimates of effect. The hazard ratios were between 1.4 and 1.5 in the new-user cohorts and between 1.1 and 1.3 in the prevalent-user cohorts.

In parallel analyses, there were 1,293 patients in the clozapine cohort (110 without a prescription in the first 12-week period), and 106 developed new-onset diabetes during follow-up. Clozapine patients tended to be younger, and fewer of them were married or members of racial/ethnic

TABLE 2. Risk of developing diabetes according to initiation of use of second-generation antipsychotic medication among US veterans with schizophrenia, 1999–2001*

Analysis	Second-generation antipsychotic agent					
	Olanzapine ($n = 5,981$)		Risperidone ($n = 5,901$)		Quetiapine ($n = 877$)	
	HR†	95% CI†	HR	95% CI	HR	95% CI
Unadjusted (all ages)	1.63	1.22, 2.18	1.58	1.18, 2.11	1.66	1.01, 2.73
Adjusted						
All ages‡	1.64	1.22, 2.19	1.60	1.19, 2.14	1.67	1.01, 2.76
All ages + 30 days to follow-up§	1.57	1.19, 2.08	1.55	1.17, 2.05	1.67	1.04, 2.70
By age group (years)						
<45 ($n = 4,928$)	3.06	1.41, 6.63	3.40	1.56, 7.42	2.98	0.95, 9.31
45–54 ($n = 6,312$)	1.54	0.99, 2.39	1.38	0.88, 2.16	1.04	0.44, 2.41
55–64 ($n = 2,177$)	0.84	0.44, 1.60	1.15	0.63, 2.10	1.11	0.36, 3.44
65–74 ($n = 1,329$)	1.22	0.55, 2.72	1.14	0.49, 2.65	2.59	0.74, 8.97
≥75 ($n = 1,021$)	3.15	0.66, 15.21	2.46	0.52, 11.51	3.21	0.26, 39.23

* Cox proportional hazards regression analysis of new-user cohorts. Users of haloperidol were the reference category.

† HR, hazard ratio; CI, confidence interval.

‡ Models included terms for sex, age, race/ethnicity, marital status, use of other potentially diabetes-inducing medications (beta-blockers, thiazide diuretics, lithium, phenytoin, and corticosteroids), and number of basic or comprehensive metabolic panels performed during follow-up.

§ Follow-up extended to 30 days after discontinuing medication and switching to a new antipsychotic agent.

minority groups. The hazard ratio for clozapine from the prevalent-user cohort analysis was 2.15 (95 percent confidence interval: 1.74, 2.66) and was significantly higher than the hazard ratios for olanzapine, risperidone, and quetiapine ($p < 0.001$). From the case-control analyses, the odds ratio was 1.34 (95 percent confidence interval: 0.98, 1.82) for the 12-week exposure period, and it increased to 1.41 and 1.60 for the 24- and 52-week periods, respectively.

DISCUSSION

Second-generation antipsychotic agents are widely used as first-line therapy for psychotic illnesses, accounting for 80 percent of all antipsychotic medications prescribed in the United States in 2002 (59). Conventional antipsychotic drugs such as haloperidol may cause movement disorders and tardive dyskinesia—stigmatizing and sometimes debilitating side effects that harm patients' functioning and well-being (60). Some second-generation antipsychotic drugs may cause these side effects, but at a lower rate, while offering efficacy equal to or better than that of the older drugs (11, 61).

There is growing evidence of metabolic side effects, such as hyperglycemia and weight gain, following the use of certain second-generation antipsychotic agents. This complicates the comparison between newer and older antipsychotic drugs (59, 61, 62). Prescribing choices must now be based on an assessment of each drug's efficacy as well as its potential to cause movement disorders or metabolic side effects. Apart from clozapine, the evidence is equivocal as to whether or not second-generation antipsychotic drugs differ from one another in effectiveness, and it is not certain that they are more effective than their older counterparts (11, 59, 61–64). If and when additional benefits of second-generation agents are confirmed, they must be weighed against the risk of metabolic problems and their higher acquisition costs.

The association between second-generation antipsychotic agents and diabetes risk first came to light in case reports. In most of these, observers reported diabetic ketoacidosis, new-onset diabetes, or hyperglycemia among patients initiating either clozapine (26–33, 65) or olanzapine, the two second-generation antipsychotic agents that have been on the market for the longest time and have most often been associated with weight gain (66). Subsequently, there appeared reports of diabetes occurring in patients taking one of the other second-generation antipsychotic agents, risperidone (32, 43–46) or quetiapine (32, 41, 42), leading to uncertainty about which agents in this class carry the highest risk of diabetes. While the weight gain associated with use of these agents may contribute to the increased risk of diabetes, the mechanism appears to be complex, possibly involving direct effects of the agents on insulin sensitivity and serotonin receptor activity (22, 32, 67).

Epidemiologic studies have largely confirmed the association of new-onset diabetes with use of second-generation antipsychotic agents. However, the increase in risk is relatively small, and there are inconsistencies in the findings, particularly with respect to variation in risk among individual agents (23, 25, 47–49, 68). Compared with conventional antipsychotic agents, clozapine has been associated with more than a twofold increased risk of diabetes in younger

TABLE 3. Results from cohort and case-control analyses of diabetes risk according to use of second-generation antipsychotic medication among US veterans with schizophrenia, 1999–2001*

Second-generation antipsychotic agent	Cohort study design							Case-control study design							
	New-user cohorts			Prevalent-user cohorts†				12-week exposure period‡				24-week exposure period§			
	No. of cases	HR#	95% CI#	No. of cases	HR	95% CI		No. of cases	No. of controls	OR#	95% CI	No. of cases	No. of controls	OR	95% CI
Olanzapine	5,981	1.64	1.22, 2.19	19,780	1.39	1.26, 1.54		1,302	3,270	1.37	1.19, 1.58	1,138	2,886	1.39	1.20, 1.62
Risperidone	5,901	1.60	1.19, 2.14	19,369	1.26	1.14, 1.40		1,001	2,808	1.20	1.03, 1.38	869	2,484	1.21	1.04, 1.42
Quetiapine	877	1.67	1.01, 2.76	1,578	1.19	0.89, 1.59		147	348	1.46	1.14, 1.87	124	293	1.47	1.13, 1.92

Second-generation antipsychotic agent	52-week exposure period¶		
	No. of cases	No. of controls	OR	95% CI
Olanzapine	801	2,147	1.32	1.11, 1.58
Risperidone	668	1,763	1.35	1.12, 1.62
Quetiapine	89	186	1.82	1.32, 2.49

* In all analyses, patients exposed to haloperidol were the reference group.
† In the prevalent-user cohort analysis, the hazard ratios for olanzapine and risperidone were significantly different from each other at $p < 0.05$. There were no other significant differences between antipsychotic drugs within each design.
‡ The 12-week case-control study included 414 haloperidol cases and 1,378 controls.
§ The 24-week case-control study included 351 haloperidol cases and 1,180 controls.
¶ The 52-week case-control study included 244 haloperidol cases and 821 controls.
# HR, hazard ratio; CI, confidence interval; OR, odds ratio.

patients (ages 20–34 years) with schizophrenia. This was reported from a cohort analysis of Iowa Medicaid claims data (49) and subsequently confirmed in a larger study of VHA patients with schizophrenia (48). In most studies, more modest risk increases of 20–80 percent have been reported for the other, newer second-generation antipsychotic agents.

Two previous studies of VHA patients have provided much of the published evidence on this issue (23, 48). In a prevalent-user cohort analysis of VHA patients with schizophrenia, persons taking second-generation antipsychotic agents were just 9 percent more likely to have diabetes than persons taking conventional antipsychotic medications (48), with relative risks ranging from 1.1 to 1.3 for clozapine, olanzapine, quetiapine, and risperidone. Risk increases were greater in younger patients (age <50 years). This study was limited by its mixing of new and ongoing users of one or more of these agents, its failure to differentiate between new and existing cases of diabetes, and limited adjustment for potential confounders. In a second study of VHA patients from Ohio, a prevalent-user cohort analysis was performed that included all patients prescribed antipsychotic agents, not just those with schizophrenia. Compared with haloperidol, olanzapine (but not risperidone) was associated with an approximately 50 percent increased risk of diabetes (23). While the investigators attempted to address the effect of medication-switching in the analysis, they did not examine the potential influence of the pattern of switching (i.e., whether different drugs were taken simultaneously or sequentially and, if so, in what sequence), nor did they consider potential bias related to the functional form of their time-dependent covariates (69).

Findings bearing on this question have been reported from two other studies. In a nested case-control analysis of the United Kingdom General Practice Research Database, high odds ratios for diabetes were found for use of olanzapine (odds ratio = 4.2) and risperidone (odds ratio = 1.6) relative to conventional antipsychotic medication ($p > 0.05$) (47). In a second study (25), a follow-up analysis of a large prescription claims database, risk of diabetes was increased with use of any antipsychotic medication as compared with the general (nonpsychiatric) population. Compared with haloperidol, diabetes risk was greater with use of risperidone (hazard ratio = 1.23) but not with olanzapine or quetiapine use. These investigators also restricted their sample to new users and evaluated risks for patients using single antipsychotic agents. However, the sample was not limited to patients with schizophrenia, diagnosis of diabetes was based solely on prescription data, and there was more limited adjustment for confounders.

In the present study, there were negligible differences in diabetes risk associated with use of olanzapine, risperidone, and quetiapine. Each appeared to increase risk by 60–70 percent in comparison with haloperidol. Elevations in risk were higher among younger patients with schizophrenia. However, since the incidence of diabetes climbs steeply with age, a greater number of diabetes cases may be attributable to second-generation antipsychotic agents in older users as compared with younger users, and switching to lower-risk agents may actually prevent more cases of diabetes among older patients.

TABLE 4. Characteristics of five cohorts of prevalent users of antipsychotic medication ($n = 55,808$) among US veterans with schizophrenia, 1999–2001

Variable	Antipsychotic agent				
	Olanzapine ($n = 19,780$)	Risperidone ($n = 19,639$)	Quetiapine ($n = 1,578$)	Clozapine ($n = 1,293$)	Haloperidol ($n = 13,518$)
Mean age (years)	50.0 (11.5)*	51.1 (12.4)	49.8 (11.6)	47.6 (8.7)	53.0 (12.3)
Sex (%)					
Male	93.7	93.2	90.4	95.1	95.6
Female	6.3	6.8	9.6	4.9	4.4
Race/ethnicity (%)					
White	53.2	52.2	56.5	75.8	49.0
African-American	24.4	26.4	20.3	14.1	33.2
Hispanic	6.8	5.0	3.3	2.9	5.8
Other	1.0	0.9	1.0	1.2	1.0
Unknown	14.6	15.5	18.9	5.9	11.2
Marital status (%)					
Married	23.0	23.1	22.0	9.5	19.2
Never married	43.2	42.6	40.2	66.4	48.0
Divorced, separated	29.1	29.1	33.0	21.0	26.7
Widowed	2.7	3.6	2.9	1.2	3.3
Unknown	2.0	1.6	2.0	2.0	2.6
Use of medications potentially inducing diabetes (%)					
Beta-blockers/thiazide diuretics	14.0	13.7	15.5	15.5	14.9
Lithium	6.6	5.8	7.2	4.4	6.6
Corticosteroids	1.6	1.6	1.1	0.6	1.6
Phenytoin	1.6	1.7	1.2	0.5	2.0
No. of metabolic panels per patient	0.24 (0.92)	0.22 (0.86)	0.18 (0.81)	0.22 (0.91)	0.24 (0.92)
Mean duration of follow-up (days)	495.5 (391.8)	522.5 (389.5)	270.9 (288.1)	609.5 (441.7)	505.5 (399.1)
Mean time to event (days)	290.3 (280.8)	301.1 (288.5)	137.5 (151.6)	350.6 (349.0)	295.8 (285.2)
No. of new cases of diabetes diagnosed during study period	1,098	1,026	50	106	571
Diabetes incidence per 100 person-years of exposure	4.1	3.9	4.3	4.9	3.0

* Numbers in parentheses, standard deviation.

We believe that the risk of diabetes can be attributed confidently to each agent evaluated in this study because of the new-user cohort design and because each study patient was exposed to one and only one drug during the follow-up period. Without this design, there may be important confounding related to discontinuation or switching of medications, and the effects of the agent under study may be biased by other prior or concurrent medications used (50). To our knowledge, all previous studies but one (25) either have not addressed these potential problems or have accounted for them using other methods (23, 48, 49, 68, 70). The estimates from our study suggest that, in patients with schizophrenia using olanzapine, quetiapine, or risperidone, approximately one case per 100 patients per year or one third of new-onset diabetes is attributable to use of these agents as compared with use of haloperidol.

Differences in study design may explain why our results are partially at variance with those of other studies. We evaluated this by analyzing our data using alternative study designs. Results from the prevalent-user cohort analysis are comparable to those that have been reported for studies of this kind, in that the relative risk estimates are somewhat closer to 1.0 and diabetes risk is higher with use of olanzapine compared with risperidone (23, 48). The other

finding from this analysis is a higher risk of diabetes associated with clozapine use—about a doubling of risk—and this is also consistent with previous reports (48, 49). Risk estimates from the case-control analysis are similar to those from our new-user cohort analysis. Indeed, while there are some differences in risk estimates coming from the analyses using different designs, they are similar and are statistically consistent with one another in suggesting a modestly increased risk of diabetes with use of clozapine, olanzapine, quetiapine, and risperidone. In making these comparisons, caution is warranted in using large study samples to evaluate such small differences in risk estimates—differences that may be the result of unexplained bias.

In comparison with the new-user cohort analysis, more modest associations with diabetes risk were found in the prevalent-user cohort design. This sampling strategy is more likely to include patients who were long-term users and tolerated their drugs well, since patients who gained more weight or had other metabolic problems may have had their medications discontinued or changed prior to the time of our study. Their underrepresentation in the sample may have resulted in the somewhat weaker associations observed with the prevalent-user cohort design. It is important to recognize that potential confounding or problems of differences between switchers and long-term users cannot be resolved entirely through the use of a cohort design. Nevertheless, we believe that the new-user cohort design is preferable as a method of reducing these potential problems (50).

Other considerations warrant caution in interpreting these findings. The pharmacy or diagnostic data may have been inaccurate or incomplete, and there may have been misclassification in the identification of schizophrenia and diabetes, although conservative definitions were used (52). Confounding by contraindication remains a possible explanation for our results, particularly since we lacked critical information with which to adjust for baseline diabetes risk, such as data on initial weight, change in weight, caloric intake, existing hypertension or hypercholesterolemia, and family history of diabetes. Prescribers who believed that some drugs (e.g., clozapine or olanzapine) caused more weight gain than others may have steered patients with high diabetes risk away from these agents. If this did occur, the risk for these drugs may have been underestimated, while risk for more weight-neutral drugs (e.g., risperidone or quetiapine) may have been overestimated. Concern about this potential source of confounding is mitigated by our finding of only minute differences in the intensity of diagnostic screening between users of the different drugs. Nevertheless, confounding by contraindication remains a possible source of bias in this study and in previously conducted observational studies of antipsychotic agents and diabetes, none of which controlled for baseline diabetes risk.

There are other limitations to our research. Medications taken prior to the 3-month period used to identify patients for the new-user cohort analysis may have influenced subsequent risk, and we had no information on those prescriptions. Restricting our study to patients exposed to only one antipsychotic agent limited our ability to assess the potential diabetogenic effects of simultaneous or sequential exposures to more than one antipsychotic drug—patterns that may be common in clinical practice. Since we did not study ziprasidone or aripiprazole, the newest second-generation antipsychotic agents, no conclusions should be drawn from our study about their potential for causing diabetes.

Some caution in generalizing the results of our study to users of other antipsychotic agents is also warranted. We studied patients with schizophrenia, and effects may be different in patients taking antipsychotic drugs for other indications. Patients in our new-user cohorts who did not receive antipsychotic medication at the VHA for at least 3 months may have been different from the larger population of VHA patients with schizophrenia. Although some of these patients may have used non-VHA services during that time, they were unlikely to obtain outpatient medications from non-VHA sources, where costs are higher and access is more limited (71, 72). Poor adherence to treatment is a significant issue in schizophrenia (73–75), and substantial time periods without treatment are not unusual. The lack of differences in patient characteristics between the new-user cohorts and the prevalent-user cohorts partially mitigates these concerns. Generalizing these results beyond the VHA population should be done with caution, especially since there were so few women in the sample.

The evidence presented here for an association between selected second-generation antipsychotic medications and metabolic problems should be placed in a broad context. Decisions concerning selection of specific antipsychotic medications should be based on safety, efficacy, tolerability, and cost (61, 63). The relative weights assigned to these factors will depend on the clinical and financial context of treatment (76, 77).

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ORIGINAL REPORT

Antipsychotic exposure and type 2 diabetes among patients with schizophrenia: a matched case-control study of California Medicaid claims†

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SUMMARY

Purpose To examine the risk of developing type 2 diabetes mellitus among people with schizophrenia exposed to atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone) compared to those exposed to conventional antipsychotics.
Methods A matched case-control design was used to examine California Medicaid beneficiaries. Cases developed diabetes subsequent to being diagnosed with schizophrenia (ICD-9295), were 18 years or older, and were exposed to at least one antipsychotic medication at some point during the 12 weeks preceding diabetes diagnosis. Diabetes was defined by diagnostic claim (ICD-9250) or prescription for antidiabetic agents. A total of 3663 cases were matched to 14 523 non-diabetic controls (people with schizophrenia matched on gender and age ±5 years). All had to be continuously eligible for benefits during the 12-week period preceding diabetes onset in the case. Conditional logistic regression modeled the risk of exposure, controlling for age, ethnicity, and exposure to selected concomitant medications. Analyses were repeated with 24- and 52-week exposure windows.
Results Using a 12-week exposure window, olanzapine (OR = 1.36, 95%CI 1.20–1.53), clozapine (OR = 1.34, 95%CI 1.16–1.55), and combination atypical therapy (OR = 1.58, 95%CI 1.33–1.88), but not risperidone or quetiapine, were associated with increased odds of developing diabetes compared to conventional antipsychotics. Changing to a 24-week exposure window, the risks were: olanzapine (OR = 1.38, 95%CI 1.22–1.56), clozapine (OR = 1.32, 95%CI 1.14–1.53), or combinations (OR = 1.54, 95%CI 1.29–1.84). With a 52-week exposure window, the risks were: olanzapine (OR = 1.41, 95%CI 1.24–1.60), clozapine (OR = 1.41, 95%CI 1.21–1.65), combinations (OR = 1.58, 95%CI 1.31–1.90). Risk for olanzapine increased with dose. Hispanic, African American, and unknown ethnicity were significant risks for development of type 2 diabetes as was exposure to selected concomitant medications.
Conclusions Exposure to olanzapine or clozapine is associated with a 34–41% increase in the developing of type 2 diabetes among California Medicaid recipients with schizophrenia. Prospective, randomized trials are needed to confirm these retrospective, observational findings. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotic; neuroleptic; adverse effects; type 2 diabetes mellitus; schizophrenia; Medicaid; matched case-control study

INTRODUCTION

Atypical antipsychotic medications have proven to be at least as effective as older medications (e.g., haloperidol) in the treatment of schizophrenia.[1–8] At the same time, they are less likely to cause extrapyramidal symptoms and tardive dyskinesia, serious

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side effects caused by typical antipsychotics.[9] Certain atypical antipsychotic medications cause substantially more weight gain than their predecessors.[10–14] In several recent studies, these medications have been linked to development of impaired glucose tolerance and type 2 diabetes,[15–19] hyperlipidemia,[15,20,21] and increased mortality.[22] The present study assesses the extent to which an increased risk of new-onset type 2 diabetes among patients with schizophrenia may be associated with exposure to new generation antipsychotic medications when compared to the older antipsychotic medications.

Evidence of a possible link between diabetes and atypical antipsychotic medications first appeared in the form of case reports.[17] New-onset type 2 diabetes, glucose dysregulation, or diabetic ketoacidosis have been reported in patients taking clozapine,[23–31] olanzapine,[24–27,30–38] quetiapine,[30,39,40] and risperidone.[30,41–44] In addition to the case reports, several retrospective studies have reported an association between new generation antipsychotic medications and type 2 diabetes mellitus.[18,45–49]

Lund *et al*. used Iowa Medicaid claims data to compare the incidence of new-onset diabetes among patients receiving either clozapine or any conventional antipsychotic medication. They found a null overall effect of exposure to clozapine. However, there was a significantly increased risk of diabetes for clozapine among the youngest age group only (20–34 years of age).[46] This study, which was limited to clozapine, did not control for the concomitant use of other medications that might cause diabetes (e.g., beta-blockers, thiazide diuretics, corticosteroids).

A more recent study of national data from the Veterans Health Administration of the Department of Veterans Affairs examined the risk of diabetes associated with exposure to clozapine, olanzapine, quetiapine, and risperidone.[45] A 9% increased risk of diabetes was reported for patients taking any atypical antipsychotic medication compared to those taking any conventional antipsychotic. In the overall analysis, the risk was significantly greater than conventional medications for clozapine, olanzapine, and quetiapine but not for risperidone. As in the study of clozapine, the risk appeared to be greatest among the youngest cohort of patients with schizophrenia. Important limitations of the VA study included failure to differentiate between new and existing cases of diabetes and failure to control for the concomitant use of other potentially diabetogenic medications.

Fuller *et al*.[18] compared olanzapine and risperidone to haloperidol and fluphenazine using 4 years of electronic data on veterans receiving treatment in Ohio. After controlling for a number of other covariates, they found that olanzapine increased the risk of new-onset diabetes by 37%. This study included all users of antipsychotics, regardless of diagnosis. In yet another recent database study, Buse *et al*.[49] used data from a pharmacy benefit manager (AdvancePCS) to compare old and new generation antipsychotics to one another and to patients with no antipsychotic exposure. They found no differences in head-to-head comparisons between older and newer drugs. This study was limited by the absence of information on diagnostic data and by its failure to control for exposure to other medications that may cause diabetes.

The current study seeks to extend this line of research. Our objective was to quantify the risk of type 2 diabetes mellitus associated with exposure to selected atypical antipsychotic medications, as compared to the risk for patients taking conventional antipsychotics.

METHOD

Design

The present study used a matched case-control design, with cases and controls matched on gender and age ±5 years.[50,51] The case-control study was nested within a cohort of people with schizophrenia and within a larger cohort of California Medicaid beneficiaries.

Data source, case-control selection, and matching

Data came from California Medicaid (i.e., Medi-Cal) medical and prescription claims filed between 1 January 1995 and 30 September 2000.[52] Figure 1 illustrates the process of case and control selection as well as eligibility determination. Cases were adult patients who developed type 2 diabetes mellitus after being diagnosed with schizophrenia. Controls were adult patients who were diagnosed with schizophrenia but did not have type 2 diabetes mellitus at the time diabetes was diagnosed in the matched case. Patients who subsequently developed diabetes were eligible to serve as controls until the date of their diabetes diagnosis. As such, one individual could serve as both a case and a control.[53] The same individual could not serve as a control for more than one case.

To identify cases, first all patients with schizophrenia were identified by the presence of a diagnostic claim for ICD-9 code 295.00-295.99 on two separate days. Next, all patients with diabetes were identified by the presence a diagnostic claim for ICD-9 code 250 on two

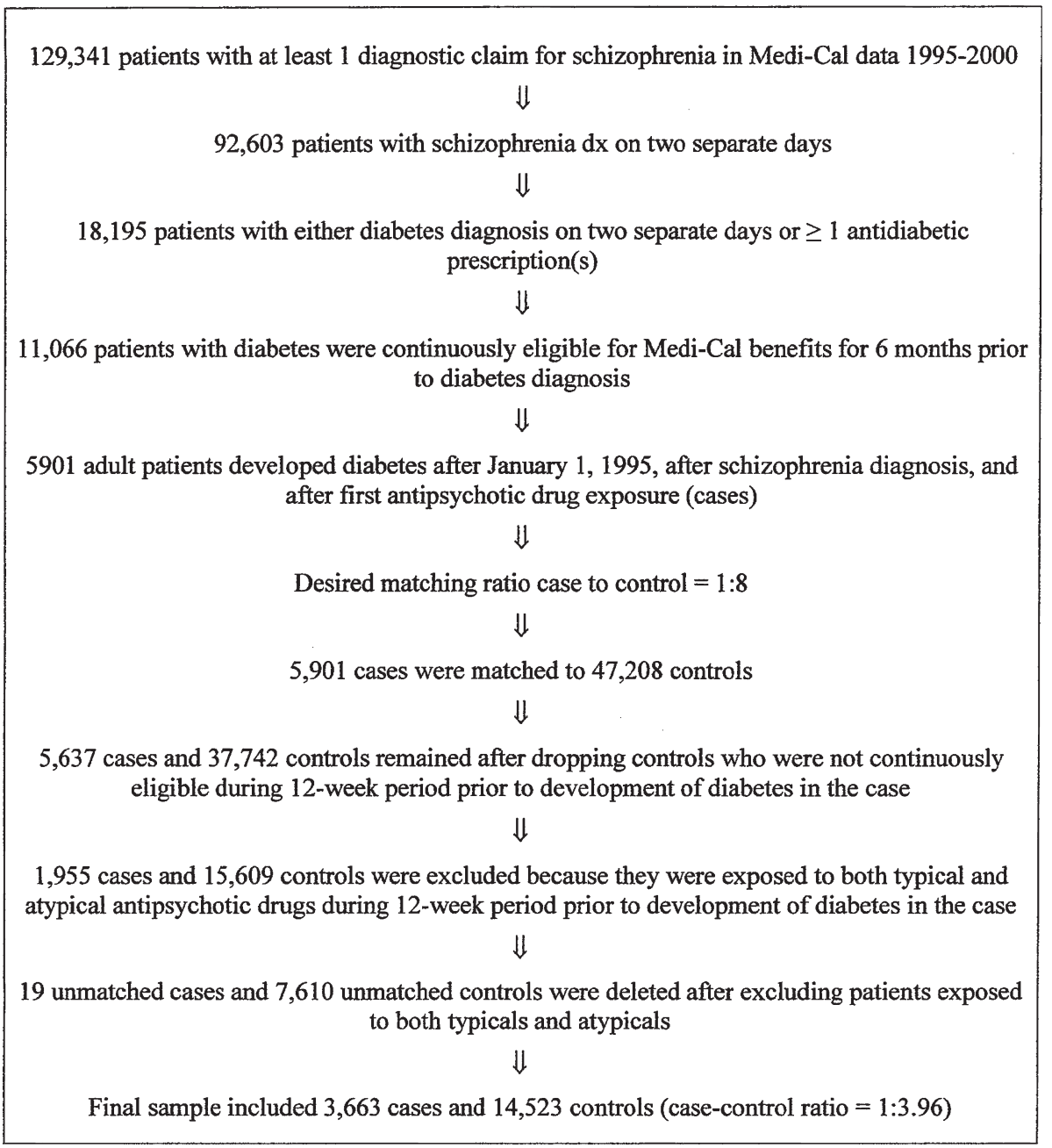

Figure 1. Flow chart for case selection and matching (12-week retrospective exposure window)

separate days (excluding juvenile types indicated by ICD-9 code 250.x1 or 250.x3) or by receipt of an antidiabetic agent (glimepiride, chlorpropamide, glyburide, glipizide, metformin hydrochloride, insulin, acarbose, or troglitazone).

Definition of antipsychotic exposure

In the main analysis, medication exposure was defined with reference to prescription claims filed during the 12 weeks prior to diabetes diagnosis. Subsequent

analyses extended the exposure window to 24 and 52 weeks. Drug exposure did not need to be continuous. Both cases and controls had to have been exposed to at least one antipsychotic medication at some point during the exposure window. We defined four categories of exposure: (a) exposure to any typical or combination of typicals; (b) exposure to a single atypical; (c) exposure to any combination of atypicals; and (d) exposure to any combination of typicals and atypicals. Patients exposed to both typical and atypical antipsychotics (category (d)) during exposure window were excluded. All other exposure patterns were included.

The atypical antipsychotic medications studied were clozapine, olanzapine, quetiapine, and risperidone. The typical antipsychotic medications studied were chlorpromazine, fluphenazine, loxapine, pimozide, promazine, trifluoperazine, haloperidol, perphenazine, prochlorperazine, thioridazine, chlorprothixine, molindone, thiothixene, and mesoridazine. Within the Medi-Cal database, all medications were identified by their National Drug Codes (NDC).[54,55] To get strength data for the dose-response analyses, NDC codes were used to index into FDAs NDC database.[55]

Additional exclusion criteria

The diagnosis of diabetes or receipt of an antidiabetic medication had to occur after the date of the first diagnostic claim for schizophrenia. For cases, a minimum 6-month continuous eligibility period prior to the index date was used to screen for prevalent diabetes. Prevalent cases were excluded. Both cases and controls had to be continuously eligible for Medicaid benefits during the 12 (24- or 52-) week exposure window prior to diabetes onset in the case. Our goal was to achieve a final 1:4 ratio of cases to controls.[56] Anticipating losses due to our exclusion criteria, we initially searched for eight controls for every case.[50,51] After eliminating patients who were exposed to both typical and atypicals or who were not continuously eligible for Medicaid benefits during the 12 weeks prior to the onset of diabetes in the case, the final ratio of cases to controls was 1:3.96 (see Figure 1).

Analysis plan

The first step in our analysis was to compute simple descriptive statistics for the cases and controls. Next, we built conditional logistic regression models to predict new-onset type 2 diabetes. Conditional logistic regression is more appropriate than standard logistic regression when highly stratified data (as in matched case-control designs) result in small sample sizes within each stratum.[57] We used SASs PROC PHREG to form our conditional logistic models.[58] Hypothesis tests involving planned comparisons between different atypicals were done using the TEST option to PROC PHREG. The independent variables were five dummy-coded dichotomous variables corresponding to exposure to a single atypical antipsychotic medications (clozapine, olanzapine, quetiapine, or risperidone) or any combination of atypicals, the reference group being any typical antipsychotic (or combination thereof). The control variables were: (a) four dummy-coded dichotomous variables representing Hispanic, African American, other and unknown ethnicity, the reference group being whites and (b) nine dichotomous variables representing exposure to (classes of) medications associated with new-onset diabetes (corticosteroids, phenytoin, oral contraceptives containing norgestrel, beta-blockers, alpha-blockers, thiazide diuretics, tricyclic antidepressants, SSRIs, and ACE inhibitors). The list of generic names for these medications can be obtained from the first author.

For each atypical antipsychotic, we conducted dose-response analyses. We defined high, medium, and low doses, based on the empirical distribution of actual doses and on expert clinical judgment (see Table 1). For each atypical drug, we built a separate conditional logistic regression model with dose represented by three dichotomous variables corresponding to low, medium, and high doses. Any dose of a typical was the reference. Differences between doses were tested using the TEST option to SAS PROC PHREG. Only when the omnibus test of equality between all doses (i.e., low = medium = high) was significant did we report differences between dose levels. Note that for a given drug's (e.g., clozapine's) dose-response model, cases and controls not on either clozapine or typicals were excluded. When this process resulted in a case or control being unmatched, those patients were excluded also. Asa result, the n's for each dose level do not sum to the overall N for given drug in main analysis.

Finally, because the exact time course of the development of antipsychotic-associated diabetes is unknown, we repeated all analyses after lengthening the exposure window to 24 and 52 weeks, respectively. We report results from the extended exposure windows briefly in the text.

RESULTS

Table 1 shows the results of analyses based on the 12-week exposure window. Controlling for ethnicity and exposure to other diabetes-causing medications,

Table 1. Association between antipsychotic exposure and development of type 2 diabetes among patients with schizophrenia (12-week exposure window)

Characteristic	Cases ($N = 3663$)		Controls ($N = 14\,523$)		Crude OR	Adjusted OR
	Mean	SD	Mean	SD		
Age					1.04 (1.03–1.05)	1.04 (1.03–1.06)
Mean (SD)	45.3	13.7	45.3	13.3		
Min	18		18			
Max	94		99			
	n	%	*n*	%		
Gender (1, male)						
Male	1709	46.7	6634	45.7		
Female	1954	53.3	7889	54.3		
Ethnicity						
White	1745	47.6	8237	56.7		
Hispanic	61	1.7	200	1.4	1.2 (0.9–1.6)	1.4 (1.0–1.9)
African American	769	21.0	2342	16.1	1.4 (1.3–1.5)	1.6 (1.4–1.8)
Others	41	1.1	133	0.9	1.2 (0.8–1.7)	1.4 (1.0–2.0)
Unknown	1046	28.6	3608	24.8	1.2 (1.1–1.3)	1.4 (1.3–1.5)
Concomitant medications						
ACE inhibitors	491	13.4	1056	7.3	2.0 (1.8–2.2)	1.8 (1.6–2.0)
Alpha-blockers	59	1.6	187	1.3	1.3 (0.9–1.7)	0.9 (0.7–1.3)
Beta-blockers	337	9.2	970	6.7	1.4 (1.2–1.6)	1.3 (1.1–1.5)
Corticosteroids	470	12.8	1130	7.8	1.7 (1.6–2.0)	1.7 (1.5–1.9)
Oral contraceptives containing norgestrel	15	0.4	52	0.4	1.1 (0.6–2.0)	1.1 (0.6–2.0)
Phenytoin	176	4.8	688	4.7	1.0 (0.9–1.2)	1.0 (0.8–1.2)
SSRIs	534	14.6	1696	11.7	1.3 (1.2–1.4)	1.2 (1.1–1.3)
Thiazide diuretics	165	4.5	353	2.4	1.9 (1.6–2.3)	1.4 (1.2–1.7)
Tricyclic antidepressants	759	20.7	2616	18.0	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Antipsychotic exposure (mean daily dose)						
Typicals	1993	54.4	8657	59.6		
Olanzapine	576	15.7	1857	12.8	1.3 (1.2–1.5)	1.4 (1.2–1.5)
Low (<7.5 mg)	81	4.0	214	3.3	1.2 (1.0–1.6)	1.1 (0.9–1.5)
Medium ($7.5 \leq x \leq 12.5$ mg)	182	7.3	356	4.7	1.6 (1.3–1.9)	1.6 (1.3–1.9)
High (>12.5 mg)	285	11.4	598	7.9	1.5 (1.3–1.7)	1.5 (1.2–1.8)
Risperidone	521	14.2	2169	14.9	1.0 (0.9–1.2)	1.0 (0.9–1.2)
Low (<3 mg)	108	4.4	284	3.6	1.2 (1.0–1.6)	1.0 (0.8–1.3)
Medium ($3 \leq x \leq 6$ mg)	241	9.9	735	9.3	1.1 (0.9–1.2)	0.9 (0.8–1.1)
High (>6 mg)	143	5.9	444	5.6	1.0 (0.9–1.3)	1.0 (0.8–1.3)
Clozapine	303	8.3	1061	7.3	1.2 (1.1–1.4)	1.3 (1.2–1.5)
Low (<300 mg)	73	3.3	154	2.3	1.5 (1.1–2.0)	1.5 (1.1–2.0)
Medium ($300 \leq x \leq 600$ mg)	157	7.1	345	5.0	1.4 (1.2–1.8)	1.5 (1.2–1.8)
High (>600 mg)	59	2.7	188	2.8	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Quetiapine	47	1.3	169	1.2	1.2 (0.9–1.7)	1.2 (0.8–1.7)
Low (<250 mg)	15	0.8	17	0.3	2.6 (1.3–5.2)	1.9 (0.9–4.1)
Medium ($250 \leq x \leq 500$ mg)	12	0.6	22	0.4	1.6 (0.8–3.2)	1.2 (0.6–2.4)
High (>500 mg)	11	0.6	16	0.3	2.0 (0.9–4.3)	1.6 (0.7–3.6)
Combination	223	6.1	610	4.2	1.6 (1.4–1.9)	1.6 (1.3–1.9)

Note: Crude and adjusted odds ratios are not given for gender because it was used as a matching variable, and they are not given for white ethnicity or typical antipsychotics because those categories served as the reference groups.

patients with schizophrenia who developed type 2 diabetes were more likely than controls to have been exposed to clozapine (OR = 1.34, 95%CI 1.16–1.55), olanzapine (OR = 1.36, 95%CI 1.20–1.53), or combination atypical therapy (OR = 1.58, 95%CI 1.33–1.88). The reference group for exposure was any typical antipsychotic. Tests comparing the model coefficients for each drug to each other drug revealed that the coefficient for olanzapine was significantly greater than risperidone ($\chi^2 = 12.54$, $p = 0.0004$); clozapine was greater than risperidone ($\chi^2 = 8.23$, $p = 0.004$); and combination therapy was greater than risperidone ($\chi^2 = 17.82$, $p < 0.0001$). A statistically significant additive risk of new-onset type 2 diabetes

was also associated with African American and unknown ethnicity, as well as with exposure to several concomitant medications. For the 12-week exposure window, dose did not affect the odds of developing diabetes for clozapine, olanzapine, quetiapine, or risperidone. For olanzapine, there was a trend towards increasing risk with higher doses, but it did not reach conventional levels of statistical significance.

Using a 24-week exposure window, the odds ratios for olanzapine (OR = 1.38, 95%CI 1.22–1.56) and clozapine (OR = 1.32, 95%CI 1.14–1.53) changed only slightly. The odds ratio for combinations of atypicals decreased slightly (OR = 1.54, 95%CI 1.29–1.84). Odds ratios for clozapine, olanzapine, and combination therapy were all significantly greater than for risperidone. Neither quetiapine nor risperidone were associated with increased odds of developing diabetes. None of the drugs showed significant dose-response relationships.

With a 52-week exposure window, the odds ratios increased for olanzapine (OR = 1.41, 95%CI 1.24–1.60), clozapine (OR = 1.41, 95%CI 1.21–1.65), and combinations of atypicals (OR = 1.58, 95%CI 1.31–1.90). Odds ratios for clozapine, olanzapine, and combination therapy were all significantly greater than for risperidone. Neither quetiapine nor risperidone was associated with increased odds of developing diabetes. There was a significant dose response only for olanzapine when using the 52-week exposure window. The odds ratio for low doses (OR = 1.25, 95%CI 1.00–1.57) was significantly smaller than for medium (OR = 1.84, 95%CI 1.53–2.22) or high doses (OR = 1.87, 95%CI 1.58–2.21).

DISCUSSION

Exposure to clozapine or olanzapine, but not quetiapine or risperidone, was associated with a 34–41% increase in the odds of developing new-onset type 2 diabetes when compared to typical antipsychotics. The odds increased 58% for patients exposed to combinations of atypical drugs. These associations were present when the effects of age, gender, ethnicity, and exposure to other medications were controlled and when the retrospective exposure window was 12, 24, or 52 weeks. These findings are largely consistent with recently published studies.[18,45–48] The small number of patients on quetiapine in our sample and the consequent imprecision and low power may explain why we did not detect a significant association between quetiapine exposure and diabetes as others have.[45] Other discrepancies between previous findings and our own are likely due to differences in populations studied, definitions of diabetes and antipsychotic exposure, covariates, and statistical analysis plans.[19] The present study adds to the body of observational evidence indicating that certain atypical antipsychotics may be associated with a significantly increased risk of developing new-onset type 2 diabetes.[18,45–48] To our knowledge, we are the first to report that the magnitude of the association between olanzapine exposure and diabetes risk may be dose-dependent.

For many clinicians, the broader implications of this study and of the emerging consensus about the risk of diabetes associated with exposure to certain antipsychotics boil down to a simple set of questions: How can I quantify the risks (and benefits) in terms my patients and I can understand and relate to? When is it safe to use these medications? In which patient populations? What sort of monitoring is necessary when these medications are used? There are no simple answers to these questions, although some recommendations have begun to appear.[19,48,59,60]

One way of illustrating the risk is to move from odds ratios to more easily interpretable numbers. For example, we estimated that the odds of developing type 2 diabetes among patients of all ages exposed to olanzapine was 36% greater than the risk for those on typical antipsychotic medications (34% greater for clozapine). To move the discussion from relative to absolute risk, we need to know the incidence of type 2 diabetes among patients with schizophrenia generally. That number is not, to our knowledge, available in the literature.[61] The incidence of type II diabetes is approximately 0.35% per year in the general population.[61,62] Under the conservative assumption that the risks of diabetes among adults with schizophrenia is no greater than that of the general population, exposure to olanzapine would increase the incidence of diabetes from approximately 1 in 286 to 1 in 210 or from 3.5 per thousand to 4.8 per thousand. Assuming the risk of diabetes among adults with schizophrenia is at least twice that of the general population, arguably a more realistic assumption,[61–64] exposure to olanzapine, for example, would increase diabetes incidence from 1 in 143 to 1 in 105 or from 7 per thousand to 9.6 per thousand.

The clinical implications of the increased diabetes risk are different for clozapine and olanzapine. Clozapine is indicated for patients with treatment-refractory psychosis, but because of its known risk of agranulocytosis, its use is restricted and must be carefully monitored. Any additional risk of diabetes for patients using clozapine might need to be tolerated, since patients on clozapine have few alternatives. On

the other hand, olanzapine is one among several equally effective options. If it were definitively shown to have a substantially different risk-benefit profile than other atypical antipsychotics, then clinicians could choose another drug.

Finally, when considering whether or not to use one of the potentially diabetogenic atypical drugs, prescribers must also consider other risk factors for diabetes as well as the clinical, psychosocial, and economic context of treatment. Most salient in the current study were ethnicity and several classes of concomitant medications (e.g., beta-blockers, thiazide diuretics, corticosteroids, and ACE inhibitors). The greater risk of diabetes faced by Hispanics and African Americans is well known and was reinforced by our data.[61,65]

The results of this investigation should be interpreted in light of several limitations. Diagnostic (ICD-9) codes were not independently validated. Thus it is possible that some patients identified in the database as having schizophrenia or diabetes may have been misdiagnosed. Due to limitations in the Medi-Cal claims database, we were unable to control for body mass index, a known risk factor for type 2 diabetes and a factor thought to mediate the relationship between atypical exposure and the development of diabetes. For similar reasons, we are unable to control for family history of diabetes.

Because of left censoring, we cannot be certain that all of the first-listed claims for diabetes represented new onsets of illness. However, the requirement of a 6-month diabetes-free eligibility window prior to the index date mitigates this concern. Also, diabetes has a prolonged, asymptomatic clinical course, and its detection is dependent on contact with a clinician. This may have resulted in biased selection of control patients.[66] We did not examine the effects of exposure to ziprasidone or aripirazole because neither was on the California Medicaid formulary during the period covered by the claims data we studied.

Children (under the age 21), women, people with low incomes, and people of African American and Hispanic ethnicity are overrepresented in the Medicaid population compared to the general population.[67–70] Our results may or may not generalize to the increasing number of patients who take atypical antipsychotic medications for conditions other than schizophrenia. Also, we studied ongoing users, without any antipsychotic-free washout period. Studies of ongoing users may be vulnerable to certain biases that are not present when observations are restricted to new users.[71] The results reported here give evidence of association between exposure and disease, but they do not establish causation. Prospective, randomized trials are needed to confirm and more precisely quantify findings from this and similar observational studies.

CONCLUSION

Among people with schizophrenia in the California Medicaid system, exposure to clozapine or olanzapine but not quetiapine or risperidone, was associated with an increased risk of developing type 2 diabetes when compared to typical antipsychotic medications. These effects persisted after adjustment for age, gender, ethnicity, and concomitant exposure to other potentially diabetogenic medications. Age, Hispanic and African American ethnicity as well as exposure to other medications were significant, independent risk factors. More research needs to be done to quantify the personal and societal risk/benefit ratio associated with use of these medications. In the meantime, clinicians should carefully weigh the risk of type 2 diabetes when deciding whether or not to prescribe clozapine or olanzapine, especially among patients who may be predisposed to develop diabetes (e.g., due to ethnicity, positive family history, age, or body mass). Patients who do receive these medications should be monitored in accordance with recently published guidelines.[19]

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New-onset type-2 diabetes associated with atypical antipsychotic medications

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Abstract

Purpose: This study compared the one-year incidence of new-onset type-2 diabetes mellitus (DM) and changes in weight in patients with a variety of psychiatric diagnoses prescribed olanzapine, risperidone, or quetiapine, compared to a reference group receiving haloperidol and no other antipsychotic medication.
Research design and methods: Data was abstracted from charts of subjects newly initiated and then maintained for one year on olanzapine ($n=112$), risperidone ($n=100$), quetiapine ($n=100$), and haloperidol ($n=100$). Baseline and one-year DM status, height, and weight were collected, as well as concurrent psychotropic medications, medical and psychiatric comorbidities.
Findings: Using a multivariate model, logistic regression identified a significant association between olanzapine (but not other atypical agents) and the development of diabetes compared to haloperidol over the one-year period (odds ratio 8.4, 95% CI 1.8–38.7). Baseline obesity was independently associated with new-onset DM, but only marginally greater weight gain was found among olanzapine users.
Conclusions: The middle-aged American veterans in this study cohort were highly vulnerable to the diabetogenic effects of olanzapine, but a close correlation with weight change was not found. Patients administered olanzapine should receive careful laboratory monitoring for elevated plasma glucose in addition to weight measurement.
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Keywords: Atypical antipsychotic agents; Body mass index; Type-2 diabetes mellitus

1. Introduction

New generation "atypical" antipsychotic medications carry an increased risk of weight gain and new-onset type-2 diabetes mellitus (DM) (American Diabetes Association, 2004; Department of Veterans Affairs, 2002; Melkerson and Dahl, 2004; Cohen, 2004; Jin et al., 2002; Wirshing et al., 2002; Caro et al., 2002). While the association between atypical antipsychotics and these metabolic side effects is clear, especially in patients with schizophrenia, information about comparative risks of weight gain and diabetes between specific atypical medications, the exact relationship between weight gain and diabetes, and comparative risks for patients with diagnoses other than schizophrenia remain important areas of concern (Kornegay et al., 2002; Koro et al., 2002; Kropp et al., 2004; Beliard et al., 2003).

In the United States Department of Veterans Affairs Veterans Health Administration (VA), olanzapine, risperidone, and quetiapine are the most frequently prescribed atypical antipsychotic medications. Leslie and Rosenheck (2004), in a VA administrative data base study, found the risk for new-onset diabetes in schizophrenia patients was highest for clozapine (2.03%), with lower risks for quetiapine (0.80%), olanzapine (0.63%), and risperidone (0.05%) compared to a

Abbreviations: DM, type-2 diabetes mellitus; BMI, body mass index; VA, United States Department of Veteran Affairs.

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reference cohort of patients on haloperidol. However, a high percentage of atypical use in VA care is for diagnoses other than schizophrenia: 34.8% of olanzapine, 14.7% of quetiapine, and 46.8% of risperidone prescriptions were for other disorders, such as posttraumatic stress disorder (PTSD), mood disorders, or dementia (Blow et al., 2003).

Characteristics of the VA population such as older age, polypharmacy, and pre-existing obesity may increase the risk for development of diabetes. Costs of additional weight gain and DM on health, quality of life, survival, and health care expenditures are enormous (Wolf and Colditz, 1998; Nasrallah, 2002). Given the need for information about the relative risk DM with this population, the current study was conducted to compare the incidence of new-onset DM in veterans with a variety of psychiatric diagnoses.

2. Methods

2.1. Study design

The study, conducted with Institutional Review Board (IRB) approval, was an electronic chart review of the occurrence of new-onset DM in patients maintained on olanzapine, risperidone or quetiapine for a one-year period compared to a haloperidol reference group. Data was collected from care episodes occurring between December 2000 and January 2003 in the greater North Texas catchment area, which includes three major VA mental health care settings. Change in weight and body mass index (BMI), (Gray and Fujioka, 1991) were also assessed.

2.2. Study criteria and patient population

Potential study charts were selected from a pharmacy list of patients newly initiated on the study medications who continued the medication for a full year as indicated by a minimum of four outpatient refills in the year following medication initiation. A baseline weight measurement was required in the medical record within two months of medication initiation and another within two months of the anniversary of medication initiation. A measurement of height was required as well as documentation of medical and psychiatric diagnoses. Exclusion criteria included concurrent prescription of any other study medication or death during the study year. The number of subjects per cell was determined a priori by a statistical power analysis indicating 100 subjects per cell would yield >80% power for detecting significant change in outcome variables of new-onset DM and weight change. To obtain subjects required by the protocol, 1034 olanzapine, 889 quetiapine, 987 risperidone, and 730 haloperidol records were screened in an identical manner applying study criteria in sequence by unique identifying number. Twelve olanzapine chart reviews unintentionally collected in excess of protocol due to an error in collection count between investigators were not discarded. Data was extracted from the electronic medical record applying a standardized study data collection form.

2.3. Measures

The dependent variables included new-onset DM and change in weight. New-onset DM was defined by American Diabetic Association (1997) criteria of a fasting plasma glucose of 126 mg/dl or higher, indication of a new diagnosis of DM in any medical progress note, or initiation of an anti-diabetic medication during the follow-up period. New-onset DM was classified as a dichotomous variable (yes/no). Change in weight in pounds over the study period was determined. Baseline and follow-up weights and BMI were recorded.

2.4. Statistical analyses

2.4.1. Independent variables and covariates

The independent variable of primary interest was type of antipsychotic medication: olanzapine, quetiapine, risperidone, or the reference medication haloperidol. Potential covariates included medical comorbidity, psychiatric diagnoses associated with weight loss, concurrent psychotropic medications associated with weight gain, baseline obesity, and demographic characteristics (age, gender, and race). Based on literature review of co-administered psychiatric medications associated with significant weight gain (Thompson Healthcare, 2004), a dichotomous marker (yes vs. no weight gain) was created for co-administered psychotropic medications. Dichotomous indicators (any vs. none) for baseline medical comorbidity and psychiatric conditions associated with weight loss were applied to assess possible influences of comorbidity. To designate these comorbid conditions, a panel of 5 academic psychiatrists rated the likelihood of weight loss associated with each of the diagnoses found in the study sample. The consensus results were used to develop the dichotomous indicators. A final indicator denoted pre-existing obesity defined by a baseline BMI of 30 or higher. Three age categories were devised: young (age 21–35), middle (age 36–50), and older (age 50–88). Other demographic variables included gender and race, coded white vs. non-white; non-white was primarily Black with one Asian and 12 Hispanic patients.

2.4.2. Multivariate model refined for the analyses

Frequencies and means were calculated to provide descriptive information about the sample. Multivariate models that included gender, race, and psychiatric and medical comorbid diagnoses associated with weight loss were tested but these measures were found to have no effect ($p>0.40$). Accordingly, these variables were omitted from the analyses to conserve power. A diagnosis of schizophrenia may be a risk factor for diabetes, (Ryan et al., 2003; Citrome et al., 2005), so a preliminary analysis of the effect of schizophrenia was performed. Finding no association, schizophrenia was not used in subsequent models. Therefore, a logistic regression model was refined that determined the association of antipsychotic medication with development of diabetes, controlling for gender, race, age, baseline obesity, and use of weight-gain medications. This analysis was necessarily restricted to patients without pre-existing diabetes ($n=332$). Analysis of

Table 1
Demographic and clinical characteristics of patients on antipsychotic medications (n=412)

Characteristic	Percent (n)	Mean (SD)	Range
Age		55.4 (12.3)	24–88
Age group			
Young (21–35 years)	3% (14)		
Middle-aged (36–50 years)	30% (125)		
Older (51–88 years)	66% (273)		
Race			
White	70% (288)		
Black	27% (110)		
Other	3% (13)		
Female	13% (53)		
Other weight-gain associated psychiatric medication	23% (96)		
Baseline weight in pounds		198 (41.7)	98–331
Baseline body mass index		29.1 (6.0)	14–51
Baseline obesity (BMI≥30)	42% (173)		
Pre-existing diabetes	19% (80)		
New-onset diabetes	6.9% (23 of 332)		
Comorbid medical diagnosis	87% (360)		

co-variance (ANCOVA) was used to determine differences in weight change among patients taking the four antipsychotic medications, controlling for age, baseline obesity, baseline diabetes (based on BMI), and use of weight-gain medications (n=412). Dummy variables were created for the three atypical antipsychotic medications compared to patients on haloperidol. Post hoc pair-wise comparisons assessed differences in weight by antipsychotic medication using Tukey's adjustment for multiple comparisons. We report both significant (p<0.05) and trend (p<0.10) results from the analysis of variance of weight.

3. Results

Demographic and clinical data are presented in Table 1. Patients ranged in age from 24 to 88 with a mean of 55 (±12) years. Only 3.4% (n=14) were young adults aged 21–35. Thirteen percent (n=53) were females and 27% (n=110) were African-American. A total of 19.4% (n=80) subjects had pre-existing DM; 332 (80.6%) had no history of DM and therefore were at risk for new-onset DM. Overall, 23 (6.9%) of 332 subjects without pre-existing diabetes developed new-onset diabetes (Table 1). Table 2 presents absolute change in weight and BMI, and change in weight and BMI as a percent of baseline for each medication groups, as well as raw differences in new-onset diabetes between the medication groups.

Table 2
Comparison of patient characteristics by type of antipsychotic agent

	Haloperidol n=100	Olanzapine n=112	Quetiapine n=100	Risperidone n=100
Age in years	56.0	53.8	54.2	57.8
No pre-existing DM (%)	88	83	75	76
New-onset diabetes (%)	2	13	5	1
Pre-treatment weight (lb)	193.7	197.0	205.5	196.5
Post-treatment weight (lb)	196.0	203.7	208.2	200.9
Average weight change (lb)	2.3	6.7	2.7	4.4
Lost more than 10 lb (%)	7	11	12	15
Gained>10–20 lb (%)	13	14	12	17
Gained more than 20 lb (%)	4	18	11	13

Table 3
Estimated odds ratios for factors predicting new-onset diabetes among veterans taking antipsychotic medications in comparison to haloperidol (n=332)

Effect	Odds ratio estimates	
	Point	95% Wald
	Estimate	Confidence limits
Olanzapine	8.7[a]	1.9–40.5
Quetiapine	2.7	0.5–14.7
Risperidone	0.5	0.0–5.7
Obese at baseline	5.2[a]	1.9–14.4
WeightGainMeds	1.5	0.5–4.5
PsyDxWgtLoss	1.0	0.4–2.6
Female	0.4	0.1–2.2
White	1.7	0.5–5.5
Age	1.0	<1.0–1.1

[a] Statistically significant effects.

Controlling for age, race, gender, baseline obesity, and weight-gain medications, there was a strong association between the use of olanzapine (compared to haloperidol) and the development of diabetes over the one-year period. Table 3 presents odds ratios for factors predicting new-onset diabetes, indicating a significant risk effect for olanzapine (odds ratio 8.7, 95% CI, 1.9–40.7). Quetiapine and risperidone were not associated with increased risk of the onset of diabetes. Demographic characteristics and weight-gain medications were not associated with the development of new-onset DM. The only other factor significantly related to diabetes onset was baseline obesity (odds ratio 5.2; 95% CI, 1.9–14.4). Similarly controlling for age, baseline diabetes, baseline obesity, and weight-gain medications, the association of type of antipsychotic with weight change was only marginally significant in the analysis of variance (omnibus F=2.56; df=8, 403; p=0.01). Young age, weight-gain medications, and baseline obesity were significantly associated with changes in weight. Examination of adjusted means revealed that baseline obesity was associated with less gain in weight over the year while youthful age was associated with more.

4. Discussion

4.1. Key findings

The key finding was the effect of olanzapine exposure on the risk of developing DM over a one-year period, while quetiapine and risperidone showed no effect relative to haloperidol. Weight change was not strongly associated with risk of new-onset DM. Clearly, patients prescribed olanzapine

should receive careful laboratory monitoring for DM and relying on weight assessment alone is inadequate. Patients with additional risk factors, such as older age or pre-existing obesity should be very closely monitored for new-onset diabetes by baseline and repeat assessments of glucose status (fasting serum glucose, HbA1c).

In this study, subjects in all groups developed newly diagnosed DM at a higher rate (10 to 130 per 1000) than the annual incidence reported by the U.S. Department of Health and Human Services (2002) among the general U.S. population (6.3 per 1000). Olanzapine subjects had a higher rate of new-onset DM than that reported in a previous study of VA patients with schizophrenia: 7.3% over a 12–24 month follow-up period (Leslie and Rosenheck, 2004). This difference may in part be due to the high prevalence of pre-existing obesity in our subjects increasing DM risk. The U.S. Preventive Services Task Force (McTigue, 2003) designates a BMI of 30 or greater as "Class I Obesity." On average the study population was near the cutoff for Class I Obesity and 42% met criteria for Class I Obesity at baseline.

Atypical antipsychotic medications have many useful applications for patients other than those with schizophrenia. In our clinical experience, the mood-stabilizing and calming effects are useful in patients with mood disorders, PTSD, and in some patients with unstable personality disorder. Additional research is needed to identify the specific effect of diagnosis on relative risk of diabetes and weight gain with these medications. At the current time, only schizophrenia has been identified as frequently having an independent risk of type-2 DM (Citrome et al., 2005), although our analyses did not find an increased risk in this study.

Metabolic side effect screening guidelines for atypical antipsychotic medications, such as those based on the Mount Sinai Conference on the Pharmacotherapy of Schizophrenia, emphasize weight assessment (Marder et al., 2002). Monitoring weight alone may be insufficient to screen for DM risk. Further research needs to refine guidelines that adequately monitor adverse effects in light of the lack of a strong association between DM and weight gain.

4.2. Limitations and strengths of the study

Retrospective studies are limited by reliance on documented data. Surveillance bias may exist in the subject selection process as patients on certain atypical agents may have been more closely monitored for adverse effects. The subjects may not represent typical VA care in that extensive documentation was required for study inclusion. Data on family history of diabetes was not available for the analyses. However, detailed clinical information from individual patient charts improved the validity of the data compared to information derived from batch administrative databases.

5. Conclusion

The results indicate a high risk of new-onset DM associated with olanzapine in this VA population of individuals with a variety of psychiatric diagnoses, predominantly composed of late middle-aged overweight males. Good clinical practice should include frequent monitoring for new-onset diabetes, including baseline and repeat laboratory assessments of glucose status in veterans prescribed olanzapine. Further research is needed to clarify specific risk factors associated with DM in patients prescribed atypical antipsychotic medications.

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Risk of Diabetes Mellitus Associated With Atypical Antipsychotic Use Among Patients With Bipolar Disorder: A Retrospective, Population-Based, Case-Control Study

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Background: Drug-induced diabetes onset has not been adequately quantified in patients with bipolar disorder, although atypical antipsychotics have been widely used as new mood stabilizers.

Objectives: To quantify the association between atypical antipsychotics and diabetes mellitus.

Method: A retrospective, population-based, case-control study was conducted using the medical claims database from U.S. managed care organizations from January 1, 1998, to December 31, 2002. Nine hundred twenty incident cases of diabetes were matched with 5258 controls by age, sex, and bipolar index month and year. Diabetes cases were identified by either diagnosis of ICD-9 codes or diabetic medications. Patients with diabetes had a minimum 3-month exposure to any medications or at least 3 prescriptions for their bipolar or comorbidity treatment. Cox proportional hazard regression was conducted to assess the risk of diabetes associated with antipsychotic use.

Results: Of 920 cases, 41% received atypical antipsychotics (e.g., olanzapine, risperidone, quetiapine, ziprasidone, clozapine) and 34% received conventional antipsychotics. Compared to patients receiving conventional antipsychotics, the risk of diabetes was greatest among patients taking clozapine (hazard ratio [HR] = 7.0, 95% confidence interval [CI] = 1.7 to 28.9), risperidone (HR = 3.4, 95% CI = 2.8 to 4.2), olanzapine (HR = 3.2, 95% CI = 2.7 to 3.8), and quetiapine (HR = 1.8, 95% CI = 1.4 to 2.4), with controlling covariates of age; sex; duration of follow-up; use of lithium, anticonvulsants, antidepressants, or concomitant drugs; and psychiatric and medical comorbidities.

Conclusion: Development or exacerbation of diabetes mellitus is associated with antipsychotic use in bipolar patients. Metabolic complications are a major issue in patients receiving antipsychotic therapy. Thus, the propensity of an antipsychotic to induce diabetes should be a consideration when selecting an agent for patients with bipolar disorder.

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The opinions and conclusions expressed in this manuscript are solely those of the authors.

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Mood stabilizers like lithium, divalproex, and carbamazepine are traditionally used for bipolar treatment. Antiepileptic drugs (lamotrigine) and atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) are emergent therapies for bipolar disorder.[1,2] Atypical antipsychotic agents with different mechanisms of action from conventional antipsychotics have been widely adopted in the treatment of bipolar disorder since the mid-1990s.[3] Although atypical antipsychotics reduce extrapyramidal side effects, they have a different spectrum of side effects, including weight gain, alterations in glucose metabolism, increased concentrations of blood cholesterol and lipids, myocarditis, and cardiomyopathy.[4–9]

Evidence has shown an association between some antipsychotics and diabetes in patients with schizophrenia.[7,10–15] Recently, some cases of diabetic ketoacidosis and diabetes associated with antipsychotics were also reported in adult[16–18] and pediatric[19,20] bipolar patients. Although most of the articles were case reports documenting the incidence of diabetes or hyperglycemia with use of atypical antipsychotics, some studies reported that patients with schizophrenia exposed to clozapine, olanzapine, and risperidone were significantly associated with an increased risk of glucose intolerance ranging from a hazard ratio (HR) of 1.2 based on the Veterans Affairs database,[21,22] to HRs of 4.7 and 5.8 based on the United Kingdom General Practice Research (GPRD) database,[7,23] to an HR of 10.22 based on the World Health Organization adverse drug reaction database.[24] Very few case reports exist for quetiapine or ziprasidone despite these drugs having similar pharmacotherapy characteristics.

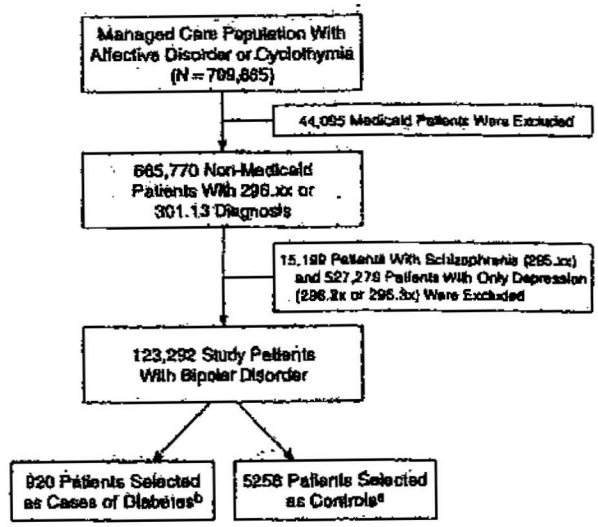
Diabetes is a known and infrequent adverse effect of olanzapine and risperidone. Drug-induced diabetes onset has not been adequately quantified in patients with bipolar disorder, although atypical antipsychotics are being increasingly used in the treatment of bipolar disorder. Published reports indicated some drugs are known to affect the risk of developing diabetes or hyperglycemia, including α-adrenergic blockers (e.g., doxazosin, prazosin, terazosin), β-adrenergic blockers (e.g., atenolol, betaxolol, bisoprolol), thiazide diuretics (e.g., chlorothiazide, chlorthalidone, polythiazide), corticosteroids (e.g., methylprednisolone, hydrocortisone), phenytoin, oral contraceptives containing norgestrel, and valproic acid.[8,25,26] We used medical claims data from U.S. managed-care organizations to quantify the risk of diabetes associated with antipsychotics, especially atypical antipsychotics, in patients with bipolar disorder.

PATIENTS AND METHOD

Study Design and Population

The primary data source was a multi-state managed care claims database (PharMetrics) covering January 1, 1998, to December 31, 2002 (5 calendar years). The database included all pharmacy, medical, and institutional claims. Each medical claim was recorded with accompanying diagnostic codes (*International Classification of Diseases*, Ninth Revision [ICD-9]) that justified the medical service. The database includes over 45 million lives enrolled in managed care organizations with 70 health plans, including managed care Medicaid programs, in 4 U.S. regions: mid-west (34.1%), east (15.6%), south (23.9%), and west (26.4%). Population distributions are similar to the U.S. population distribution by age and gender distributions (PharMetrics, 2004).[27] This geographically diversified claims database provides a large population perspective of health information. The use of managed care claims databases to conduct pharmacoepidemiologic studies has been well documented.[28–30]

Figure 1. Selection of Incident Cases of Diabetes[a] and Controls From Patients With Bipolar Disorder in a Large Managed Care Population, 1998–2002



[a]Incident cases of diabetes were identified by either earliest diagnosis of ICD-9 code 250.xx or treatment for diabetes.
[b]Patients were selected if they had at least a minimum of 3 months' exposure to medications or at least 3 prescriptions during the study period.
[c]Each case was matched with 6 controls by age, sex, and bipolar index month and year. Eighty-two case subjects with fewer than 6 matched controls were included in the analysis.

To protect patient confidentiality, patient names, insurance plan identification numbers, and other patient identifiers were deleted from the claims database. Randomized patient numbers and patient birth years were used for identification and calculation of age, respectively. The research project was approved by the University of Cincinnati Medical Center Institutional Review Board.

A retrospective, population-based, case-control (nested case-control) study was conducted. From 1998 to 2002, a total of 709,865 patients, including 6.2% Medicaid enrollees, had at least 1 diagnosis of an affective disorder or cyclothymia (Figure 1). Due to different socioeconomic characteristics of the Medicaid population, we selected a cohort of 123,292 non-Medicaid patients who had a bipolar diagnosis indicated by any of the following ICD-9 codes: 296.0, 296.1, 296.4–296.8. Patients with a diagnosis of depression only (ICD-9 code = 296.2x or 296.3x) or schizophrenia (ICD-9 code = 295.xx) during the study period were excluded from this population. Because numbers of patients with cyclothymia were less than 0.1%, patients with cyclothymia were not categorized separately.

Patient Selection

Because published reports show that drug-induced diabetes usually occurs with recent or current use of anti-

psychotic drugs,[10–23] we selected a cohort of patients who had at least a minimum of 3 months exposure to any medications or at least 3 prescriptions for their bipolar or comorbidity treatment during the study period. Incident cases of diabetes were identified by either earliest diagnosis of ICD-9 code 250.xx or treatment for diabetes. The date for the first diabetes diagnosis or use of diabetic medication was defined as the diabetes index date. To ensure that the patients with diabetes were incident cases, we checked the medical and prescription claim records for any diagnosis of or treatment for diabetes before the diabetes index date. Patients identified as cases should not have had a prescription for oral antidiabetic agents before the diabetes index date. A total of 78 patients who had received insulin and/or oral antidiabetic agents before the diabetes index date were excluded in order to eliminate potential patients with preexisting diabetes. The oral antidiabetic agents included sulfonylurea drugs (e.g., acetohexamide, glipizide, glyburide), biguanide (metformin), glitazones (e.g., pioglitazone, rosiglitazone), α-glucosidase inhibitors (e.g., miglitol, acarbose), and other new drugs like repaglinide and nateglinide.

For each case, we matched 6 controls with age at index date (standard deviation of 5 years), sex, and bipolar diagnosis index month and year. Controls that met the matching criteria were selected at random with SAS version 8.0 software (SAS Institute, Cary, N.C.). Controls were selected from patients who had been diagnosed as having bipolar disorder but had not been diagnosed as having diabetes and were not treated for diabetes at any time during the study period. Because bipolar diagnosis index month and year were part of matching criteria, the calendar time distributions of the bipolar index date were the same for both cases and controls.

Drug Use

We classified antipsychotics as conventionals and atypicals. Atypical antipsychotics included olanzapine, risperidone, quetiapine, ziprasidone, and clozapine. Aripiprazole was not included for this analysis as it was not available during the study period. Patients might switch from one atypical antipsychotic to another during the defined study period. Conventional antipsychotics included haloperidol, chlorpromazine, fluphenazine, loxapine, molindone, perphenazine, thioridazine, trifluoperazine, thiothixene, and pimozide.

For both cases and controls, we abstracted all prescription drug claims dispensed and reimbursed for the treatment of bipolar disorder and diabetes between the start of the study period and the index date of diabetes, the end of the study period, or the end of enrollment, whichever came first. We used dichotomous variables to indicate whether a patient had received concomitant drugs that have known association with diabetes or hyperglycemia, that is, α-blockers, β-blockers, corticosteroids, thiazide diuretics, phenytoin, oral contraceptives, or valproic acid.

Table 1. Characteristics for Study Population, Incident Cases of Diabetes, and Controls

Characteristic	Study Population (N = 123,292), N (%)	Cases (N = 920), N (%)	Controls (N = 5258), N (%)
Age, y			
≤ 12	5515 (4.47)	19 (2.07)	101 (1.92)
13–17	12,006 (9.74)	39 (4.24)	234 (4.45)
18–34	35,916 (29.13)	144 (15.65)	854 (16.24)
35–49	45,191 (36.65)	413 (44.89)	2477 (47.11)
50–64	21,754 (17.64)	263 (28.59)	1504 (28.60)
65+	2910 (2.36)	42 (4.57)	88 (1.67)
Sex			
Female	74,786 (60.66)	601 (65.33)	3473 (66.05)
Male	48,506 (39.34)	319 (34.67)	1785 (33.95)
Use of medications[a]			
Lithium	13,014 (10.56)	177 (19.24)	666 (12.67)
Anticonvulsants	30,313 (24.59)	395 (42.93)	1355 (25.77)
Atypical antipsychotics	13,560 (11.00)	378 (41.09)	592 (11.26)
Olanzapine	6020 (4.88)	186 (20.22)	258 (4.91)
Quetiapine	3228 (2.62)	79 (8.59)	166 (3.16)
Risperidone	4566 (3.70)	130 (14.13)	186 (3.54)
Ziprasidone	472 (0.38)	9 (0.98)	11 (0.21)
Clozapine	30 (0.02)	2 (0.22)	3 (0.06)
Switched atypicals	627 (0.51)	20 (2.17)	29 (0.55)
Antidepressants	40,521 (32.87)	436 (47.39)	1912 (36.36)
Conventional antipsychotics	20,042 (16.26)	314 (34.13)	1005 (19.11)

[a]Use of different medications was not mutually exclusive for one patient.

Statistical Analysis

The age of each patient was calculated as the number of years between the index date of bipolar diagnosis and birth year. The index date of bipolar diagnosis was the first date of diagnosis indicated by defined ICD-9 codes for bipolar during the study period. Age categories were ≤ 12, 13–17, 18–34, 35–49, 50–64, and 65 years or older.

We conducted all analyses with SAS version 8.0. We conducted the Cox proportional hazard regression to assess the risk of development diabetes associated with antipsychotic use due to the consideration of time-to-event with censoring and covariates. We used 2 different referent groups to compare the risk of diabetes developing among patients receiving different antipsychotics. The first group included all patients except those receiving the specific atypical antipsychotic drug of interest. The second group included patients taking conventional antipsychotics.

In addition to matching variables, we adjusted the analysis for use of other drugs known to affect the risk of diabetes, psychiatric comorbidities (alcohol abuse, substance abuse disorder, personality disorder, anxiety disorder, and impulse-control disorder), and medical comorbidities (hypertension, obesity, arthritis, cerebral

Table 2. Exposure Hazard Ratios and 95% Confidence Intervals (CIs) for Development of Diabetes in Patients Using Different Antipsychotics[a]

Use of Antipsychotics	Unadjusted Hazard Ratio[b] (95% CI)	p Value	Adjusted Hazard Ratio[c] (95% CI)	p Value
Atypical antipsychotics				
Olanzapine	5.378 (4.556 to 6.348)	< .0001	4.045 (3.384 to 4.834)	< .0001
Quetiapine	3.588 (2.833 to 4.545)	< .0001	2.300 (1.799 to 2.943)	< .0001
Risperidone	4.868 (4.025 to 5.888)	< .0001	3.484 (2.842 to 4.270)	< .0001
Ziprasidone	6.643 (3.423 to 12.891)	< .0001	4.642 (2.383 to 9.042)	< .0001
Clozapine	7.289 (1.811 to 29.335)	.0052	6.872 (1.702 to 27.746)	< .0001
Switched atypicals	3.896 (2.490 to 6.095)	< .0001	2.293 (1.452 to 3.621)	< .0001
Conventional antipsychotics	2.127 (1.849 to 2.447)	< .0001	1.495 (1.263 to 1.770)	< .0001

[a]For each Cox proportional hazard regression, the referent group involved all patients except those receiving the drug of interest.
[b]Unadjusted model includes age, sex, and bipolar follow-up months.
[c]Adjusted for age, sex, bipolar follow-up months, and use of medication (lithium, anticonvulsants, antidepressants, α-blockers, β-blockers, corticosteroids, thiazide diuretics, phenytoin, valproic acid, or oral contraceptives).

vascular disease [CVD], chronic obstructive pulmonary disease [COPD], dyslipidemia, and coronary heart disease [CHD]).

RESULTS

For study patients with bipolar disorder, females were more frequent than males (see Table 1). During the study period from 1998 to 2002, 13,560 study patients (11%) had at least 1 prescription for atypical antipsychotics, 20,042 patients (16%) had at least 1 prescription for conventional antipsychotics, 13,014 patients (11%) had at least 1 prescription for lithium, 30,313 patients (25%) had at least 1 prescription for anticonvulsants, and 40,521 patients (33%) had at least 1 prescription for antidepressants.

Based on the study inclusion and exclusion criteria, 920 cases of diabetes were identified and matched with 5258 controls. Eighty-two cases that had fewer than 6 controls per case were kept for the analysis. The majority of those cases were older patients who had a range of matched controls from 2 to 4 patients. The age and sex of these cases and controls were similar. Compared to controls, the cases more frequently used atypical antipsychotics and conventional antipsychotics, as well as lithium, anticonvulsants, and antidepressants (see Table 1). Of 920 cases, 41% received atypical antipsychotics, including 20% olanzapine, 14% risperidone, 9% quetiapine, and 1% ziprasidone. About 2% of patients in the case group switched from one atypical antipsychotic to another.

Table 2 summarizes the Cox proportional hazard regression analyses. The risk of developing diabetes was greatest among clozapine users (HR = 6.9, 95% CI = 1.7 to 27.7), ziprasidone users (HR = 4.6, 95% CI = 2.4 to 9.0), olanzapine users (HR = 4.0, 95% CI = 3.4 to 4.8), risperidone users (HR = 3.5, 95% CI = 2.8 to 4.3), quetiapine users (HR = 2.3, 95% CI = 1.8 to 2.9), patients receiving switched atypical antipsychotics (HR = 2.3, 95% CI = 1.5 to 3.6), and patients receiving conventional antipsychotics (HR = 1.5, 95% CI = 1.3 to 1.8), with adjusted models for age, sex, duration of bipolar follow-up, use of medications, and concomitant drugs.

Compared to patients receiving conventional antipsychotics, the risk of diabetes was also greatest among patients taking clozapine (HR = 7.0, 95% CI = 1.7 to 28.9), olanzapine (HR = 3.2, 95% CI = 2.7 to 3.8), risperidone (HR = 3.4, 95% CI = 2.8 to 4.2), and quetiapine (HR = 1.8, 95% CI = 1.4 to 2.4), with controlling covariates of age; sex; duration of follow-up; use of lithium, anticonvulsants, antidepressants, or concomitant drugs; and psychiatric and medical comorbidities (see Table 3).

DISCUSSION

This is a multi-state, population-based, case-control study examining the risk of developing diabetes associated with antipsychotics in patients with bipolar disorder. After controlling for personal risk factors and concomitant drug use, we found that patients receiving conventional or atypical antipsychotics for bipolar disorder have an increased risk of diabetes. It is unclear how much diabetes mellitus in the study population might be due to the use of antipsychotics compared to the underlying disease of bipolar disorder, poorer overall physical health, less healthy lifestyles, or poorer access to health care services.

Atypical and conventional antipsychotics are often distinguished by their adverse effects. Atypical antipsychotics are generally regarded as having low potential for causing extrapyramidal symptoms and a high serotonin-to-dopamine receptor affinity.[9,31] Literature indicates that clozapine and olanzapine are more likely to be associated with diabetes mellitus (indicated by diabetic ketoacidosis and atherogenic lipid profile) than other atypical agents.[7,21,22,32,33] One possible mechanism for hyperglycemia is impairment of insulin resistance, which may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues.[7,34]

Compared to published pharmacoepidemiologic studies of patients with schizophrenia,[7,21–24] our findings from

Table 3. Exposure Hazard Ratios (HRs) for Development of Diabetes in Patients Receiving Atypical Antipsychotics Compared With Patients Receiving Conventional Antipsychotics

Variable	Cases (N = 920), N (%)	Controls (N = 5258), N (%)	Model 1,[a] HR (95% CI)	Model 2,[b] HR (95% CI)	Model 3,[c] HR (95% CI)
Use of medication					
Atypical antipsychotics					
Olanzapine	186 (20.22)	258 (4.91)	4.032 (3.363 to 4.834)	3.889 (3.238 to 4.670)	3.188 (2.650 to 3.834)
Quetiapine	79 (8.59)	166 (3.16)	2.197 (1.703 to 2.836)	2.121 (1.641 to 2.741)	1.824 (1.413 to 2.357)
Risperidone	130 (14.13)	186 (3.54)	3.524 (2.864 to 4.337)	3.409 (2.767 to 4.201)	3.403 (2.757 to 4.199)
Ziprasidone	9 (0.98)	11 (0.21)	1.237 (0.614 to 2.491)	1.279 (0.636 to 2.571)	1.685 (0.844 to 3.365)
Clozapine	2 (0.22)	3 (0.06)	6.217 (1.525 to 25.338)	5.313 (1.285 to 21.967)	7.003 (1.698 to 28.877)
Lithium	177 (19.24)	666 (12.67)	1.034 (0.867 to 1.233)	1.077 (0.902 to 1.287)	1.077 (0.900 to 1.287)
Anticonvulsants	395 (42.93)	1355 (25.77)	1.414 (1.192 to 1.677)	1.399 (1.176 to 1.664)	1.359 (1.139 to 1.621)
Antidepressants	436 (47.39)	1912 (36.36)	0.832 (0.707 to 0.978)	0.80 (0.681 to 0.948)	0.820 (0.694 to 0.969)
Conventional antipsychotics[d]	314 (34.13)	1005 (19.11)	1.000	1.000	1.000
Concomitant drugs					
β-Blocker	128 (13.91)	408 (7.76)	1.339 (1.098 to 1.634)	1.327 (1.088 to 1.620)	1.025 (0.839 to 1.252)
α-Blocker	29 (3.15)	45 (0.86)	1.760 (1.175 to 2.634)	1.785 (1.192 to 2.674)	1.012 (0.678 to 1.511)
Corticosteroid	149 (16.20)	593 (11.28)	1.120 (0.932 to 1.345)	1.093 (0.910 to 1.314)	0.941 (0.778 to 1.139)
Thiazide diuretic	67 (7.28)	134 (2.55)	1.877 (1.444 to 2.440)	1.886 (1.449 to 2.454)	1.249 (0.959 to 1.627)
Oral contraceptive	17 (1.85)	101 (1.92)	0.707 (0.426 to 1.174)	0.677 (0.406 to 1.130)	0.750 (0.451 to 1.248)
Valproic acid	7 (0.76)	29 (0.55)	1.181 (0.557 to 2.501)	1.179 (0.557 to 2.497)	1.172 (0.554 to 2.482)
Phenytoin	4 (0.43)	24 (0.46)	0.373 (0.137 to 1.013)	0.364 (0.133 to 1.001)	0.345 (0.126 to 0.946)
Psychiatric comorbidities					
Alcohol abuse	81 (8.80)	325 (6.18)	...	1.180 (0.922 to 1.510)	1.258 (0.984 to 1.609)
Substance abuse disorder	58 (6.30)	240 (4.56)	...	1.082 (0.808 to 1.449)	1.112 (0.831 to 1.489)
Anxiety disorder	415 (45.11)	1916 (36.44)	...	1.211 (1.057 to 1.387)	1.050 (0.914 to 1.206)
Impulse-control disorder	26 (2.83)	65 (1.24)	...	1.744 (1.153 to 2.638)	1.634 (1.080 to 2.470)
Personality disorder	66 (7.17)	215 (4.09)	...	1.261 (0.971 to 1.637)	1.200 (0.925 to 1.557)
Medical comorbidities					
Hypertension	451 (49.02)	1009 (19.19)	...	...	2.741 (2.343 to 3.217)
Obesity	203 (22.07)	331 (6.30)	...	...	2.244 (1.897 to 2.656)
Arthritis	48 (5.22)	152 (2.89)	...	...	1.155 (0.851 to 1.568)
COPD	76 (8.26)	182 (3.46)	...	...	1.201 (0.933 to 1.546)
CVD	65 (7.07)	124 (2.36)	...	...	1.467 (1.118 to 1.925)
CHD	21 (2.28)	19 (0.36)	...	...	2.558 (1.616 to 4.048)
Dyslipidemia	28 (3.04)	58 (1.10)	...	...	2.703 (1.825 to 4.005)

[a]Model for age, sex, bipolar follow-up months, and use of medications; $\chi^2 = 620.90$, $p < .0001$.
[b]Model for age, sex, bipolar follow-up months, use of medications, and psychiatric comorbidities; $\chi^2 = 643.82$, $p < .0001$.
[c]Model for age, sex, bipolar follow-up months, use of medications, and psychiatric and medical comorbidities; $\chi^2 = 987.54$, $p < .0001$.
[d]HR = 1.000, because use of conventional antipsychotics was considered as the reference group.
Abbreviations: CHD = coronary heart disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CVD = cerebral vascular disease.

the present study of bipolar patients are similar or comparable. For example, patients with schizophrenia had the risk of developing diabetes associated with clozapine (HR = 7.4–8.4),[34,35,37] olanzapine (HR = 1.2–5.8),[7,21–23] and risperidone (HR = 1.1–2.2),[7,21–24] compared to the risk among bipolar patients for clozapine (HR = 7.0), olanzapine (HR = 3.2), and risperidone (HR = 3.4) reported in Table 3. Our results indicated the risk of developing diabetes is statistically significant for bipolar patients taking clozapine, olanzapine, risperidone, and quetiapine antipsychotics after controlling for comorbidities, personal risk factors, and concomitant drug use. The hazard ratio associated with ziprasidone was large (HR = 4.6) without controlling for comorbidities; then it became smaller (HR = 1.7) and not statistically significant after controlling for comorbidities. This indicated that comorbidities are critical covariates for assessing the risk of drug-induced diabetes.

In addition to antipsychotic use, the present study indicates that the risk of developing diabetes is also associated with a patient's comorbidity, especially obesity (HR = 2.2, 95% CI = 1.9 to 2.7), hypertension (HR = 2.7, 95% CI = 2.3 to 3.2), CVD (HR = 1.5, 95% CI = 1.1 to 1.9), CHD (HR = 2.6, 95% CI = 1.6 to 4.0), and dyslipidemia (HR = 2.7, 95% CI = 1.8 to 4.0) (Table 3). As the literature indicates, some antipsychotics like olanzapine, clozapine, and risperidone are associated with weight gain,[5,38,39] hyperlipidemia, and hypertriglyceridemia, which are independent risk factors for heart disease.[7,8,40,41] It is likely that incident diabetes was associated with metabolic syndrome, as indicated by higher HRs for obesity, hypertension, CVD, CHD, and dyslipidemia in this study. This study also suggested that patients with impulse-control disorder or anxiety disorder had higher risk for diabetes. It is possible that patients with impulse-control disorder or anxiety disorder might have

less healthy lifestyles, less medication compliance, or poorer access to health care services.[42,43]

Our study has several limitations. Drug use was inferred from automated pharmacy claims data. Because of the retrospective nature of a claims database review, it is not possible to review the direct information on the severity of bipolar disorder, socioeconomic class, lipid profiles, fasting glucose, or body mass index related to weight gain. We were unable to adjust the patients' ethnicity because the variable was missing when PharMetrics (data vendor) collected the medical claim data from different managed care organizations. It is unclear whether different medications prescribed before the study period might be partially limited to the increased risk of diabetes. Because clinicians may have prescribed one drug over the other based on the different moods of bipolar patients, we attempted to reduce this potentially confounding bias by adjusting for known concomitant drugs and comorbidities. We also included comorbidities of dyslipidemia and CHD as a rough proxy for controlling high risk patients for diabetes. It is possible that this study underestimated the prevalence of diabetes due to the limited time window and changes of managed care enrollment and other mental services not billed to patients' managed care organizations. Comorbid conditions were identified by diagnostic codes without considering the combination of medications for obesity, hypertension, CVD, and other diseases.

Despite the above limitations, the present study is a contribution to the limited literature about diabetes risk in bipolar patients and provides useful information for disease management strategies in terms of selection of mood stabilizers and consideration of relevant comorbidities for patients with bipolar disorder. Atypical antipsychotics provide great benefit to a wide variety of people with psychiatric disorders and have one constellation of adverse effects related to increased risk of obesity, diabetes, and dyslipidemia.[9,34]

In conclusion, some atypical antipsychotics like clozapine, olanzapine, risperidone, and quetiapine are consistently associated with a clinically important increased risk of diabetes mellitus in bipolar patients after adjustment for relevant risk factors. Metabolic complications are a major issue for patients receiving antipsychotic therapy. The choice of atypical antipsychotics for a specific bipolar patient should consider the risk-benefit of antipsychotics and depends on relevant high-risk comorbid conditions. Thus, the propensity of an antipsychotic to induce diabetes is a critical consideration when selecting an agent for patients with bipolar disorder.

Drug names: acarbose (Precose), aripiprazole (Abilify), atenolol (Tenormin and others), betaxolol (Kerlone, Betoptic, and others), bisoprolol (Zebeta and others), carbamazepine (Carbatrol, Equetro, and others), chlorothiazide (Diuril and others), chlorpromazine (Thorazine, Sonazine, and others), chlorthalidone (Thalitone and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), doxazosin (Cardura and others), fluphenazine (Prolixin and others), glipizide (Glucotrol and others), glyburide (Diabeta, Micronase, and others), hydrocortisone (Hydrocortone, Cortef, and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), loxapine (Loxitane and others), metformin (Riomet, Fortamet, and others), methylprednisolone (Medrol, A-Methapred, and others), miglitol (Glyset), molindone (Moban), nateglinide (Starlix), olanzapine (Zyprexa), phenytoin (Dilantin, Phenytek, and others), pimozide (Orap), pioglitazone (Actos), polythiazide (Renese), prazosin (Minipress and others), quetiapine (Seroquel), repaglinide (Prandin), risperidone (Risperdal), rosiglitazone (Avandia), terazosin (Hytrin and others), thiothixene (Navane and others), trifluoperazine (Stelazine and others), valproic acid (Depakene and others), ziprasidone (Geodon).

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A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States

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Abstract

Treatment-emergent diabetes mellitus (DM) has been described for conventional and atypical antipsychotics. In our study, antipsychotic prescription claims from AdvancePCS's database were used to identify patients starting antipsychotic monotherapy. The relative risk of developing DM was determined using prescription claims for antidiabetic agents in the following cohorts: AdvancePCS general patient population, combined conventional antipsychotics, and combined atypical antipsychotics. Cox proportional hazards regression was used to adjust for differences in age, gender, and duration of antipsychotic exposure between cohorts in the estimation of risk of developing diabetes. Hazard ratios for developing DM in the combined conventional, combined atypical, and individual conventional and atypical antipsychotic treatment cohorts were greater than the AdvancePCS general patient population cohort. An increased risk of developing diabetes compared with the AdvancePCS general patient population was observed during treatment with conventional or atypical antipsychotics.

*Keywords: A*ntipsychotics; Diabetes; Epidemiologic study

1. Introduction

Studies over several decades have suggested that diabetes mellitus (DM), impaired glucose tolerance, and insulin resistance are more common in patients with psychiatric disorders, including major mood disorders and schizophrenia, than in the general population [1–6]. Literature reports have associated treatment-emergent glucose intolerance with conventional antipsychotics [7–15] and atypical antipsychotics [16–23] in humans. This possibility has been supported also by animal studies, where chlorpromazine was shown to cause hyperglycemia in normal animals [24,25]. However, a role of neuroleptics in the development of DM has not been supported by all investigations [26,27] because higher than expected rates of insulin resistance and impaired glucose tolerance had been reported in patients with schizophrenia before the introduction of neuroleptics [28–32].

A number of recent studies have attempted to clarify whether the rate of diabetes is elevated in patients treated with antipsychotics. However, reports in the literature have consisted primarily of small case series and prevalence studies in relatively small population samples [33–36]. These studies have been marked by significant methodologic limitations, and the results have been largely inconclusive. Questions regarding the frequency of DM in patients treated with antipsychotics are most effectively answered in epidemiologic studies. Due to their large sample size and less rigorous exclusion criteria compared with prospective clinical trials, epidemiologic studies can accurately assess the frequency of relatively rare events and provide results that are more representative of the general population.

Recently, there has been increasing interest in the pharmacoepidemiology of antipsychotics and DM. Mahmoud et al [37] examined prescription claims data from two large mixed indemnity and managed health care plans in the United States and determined the hazard ratios (HR) for developing DM during exposure to antipsychotic medications. They identified treatment-emergent diabetes by prescription claims and ICD-CM-9 diagnostic criteria over a 2-year period, with 4- and 8-month prescreening periods before the initiation of antipsychotic therapy. They reported an increased risk of developing DM in patients exposed to high- and low-potency

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conventional antipsychotics, clozapine, and olanzapine. Another recent epidemiologic study by Caro et al retrospectively examined treatment-emergent diabetes during exposure to risperidone or olanzapine from prescription claims and physician diagnoses from the Régie de l'Assurance Maladie du Québec (RAMQ) [38]. The results of this study showed a greater incidence of DM for the olanzapine cohort (1.7%) as compared with the risperidone (1.5%) cohort. On the basis of a crude relative risk of 1.08 (95% confidence interval [CI] 0.89–1.31) and HR of 1.2 (95% CI 1.0–1.43), the authors concluded that the risk of developing diabetes was higher for patients treated with olanzapine than for those who had been treated with risperidone. The Mahmoud [37] and RAMQ [38] studies included patients in their cohorts who were taking more than one antipsychotic medication concurrently. To our knowledge, no large-scale, peer-reviewed epidemiologic study evaluating the potential association of diabetes with antipsychotic treatment has been published.

In the present retrospective cohort study, the AdvancePCS (Scottsdale, AZ) prescription claim database was used to identify large cohorts of patients treated with a single antipsychotic during a defined period of observation. The purpose of this study was to estimate the incidence and risk of developing DM among patients in the United States who received a single antipsychotic drug, irrespective of indication. Individual antipsychotic cohorts were compared with each other and with the AdvancePCS general patient population.

2. Methods

This is a retrospective cohort study that determined the risk of developing DM during antipsychotic treatment using prescription claim data from AdvancePCS, Inc. AdvancePCS processes over 300 million prescription claims per year for the over 50 million members covered by the over 2000 nationwide employers and managed care plans represented in this database. Most of these claims are submitted by pharmacies handling the outpatient prescription needs for this membership; however, some prescriptions are filled in long-term care settings. There was no difference among study groups in terms of how patients received their prescriptions. In this study, we followed patients who maintained coverage with AdvancePCS. Once a patient discontinued their coverage, they were censored in the data analyses. Approximately 15% of the AdvancePCS members are over 65, and the >65 group represents over 24% of AdvancePCS's patient population. As of 1997, 42% of the patients starting an antipsychotic prescription were covered by Medicaid. The data cut-off point for this study was August 31, 2000.

2.1. Study cohorts

Only subjects who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. For the purpose of this study, monotherapy refers only to antipsychotics and not to any other medications. The cohorts studied (1) a combined conventional antipsychotic cohort (comprised of subjects treated with all agents in this class), (2) a combined atypical antipsychotic cohort, (3) cohorts of individual antipsychotics (comprised of subjects treated with a particular agent [eg, the haloperidol cohort]), and (4) the AdvancePCS general patient population cohort. The general patient population cohort included all subjects who had made a prescription claim for any AdvancePCS-covered benefit during a 2-month enrollment window (1 January 2000 to 29 February 2000). They must not have made a claim for diabetes drug(s) for at least 12 months before enrollment. In addition, they must not have been dispensed an antipsychotic for at least 6 months before and 6 months after enrollment.

Antipsychotic agents included conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychotics (clozapine, olanzapine, quetiapine, and risperidone).

The enrollment window for subjects in the antipsychotic cohorts was 1 December 1998 through 29 February 2000. Subjects who started therapy during this period and continued to be treated with the same single antipsychotic during this period were included in the antipsychotic cohorts. Only subjects who were eligible for prescription claims through the AdvancePCS system for at least 12 months before enrollment were included in any of the cohorts. There were no significant differences among the number of patients using a diabetes medication when comparing a 12-month pre-enrollment period versus a 24-month pre-enrollment period. Thus, for this study, the 12-month pre-enrollment period was used. The exclusion criteria applicable to all cohorts were (1) a pre-existing history of DM as evidenced by a prescription claim for any anti-diabetic medication during the 12-month period before enrollment, (2) a prescription claim for any antipsychotics within the 6-month period before enrollment date, (3) the absence of information on sex or the year of birth, and (4) being <18 years of age. For all antipsychotic cohorts, patients who received more than one antipsychotic during the evaluation period were excluded. Although the enrollment windows differ between the general patient population and the antipsychotic groups, age at the point of entry into the study was used as the reference age for each study subject for the data analysis. In addition, adjustments for age differences were addressed by including an age variable in the regression analyses.

2.2. Identification of incident cases of DM

New onset of DM during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of diabetes, regardless of the route of administration. For subjects in any cohort, the earliest date during the enrollment window that any given subject received an antipsychotic agent (in the case of antipsychotic cohorts) or a nonantipsychotic agent (in the case of the AdvancePCS gen-

eral patient population) was considered the enrollment date for that subject. To identify the timing of onset of new cases of DM, the date of the first antidiabetic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for a new onset of DM from the enrollment date (ie, the start of antipsychotic therapy for the antipsychotic cohorts) to the time that the antipsychotic was discontinued for more than 15 days or until 31 August 2000 (the data set cut-off point), whichever came first. Thus, length of therapy was used as the dependent variable in the proportional hazards model.

2.3. Comparison of the risk of developing diabetes among cohorts

To compare the risk of developing DM among cohorts, incidence density and HRs were determined. Because the incidence of DM for antipsychotic cohorts might not be linearly related to time with more cases being experienced early, annualization of incidence density could inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, gender, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of DM, the Cox proportional hazard regression was used to determine the HR of DM for antipsychotic cohorts relative to the AdvancePCS general patient population. Using the PHREG procedure in SAS, several proportional hazards models were created using various combinations of the following covariates: age (three categories), gender (two categories), and amount of exposure (five categories). The reference categories for these covariates, represented by zero in the model, were the 18 to 44 group for age and female patients for gender. Amount of exposure was viewed as continuous days of treatment determined from the date of first antipsychotic prescription filled and the last successive prescription(s) that was not separated by more than 15 days. Individual doses were determined for each subject by summing the product(s) of strength and number of tablets for the successive prescriptions and dividing that sum by the number of continuous days of treatment. Because these doses varied widely within and among the antipsychotic cohorts, subjects within a cohort were grouped into dose quartiles. Subjects in the AdvancePCS general patient population were assigned a fifth dose "quartile" with a value of zero. Age was also standardized into the 18 to 44, 45 to 64, and 65 years of age and older categories because these ranges correspond with those cited for the incidence of diabetes in the United States general population [39]. In addition, given the wide doses observed in the antipsychotic cohorts, the HRs of DM were determined for each dose quartile relative to the AdvancePCS general patient population. The HRs of DM between selected antipsychotic cohorts were also determined. The alpha level for staistical significance was 0.05.

3. Results

The characteristics of the antipsychotic cohorts studied are summarized in Table 1. Haloperidol, thioridazine, risperidone, and olanzapine were the most commonly prescribed agents in their respective antipsychotic classes in the AdvancePCS database. Compared with the AdvancePCS general patient population, patients in the combined conventional and combined atypical antipsychotic cohorts were older. Among individual antipsychotic cohorts, the average age of the haloperidol cohort was notably older, with almost two thirds of patients over 64 years of age. There were more women than men in all cohorts, with the exception of the clozapine cohort. The average duration of antipsychotic treatment, ranging from 67 to 137 days, was longer for the atypical antipsychotic cohorts.

Separate regression analyses were performed to determine the association between the covariates and the development of DM (Table 2). A significant HR for age was found for most cohorts (excluding the thioridazine and clozapine cohorts), and a significant HR for gender was found for the AdvancePCS

Table 1
Characteristics of cohorts studied

	AdvancePCS general patient	Conventional antipsychotic			Atypical antipsychotic				
Number of subjects in cohort	population 5,816,473	All agents 19,782	Haloperidol 8476	Thioridazine 3133	All agents 38,969	Clozapine 277	Olanzapine 13,863	Quetiapine 4196	Risperidone 20,633
Age distribution, y									
18–44, %	36.5	20.8	11.9	25.7	30.2	36.8	36.6	35.8	24.6
45–64, %	39.3	26.0	15.3	26.7	23.6	25.3	28.7	28.1	19.2
65 and older, %	24.2	53.2	72.8	47.7	46.3	37.9	34.7	36.0	56.2
Mean age, y	52	64	72	61	60	55	55	55	64
Male, %	37	44	41	38	38	53	39	37	37
Average duration of antipsychotic treatment, d (SD)	NA	67 (74)	68 (70)	76 (81)	90 (83)	137 (125)	89 (85)	89 (79)	90 (82)
Mean dose of antipsychotic, mg (SD)	NA	NA	2.5 (5.2)	43.9 (54.6)	NA	183.1 (198.6)	5.1 (4.2)	79.9 (96.7)	1.2 (1.0)

Table 2
Hazard ratio of diabetes mellitus for covariates in the proportional hazard regression model stratified by antipsychotic cohorts

Variable	HR	95% CI	*P* value
Conventional antipsychotic cohort (n = 19,782)			
Age 45–64 y[a]	2.4	1.5–3.9	0.0003
Age ⩾65 y[a]	3.4	2.2–5.3	⩽0.0001
Gender (male)[b]	1.0	0.8–1.2	0.8158
Haloperidol cohort (n = 8476)			
Age 45–64 y	4.5	1.3–15.2	0.0162
Age ⩾65 y	5.9	1.9–18.4	0.0025
Gender (male)	1.3	0.9–1.8	0.1218
Thioridazine cohort (n = 3133)			
Age 45–64 y	1.7	0.7–4.0	0.2061
Age ⩾65 y	2.1	1.0–4.5	0.0610
Gender (male)	0.8	0.5–1.4	0.4729
Atypical antipsychotic cohort (n = 38,969)			
Age 45–64 y	2.8	2.0–4.0	⩽0.0001
Age ⩾65 y	6.1	4.5–8.2	⩽0.0001
Gender (male)	1.3	1.1–1.6	0.0003
Clozapine cohort (n = 277)			
Age 45–64 y	3.0	0.3–33.6	0.3677
Age ⩾65 y	3.4	0.4–31.3	0.2716
Gender (male)	0.7	0.2–3.2	0.6497
Olanzapine cohort (n = 13,863)			
Age 45–64 y	2.6	1.5–4.5	0.0006
Age ⩾65 y	6.5	4.2–10.5	⩽0.0001
Gender (male)	1.3	1.0–1.8	0.0585
Quetiapine cohort (n = 4196)			
Age 45–64 y	1.0	0.3–2.9	0.9670
Age ⩾65 y	3.0	1.3–7.0	0.0095
Gender (male)	1.1	0.6–2.1	0.7649
Risperidone cohort (n = 20,633)			
Age 45–64 y	3.7	2.2–6.2	⩽0.0001
Age ⩾65 y	6.6	4.2–10.3	⩽0.0001
Gender (male)	1.3	1.1–1.7	0.0010
AdvancePCS general patient population cohort (n = 5,816,473)			
Age 45–64 y	3.4	3.3–3.5	⩽0.0001
Age ⩾65 y	4.0	3.9–4.2	⩽0.0001
Gender (males)	1.1	1.1–1.2	⩽0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] For all cohorts, age 18–44 used as reference group.

[b] For all cohorts, female gender used as reference group.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

general patient population, combined atypical antipsychotic, and risperidone cohorts. The gender effect was smaller than the age effect. Male gender was associated with a 30% increased risk of DM for the combined atypical antipsychotic cohort (P = 0.0003) and a 10% increased risk for the AdvancePCS general patient population cohort ($P \leqslant 0.0001$).

The incidence of diabetes per 1000 patient-years of antipsychotic treatment and the HR of diabetes of the various cohorts are shown in Table 3. Compared with the incidence density of the AdvancePCS general patient population, the incidences of diabetes during exposure to antipsychotics were several times higher. The Cox proportional hazards regression, adjusting for age, gender, and duration of antipsychotic exposure, showed that the risk of DM for the combined conventional and combined atypical antipsychotic cohorts was significantly higher than in the AdvancePCS general patient population. The HRs for all individual atypical antipsychotic cohorts (clozapine, olanzapine, risperidone, and quetiapine) were significantly higher than those of the AdvancePCS general patient population.

The risk of DM for the combined conventional cohort was not significantly different from that of the combined atypical cohorts (HR 0.97, CI 0.84–1.11; P = 0.626) (Table 4). No significant increase in the risk of DM was observed for the olanzapine (HR 1.09, CI 0.86–1.37; P = 0.479) or the clozapine (HR 1.31, CI 0.60–2.86; P = 0.496) cohort when compared with the haloperidol cohort. The number of patients in the clozapine cohort was small (n = 277) and lacked power to detect a significant difference in the HR ratio within the range of the HRs observed in the other antipsychotic cohorts. The risk of DM for the quetiapine cohort was lower than the risk for the haloperidol cohort (HR 0.67, CI 0.46–0.97; P = 0.033). The risk of DM in the risperidone cohort, relative to the haloperidol cohort, was 1.23 (CI 1.01–1.50; P = 0.040). When comparing the two largest atypical antipsychotic cohorts (olanzapine and risperidone), the HR was 0.90 (CI 0.76–1.07; P = 0.234).

The age- and gender-adjusted HRs for the dose quartiles relative to the AdvancePCS general patient population are displayed in Table 5. A positive dose relationship for the risk of DM was observed for the thioridazine cohort because the 95% CI of the first and fourth dose quartile did not overlap. A significant dose-response relationship was not observed in the atypical antipsychotic cohorts, with the possible exception of quetiapine. Although the HR of the quetiapine cohort was not statistically significant in the first dose quartile relative to the AdvancePCS general patient population (HR 1.8, CI 0.9–3.4; P = 0.096), the HR was statistically significant in the fourth dose quartile (HR 3.1, CI 1.9–5.1; $P \leqslant 0.0001$).

4. Discussion

This large pharmacoepidemiologic study examined at least two important questions: (1) Did patients on atypical agents experience a different risk of treatment-emergent diabetes than those on conventional antipsychotics? and (2) Were there clinically significant differences in the risks of diabetes between antipsychotics? Consistently, the HRs of all antipsychotic treatment cohorts studied were significantly higher than those of the AdvancePCS general patient population. Although the risk of DM was comparable between the combined conventional cohort and the combined atypical cohort, some significant differences were observed when pairwise comparisons were made between individual antipsychotics. Of the atypical antipsychotic cohorts, only the risperidone cohort was associated with a significantly greater risk of diabetes than the haloperidol cohort. Direct comparison of the olanzapine and risperidone cohorts indicated no significant difference in the risk of diabetes during treatment with these agents.

Table 3
Incidence and hazard ratio of diabetes mellitus in patients during treatment with antipsychotics

Cohort	New cases (*n*)	Patients (*n*)	Patient-years	Incidence (per 1000 patient-years)		HR[a]		
				Rate	95% CI	Ratio	95% CI	*P* value
Conventional antipsychotics								
All combined	307	19,782	3645.57	84	75–94	3.5	3.1–3.9	⩽0.0001
Haloperidol	133	8476	1568.39	85	70–100	3.1	2.6–3.7	⩽0.0001
Thioridazine	62	3133	654.28	95	71–119	4.2	3.2–5.5	⩽0.0001
Atypical antipsychotics								
All combined	641	38,969	9571.18	67	62–72	3.1	2.9–3.4	⩽0.0001
Clozapine	7	277	103.95	67	16–118	3.3	1.4–8.0	0.0070
Olanzapine	194	13,863	3374.57	58	49–66	3.0	2.6–3.5	⩽0.0001
Quetiapine	40	4196	1025.75	39	27–51	1.7	1.2–2.4	0.0020
Risperidone	400	20,633	5066.90	79	71–87	3.4	3.1–3.8	⩽0.0001
General patient population	45,513	5,816,473	2,908,236.5	15.7	15.5–15.8			

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.
HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.

For all antipsychotic cohorts, increasing age was a significant risk factor for DM. This finding is in keeping with well-established epidemiologic data indicating that the prevalence of diabetes increases with age [40], with an almost two-fold increase past age 49 [39]. Male gender was a significant predictor of increased risk of diabetes only for the combined atypical antipsychotic, the risperidone, and the AdvancePCS general patient population cohorts.

Factors related to diagnostic heterogeneity and illness severity may also underlie some of the findings in the dose quartile analysis. The antipsychotic cohorts included all subjects treated with antipsychotics, irrespective of diagnosis and illness severity. The fourth dose quartile in the antipsychotic cohorts contains patients who received the highest doses of antipsychotics that may define a subpopulation of more severely ill, diagnostically homogeneous patients. Compared with other psychiatric disorders commonly treated with antipsychotics, schizophrenic patients often require higher doses of antipsychotics. Thus, the risk of DM associated with the fourth dose quartile may be particularly relevant to patients with schizophrenia.

Recently, there have been a number of reports on the prevalence [36] or the risk [37,38] of DM in subjects treated with antipsychotics. Some of these reports have been limited by relatively small sample sizes, the concurrent use of multiple antipsychotic drugs in the cohorts, or the absence of a reference (control) population. Our study presents a number of strengths: (1) The sample sizes of cohorts were large; (2) only patients who were antipsychotic free for at least 6 months and who received only a single antipsychotic during the evaluation period were included in the antipsychotic cohorts, and thus the study was not confounded by antipsychotics that were recently or concurrently administered; and (3) the use of the AdvancePCS general patient population enabled us to compare the rates of developing DM relative with a reference population that was not exposed to antipsychotic medications.

The major limitation of this study was that psychiatric diagnostic information was not available in the database. Other limitations were that only incident cases of DM that resulted in intervention with antidiabetic medications were identified and that all indications for antipsychotic prescriptions were included, regardless of psychiatric illness spectrum or severity. Furthermore, the selection of a given antipsychotic reflects clinical choices rather than randomized assignment. Potentially, certain patient attributes that influence treatment selection might also affect likelihood of developing DM. While pharmacoepidemiological studies can control for some important factors (e.g., age), others cannot be addressed with available data (e.g., severity of illness); 3) the average duration of antipsychotic treatment was not long, ranging from 68 days to 137 days; 4) the database did not

Table 4
Hazard ratio of developing diabetes comparing other antipsychotic cohorts to the haloperidol cohort

Treatment cohort	New cases (*n*)	Subjects in cohort (*n*)	HR[a]		
			Ratio	95% CI	*P* value
Olanzapine	194	13,863	1.09	0.86–1.37	0.479
Risperidone	400	20,633	1.23	1.01–1.50	0.040
Quetiapine	40	4,196	0.67	0.46–0.97	0.033
Clozapine	7	277	1.31	0.60–2.86	0.496

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.
HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.
In the haloperidol cohort, there were 133 new cases in a total of 8476 patients.

Table 5
Hazard ratios for antipsychotic cohort dose quartiles relative to the AdvancePCS general patient population

Cohort	Mean dose/quartile (± SD)	Mean age (± SD)	HR[a]		
			Ratio	95% CI	*P* value
Conventional					
Haloperidol					
Q1	0.5 ± 0.3	77.1 ± 30.6	2.6	1.9–3.7	≤0.0001
Q2	0.9 ± 0.3	75.8 ± 31.5	2.9	2.0–4.2	≤0.0001
Q3	1.7 ± 0.7	72.6 ± 34.1	2.9	2.0–4.1	≤0.0001
Q4	7.0 ± 17.5	61.5 ± 39.5	4.3	3.1–5.9	≤0.0001
Thioridazine					
Q1	9.9 ± 6.3	66.1 ± 39.6	2.1	1.0–4.5	0.0453
Q2	20.1 ± 6.3	63.6 ± 38.8	3.0	1.7–5.4	≤0.0001
Q3	37.3 ± 14.4	60.2 ± 37.9	2.9	1.6–5.2	0.0005
Q4	110.8 ± 151.1	54.9 ± 37.0	8.9	6.2–12.7	≤0.0001
Atypical					
Olanzapine					
Q1	1.7 ± 0.9	60.1 ± 42.2	3.4	2.6–4.5	≤0.0001
Q2	3.1 ± 0.7	55.0 ± 41.0	2.6	1.9–3.6	≤0.0001
Q3	5.3 ± 2.0	53.4 ± 39.6	2.5	1.9–3.3	≤0.0001
Q4	11.3 ± 9.8	50.0 ± 37.1	3.6	2.8–4.7	≤0.0001
Risperidone					
Q1	0.4 ± 0.2	70.9 ± 40.6	3.7	3.0–4.5	≤0.0001
Q2	0.7 ± 0.1	65.1 ± 43.5	3.0	2.4–3.8	≤0.0001
Q3	1.1 ± 0.3	63.6 ± 43.0	3.0	2.5–3.7	≤0.0001
Q4	2.5 ± 2.4	56.0 ± 42.2	4.0	3.3–4.8	≤0.0001
Quetiapine					
Q1	17.0 ± 8.6	60.2 ± 40.7	1.8	0.9–3.4	0.0957
Q2	34.5 ± 11.3	57.1 ± 41.2	1.4	0.7–2.9	0.3347
Q3	64.5 ± 24.4	53.3 ± 37.8	0.6	0.2–1.8	0.3938
Q4	203.7 ± 245.1	49.8 ± 36.4	3.1	1.9–5.1	≤0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.
[a] Cox proportional hazards regression analysis adjusted for age and gender.
HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.
The sample size of the clozapine cohort (277 subjects with 7 cases of diabetes mellitus) was too small for a meaningful quartile analysis.

contain information on well known risks for DM, including obesity, ethnic origin, or family history. Thus it was not possible to adjust for differences in these risk factors between cohorts; 5) the mean daily doses in antipsychotic cohorts were low. However, the dose quartile analysis showed that relatively higher doses were represented. Thus our findings can only be generalized to populations similar to that represented in the AdvancePCS database; 6) we did not account for exposure to other drugs that may be temporally associated with glucose dysregulation (e.g. protease inhibitors, thiazide diuretics and β-blockers). Therefore, if these drugs were not prescribed uniformly across the cohorts studied, the hazard ratio for developing diabetes may have been overestimated in individual cohorts containing patients prescribed these drugs.

Elevated HR during antipsychotic treatment may reflect a number of factors. While one possibility is an adverse glycemic effect of antipsychotics, other major considerations include (1) a vulnerability for DM which may be genetically or behaviorally linked to the disorder being treated; (2) an indirect medication effect, e.g., via an effect on diet or exercise; and (3) enhanced recognition of DM coinciding with the prescription of antipsychotic medication or illness severity, e.g., increased probability of detecting diabetes for patients who had more frequent contact with medical professionals due to their illness. These additional factors need to be taken into account in determining the risk of developing DM during treatment with antipsychotics. Further, given that differences in background incidence and risk factors for DM might exist between populations commonly treated with antipsychotics and the general population, comparisons between antipsychotic-treated cohorts and a reference population without psychosis may overestimate the potential effect of antipsychotics on the emergence of DM.

In conclusion, our study suggests that patients treated with either conventional or atypical antipsychotics may be at higher risks of developing DM than the AdvancePCS general patient population. The risk of developing diabetes was comparable between conventional and atypical antipsychotic cohorts. What remains unclear is to what extent the observed increases in incidence and risk of DM may be related to factors intrinsic or extrinsic to those psychiatric disorders commonly treated with antipsychotic drugs. Finally, though the potential morbidity and mortality related to DM is serious, it must be evaluated in the context of the significant morbidity and mortality associated with major psychiatric illnesses. Findings from the present study suggest that the decisions regarding the choice of antipsychotic for treat-

ing major psychiatric illness should not be based solely on the relatively modest differences in DM rates observed during treatment with these agents. In patients with schizophrenia as in the general population, consideration should be given to the presence of known risk factors for diabetes [41], including obesity and glucose intolerance and psychotropic therapy should be evaluated in the context of the patient's overall response and tolerability to therapy.

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Risk of Diabetes Mellitus Associated with Atypical Antipsychotic Use Among Medicaid Patients with Bipolar Disorder: A Nested Case-Control Study

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Study Objective. To quantify the risk of diabetes mellitus associated with atypical antipsychotics compared with conventional antipsychotics in managed care Medicaid patients with bipolar disorder.

Design. Retrospective nested case-control study.

Data Source. Integrated seven-state Medicaid managed care claims database from January 1, 1998–December 31, 2002.

Patients. Two hundred eighty-three patients with diabetes (cases) and 1134 controls matched by age, sex, and the index date on which bipolar disorder was diagnosed.

Measurements and Main Results. Cases were defined as those having an *International Classification of Diseases, Ninth Revision* diagnosis of diabetes or those receiving treatment with antidiabetic drugs. Both case and control patients had at least a 3-month exposure to either conventional or atypical antipsychotic agents or three filled prescriptions related to treatment for bipolar disorder. Of the 283 cases, 139 (49%) received atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and clozapine) and 133 (47%) were prescribed conventional antipsychotics. To compare the risk for new-onset diabetes associated with atypical versus conventional antipsychotics, we conducted a Cox proportional hazard regression, in which we controlled for age; sex; duration of bipolar disorder follow-up; use of lithium, anticonvulsants, antidepressants, and other drugs; and psychiatric and medical comorbidities. Compared with patients receiving conventional antipsychotics, the risk of diabetes was greatest among patients taking risperidone (hazard ratio [HR] 3.8, 95% confidence interval [CI] 2.7–5.3), olanzapine (3.7, 95% CI 2.5–5.3), and quetiapine (2.5, 95% CI 1.4–4.3). The risk for developing diabetes was also associated with weight gain (HR 2.5, 95% CI 1.9–3.4), hypertension (HR 1.6, 95% CI 1.2–2.2), and substance abuse (HR 1.5, 95% CI 1.0–2.2).

Conclusion. Olanzapine, risperidone, and quetiapine are all associated with development or exacerbation of diabetes mellitus in patients with bipolar disorder. When prescribing therapy for this patient population, metabolic complications such as diabetes, weight gain, and hypertension need to be considered.

Key Words: diabetes, bipolar disorder, atypical antipsychotics, managed care, Medicaid.

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Traditionally, mood stabilizers such as lithium, divalproex, and carbamazepine have been the primary agents used to treat bipolar disorder. Although conventional antipsychotics also have

been prescribed to treat acute mania, long-term maintenance use of these agents is limited due to their intolerable adverse events, including akathisia, extrapyramidal symptoms, and tardive dyskinesia. Atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) are generally regarded as having lower risk for causing extrapyramidal symptoms than conventional antipsychotics; they have been used with increasing frequency in the treatment of bipolar disorder since the mid-1990s.[1–4] This trend may reflect the antimanic or mood-stabilizing properties of atypical antipsychotics and their favorable tolerability profiles compared with conventional agents.[5–7] Recent clinical trials suggest that antipsychotic augmentation might be efficacious for treatment of bipolar depression.[7–9] Unfortunately, atypical antipsychotics are associated with metabolic complications that place patients at risk for weight gain, altered glucose metabolism, dyslipidemia, myocarditis, and cardiomyopathy.[10–13]

The increased risk for diabetes associated with atypical antipsychotics may reflect direct effects of these drugs on β-cell function and insulin action.[10, 11] Several published studies, including a number of retrospective cohort studies, have shown associations between the development of diabetes or glucose intolerance and the atypical antipsychotics clozapine, olanzapine, and risperidone in patients with schizophrenia.[14–23] A research group reported hazard ratios (HRs) for diabetes risk of 1.1–1.2 in Veterans Affairs patients who received atypical antipsychotics.[24] Two groups in the United Kingdom found that atypical antipsychotics were associated with HRs for diabetes of 4.7–5.8.[24, 25] An analysis based on the World Health Organization's adverse drug reaction database found that these agents had an HR for diabetes as high as 10.22.[26] Several cases of diabetic ketoacidosis and diabetes associated with atypical antipsychotics have been reported among adult[27] and pediatric[28, 29] patients with bipolar disorder. Although atypical antipsychotics are widely used to treat mania, their association with diabetes onset has not been adequately quantified in patients with bipolar disorder.[30]

Not only is the Medicaid program the dominant payer for mental health services in the United States,[31] but the number of Medicaid enrollees in managed care organizations has increased since the mid-1990s.[32] Studies using Iowa and California Medicaid claims databases have found that patients with schizophrenia exposed to clozapine or olanzapine were at increased risk for type 2 diabetes.[33, 34] Yet, very little information exists about the risk of diabetes associated with antipsychotic drug use among patients with bipolar disorder in the managed care Medicaid population.

We hypothesized that atypical antipsychotics would present a different risk for diabetes than conventional antipsychotics. Our objectives were to investigate the association between atypical antipsychotics and diabetes mellitus in patients with bipolar disorder in the managed care Medicaid population and compare it with the association between conventional antipsychotics and diabetes in the same patient population. In assessing the risk for diabetes, we controlled for key covariates such as age, sex, and psychiatric and medical comorbidities, as well as concomitant drugs that affect patients' risk for hyperglycemia.

Methods

Data Source

Our data source was a multistate managed care claims database (PharMetrics, Watertown, MA). The database covered over 45 million individuals enrolled in managed care organizations with 70 health plans, including seven state Medicaid managed care programs, in four U.S. regions: Midwest (34.1%), East (15.6%), South (23.9%), and West (26.4%).[35] The database included each patient's date of enrollment and pharmacy, medical, and institutional claims. Each medical claim was recorded with accompanying diagnostic codes from the *International Classification of Diseases, Ninth Revision* (ICD-9) that justified

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the medical service. This geographically diversified claims database provides a large quantity of health information pertaining to the Medicaid population. The use of Medicaid or managed care claims databases for pharmacoepidemiologic studies has been well documented.[14, 23, 24, 33, 34]

Study Design

We used a retrospective nested case-control (population-based case-control) design. Claims data from January 1, 1998–December 31, 2002 (5 calendar years) were reviewed. To protect patient confidentiality, we deleted patient names, insurance plan identification numbers, and other patient identifiers from the claims database. Randomized patient numbers and patients' birth years were used for identification and calculation of age. The research project was approved by the University of Cincinnati Medical Center's institutional review board.

Study Cohort Identification

As shown in Figure 1, from 1998–2002 a total of 48,965 managed care Medicaid patients had at least one diagnosis of an affective disorder (ICD-9 code 296.xx) or cyclothymia (ICD-9 code 301.13). We excluded 4841 patients with schizophrenia (295.xx), 30,624 patients with depression only (296.2x and/or 296.3x), and 29 patients aged 65 years or greater during the study period. These exclusions enabled us to assess patients with bipolar disorder while avoiding confounding due to patients who had schizophrenia and/or depression or who were eligible for both Medicare and Medicaid. The final cohort consisted of 13,471 patients with bipolar disorder indicated by any of the following ICD-9 codes: 296.0, 296.1, and 296.4–296.8. Because less than 0.1% of the study group had cyclothymia, patients with that disorder were not categorized separately.

In keeping with other published retrospective cohort studies,[15–25] we selected a cohort of patients who had a minimum of 3 months of exposure to atypical or conventional antipsychotics or at least three filled prescriptions related to treatment of bipolar disorder during the study period. Incident cases of diabetes were identified by either the earliest diagnosis of ICD-9 code 250.xx or treatment for diabetes after the first identified use of antipsychotics. The date for the first diabetes diagnosis or first use of antidiabetic drugs was defined as the diabetes index date. To ensure that we were identifying incident cases of diabetes, we checked medical and prescription claim records for any diagnosis or treatment of diabetes before the diabetes index date. Patients were rejected as cases if they had a prescription for oral antidiabetic agents before the diabetes index date. The oral antidiabetic agents identified were sulfonylurea drugs (acetohexamide, glipizide, glyburide), a biguanide (metformin), thiazolidinediones (pioglitazone, rosiglitazone), α-glucosidase inhibitors (acarbose, miglitol), and the new drugs repaglinide and nateglinide.

The index date of bipolar diagnosis was the first date of diagnosis indicated by designated ICD-9 codes for bipolar disorder during the study period. For each case we matched five controls according to age at bipolar diagnosis index date (standard deviation of 5 yrs), sex, and the month and year of diagnosis of bipolar disorder. Controls meeting the matching criteria were selected at random using SAS, version 8.0 (SAS Institute Inc., Cary, NC), software. Controls were selected from a population of patients who had been diagnosed with bipolar disorder but were not diagnosed with or treated for diabetes at any time during the study period. Because the

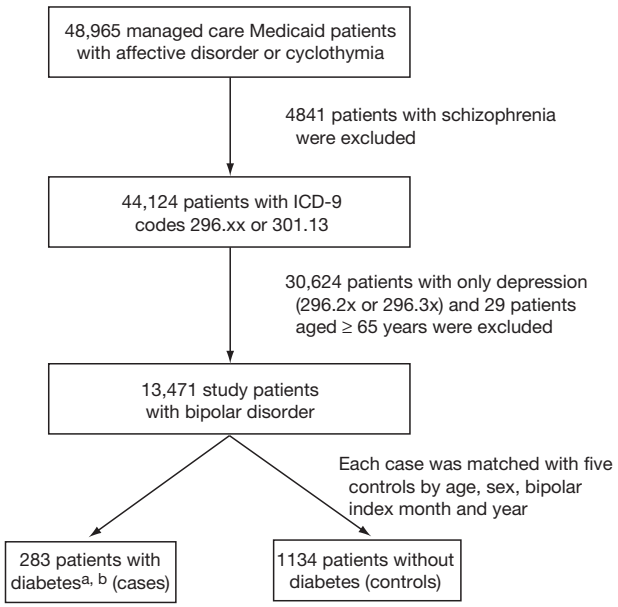

Figure 1. Patient flow diagram of incident cases of diabetes mellitus and controls from patients with bipolar disorder in the United States managed care Medicaid population, 1998–2002. [a]Incident cases of diabetes were identified by either earliest diagnosis of *International Classification of Diseases, Ninth Revision* (ICD-9) code 250.xx or treatment for diabetes. [b]Eighty-nine case patients with fewer than five matched controls were included in the analysis.

month and year of bipolar diagnosis were part of the matching criteria, the calendar time distributions of the bipolar index date were the same for both cases and controls.

Drug Use and Covariates

We classified antipsychotics as either conventional or atypical. The atypical antipsychotics were olanzapine, risperidone, quetiapine, ziprasidone, and clozapine. Aripiprazole was not included in this analysis as it was not available during the study period. The conventional antipsychotics were haloperidol, chlorpromazine, fluphenazine, loxapine, molindone, perphenazine, thioridazine, trifluoperazine, thiothixene, and pimozide. Other antipsychotics, such as thioxanthenes (flupenthixol, zuclopenthixol), pipotiazine, and methotrimeprazine were not included in this study because they were not available in the United States.

Published reports indicate that some drugs elevate blood glucose levels in some patients. Thus, our analysis incorporated data on administration of any of the following drugs during the study period: α-blockers (e.g., doxazosin, prazosin, terazosin), β-blockers (e.g., atenolol, betaxolol, bisoprolol), thiazide diuretics (e.g., chlorothiazide, chlorthalidone, polythiazide), corticosteroids (e.g., methylprednisolone, hydrocortisone), phenytoin, oral contraceptives containing norgesterol, and valproic acid.[30, 36, 37]

For both cases and controls, all prescription drug claims for treatment of bipolar disorder and diabetes were abstracted and reviewed. The follow-up period began with each patient's first bipolar diagnosis date and ended with the index date of diabetes, the end of the study period, or the end of the patient's enrollment in the managed care Medicaid program, whichever came first. We used dichotomous variables to indicate whether a patient had received concomitant drugs known to be associated with diabetes or hyperglycemia. All drug claims were identified by national drug codes.

In addition to drugs known to affect the risk of diabetes, we adjusted the analysis for psychiatric comorbidities (alcohol abuse, substance abuse disorder, personality disorder, anxiety disorder, and impulse-control disorder) and medical comorbidities (hypertension, weight gain, arthritis, cerebral vascular disease, chronic obstructive pulmonary disease, dyslipidemia, and coronary heart disease. The ICD-9 codes were used to identify comorbid conditions from either hospital or clinical encounters.

Statistical Analysis

All analyses were performed with SAS, version 8.0. Descriptive statistics were used to explore patient demographics and drug use categories. The age of each patient was simply the age at bipolar diagnosis. We conducted the Cox proportional hazard regression to assess the risk for diabetes associated with antipsychotic drugs due to the consideration of time-to-event with censoring and covariates. We determined hazard ratios for each risk factor with 95% confidence intervals. Patients taking conventional antipsychotics were the referent group in our comparison of diabetes risk among patients.

Results

Table 1 summarizes the characteristics of the study population. During the 5-year study period (1998–2002), of the 13,471 managed care Medicaid patients with bipolar disorder, 1730 (13%) had at least one prescription for atypical antipsychotics, 1918 (14%) had prescriptions for conventional antipsychotics, 1048 (8%) for lithium, 3013 (22%) for anticonvulsants, and 4011 (30%) for antidepressants.

The first cohorts we selected consisted of 323 case patients who developed diabetes after the bipolar index date and after their first antipsychotic drug exposure and 12,432 control patients who had bipolar disorder but not diabetes during the study period. We then excluded eight case patients who received insulin for type 1 diabetes and 32 case patients who were unmatched with controls. This resulted in 283 cases of diabetes and matched 1134 controls. Eighty-nine cases that had fewer than five controls/case were kept for the study. Most of those cases were adults older than 50 years. The age and sex of these cases and controls were similar.

As shown in Table 1, treatment with atypical antipsychotics, conventional antipsychotics, lithium, anticonvulsant drugs, and antidepressant drugs was more prevalent among cases than controls. Of the 283 cases, 133 (47%) received conventional antipsychotics, and 139 (49%) received atypical antipsychotics. Because only five patients (< 2%) received more than one atypical antipsychotic during the study period, we did not categorize this patient group.

Compared with patients receiving conventional antipsychotics, the risk for diabetes was greatest among patients taking risperidone (HR 3.8, 95% CI 2.7–5.3), olanzapine (HR 3.7, 95% CI

Table 1. Characteristics of the Study Patients

Characteristic	No. (%) of Patients	
	Cases (n=283)	Controls (n=1134)
Age (yrs)		
≤ 12	5 (1.77)	25 (2.20)
13–17	10 (3.53)	50 (4.41)
18–34	70 (24.73)	329 (29.01)
35–49	129 (45.58)	562 (49.56)
50–64	69 (24.38)	168 (14.81)
Sex		
Female	227 (80.21)	916 (80.78)
Male	56 (19.79)	218 (19.22)
Psychotherapeutic drugs[a]		
Lithium	153 (54.06)	119 (10.49)
Anticonvulsants[b]	164 (57.95)	289 (25.48)
Atypical antipsychotics	139 (49.12)	164 (14.46)
Olanzapine	51 (18.02)	79 (6.97)
Quetiapine	18 (6.36)	20 (1.76)
Risperidone	65 (22.97)	61 (5.38)
Ziprasidone	2 (0.71)	3 (0.26)
Clozapine	3 (1.06)	2 (0.18)
Antidepressants	174 (61.48)	374 (32.98)
Conventional antipsychotics	133 (47.00)	213 (18.78)
Other concomitant drugs[a]		
β-Blockers	63 (22.26)	86 (7.58)
α-Blockers	4 (1.41)	7 (0.62)
Corticosteroids	78 (27.56)	171 (15.08)
Thiazide diuretics	30 (10.60)	38 (3.35)
Oral contraceptives	9 (3.18)	17 (1.50)
Valproic acid	1 (0.35)	8 (0.71)
Phenytoin	5 (1.76)	18 (1.59)
Psychiatric comorbidities[c]		
Alcohol abuse	22 (7.77)	147 (12.96)
Substance abuse	41 (14.48)	146 (12.87)
Anxiety disorder	150 (53.00)	445 (39.24)
Impulse-control disorder	5 (1.76)	22 (1.94)
Personality disorder	21 (7.42)	65 (5.73)
Medical comorbidities[c]		
Hypertension	130 (45.94)	194 (17.11)
Weight gain	79 (27.92)	90 (7.94)
Arthritis	16 (5.65)	30 (2.65)
Chronic obstructive pulmonary disease	41 (14.49)	71 (6.26)
Cerebral vascular disease	15 (5.30)	27 (2.38)
Coronary heart disease	11 (3.88)	5 (0.44)
Dyslipidemia	8 (2.83)	5 (0.44)

[a]Some patients received more than one drug.
[b]Anticonvulsants were divalproex and carbamazepine.
[c]Some patients were diagnosed with more than one comorbid condition.

2.5–5.3), quetiapine (HR 2.5, 95% CI 1.4–4.3), and the anticonvulsants divalproex and carbamazepine (HR 1.6, 95% CI 1.2–2.1; Table 2). These data were obtained in a process that controlled for the covariates of age, sex, and duration of follow-up; use of lithium, anticonvulsants, and antidepressants; concomitant drugs (not related to bipolar disorder); and psychiatric and medical comorbidities. In addition, patients whose bipolar disorder was coupled with substance abuse, hypertension, and/or weight gain had a significantly higher risk for diabetes than their counterparts.

Discussion

This multistate, population-based, nested case-control study examined the risk of diabetes

associated with use of antipsychotics in Medicaid patients with bipolar disorder. After controlling for personal risk factors and concomitant drug use, we found that patients receiving atypical antipsychotics for bipolar disorder are at increased risk for diabetes. Our findings add to the body of observational evidence indicating that certain atypical antipsychotics may be associated with an increased risk for diabetes among patients with bipolar disorder.[27–29] It is unclear, however, whether the diabetes in the study population is due to the use of atypical antipsychotics versus the underlying condition of bipolar disorder versus characteristics of the Medicaid population, such as low socioeconomic status, poor overall physical health, unhealthy lifestyles, and poor access to health care services.

Atypical antipsychotics are generally regarded as having less potential for causing extrapyramidal symptoms and a higher serotonin:dopamine receptor affinity compared with conventional antipsychotics.[11, 12] Recent literature indicates that clozapine, olanzapine, and risperidone are more likely to be associated with diabetes (indicated by diabetic ketoacidosis and an atherogenic lipid profile) than other atypical agents.[14, 28, 29, 38, 39] One possible mechanism for hyperglycemia is impairment of insulin resistance, which may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues.[2, 10, 11]

Our findings are comparable to data from published pharmacoepidemiologic studies of patients with schizophrenia.[14, 23–25] For example, reported HRs for diabetes in patients with schizophrenia were 1.2–5.8 for olanzapine and 1.1–2.2 for risperidone.[14, 23–25, 33] These values can be compared with the HRs we obtained for the same drugs in patients with bipolar disorder: HR 3.7 (95% CI 2.5–5.3) for olanzapine and 3.8 (95% CI 2.7–5.3) for risperidone (Table 2). After controlling for comorbidities, personal risk factors, and concomitant drugs, we also found that quetiapine increases the risk for diabetes in patients with bipolar disorder (HR 2.5, 95% CI 1.4–4.4). Although quetiapine has been linked to diabetes in case reports,[40–43] earlier studies have failed to confirm this association.[33] This may be due to their small sample sizes or lack of control for confounding variables.[44] The HRs associated with clozapine (HR 2.9, 95% CI 0.9–9.6) and ziprasidone (HR 4.3, 95% CI 1.0–18.9) in our study were large, but they were not statistically significant. This might be due to the small number of patients in our study who received either clozapine or ziprasidone. Long-term data from large, randomized, controlled trials are needed to more explicitly examine the association between diabetes and various atypical antipsychotic drugs.

As shown in Table 2, in addition to antipsychotic use, diabetes risk is also associated with weight gain and hypertension. As the literature indicates, olanzapine, clozapine, and risperidone are associated with weight gain,[13, 45, 46] hyperlipidemia, and hypertriglyceridemia, all of which are independent risk factors for heart disease.[14, 47, 48] Our findings of elevated HRs for weight gain and hypertension make it likely that the incident cases of diabetes we identified were associated with metabolic syndrome. Our data also show that patients with substance abuse have a heightened risk for diabetes. It is possible that these patients might have less healthy lifestyles, poorer drug compliance, or poorer access to health care services than patients without substance abuse.[49, 50] Poor drug compliance might lead to drug overdose, which could increase the risk for diabetes in this population.[33]

Our study had several limitations. Children, women, and low-income populations are overrepresented in the Medicaid population. Thus, our findings might not be indicative of the general population. We inferred drug use from automated pharmacy claims data. Although baseline drug use differed between cases and controls, we tried to adjust for these differences with the Cox proportional hazard model. Because of the retrospective nature of a claims database review, we could not assess individual patients with regard to severity of bipolar disorder, socioeconomic class, lipid profiles, fasting glucose concentrations, or changes in body mass index related to weight gain.

Moreover, data on patients' ethnicity were missing when PharMetrics (data vendor) collected medical claims information from participating managed care organizations. Another concern is that clinicians may have prescribed one drug versus another based on patients' specific symptoms. We attempted to reduce this potential confounding bias by adjusting for known concomitant drugs and comorbidities. We also included dyslipidemia and coronary heart disease as comorbidities, as these provide a rough proxy for patients at high risk for diabetes. It is possible that we underestimated the prevalence of diabetes due to our study's limited time window, changes in

Table 2. Hazard Ratios for Diabetes Risk

Variable	Hazard Ratio[a]	95% CI
Pyschotherapeutic drugs		
Conventional antipsychotic	1.000	1.000
Olanzapine	3.664	2.542–5.281
Quetiapine	2.476	1.427–4.296
Risperidone	3.771	2.699–5.269
Ziprasidone	4.297	0.976–18.923
Clozapine	2.872	0.862–9.575
Lithium	1.016	0.729–1.416
Anticonvulsant[b]	1.571	1.153–2.140
Antidepressant	1.138	0.842–1.538
Other concomitant drugs		
β-Blocker	1.329	0.960–1.839
α-Blocker	0.669	0.235–1.907
Corticosteroid	1.048	0.775–1.417
Thiazide diuretic	1.254	0.807–1.947
Oral contraceptive	1.766	0.829–3.761
Valproic acid	0.359	0.049–2.640
Phenytoin	0.428	0.167–1.098
Psychiatric comorbidities		
Alcohol abuse	0.623	0.390–0.996
Substance abuse	1.491	1.033–2.152
Anxiety disorder	1.257	0.963–1.640
Impulse-control disorder	0.499	0.183–1.360
Personality disorder	1.096	0.673–1.783
Medical comorbidities		
Hypertension	1.636	1.208–2.216
Weight gain	2.516	1.876–3.375
Arthritis	0.920	0.535–1.582
Chronic obstructive pulmonary disease	1.289	0.865–1.921
Cerebral vascular disease	1.223	0.702–2.129
Coronary heart disease	1.134	0.588–2.188
Dyslipidemia	1.844	0.813–4.182

CI = confidence interval.
[a]Model for age, sex, bipolar follow-up months, use of drugs, psychiatric and medical comorbidities.
[b]Anticonvulsants were divalproex and carbamazepine.

managed care enrollment, and the fact that some mental services may not have been billed to patients' managed care organizations. Finally, we identified comorbid conditions by diagnostic codes without considering the contribution of drugs to weight gain, hypertension, cerebral vascular disease, and other disorders.

Despite the above limitations, our study adds to the limited literature about diabetes risk in patients with bipolar disorder in managed care Medicaid programs. It provides useful information on disease management strategies in terms of selection of mood stabilizers and consideration of relevant comorbidities for patients with bipolar disorder, especially the managed care Medicaid population. Atypical antipsychotics provide great benefit to a wide variety of individuals with psychiatric disorders; nevertheless, they have a constellation of adverse effects related to increased risk for weight gain, diabetes, and dyslipidemia.[10, 11]

Conclusion

The atypical antipsychotics olanzapine, risperidone, and quetiapine are consistently associated with increased risk for diabetes in patients with bipolar disorder after adjustment for relevant risk factors. Metabolic complications are a clinically important issue for patients receiving antipsychotic therapy. The choice of olanzapine, risperidone, or quetiapine for a specific patient with bipolar disorder should involve consideration of each agent's risks and benefits, with attention to comorbid conditions relevant to the patient's risk for diabetes. Thus,

the propensity of an antipsychotic agent to induce or exacerbate diabetes is a critical consideration in the selection of an agent to treat bipolar disorder.

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Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in a Geriatric Population in the United States

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Objectives: The objective of this study was to investigate risk of diabetes among elderly patients during treatment with antipsychotic medications.

Design: We conducted a longitudinal, retrospective study assessing the incidence of new prescription claims for antihyperglycemic agents during antipsychotic therapy.

Setting: Prescription claims from the AdvancePCS claim database were followed for 6 to 9 months.

Participants: Study participants consisted of patients in the United States aged 60+ and receiving antipsychotic monotherapy. The following cohorts were studied: an elderly reference population (no antipsychotics: n = 1,836,799), those receiving haloperidol (n = 6481) or thioridazine (n = 1658); all patients receiving any conventional antipsychotic monotherapy (n = 11,546), clozapine (n = 117), olanzapine (n = 5382), quetiapine (n = 1664), and risperidone (n = 12,244), and all patients receiving any atypical antipsychotic monotherapy (n = 19,407).

Measurements: We used Cox proportional hazards regression to determine the risk ratio of diabetes for antipsychotic cohorts relative to the reference population. Covariates included sex and exposure duration.

Results: New antihyperglycemic prescription rates were higher in each antipsychotic cohort than in the reference population. Overall rates were no different between atypical and conventional antipsychotic cohorts. Among individual antipsychotic cohorts, rates were highest among patients treated with thioridazine (95% confidence interval [CI], 3.1– 5.7), lowest with quetiapine (95% CI, 1.3–2.9), and intermediate with haloperidol, olanzapine, and risperidone. Among atypical cohorts, only risperidone users had a significantly higher risk (95% CI, 1.05–1.60; $P = 0.016$) than for haloperidol. Conclusions about clozapine were hampered by the low number of patients.

Conclusion: These data suggest that diabetes risk is elevated among elderly patients receiving antipsychotic treatment. However, causality remains to be demonstrated. As a group, the risk for atypical antipsychotic users was not significantly different than for users of conventional antipsychotics. **(J Am Med Dir Assoc 2004; 5: 38–46)**

Keywords: Antipsychotics; diabetes mellitus; geriatrics; prescriptions; drug

Use of antipsychotic medications among the elderly is substantial, with as much as half of all repeat prescriptions for antipsychotics being accounted for by patients over age 65.[1] It has been estimated that 38% to 43% of all elderly patients residing in skilled care facilities receive antipsychotic medication,[2,3] although as many as 60% to 80% of elderly patients at facilities for the mentally ill could be receiving such treatment.[4,5] Fully 20% of the population aged 80 and older are affected by dementia,[6] and approximately one fourth to one half of these develop psychotic features that require the use of an antipsychotic agent.[7,8] In addition to being prescribed for this condition, however, a considerable proportion of antipsychotic prescriptions for the elderly are for use as a tranquilizer or anxiolytic.[9,10]

Use of conventional high-potency antipsychotics such as

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haloperidol is associated with high levels of extrapyramidal symptoms,[11,12] to which elderly patients are particularly vulnerable.[13,14] In contrast, extrapyramidal symptoms in patients treated with atypical antipsychotics are less common.[15] Nevertheless, an issue has been raised recently regarding the safety of both conventional and atypical antipsychotics, as it has been suggested that their use could be associated with induction of insulin resistance and an increased risk of type 2 diabetes mellitus.[16–18] For example, one study[19] reports that 12% of patients treated with clozapine developed type 2 diabetes compared with a prevalence in the general population of 5.1%.[20] Some studies appear to associate the use of specific antipsychotic medications with a higher rate of new-onset hyperglycemia or type 2 diabetes.[16,17,19] This is still a point of controversy, however, because such studies have largely relied on case reports and chart reviews and might not accurately reflect the actual incidence of hyperglycemia among antipsychotic users relative to the general population, let alone the population of patients with mental illness. Moreover, the contribution of undiagnosed diabetes or impaired glucose tolerance among patients before their use of antipsychotics is unknown.[21] By contrast, other studies have concluded that antipsychotic use is merely coincidental to an underlying predisposition to diabetes among patients with schizophrenia.[22]

Many attempts to investigate the potential link between antipsychotic use and an increased risk of diabetes have been hampered by limited sample size, and studies have yielded largely inconclusive results. However, a recent analysis[21] has been conducted using a drug prescription claim database maintained by AdvancePCS (Scottsdale, AZ), the United States' largest health plan provider, with more than 75 million members linked to 58,000 pharmacies throughout the country. The analysis suggested that there is a statistically significant increase in the risk of diabetes during treatment with either conventional or atypical antipsychotics. However, large-scale studies of this sort that focus on an elderly population have received little attention. Accordingly, the current analysis was undertaken, using the AdvancePCS prescription claim database, to investigate the risk of diabetes among patients aged 60 and older who had been receiving either conventional or atypical antipsychotic medications.

METHODS

Study Design and Patient Sample

This longitudinal study was conducted retrospectively to compare the risk of new development of diabetes mellitus among selected antipsychotic cohorts drawn from the AdvancePCS prescription claim database. The validity and reliability of their prescription database has been verified independently. Over 300 million prescription claims per year are processed in this database for more than 50 million members covered by over 2000 managed care plans and employers. Most claims were submitted by pharmacies handling the outpatient prescription needs for these patients, although some prescriptions were filled in long-term care settings. Only patients who maintained coverage with AdvancePCS were followed; if patients discontinued their coverage, they were censored from the analysis. This analysis examines the data from patients aged 60 and older, amounting to a total patient sample of nearly two million patients. Because this was an examination of only the potential effects of exposure to antipsychotic medications, diagnostic information was not captured. Information regarding patients' ethnicity was also not available. For the purposes of this analysis, patients were examined both together as a single geriatric population (all patients aged ≥60 years) and stratified as two separate subgroups, a younger one consisting of patients aged 60 to 74 and an older one of patients aged 75 and older.

Inclusion/Exclusion Criteria

Patients who were qualified for prescription claims through AdvancePCS for the entire 12 months before enrollment were eligible for inclusion in the analysis. No obvious differences were seen in the number of patients using a diabetes medication when comparing a 12-month preenrollment period versus a 24-month preenrollment period; thus, the 12-month preenrollment period was used.[21] The exclusion criteria applicable to all cohorts included (1) a preexisting history of diabetes mellitus, as evidenced by a prescription claim for any antihyperglycemic medication during the 12-month period before enrollment; (2) a prescription claim for any antipsychotics within the 6-month period before the enrollment date; and (3) absence of information on sex or year of birth.

Cohort Studies

A "general patient population" cohort, consisting of all subjects who had made any AdvancePCS-covered prescription claim during a 2-month enrollment window (January 1 to February 29, 2000), was used as a standard reference population. Patients in the general population cohort must not have made a claim for any diabetes drug for at least 12 months before enrollment. In addition, they must not have received a prescription for an antipsychotic for at least 6 months before and 6 months after enrollment.

Only patients who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. The antipsychotic cohorts studied consisted of the following: (1) patients receiving haloperidol monotherapy; (2) patients receiving thioridazine monotherapy; (3) all patients receiving monotherapy with any single conventional antipsychotic, referred to as the "combined conventional antipsychotic" cohort; (4) patients receiving clozapine monotherapy; (5) patients receiving olanzapine monotherapy; (6) patients receiving quetiapine monotherapy; (7) patients receiving quetiapine monotherapy; (8) patients receiving risperidone monotherapy; and (9) all patients receiving monotherapy with any single atypical antipsychotic, referred to as the "combined atypical antipsychotic" cohort. Antipsychotic agents included both conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychot-

ics (clozapine, olanzapine, quetiapine, and risperidone). Haloperidol and thioridazine were chosen as separate cohorts from among the conventional antipsychotics as a result of their sufficient numbers, whereas the remaining conventional antipsychotics individually formed less than 10% of the total prescriptions for typical antipsychotics, yielding cohorts that were too small for analysis. Clozapine was included as a separate cohort from among the atypical antipsychotics as a result of the intense focus it has received for a possible association with diabetes risk.

The enrollment window for subjects in the antipsychotic cohorts was December 1, 1998, through February 29, 2000. Subjects who started therapy during this period and continued treatment with the same single antipsychotic were included in the antipsychotic cohorts. Patients receiving antipsychotics were studied for as long as they had continuous therapy and did not terminate AdvancePCS coverage. The data cutoff point for this study was August 31, 2000. For all antipsychotic cohorts, patients who received more than one antipsychotic during the enrollment window were excluded. The earliest date during the enrollment window that any patient filed a prescription claim, either an antipsychotic agent in the case of the antipsychotic cohorts or a nonantipsychotic agent in the case of the general patient population, was considered the enrollment date for that subject.

Incidence of Diabetes Mellitus

New onset of diabetes mellitus during antipsychotic exposure was identified by claims for any medication indicated for the treatment of diabetes regardless of the route of administration. For the purposes of this analysis and of the language in this report, the incidence of new prescriptions for antihyperglycemic medications is equated with the incidence of new-onset diabetes without regard to clinicians' standards for diagnosis or choices of treatment. To identify the timing of onset of new cases of diabetes, the date of the first antihyperglycemic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for new onset of diabetes from the enrollment date to the time that the antipsychotic was discontinued for more than 15 days, or until the data cutoff point, whichever came first.

Comparison of Risk Between Cohorts

To compare the risk of developing diabetes among cohorts, both incidence density and risk ratios were determined. Incidence of diabetes for antipsychotic cohorts might not be linearly related to time, with more cases being experienced earlier during treatment exposure. Annualization of incidence density might therefore be likely to inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, sex, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of diabetes, the Cox proportional hazards regression was used to determine the risk ratio of diabetes for antipsychotic cohorts relative to the general AdvancePCS population, matching the antipsychotic cohort with the reference population by age ($\geq$60 years, 60–74 years, or $\geq$75 years). Several Cox proportional hazard models were analyzed with the "PHREG" (proportional hazards regression) procedure in SAS (Statistical Analysis Systems, SAS Institute, Cary, NC) using covariates for sex and duration of exposure. For comparisons of diabetic risk among the atypical antipsychotic treatment groups, the haloperidol cohort was used as a reference standard because of its status as the most widely used conventional antipsychotic agent. The alpha level for statistical significance was 0.05.

RESULTS

Observational Results

A total of 30,953 elderly outpatients who had received prescriptions for antipsychotic treatment were included in this analysis (Tables 1 and 2), and an additional 1,836,799 outpatients from the general population who had received prescriptions for other, nonantipsychotic medications were used as the standard for comparison. Prescriptions for atypical antipsychotic medications (Table 2) outnumbered those for conventional antipsychotics (Table 1) by nearly 70%. In terms of raw numbers of patients, relative rates of prescribing for the atypical agents were as follows: risperidone > olanzapine > quetiapine > clozapine. For conventional antipsychotic agents, prescription rates were highest for haloperidol, followed by thioridazine, and finally by all other conventional agents. It was noted that, in terms of chlorpromazine equivalents (doses converted to an equivalent daily dose of chlorpromazine, based on minimum effective doses[23]) and relative to dose recommendations for older patients with schizophrenia, the mean administered doses were low for thioridazine (36.1 mg chlorpromazine equivalents), risperidone (75.0 mg), quetiapine (87.2 mg), haloperidol (90.0 mg), and clozapine (90.3 mg), but moderate to high for olanzapine (165.0 mg). Mean durations of treatment were, for the most part, in the vicinity of 70 to 100 days. The one exception was clozapine, which was administered for a mean duration of over 140 days.

As shown in Tables 1 and 2, a higher proportion of patients in the older group of patients had prescriptions for antipsychotics compared with the younger group ($\geq$75 years: 21,742 patients compared with a corresponding general population of 690,545 patients, or an equivalent frequency of 32 per thousand; 60–74 years: 9211 of 1,146,254 patients, or an equivalent frequency of 8 per thousand). The older group of patients had a higher proportion of females relative to the younger subgroup, both overall and within each drug cohort, presumably reflecting age-related changes in demographics. Mean doses of each drug were lower among the older patients relative to their corresponding drug-matched younger counterparts. Mean treatment durations were much longer among the clozapine-treated patients relative to the other drug cohorts, both overall and within each of the two age subgroups.

Comparison of Antipsychotic Users and Nonusers

Compared with the general patient population of patients aged 60+ who received only nonantipsychotic prescriptions, an increased risk of development of diabetes was seen in every antipsychotic cohort (Table 3). The risk was lowest for the

Table 1. *Characteristics of Patients Receiving Conventional Antipsychotics versus the General Patient Population*

Characteristic	General Patient Population	Conventional Antipsychotics		
		All Agents	Haloperidol	Thioridazine
All patients, aged ≥60				
No. of subjects	1,836,799	11,546	6481	1658
Age, mean (SD)	72.1(8.3)	78.4(9.1)	80.8(8.4)	77.8(9.1)
Percent males	39.2	43.1	39.8	35.3
Treatment duration days (SD)		70.2(75.9)	68.5(69.8)	84.7(87.2)
Dose (mg/day)				
mean (SD)			1.8(3.4)	36.1(43.4)
CPZ equivalents			90.0	36.1
Patients aged 60–74				
No. of subjects	1,146,254	3778	1389	564
Age mean (SD)	66.7(4.4)	67.8(4.4)	68.6(4.4)	67.4(4.4)
Percent males	41.1	47.6	46.2	34.0
Treatment duration days (SD)		69.7(80.0)	67.4(71.4)	83.9(88.5)
Dose (mg/day)				
mean (SD)			2.7(6.0)	48.7(58.7)
CPZ equivalents			135.0	48.7
Patients aged ≥75				
No. of subjects	690,545	7768	5092	1094
Age mean (SD)	81.0(5.0)	83.5(5.7)	84.2(5.7)	83.1(5.6)
Percent Males	36.1	40.9	38.0	35.9
Treatment duration days (SD)		70.4(73.8)	68.8(69.4)	85.1(86.5)
Dose (mg/day)				
mean (SD)			1.5(2.3)	29.6(30.9)
CPZ equivalents			75.0	29.6

SD, standard deviation; CPZ, chlorpromazine.

quetiapine cohort, with patients nevertheless being approximately twice as likely to have received a new prescription for antihyperglycemic medication as patients in the general patient population, whereas patients receiving thioridazine had the greatest risk, being four times as likely to have received new antidiabetic treatment. Risk did not appear to be related to dose, however, because the two groups with the highest risk ratios, thioridazine and risperidone, were also associated with the lowest relative doses.

A comparison of patients within each of the stratified age groups (Table 3) showed the risk ratio (RR) among younger patients (60–74 years of age) to be highest for the risperidone (RR = 5.1) and haloperidol (RR = 5.0) cohorts. It should be pointed out, however, that the number of younger patients in the clozapine cohort was too low to permit a meaningful statistical analysis, and therefore no comparisons could be made regarding the risk ratio in patients treated with clozapine compared with the other antipsychotics. Among older patients (75+), diabetes risk was highest for the clozapine and thioridazine cohorts. In fact, older patients receiving clozapine had the highest risk of any subgroup, being 5.8 times as likely as older patients in the reference population to have received new antidiabetic treatment. This figure takes into account the longer duration of exposure in the clozapine cohort, because the Cox proportional hazards regression analysis was adjusted for duration of exposure as well as sex. However, this figure must nevertheless be regarded as tentative, again as a result of the large confidence interval associated with this small group of patients. Younger patients receiving quetiapine were unique in being the only subgroup not to have a significantly higher risk of diabetes (95% confidence interval [CI], 0.5–2.7; $P = 0.794$) than their age-matched general reference population; similarly, among older patients, quetiapine use was temporally associated with the lowest risk of any cohort compared with their age-matched general patient population.

Comparison of Atypical Antipsychotic Users and Conventional Antipsychotic Users

The risk for patients receiving prescriptions for atypical antipsychotics was not significantly different from that for patients taking conventional antipsychotics (Table 4). This was true for the overall patient sample (95% CI, 0.92–1.25; $P = 0.382$) and within each age-stratified group (aged 60–74: 95% CI, 0.74–1.22; $P = 0.686$; aged ≥75: 95% CI, 0.97–1.44; $P = 0.104$). For a comparison of diabetes risk among the different drug cohorts, risk ratios were calculated using the haloperidol drug cohort as the reference population (Table 4). Of the atypical antipsychotics, only the risperidone cohort had a significantly higher diabetes risk relative to haloperidol. This was seen both overall (95% CI, 1.05–1.60; $P = 0.016$) and among the older patients (95% CI, 1.05–1.75; $P = 0.019$). Among younger patients (60–74 years of age), the quetiapine cohort was again seen to have the lowest risk of diabetes, with an incidence rate

TABLE 2. *Characteristics of Patients Receiving Atypical Antipsychotics versus the General Patient Population*

Characteristic	General Patient Population	Atypical Antipsychotics				
		All Agents	Clozapine	Olanzapine	Quetiapine	Risperidone
All Patients aged ≥60						
No. of subjects	1,836,799	19,407	117	5382	1664	12,244
Age mean (SD)	72.1 (8.3)	79.2 (8.8)	75.2 (7.2)	77.4 (9.1)	76.9 (8.5)	80.4 (8.4)
Percent males	39.2	35.2	45.3	34.2	40.4	34.8
Treatment duration days (SD)		97.6 (89.8)	141.2 (124.3)	102.0 (96.1)	99.2 (86.9)	95.1 (86.6)
Dose (mg/day)						
mean (SD)			77.9 (120.9)	4.4 (3.8)	64.6 (83.5)	1.0 (0.8)
CPZ equivalents			90.3	165.0	87.2	75.0
Patients aged 60–74						
No. of subjects	1,146,254	5433	52	1961	619	2801
Age mean (SD)	66.7 (4.4)	68.1 (4.4)	68.6 (4.3)	67.7 (4.5)	68.0 (4.4)	68.5 (4.4)
Percent Males	41.1	38.7	48.1	38.0	42.2	38.2
Treatment duration days (SD)		91.4 (86.9)	149.0 (131.7)	93.9 (91.2)	95.9 (83.4)	87.7 (83.1)
Dose (mg/day)						
mean (SD)			114.0 (160.1)	5.1 (4.3)	75.8 (86.9)	1.2 (1.0)
CPZ equivalents			132.2	191.3	102.3	90.0
Patients aged ≥75						
No. of subjects	690,545	13,974	65	3421	1045	9443
Age mean (SD)	81.0 (5.0)	83.6 (5.7)	80.5 (3.9)	83.0 (5.7)	82.3 (5.3)	83.9 (5.7)
Percent males	36.1	33.8	43.1	32.1	39.4	33.8
Treatment duration days (SD)		100.0 (90.7)	135.0 (118.8)	106.6 (98.5)	101.1 (88.8)	97.3 (87.6)
Dose (mg/day)						
mean (SD)			49.1 (64.4)	4.0 (3.4)	58.0 (80.7)	0.9 (0.7)
CPZ equivalents			57.0	150.0	78.3	67.5

SD, standard deviation; CPZ, chlorpromazine.

in this younger subgroup of 0.97% and a risk ratio significantly lower than that of haloperidol. The older subgroup of quetiapine users, however, showed no significant difference from haloperidol. The risk ratio for the olanzapine group was not significantly different from that of the haloperidol reference group, either overall or in either age subgroup. Relative to the risperidone cohort, the olanzapine group had a risk ratio of 0.97 (95% CI, 0.76–1.24; $P = 0.814$). The risk for clozapine also was not different overall from that of the haloperidol reference group. In terms of incidence rates, however, clozapine had the highest percentage of new cases of diabetes, both overall (5 of 117 [4.27%]) and in the older subgroup (4 of 65 [6.15%]), but this must again be taken in the context of the low overall numbers of patients in the clozapine cohort.

DISCUSSION

This analysis is consistent with earlier reports that patients who receive antipsychotic medications could be at increased

Table 3. *Development of Diabetes Mellitus During Treatment With Antipsychotics, Relative to the General Population of the Same Age Group**

Cohort	All Patients (aged ≥60)			Patients (aged 60–74)			Patients (aged ≥75)		
	Risk Ratio	95% CI	*P* Value	Risk Ratio	95% CI	*P* Value	Risk Ratio	95% CI	*P* Value
Conventional antipsychotics									
All combined	3.6	3.1–4.1	<0.001	4.5	3.7–5.6	<0.001	3.2	2.7–3.8	<0.001
Haloperidol	3.2	2.7–3.9	<0.001	5.0	3.6–6.8	<0.001	2.8	2.2–3.5	<0.001
Thioridazine	4.2	3.1–5.7	<0.001	4.1	2.4–6.9	<0.001	4.3	3.0–6.3	<0.001
Atypical antipsychotics									
All combined	3.5	3.2–3.8	<0.001	4.1	3.5–4.8	<0.001	3.3	3.0–3.7	<0.001
Clozapine	3.1	1.0–9.5	0.051	†	†	†	5.8	1.9–17.8	0.002
Olanzapine	3.6	3.0–4.2	<0.001	3.8	2.9–5.0	<0.001	3.5	2.8–4.3	<0.001
Quetiapine	1.9	1.3–2.9	0.001	1.1	0.5–2.7	0.0794	2.5	1.6–3.9	<0.001
Risperidone	3.7	3.3–4.2	<0.001	5.1	4.2–6.3	<0.001	3.4	2.9–3.9	<0.001

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.
† Too few patients in cohort to yield meaningful comparison.
CI, confidence interval.

Table 4. *Development of Diabetes Mellitus Among Selected Antipsychotic Cohorts**

Cohort	No. of Patients in Cohort	New Cases No. (%)	Risk Ratio	95% CI	*P* Value
All patients (aged ≥60)					
All conventionals	11,546	238 (2.1)	(1.0)		
Haloperidol	6481	118 (1.8)	(1.0)		
All atypicals†	19,407	515 (2.7)	1.1	0.9–1.3	0.382
Clozapine‡	117	5 (4.3)	1.4	0.6–3.5	0.464
Olanzapine‡	5382	142 (2.6)	1.2	0.9–1.5	0.209
Quetiapine‡	1664	29 (1.7)	0.7	0.5–1.1	0.136
Risperidone‡	12,244	339 (2.8)	1.2	1.1–1.6	0.016
Patients aged 60–74					
All conventionals	3778	100 (2.7)	(1.0)		
Haloperidol	1389	39 (2.8)	(1.0)		
All atypicals†	5433	159 (2.9)	1.0	0.7–1.2	0.686
Clozapine‡	52	1 (1.9)	§	§	§
Olanzapine‡	1961	53 (2.7)	0.8	0.5–1.2	0.297
Quetiapine‡	619	6 (1.0)	0.3	0.1–0.7	0.003
Risperidone‡	2801	99 (3.5)	1.1	0.8–1.7	0.481
Patients aged ≥75					
All conventionals	7768	138 (1.8)	(1.0)		
Haloperidol	5092	79 (1.6)	(1.0)		
All atypicals†	13,974	356 (2.6)	1.2	1.0–1.4	0.104
Clozapine‡	65	4 (6.2)	§	§	§
Olanzapine‡	3421	89 (2.6)	1.3	1.0–1.8	0.065
Quetiapine‡	1045	23 (2.2)	1.1	0.7–1.7	0.807
Risperidone‡	9443	240 (2.5)	1.4	1.1–1.8	0.019

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.
† Versus all conventional antipsychotics.
‡ Versus haloperidol.
§ Too few patients in cohort to yield a meaningful comparison.
CI, confidence interval.

risk of hyperglycemia or diabetes mellitus. Even among the patients who received quetiapine, the cohort that had the lowest risk ratio of any of the antipsychotic cohorts, the likelihood of receiving a new prescription for antidiabetic treatment was seen to be nearly twice that of the general reference population of geriatric patients, whereas a greater than fourfold risk was seen among patients receiving thioridazine. In the middle of the spectrum of risk in our study were patients who received the remaining antipsychotics, consisting of, in descending order of risk, risperidone, olanzapine, and haloperidol. The results from the clozapine cohorts were inconclusive as a result of the considerably lower numbers of patients involved, which prevented a reliable assessment of clozapine's relative risk.

Further analysis of risk among the atypical antipsychotic cohorts, using the haloperidol cohort as the reference population, appeared to corroborate this relative order of risk, because quetiapine was uniquely found to have a significantly lower risk relative to the haloperidol cohort among younger patients (aged 60–74), whereas the risperidone cohort was uniquely found to have a significantly higher risk both overall and among the older patients (aged 75+). However, it is possible that this latter finding is simply a reflection of the substantially larger size of the patient cohort. In this analysis, the risk of diabetes in the olanzapine cohort was not significantly different from that of patients treated with haloperidol. This, in itself, is a noteworthy finding, because studies have reported an increased risk of diabetes[24,25] or glucose dysregulation[26] in patients treated with olanzapine compared with patients treated with haloperidol or other conventional antipsychotics. Clozapine had the highest risk ratio in the subgroup of patients aged 75 and older, on the order of nearly six times that of the reference population. However, the findings for clozapine throughout the rest of this analysis were inconclusive as a result of the small size of the clozapine cohort and low number of prescriptions for antihyperglycemic medications that were reported.

The prevalence of diabetes has been reported to be two to four times greater in patients with schizophrenia than in the general population,[27] and numerous analyses have concluded that patients with schizophrenia who receive antipsychotics, particularly the atypical antipsychotics, could have an increased risk of hyperglycemia.[17,28,29] For example, outpatients with schizophrenia who received atypical antipsychotics were, as a whole, 9% more likely to have an International Classification of Diseases, 9th revision, diagnosis of diabetes than those receiving conventional antipsychotics.[25] Moreover, patients receiving treatment with clozapine, olanzapine, or quetiapine have been reported to have significantly higher prevalences of diabetes relative to those receiving conventional antipsychotics, whereas patients receiving risperidone did not.[25] Glucose tolerance tests, too, have shown that

patients receiving clozapine, olanzapine, or risperidone could have higher plasma glucose levels than patients receiving haloperidol or chlorpromazine.[26] As a consequence, differences in diabetes medication prescription rates in this study could be the result of differences in the characteristics of the populations for which the antipsychotics were prescribed, for example, differences in the percentage of patients with schizophrenia or dementia.

Large-scale studies of the hypothesized link between diabetes and antipsychotic use have until recently been lacking. Many analyses that have been reported have relied on isolated case reports that are lacking matched controls of healthy subjects from the general population.[18,30–33] Such results have been largely inconclusive as a result of various methodologic limitations, and causality remains an issue. Previous analyses of information from claims databases typically have merely examined the overall incidence of diabetes, rather than the onset of new diagnoses of diabetes,[25] or have omitted use of a reference cohort of patients not receiving antipsychotics.[34] For their part, tests of glucose metabolism in patients receiving antipsychotics have typically used healthy, untreated control subjects but no healthy subjects exposed acutely to antipsychotics,[35] which might have provided information regarding the effect of the treatment itself rather than simply about differences between the patients being tested. Some have interpreted these results as indicative that antipsychotics themselves could induce hyperglycemia either through direct effects on pancreatic mechanisms[36] or secondarily through induction of body weight increases.[37] With respect to the latter, nearly all of the atypical antipsychotics have been reported to be associated with increased appetite and weight gain.[38] This appears to be an unlikely explanation of the changes occurring in the present analysis, because the incidence of weight gain in response to antipsychotic treatment among elderly patients, particularly those with dementia, tends to be overshadowed by a greater incidence of weight loss.[39,40] Moreover, weight gain is more highly associated with use of the atypical antipsychotics, whereas increased risk of hyperglycemia was also seen in the current analysis among patients receiving conventional antipsychotics. On the other hand, others have proposed that antipsychotics could merely exacerbate an underlying predisposition to diabetes in patients with schizophrenia[41]; alternatively, the use of antipsychotics could be entirely coincidental to a preexisting comorbidity for diabetes among the schizophrenic population.[22,42] The association between schizophrenia and diabetes was reported as early as the 1920s,[43] well before the development of modern antipsychotic medications, and it has been suggested that schizophrenia is itself the clinical manifestation of a metabolic disorder that can be thought of as "cerebral diabetes."[44] On the other hand, although there could be an association between the clinical condition of schizophrenia and risk of diabetes, the contribution of any schizophrenia-linked predisposition to hyperglycemia in the current analysis was likely to have been minimal, because neuroleptics are more frequently prescribed to the elderly for agitation or psychosis associated with dementia, not for schizophrenia.[9] Unfortunately, important information on patients' baseline glucose levels, underlying comorbidities, and risk factors was not available. As a result, the contribution of patients' preexisting conditions to the observed increases in the incidence of antihyperglycemic prescriptions is not known, and caution should certainly be exercised in equating "new" prescriptions for antihyperglycemic medications with the appearance of new-onset diabetes.

These findings extend the recent work of Buse and coworkers,[21] who reported the results of an analysis from the AdvancePCS database, of which the present results represent a subset. Their analysis involved 58,751 patients aged 18 and older who had received prescriptions for antipsychotics. The results of the present analysis largely reflect their findings in the broader patient population,[21] with higher risks occurring during treatment with all antipsychotics relative to the reference population but no difference in risk between conventional and atypical antipsychotics. Risk ratios for the various cohorts were quite similar between the two analyses, despite the differences in patient ages. Both studies showed the highest risk to be found in the thioridazine cohort and the lowest in the quetiapine cohort. One notable difference, however, was the finding by Buse that patients aged 65+ who received atypical antipsychotics had higher risks of diabetes than did patients aged 45 to 64, implying that, at least among patients receiving atypical agents, increasing age could be a risk factor for diabetes. By contrast, the present analysis showed that, for haloperidol and risperidone, the confidence intervals were in fact lower among patients aged ≥75 years than among those aged 60 to 74 years. It would appear, then, that any age-related increase in risk could have already reached a maximum by the time patients had entered their seventh decade of life. Alternatively, it could be that the older patients, having received considerably lower doses of antipsychotic, could merely have been exposed to a correspondingly lower risk of pharmacologically induced hyperglycemia. Both of these possibilities are, of course, entirely speculative. However, this latter hypothesis seems less likely, because weight increase with olanzapine and risperidone treatment appears uncorrelated with dose.[45] Moreover, hyperglycemic and euglycemic clamp studies failed to show a direct effect of risperidone or olanzapine on insulin production and/or sensitivity. Finally, it is likely that there are differences in the diagnostic mix of the two age groups, with the younger group containing a higher percentage of patients with schizophrenia and the older group containing a higher percentage of patients with dementia. Eventual differences in diabetes risk between these diagnostic groups could explain the differences between the two age groups.

A number of limitations of this analysis warrant mention. For example, no psychiatric diagnostic data were available, and no assessment was possible to determine the confounding effects of other nonantipsychotic drugs that could have hyperglycemic potential such as beta-adrenergic antagonists, thiazide diuretics, corticosteroids, or protease inhibitors.[46] In addition, no data were available on patients' baseline body mass index or family histories of diabetes, which might have provided crucial information regarding preexisting risk, and patients were not systematically randomized to their drug

cohort; rather, assignments were made based on the clinical choices of attending physicians. Finally, treatment exposures were of limited duration, lasting for the most part for just 2½ to 3 months. These relatively short treatment-exposure periods may not have been sufficient to fully evaluate potential treatment effects, although some reports have suggested that the majority of cases of new-onset diabetes incurred during treatment with antipsychotics occur within 3 to 6 months.[32,47,48] The short period in which an acute need for antihyperglycemic medications does appear to increase in the present analysis is therefore somewhat surprising. One explanation could be that the development of hyperglycemia is not entirely the result of the administration of antipsychotic agents, but could in fact be the result of a threshold effect in an already impaired patient population. Possibly ameliorating some of the concerns over the limitations of this analysis is the fact that it involved nearly 31,000 antipsychotic-treated patients and a control population of nearly two million patients, and it might therefore be reasonably expected that, with such a large sample, a fair degree of balancing took place between drug cohorts for such possible risk factors as obesity, family histories of diabetes, and the relative proportions of the different conditions for which these medications were being prescribed.

CONCLUSION

These data indicate that the incidence of new cases of diabetes could be higher among elderly patients who receive prescriptions for antipsychotic medications than among those not receiving antipsychotics. The risk of developing diabetes was highest overall for patients treated with thioridazine. Risk in the overall atypical antipsychotic cohort was not significantly higher than that for the overall conventional antipsychotic cohort. Among the individual atypical antipsychotic cohorts, the risperidone group's risk uniquely was significantly higher than haloperidol's. In conclusion, the risk of diabetes could be higher for patients using any antipsychotic, and clinicians must be cognizant of it, regardless of the antipsychotic selected.

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Article

Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia

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Objective: The development of both type I and type II diabetes after initiation of some atypical neuroleptics has been reported, primarily in studies involving small series of patients. This study used administrative data from a large national sample of patients with a diagnosis of schizophrenia to compare the prevalence of diabetes mellitus in patients receiving prescriptions for atypical and typical neuroleptics.

Method: All outpatients with schizophrenia treated with typical and atypical neuroleptics over 4 months in 1999 in the Veterans Health Administration of the Department of Veterans Affairs (VA) were included in this study. Patients treated with atypical neuroleptics were those who received prescriptions for clozapine, olanzapine, risperidone, or quetiapine. Patients with a diagnosis of diabetes were also identified by using ICD-9 codes in VA administrative databases. The prevalence of diabetes mellitus across age groups and among patients receiving prescriptions for different atypical neuroleptics was examined with multiple logistic regression.

Results: A total of 38,632 patients were included in the study: 15,984 (41.4%) received typical neuroleptics and 22,648 (58.6%) received any atypical neuroleptic (1,207 [5.3%] received clozapine; 10,970 [48.4%], olanzapine; 955 [4.2%], quetiapine; and 9,903 [43.7%], risperidone; 387 patients received prescriptions for more than one atypical neuroleptic). When the effects of age were controlled, patients who received atypical neuroleptics were 9% more likely to have diabetes than those who received typical neuroleptics, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone. However, for patients less than 40 years old, all of the atypical neuroleptics were associated with a significantly increased prevalence of diabetes.

Conclusions: In this large group of patients with schizophrenia, receipt of a prescription for atypical neuroleptics was significantly associated with diabetes mellitus.

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Atypical neuroleptics such as clozapine (1), olanzapine (2), quetiapine (3), and risperidone (4) have demonstrated efficacy in the treatment of schizophrenia with fewer extrapyramidal side effects than other neuroleptics (5). However, other side effects have been described. The use of olanzapine, for example, has been associated with weight gain (6), exacerbation of previously well controlled diabetes (7), and onset of type I and type II diabetes mellitus (7–9), although a recent report failed to demonstrate an association between weight gain and development of hyperglycemia (10). Clozapine use has also been associated with weight gain in several reports (11–14). Although an association between clozapine-induced weight gain and the development of either hyperglycemia or diabetes mellitus has not been demonstrated (14), there have been several reports of hyperglycemia and diabetes mellitus (both type I and type II) directly associated with clozapine use (9, 14–21). There is also a single case report of quetiapine-associated new-onset diabetes mellitus (22).

The degree to which patients who receive prescriptions for atypical neuroleptics are at risk for development of diabetes mellitus cannot be ascertained definitively from the reports thus far. To our knowledge, nearly all of the studies of this issue to date are case reports. There have been exceptions, including two uncontrolled studies (14, 21) and one study (20) that used an unmatched comparison group of patients treated with typical neuroleptics. A naturalistic study of clozapine treatment reported that 30% of patients received a diagnosis of type II diabetes during the 5-year follow-up (14). This study did not include a comparison group. In addition, a comparison of patients randomly assigned to receive olanzapine or haloperidol and followed over several years failed to demonstrate a difference in the incidence of nonfasting glucose levels equal to 160 mg/dl (10); the rate of high nonfasting glucose level was 4.6% after 2.54 years in the olanzapine-treated patients and 5.0% after 1.15 years the haloperidol-treated patients. However, this analysis failed to stratify the data for age, which might have obscured important differences between the two groups—especially in younger patients, for whom the baseline rate of diabetes is not as high as in older patients. The authors were also si-

lent about family history of diabetes in these patients and about ethnicity. However, the two groups did not differ significantly in baseline body mass index. A well-matched comparison group is particularly important, as patients with schizophrenia, regardless of treatment, have been reported to have a higher rate of diabetes than the general population (23, 24). For example, the rate of diabetes mellitus in the general U.S. male population age 20–39 years is 1.1% (25); in patients with schizophrenia age 18–44 years, rates of 5.6%–6.7% have been reported (23).

Although no pathophysiologic mechanism connecting atypical neuroleptic treatment and the development of diabetes mellitus has been delineated to date, olanzapine prescription has been associated with weight gain, hyperlipidemia, hyperinsulinemia, and insulin resistance (21), suggesting both direct and indirect mechanisms by which the medication may be involved in dysregulation of relevant metabolic pathways. Clozapine has also been found to induce insulin resistance (26). With regard to weight gain, a review has estimated that after 10 weeks of treatment a patient receiving clozapine would gain an average of 3.99 kg; a patient receiving olanzapine, an average of 3.51 kg; and a patient receiving risperidone, an average of 2 kg; and after 6 weeks of treatment, a patient receiving quetiapine would gain an average of 2.18 kg.

Thus, although researchers have reported that some patients treated with the atypical neuroleptics clozapine, olanzapine, and quetiapine develop diabetes mellitus that is sometimes, but not always, reversible, these studies have involved relatively small groups of patients. Studies have also demonstrated that prescription of olanzapine and clozapine can result in the development of metabolic abnormalities associated with diabetes mellitus (21, 26). In these studies, as well, the numbers of patients studied has been small. In summary, although the association between atypical neuroleptic prescription and development of diabetes mellitus has been observed and some potential pathophysiologic mechanisms have been elucidated, the risk of developing diabetes mellitus for patients who receive prescriptions for atypical neuroleptics has not been well studied.

This study used data for a comprehensive national sample of patients treated in the Veterans Health Administration of the Department of Veterans Affairs (VA) who had a diagnosis of schizophrenia and received prescriptions for either typical or atypical neuroleptics to test the hypothesis that prescription of atypical neuroleptics is associated with an increased prevalence of diabetes. Although the study design precluded an assessment of either a causal relationship or a mechanism of action, it provided a means for determining the potential public health risk. The large number of patients with schizophrenia treated within the VA system also allowed for examination of the prevalence of diabetes associated with each of the atypical neuroleptics available at the time of study—clozapine, olanzapine, quetiapine, and risperidone.

Method

Patients

All patients with a diagnosis of schizophrenia during fiscal year 1999 (October 1, 1998, to September 30, 1999) were identified through VA workload databases. A diagnosis of schizophrenia was operationally defined as having at least two outpatient encounters in a specialty mental health outpatient clinic for which either the primary or secondary diagnosis was schizophrenia (corresponding to ICD codes 295.00–295.99).

Data describing patient characteristics such as age, income, gender, ethnicity, receipt of VA compensation or pension, comorbid medical and psychiatric diagnoses, hospital utilization, and zip code of residence were also obtained from the VA workload databases. By using the zip code and data from the American Hospital Association annual survey, the distances from the centrum of the district designated by the patient's zip code to the nearest VA and non-VA hospitals were calculated (27). We controlled for distance as a proxy measure for access, since the likelihood of receiving a diagnosis of diabetes mellitus might increase with easier access to care.

For all patients identified as having a diagnosis of schizophrenia, records of all medications prescribed between June (when data first became available) and September (the end of the fiscal year) of 1999 were obtained from the VA Drug Benefit Management System. For each patient, the last neuroleptic prescription written between June and September 1999 was identified as the index prescription. All prescriptions written for neuroleptics in the previous week were also identified. If any of the prescriptions written during that 7-day period were for clozapine, olanzapine, quetiapine, or risperidone, then the patient was entered into the atypical neuroleptic group, regardless of whether the patient was also prescribed typical neuroleptics at the same time. If a patient received only typical neuroleptics during that week, the patient was entered into the typical neuroleptic group. If a patient had no neuroleptic prescription written for the entire 4-month period, the patient was not included in this analysis. Within the atypical group, 94% of patients received the same atypical neuroleptic for the entire 4-month period and 8.9% also received a prescription for a typical neuroleptic (28).

For the group of patients identified as having a diagnosis of schizophrenia and receiving neuroleptic medications, computerized administrative data were examined for record of a diagnosis of diabetes mellitus. A patient was operationally defined as having a diagnosis of diabetes mellitus if the patient had at least one outpatient encounter or inpatient stay with either a primary or secondary diagnosis of diabetes mellitus (corresponding to ICD codes 250.00–250.99) during the 4-month period for which the prescribing data were available.

Analysis

Because of the strong relationship between age and development of diabetes (25), the patients in both the atypical and typical neuroleptic groups were stratified into five age groups: under 40, 40–49, 50–59, 60–69, and over 70 years. Within each age division, the percentages of patients with a diagnosis of diabetes in the atypical and typical neuroleptic groups were compared with chi-square tests.

To address potentially confounding factors, we used logistic regression analysis to calculate odds ratios for the association of atypical neuroleptic prescription and the diagnosis of diabetes within each of the age strata, controlling for the effects of the demographic, diagnostic, and treatment factors listed in Table 1.

These analyses were then repeated to examine the prevalence of diabetes mellitus associated with each atypical neuroleptic. A series of four dichotomous variables was included in these analy-

TABLE 1. Characteristics of Patients With Schizophrenia Receiving Prescriptions for Atypical and Typical Neuroleptic Medication Within Department of Veterans Affairs (VA) Health Services in a 4-Month Period in 1999

Characteristic	Patients Receiving Prescriptions for Atypical Neuroleptics (N=22,648)		Patients Receiving Prescriptions for Typical Neuroleptics (N=15,984)		Analysis		
	Mean	*SD*	*Mean*	*SD*	*t*	*df*	*p*
Age (years)	50.7	11.5	54.5	11.7	31.6	33980.3	0.0001
Income (dollars/year)	14,149.49	16,973.88	15,034.72	16,902.82	5.1	38630	<0.0001
Distance to nearest VA hospital (miles)	24.8	91.0	22.0	80.1	3.2	36828.3	<0.002
	N	*%*	*N*	*%*	χ^2	*df*	*p*
Female	1,369	6.0	711	4.4	46.9	1	<0.0001
African American	5,689	25.1	3,983	24.9	0.2	1	0.65
Hispanic	945	4.2	696	4.4	0.8	1	0.38
VA service-connected compensation (rating of degree of disability)							
10%–50%	3,049	13.5	2,284	14.3	5.4	1	0.02
>50%	9,703	42.8	7,672	48.0	100.6	1	<0.0001
Comorbid diagnosis							
Organic brain syndrome or Alzheimer's disease	1,805	8.0	993	6.2	43.1	1	0.0001
Substance abuse	5,407	23.9	2,489	15.6	397.0	1	<0.0001
Alcohol abuse/dependence	4,202	18.6	1,877	11.7	327.8	1	<0.0001
Nonalcohol abuse/dependence	3,655	16.1	1,565	9.8	323.0	1	<0.0001
Major depression or bipolar disorder	9,619	42.5	4,539	28.4	799.5	1	<0.0001
Posttraumatic stress disorder	3,200	14.1	1,452	9.1	225.2	1	<0.0001
Neurosis or adjustment disorder	4,591	20.3	2,159	13.5	297.3	1	<0.0001
Personality disorder	1,724	7.6	683	4.3	178.8	1	<0.0001
Other psychiatric diagnosis	2,274	10.0	1,026	6.4	157.3	1	<0.0001
Days hospitalized in psychiatric facility in the previous year							
1–18	3,182	14.0	1,284	8.0	331.8	1	<0.0001
>18	3,389	15.0	1,061	6.6	637.3	1	<0.0001
Atypical neuroleptic prescribed[a]							
Clozapine	1,207	5.3					
Olanzapine	10,970	48.4					
Quetiapine	955	4.2					
Risperidone	9,903	43.7					

[a] Number of patients receiving prescriptions for any atypical neuroleptic is less than the total for the individual atypical neuroleptics because some patients received prescriptions for more than one atypical neuroleptic.

ses to represent each of the atypical medications available at the time of the study.

In a final analysis the five age groups were combined in a single analysis with age as a covariate to determine the population-wide prevalence of diabetes in association with atypical neuroleptic prescription and in association with each particular atypical medication.

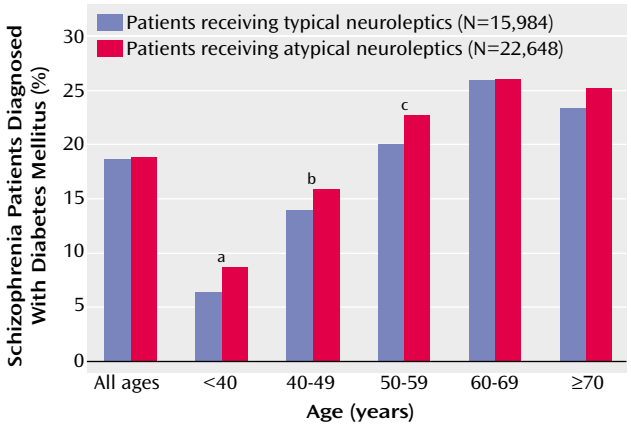
Results

In the 4-month study period, 38,632 patients identified with schizophrenia received a prescription for a neuroleptic. Of those patients, 22,648 (58.6%) received an index prescription for an atypical neuroleptic and 15,984 (41.4%) received an index prescription for typical neuroleptics alone. A comparison of the two groups is presented in Table 1. Significant differences were examined by using t tests for continuous variables and chi-square tests for dichotomous variables.

Compared to the patients who received prescriptions for typical neuroleptics, the patients who received prescriptions for atypical neuroleptics were significantly younger and had less income. They were significantly more likely to be female and have another psychiatric diagnosis, including organic brain syndrome or Alzheimer's dementia, substance abuse, major depression or bipolar disorder, posttraumatic stress disorder, neurosis or adjustment disorder, personality disorder, or other, unspecified, psychiatric disorder. Patients in the atypical group lived significantly further from the nearest VA hospital and were significantly more likely to have been hospitalized. Patients in the typical neuroleptic group were more likely to be receiving service-connected compensation from the VA.

Patients who received atypical neuroleptic medications demonstrated a statistically significant higher rate of diagnosis of diabetes in the three youngest age strata (Figure 1). Among patients less than 40 years old, for example, 8.75% of those receiving an atypical neuroleptic had a diagnosis of diabetes mellitus, compared to 6.43% of those receiving typical neuroleptics (χ^2=7.24, df=1, p=0.007). This relationship was also observed in the 40–49-year age group (15.89% versus 13.93%) (χ^2=9.81, df=1, p=0.002) and in the 50–59-year age group (22.73% versus 20.56%) (χ^2= 8.53, df=1, p=0.003). No significant association was observed in either the 60–69-year group or the group age 70 and older. Comparing across all ages, 18.84% of the patients who received a prescription for an atypical neuro-

FIGURE 1. Percentage of Patients With Schizophrenia Receiving Prescriptions for Atypical and Typical Neuroleptic Medication Who Also Had a Diagnosis of Diabetes Mellitus



[a] χ^2=7.24, df=1, p<0.07.
[b] χ^2=9.81, df=1, p=0.002.
[c] χ^2=8.53, df=1, p=0.003.

leptic and 18.64% of those who received a prescription for a typical neuroleptic also had a diagnosis of diabetes, a nonsignificant difference.

The adjusted odds ratios for the entire group and each of the age groups are presented in Table 2. For the entire group (all ages), the odds of having a diagnosis of diabetes mellitus were significantly greater for patients receiving any atypical neuroleptic and, specifically, for patients receiving clozapine, olanzapine, and quetiapine, but not risperidone. In the under-40-year age group, the odds were significantly greater for all of the atypical neuroleptics. In the 40–49-year-old age group, a prescription for clozapine, olanzapine, or quetiapine was associated with significantly increased odds for having a diagnosis of diabetes mellitus, but a risperidone prescription was not. In the 50–59-year age group, only olanzapine and risperidone were associated with a significantly increased prevalence of a diagnosis of diabetes. In the 60–69-year age group, clozapine was associated with a significantly decreased prevalence.

Discussion

This study demonstrated, overall, a significant association between prescription of clozapine, olanzapine, and quetiapine, but not risperidone, and diagnosis of diabetes mellitus, compared with prescription of typical neuroleptics. In analyses that controlled for age, the strongest effect was observed in patients less than 40 years old (odds ratio=1.63, 95% CI=1.23–2.16), and each of the atypical neuroleptics was associated with an increased prevalence of diabetes mellitus in at least two of the age groups. These results are consistent with recent reports of significantly higher serum glucose levels in patients randomly assigned to olanzapine, compared to those receiving haloperidol (10), even without adjustments for age.

TABLE 2. Logistic Regression Analysis of Association Between Prescription of Atypical and Typical Neuroleptic Medication and Presence of a Diagnosis of Comorbid Diabetes Mellitus in Patients With Schizophrenia, by Age Group

Age Group and Medication Prescribed	Odds Ratio	95% Confidence Interval	p
All ages			
Any typical (N=15,984)			
Any atypical (N=22,648)[a]	1.09	1.03–1.15	0.002
Clozapine (N=1,207)	1.25	1.07–1.46	<0.005
Olanzapine (N=10,970)	1.11	1.04–1.18	<0.002
Quetiapine (N=955)	1.31	1.11–1.55	<0.002
Risperidone (N=9,903)	1.05	0.98–1.12	0.15
<40 years			
Any typical (N=1,105)			
Any atypical (N=3,076)[a]	1.63	1.23–2.16	0.001
Clozapine (N=232)	2.13	1.36–3.35	<0.002
Olanzapine (N=1,474)	1.64	1.23–2.21	0.0009
Quetiapine (N=165)	1.82	1.05–3.15	<0.04
Risperidone (N=1,267)	1.51	1.12–2.04	<0.008
40–49 years			
Any typical (N=4,980)			
Any atypical (N=8,479)[a]	1.16	1.04–1.28	<0.006
Clozapine (N=566)	1.43	1.13–1.81	<0.003
Olanzapine (N=4,203)	1.19	1.06–1.34	<0.003
Quetiapine (N=368)	1.86	1.43–2.41	0.0001
Risperidone (N=3,518)	1.04	0.92–1.17	0.55
50–59 years			
Any typical (N=5,065)			
Any atypical (N=6,648)[a]	1.16	1.06–1.27	<0.002
Clozapine (N=322)	1.17	0.88–1.54	0.28
Olanzapine (N=3,256)	1.16	1.04–1.29	<0.008
Quetiapine (N=281)	1.19	0.89–1.59	0.24
Risperidone (N=2,891)	1.13	1.01–1.26	<0.05
60–69 years			
Any typical (N=2,547)			
Any atypical (N=2,453)[a]	0.90	0.79–1.03	0.14
Clozapine (N=69)	0.50	0.26–0.96	<0.04
Olanzapine (N=1,172)	0.90	0.77–1.07	0.23
Quetiapine (N=92)	0.90	0.55–1.46	0.66
Risperidone (N=1,156)	0.94	0.80–1.10	0.44
≥70 years			
Any typical (N=2,287)			
Any atypical (N=1,992)[a]	1.01	0.87–1.17	0.91
Clozapine (N=18)	1.61	0.59–4.37	0.35
Olanzapine (N=865)	0.99	0.82–1.19	0.91
Quetiapine (N=49)	0.62	0.30–1.28	0.19
Risperidone (N=1,071)	1.02	0.86–1.21	0.82

[a] Number of patients receiving prescriptions for any atypical neuroleptic is less than the total for the individual atypical neuroleptics because some patients received prescriptions for more than one atypical neuroleptic.

The observation that there are no overall differences in the rates of diabetes mellitus in the older age groups suggests that those with the predilection to develop diabetes in these age groups have already done so, and those left, lacking the diathesis for its development, will not develop diabetes despite being exposed to atypical neuroleptics. Thus the increased prevalence associated with atypical antipsychotics may be thought of hastening the onset of diabetes rather than precipitating it de novo. The observation of no difference at older ages may also suggest that, in those groups, age may be a more important risk factor for comorbid diabetes than the neuroleptic prescribed.

Both the typical and atypical treated groups demonstrated very high rates of diabetes mellitus. The rate of di-

abetes mellitus in the general U.S. male population age 20–39 years is 1.1% (25), whereas we observed rates of 6.2%–8.7%. These findings are consistent with previous reports of rates of 5.6%–6.7% in U.S. patients with schizophrenia age 18–44 years (23).

Several methodological limitations deserve mention. First, although this study examined data from more than 38,000 patients with a diagnosis of schizophrenia who received prescriptions for neuroleptics, the narrow time frame of 4 months yielded a virtual cross-sectional sample, precluding determination of the temporal relationship between the prescription of neuroleptics and the development of diabetes mellitus. It is possible, therefore, that patients may have been switched from an atypical to either a typical neuroleptic or another atypical secondary to development of diabetes before the 4-month prescription window. Such a switch would have the practical consequence of underestimating the risk for those medications more likely to cause diabetes and overestimating the risk for those medications less likely to cause the disease.

Second, data on changes in weight in patients who received prescriptions for atypical neuroleptics were also unavailable. These data might have clarified one potential mechanism of action for the development of diabetes.

Third, the patients who received prescriptions for typical neuroleptics may have been less likely to take the medications because of their side effect profiles than were those with prescriptions for the atypical neuroleptics. Thus, even if both groups of neuroleptics were equally likely to cause diabetes, more cases of diabetes might be seen in the atypical group if patients were taking more of their prescribed medication. We think, however, that this explanation is unlikely because empirical data show that, although patients taking atypical neuroleptics are more likely to continue on those medications for an extended period of time, they are no more likely to take the prescribed dosage than patients who take typical neuroleptics (29).

Fourth, this study relied on screening an administrative database for appropriate ICD-9 codes to identify cases of diabetes mellitus. Although the validity of this method has not been established empirically, there is no reason to believe that this method would result in any bias in the assignment of cases of diabetes to either the typical or atypical neuroleptic groups.

Finally, several possible alternative explanations for our observation deserve comment. First, it is possible that patients with preexisting diabetes mellitus were selectively switched to atypical neuroleptics. This explanation is unlikely, since the literature has implicated atypical neuroleptics in potentially inducing or exacerbating diabetes mellitus. It is more likely that clinicians, aware of case reports asserting a connection between some atypical neuroleptics and diabetes mellitus, might have avoided these medications in patients with diabetes, artificially decreasing our ability to detect an association. It is also possible, however, that clinicians who were aware of the potential risks could have chosen to monitor blood sugars more carefully in patients taking atypical neuroleptics, thereby identifying additional cases of diabetes and inflating the effect size.

A second alternative interpretation is that both atypical neuroleptic prescription and receipt of a diagnosis of diabetes could be associated with more severe forms of schizophrenia. If more severe cases of schizophrenia have a higher risk of diabetes mellitus, then more symptomatic patients may be both more likely to receive atypical antipsychotics and to be at greater risk for diabetes, although the atypical neuroleptics are not the causal agent. Although we cannot rule out these potentially confounding associations, we have attempted to adjust for them by covarying the effect of several measures of severity in our analyses.

Third, it is possible that receipt of atypical neuroleptics and having a diagnosis of diabetes both reflect a higher overall quality of medical care, including careful medical monitoring and state-of-the-art psychopharmacology.

Thus, although this study in a large national sample has demonstrated a substantial and statistically significant association between atypical neuroleptic prescription and diabetes mellitus, it did not definitively establish a causal relationship. The results are, however, strongly suggestive of such a relationship and demonstrate both the potential magnitude and public health importance of this association, as well as the potential utility of monitoring patients who receive atypical neuroleptics for signs and symptoms of diabetes mellitus.

In a recent comprehensive review of the effectiveness of atypical neuroleptics, Geddes et al. (30) concluded that the primary benefit of atypical antipsychotics was in reducing side effects. If it is established that these medications reduce the risk of extrapyramidal symptoms but increase the risk of diabetes, the risk/benefit ratio of these medications might be significantly altered.

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Relationship Between Antipsychotic Medication Treatment and New Cases of Diabetes Among Psychiatric Inpatients

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Objective: **This study examined data on patients with serious and persistent mental illness in a large state hospital system to determine whether patients who took second-generation antipsychotics were more likely to develop diabetes mellitus than patients who took first-generation antipsychotics.** ***Methods:*** **A case-control study design was used. A new prescription of an antidiabetic medication was used to identify new cases of diabetes mellitus. Odds ratios were calculated for exposure to second-generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and multiple second-generation antipsychotics) compared with exposure to first-generation antipsychotics. Cases and controls were identified by using a database that contained drug prescription information from the inpatient facilities that were operated by the New York State Office of Mental Health. Data from January 1, 2000, to December 31, 2002, were examined. Among 13,611 unique patients who received antipsychotics, 8,461 met entry criteria of being hospitalized for at least 60 days and not having an antidiabetic medication prescribed in the past. A total of 181 of these inpatients received prescriptions for an antidiabetic medication at least 30 days after their admission. Eight controls (N=1,448) for each case (N=181) were matched by calendar year, length of observation period, race, age group, and diagnosis, giving a total sample of 1,629 patients.** ***Results:*** **Statistically significant elevations in risk were seen among patients who received more than one second-generation antipsychotic or clozapine or quetiapine, compared with patients who received first-generation antipsychotics alone. Although not statistically significant, odds ratios for olanzapine and risperidone were also elevated. Conditional logistic regression adjusting for gender and age did not change the results.** ***Conclusions:*** **Exposure to multiple second-generation antipsychotics or clozapine or quetiapine significantly increased the risk of treatment-emergent diabetes mellitus. (*Psychiatric Services* 55: 1006–1013, 2004)**

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Second-generation antipsychotics are widely used in the treatment of psychotic disorders. Koller and colleagues (1–4) have reported data from the U.S. Food and Drug Administration's MedWatch surveillance program that implicated clozapine, olanzapine, risperidone, and quetiapine in new-onset diabetes mellitus, including diabetic ketoacidosis. Several pharmacoepidemiologic studies have supported the notion that second-generation antipsychotics may raise the risk of diabetes (5–15), and several mechanisms of action have been suggested for this association, including weight gain and development of insulin resistance (16,17). However, the existing pharmacoepidemiologic literature is inconsistent about the magnitude of risk of diabetes that is attributable to different antipsychotics (18). Much of this inconsistency may result from differences in study design and population or sample selection. Previous work was done mainly with outpatients in a variety of health care systems, did not control for any differences in how frequently and by what methods diabetes mellitus was screened for, and has often included patients who did not receive antipsychotics. A complete discussion of this topic can be found elsewhere (18).

We performed a case-control study among patients with serious and persistent mental illness in a large state hospital system to determine whether patients who took second-generation

antipsychotics were more likely to develop diabetes mellitus than patients who took first-generation antipsychotics. A new prescription for an antidiabetic medication was used as a proxy for treatment-emergent diabetes mellitus. All the patients who were included in our study were given antipsychotics. Because the intensity of surveillance for diabetes may also affect the identification of cases, we assessed the rate at which plasma glucose tests were ordered for patients in the control group, by type of antipsychotic prescribed.

Methods

Database

Data were collected by using the Integrated Research Database that was created by the information sciences division of the Nathan S. Kline Institute for Psychiatric Research. The database contains patient information—demographic characteristics and diagnostic information as well as dates of admission, transfer, and discharge—and drug prescription information for every inpatient within the 17 adult civil facilities of the New York State psychiatric hospital system. These psychiatric centers provide intermediate and long-term care to patients with severe and persistent mental illness. The database can produce records that can be cross-referenced with other relevant databases, including those that are related to the ordering of laboratory tests.

Approval was obtained from the institutional review board of the Nathan S. Kline Institute for Psychiatric Research and Rockland Psychiatric Center, along with a waiver for written informed consent. Patient-identifying information was removed from the data. Because the study was a retrospective review of existing data, it was found to present no more than minimal risk to the participants. The Integrated Research Database has been successfully used to examine the extent, pattern of use, and effectiveness of depot neuroleptics (19,20); the extent of prescribing or coprescribing antipsychotics (21,22); the effectiveness of newer antipsychotics (23); and the extent of the use of valproate (24,25) and other mood stabilizers (26).

Sample selection

Patients for the case group and the control group were included in the study if they were inpatients during the period of January 1, 2000, through December 31, 2002; had a length of stay of at least 60 days; and were given at least one dose of antipsychotic medication. For patients who were hospitalized in the New York State Office of Mental Health system before January 1, 2000, we also examined information in the database back to January 1, 1994, and excluded any patients who were found to have received a prescription for antidiabetic medication.

This study demonstrated an association between second-generation antipsychotics and the development of diabetes mellitus among severely and persistently ill hospitalized patients.

Case and control groups

Patients in the case group were those who received new prescriptions of antidiabetic medication—insulin, glyburide, glipizide, glimepiride, tolbutamide, chlorpropamide, tolazamide, repaglinide, metformin, troglitazone, acetohexamide, acarbose, miglitol, rosiglitazone maleate, pioglitazone hydrochloride, and nateglinide. To reduce the possibility that a prescription of an antidiabetic medication was a renewal of a medication that was received before hospitalization, patients in the case group were required to have at least a 30-day period of hospitalization before the start of the prescription of the antidiabetic medication. Nonpsychiatric physicians generally wrote these new prescriptions after clinical and laboratory evidence indicated a need for this intervention.

To control for potentially confounding variables, patients in the control group were matched to those in the case group first on calendar year, then on length of stay during the calendar year (within 45 days), then on race (white versus nonwhite), then on age group (younger than 40 years versus 40 years or older), and then on diagnosis (given a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder versus any other diagnosis). Matching on gender or total length of stay that included other calendar years was not done, because a preliminary analysis of cases for the years 1998 through 1999 did not indicate a significant association between these variables and the likelihood of receiving antidiabetic medication. Multiple rounds of matching occurred until eight controls were found for each case.

Antipsychotic exposure

The second-generation antipsychotic medications that were examined were clozapine (commercially available in the United States since 1989), risperidone (available since 1994), olanzapine (available since 1996), and quetiapine (available since 1997). Ziprasidone and aripiprazole were excluded because they were not commercially available during the entire study period. Patients who received ziprasidone or aripiprazole were excluded from being considered for either the case or control group. First-generation antipsychotic medications examined were chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine. Emergency or stat use of intramuscular antipsychotics was not considered. Antipsychotic exposure was classified by examining a 45-day period before the new prescription for

Table 1

Demographic characteristics of inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication[a]

Characteristic	Controls (N=1,448)		Cases (N=181)	
	N	%	N	%
White	464	32	58	32
Age (mean±SD years)	43.7±12.8		43.3±11.4	
Men	1,030	71	110	61
Diagnosis of schizophrenia or schizoaffective disorder	1,200	83	150	83
Length of stay (mean±SD days)	1,481±2,189		1,169±1,556	
Length of stay during the calendar year when a new antidiabetic medication was prescribed or the equivalent index date for the controls (mean±SD days)	288.7±102.3		290.7±100	

[a] Patients were matched on year of stay, length of stay during the study year (observation period), race, age, and diagnosis.

antidiabetic medication for case patients or to an equivalent index date for control patients. Six exposure categories were created a priori: patients who received first-generation antipsychotics but did not receive any second-generation antipsychotics, patients who received only clozapine, patients who received only risperidone, patients who received only olanzapine, patients who received only quetiapine, and patients who received more than one second-generation antipsychotic, either simultaneously or consecutively. For all the second-generation antipsychotic categories, patients may have also been given first-generation antipsychotics. The category of patients who received more than one second-generation antipsychotic was necessary because exposure to more than one agent is not uncommon. The many possible combinations made it unfeasible to break this category down into smaller categories for statistical analysis; however, the combinations are qualitatively described in the results section. Because this 45-day period does not equate to actual extent of exposure to the antipsychotic of interest, the amount of time that the patient was given the identified antipsychotic for the six months before the index date was also determined.

Statistical analysis

Crude odds ratios (ORs) for receiving a new prescription of an antidiabetic agent were calculated, and 95 percent confidence intervals (CIs) were determined. For the exposure variable, patients who received first-generation antipsychotics only were considered as the reference category. Conditional logistic regression analysis was used to adjust the ORs for age and gender. The use of conditional logistic regression allows data for cases to be compared directly with that of their respective controls, thus maximizing the benefit of the matched design. The analysis was performed with the Cox regression module of SPSS version 10, using syntax that stratified the data according to each case and its respective group of eight controls (27). Syntax is available from the authors on request.

Power calculations indicate that to detect at 80 percent power a crude OR of 3, with 95 percent certainty that the result is not caused by chance, a minimum sample size of 29 to 39 cases would be required for each of the categories of second-generation antipsychotics. The sample size is the sum of the number of patients in the case group who were exposed to first-generation antipsychotics only plus the number who were exposed to second-generation antipsychotics. In all exposure categories, the sample size was sufficient to detect the target OR of 3. An OR of 3 was selected for the power calculation because statistically a risk ratio of 2 is rather low and could be accounted for by many factors other than a causal connection between the suspect agent and disease (28). A risk ratio that exceeds 3—a threefold increase in risk—would indicate a strong association between the risk factor and disease (28). The actual limit of detection achieved in our study ranged from 2.3 to 2.65 for the various exposure categories.

Because the frequency of monitoring for diabetes mellitus with plasma glucose tests may vary depending on the type of antipsychotic medication prescribed, we measured this frequency among patients in the control group. The average monthly rate for plasma glucose testing was calculated by counting all plasma glucose tests that were performed for each patient in the control group during the relevant calendar year and dividing it by the number of months of observation. Information for this calculation was gathered from the administrative records that were maintained by the central laboratory that processes these tests for ten of the 17 hospitals that are operated by the New York State Office of Mental Health. Data were available for 1,154 patients in the control group (79.7 percent).

Results

Sample

Among the 13,611 unique hospitalized patients who received antipsychotic medication from January 1, 2000, to December 31, 2002, a total of 8,461 patients met our entry criteria of being hospitalized for at least 60 days and not being given antidiabetic medication in the past. Within the hospital system during this period, 1,539 patients (841 out of 8,876 men and 698 out of 4,735 women) received antidiabetic medications, for a prevalence rate of 11.31 percent among all inpatients who received antipsychotic medications (9.5 percent for men and 14.7 percent for women; χ^2=85.4, df=1, p<.001). A total of 181 patients received a new prescription for an antidiabetic agent at least 30 days after their admittance, 62 received this prescription in 2000 (out of 4,908 patients who met entry criteria), 68 received this prescription in

Table 2

Risk of developing diabetes mellitus among inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication[a]

Exposure	Cases	Controls	Crude OR	95% CI for crude OR	OR[b]	95% CI[b]	p for OR[b]
First-generation antipsychotics only	17	250	1	—	1	—	—
Clozapine only[c]	24	171	2.06	1.08–3.96	2.06	1.07–3.99	.031
Olanzapine only[c]	43	402	1.57	.88–2.82	1.57	.87–2.82	.132
Quetiapine only[c]	24	112	3.15	1.63–6.09	3.09	1.59–6.03	<.001
Risperidone only[c]	31	305	1.49	.81-2.76	1.5	.81–2.79	.196
More than one second-generation antipsychotic[c,d]	42	208	2.97	1.64–5.37	2.86	1.57–5.2	<.001

[a] Patients were matched on year of stay, length of stay during study year (observation period), race, age, and diagnosis.
[b] Calculated by logistic regression, adjusting for gender and age
[c] Patients may have also been exposed to first-generation antipsychotics.
[d] Simultaneously or consecutively within the 45-day window before the new prescription of an antidiabetic agent

2001 (out of 4,525 who met entry criteria), and 51 received this prescription in 2002 (out of 4,159 who met entry criteria), yielding percentage annual incident rates of 1.26, 1.5, and 1.27 for each respective year. Eight controls (N=1,448) for each case (N=181) were matched by calendar year, length of observation period, race, age group, and diagnosis, which gave a sample size of 1,629 patients.

Demographic information for cases and their respective controls is given in Table 1. With the exception of gender, no statistically significant differences were found between cases and controls on these demographic characteristics. A lower percentage of men were in the case group than the control group (χ^2=8.22, df=1, p=.004). This difference arose because we did not match control patients on the basis of their gender; consequently, the percentage of men in the control group is the same as the percentage of men in the inpatient population that is served by the New York State Office of Mental Health—approximately 70 percent. To adjust for this difference, gender was included in the conditional logistic regression model.

Although we used a 45-day window before the index date to classify patients by their most proximate exposure to an antipsychotic, most patients were given the antipsychotic in question for a longer period. Therefore, we also measured the amount of time that the identified antipsychotic was prescribed for the patient for the six months before the index date. The mean±SD number of days that patients received a single second-generation antipsychotic was 121±60.9 days for patients in the case group and 133.7±55 days for patients in the control group. Although the minimum length of stay that was required for study inclusion was 60 days, the sample was composed of patients with much longer stays, as can be seen in Table 1. Overall, the longer stay was associated with much longer exposure to antipsychotic medication treatment. Within the New York State psychiatric hospital system, approximately one-quarter of all inpatients have a length of stay that ranges from one to five years, and one-fourth have a length of stay that exceeds five years.

Odds ratios and 95 percent confidence intervals

Table 2 shows that when crude ORs were calculated and when the analyses used logistic regression and adjusted for gender and age, statistically significant elevations in risk were observed for patients who received more than one second-generation antipsychotic (OR=2.86, CI=1.57 to 5.2), clozapine (OR=2.06, CI=1.07 to 3.99), or quetiapine (OR=3.09, CI=1.59 to 6.03), compared with patients who received first-generation antipsychotics alone. ORs for olanza-

Table 3

Age-adjusted risk of developing diabetes mellitus among inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication, by gender

	Men (N=1,140)			Women (N=489)	
Exposure	OR	95% CI	p	OR	95% CI
First-generation antipsychotics only	1	—		1	—
Clozapine only[a]	2.52	1.04–6.13	.041	.92	.29–2.89
Olanzapine only[a]	2.09	.93–4.7		.79	.29–2.15
Quetiapine only[a]	3.89	1.54–9.81	.004	1.99	.6–6.56
Risperidone only[a]	1.85	.81–4.21		.73	.23–2.35
More than one second-generation antipsychotic[a,b]	3.72	1.61–8.57	.002	1.28	.46–3.58

[a] Patients may have also been exposed to first-generation antipsychotics.
[b] Simultaneously or consecutively within the 45-day window before the new prescription of an antidiabetic agent

Table 4

Monthly frequency of plasma glucose tests among inpatients taking an antipsychotic medication who did not receive a new prescription for an antidiabetic medication (N=1,154)

Exposure	N	Mean number of plasma glucose tests per month	SD
First-generation antipsychotics only	206	.241	.454
Clozapine only[a,c]	134	.36	.538
Olanzapine only[a,c]	312	.346	.58
Quetiapine only[a]	88	.334	.454
Risperidone only[a]	253	.258	.422
More than one second-generation antipsychotic[a,b,c]	161	.424	.739
Any antipsychotic (all controls)	1,154	.32	.543

[a] Patients may have also been exposed to first-generation antipsychotics.

[b] Simultaneously or consecutively within the 45-day window preceding the new prescription of an antidiabetic agent

c Statistically significant when compared with controls who received only first-generation antipsychotics (p=.046 for clozapine, p=.03 for olanzapine, p=.001 for more than one second-generation antipsychotic) or with controls who received risperidone as the only second-generation antipsychotic (p=.002 for more than one second-generation antipsychotic)

pine and risperidone were also elevated, although the elevations were not statistically significant.

There were 42 cases of treatment-emergent diabetes mellitus among the patients who were exposed to more than one second-generation antipsychotic. The combinations of second-generation antipsychotics were risperidone and quetiapine (12 patients, or 29 percent), risperidone and olanzapine (nine patients, or 21 percent), risperidone and clozapine (eight patients, or 19 percent), olanzapine and quetiapine (five patients, or 12 percent), olanzapine and clozapine (four patients, or 10 percent), quetiapine and clozapine (three patients, or 7 percent), and risperidone, olanzapine, and clozapine (one patient, or 2 percent).

As shown in Table 3, when the analysis was stratified by gender, ORs differed for men and women. Although men and women did not differ significantly on treatment assignment, ORs for men were statistically significant among those who received more than one second-generation antipsychotic (OR=3.72, CI=1.61 to 8.57), clozapine (OR=2.52, CI=1.04 to 6.13), or quetiapine (OR=3.89, CI=1.54 to 9.81). Statistical significance was not reached for any of the ORs for women, even after controlling for any differences in age or observation days.

Plasma glucose tests

As shown in Table 4, a comparison of the rate of plasma glucose testing that was obtained for patients in the control group revealed significant differences in surveillance rates among the exposure groups (F=3.049, df=5, 1,148, p=.01). Patients in the control group who received clozapine, olanzapine, or more than one second-generation antipsychotic were more likely to have a plasma glucose test (mean number of tests per month: .360±.538, .346±.58, or .424±.739, respectively) than control patients who received first-generation antipsychotics alone (.241±.454 tests per month; p=.046, p=.03, or p=.001, respectively, Bonferroni-corrected comparison). Patients in the control group who received more than one second-generation antipsychotic were more likely to have a plasma glucose test than those who received only risperidone (.258±.422 tests per month, p=.002 Bonferroni-corrected comparison).

Discussion

This study demonstrated an association between second-generation antipsychotics and the development of diabetes mellitus among severely and persistently ill hospitalized patients. None of the previous studies that examined this relationship included patients who were in state hospitals (5–15), and several studies included patients who were not exposed to antipsychotic medication as controls (8–10,12–14).

Both the diagnostic distribution and the choice of exposure groups for comparison may have a significant impact on the outcome of pharmacoepidemiologic studies in this area. For example, evidence exists that patients with schizophrenia may be at higher risk of developing diabetes, independent of antipsychotic use (29). In addition, second-generation antipsychotics are being used increasingly for indications outside the treatment of schizophrenia, such as for mania, dementia, and severe anxiety. Thus antipsychotic exposure groups among diagnostically heterogeneous populations are likely to differ in many patient characteristics besides the medication exposures under study. As a consequence, our restriction of the patient population to persons who were hospitalized and severely and persistently mentally ill and matching on diagnosis (schizophrenia or schizoaffective disorder versus other) may have certain methodologic advantages.

Our study is the first published case-control study to report a statistically significant increase in the risk of developing diabetes mellitus with quetiapine, compared with exposure to first-generation antipsychotics alone. This result is consistent with case reports (30–32), the "pharmacovigilance" report by Koller and colleagues (4), and the prevalence study by Sernyak and colleagues (6), in which an OR of 1.31 (CI=1.11 to 1.55) for quetiapine was reported. These results are also consistent with two presentations given at scientific meetings and whose abstracts were published (33,34). Although Buse and colleagues (12) found a hazard ratio of 1.7 (CI 1.2 to 2.4) for persons who took quetiapine, compared with persons who did not take antipsychotics, they also found a hazard ratio of .67 (CI .46 to .97) for persons who took quetiapine, compared with persons who took haloperidol, which sig-

nified a decreased risk. This result may be related to diagnostic and dosage issues. The database that was used by that study did not have information about diagnosis, and the mean dosage of quetiapine was low (79.9 mg per day). In contrast, during our study period of 2000 through 2002, within the adult civil inpatient facilities that are operated by the state of New York, 83 percent of the patients had a diagnosis of either schizophrenia or schizoaffective disorder, and the mean daily dosage of quetiapine ranged from 409 mg (first quarter of 2000, N=481) to 570 mg (fourth quarter of 2002, N=992). Similar to Buse and colleagues (12), Gianfrancesco and colleagues (14) found that patients who were given quetiapine did not have an increased risk of receiving treatment for diabetes. Although the authors stated that antipsychotic dosages did not affect their findings, they did not report on the actual dosages used. This lack of information on dosing is a particular issue for quetiapine, because it is not uncommon to see quetiapine being used as an adjunctive agent at lower doses for sedation or sleep than what is needed for a full antipsychotic effect. Moreover, in the study by Gianfrancesco and colleagues (14) only 10 percent of the patients who received quetiapine had a diagnosis of schizophrenia.

Our findings for clozapine generally confirm those of earlier published pharmacoepidemiologic studies. Reported relative risk or ORs for persons who took clozapine have been as high as 2.5 (CI=1.2 to 5.4), compared with patients who took first-generation antipsychotics (5), and 7.44 (CI=1.60 to 34.75), compared with persons who did not have any exposure to antipsychotics (10). However, one study found no difference in risk of developing diabetes mellitus among patients who were taking clozapine compared with patients who were not taking clozapine (7). In that study an almost exclusively older population was examined—the mean age of patients in the case group was 63.6 years and the mean age of patients in the control group was 61.9 years (7).

Although elevated, the OR for olanzapine in our study was not statistically significant. Our results were consistent with those of Buse and colleagues (12)—who found an elevated risk ratio of 3 for persons who took olanzapine (CI 2.6 to 3.5), compared with persons who did not take antipsychotics, but no difference when compared with persons who took haloperidol. However, our results differ from those of six published studies (8,10,11,13–15), which found relative risk or ORs for olanzapine as high as 4.2 (CI=1.5 to 12.2), compared with exposure to first-generation antipsychotics (8), and 5.8 (CI=2 to 16.7), compared with no exposure to antipsychotics (8).

Antipsychotics may put men at greater risk of developing diabetes mellitus than women, and the effect of antipsychotics on developing diabetes may be harder to detect among women because women have a higher base rate of diabetes.

Our finding that olanzapine was not associated with an increased risk of diabetes may in part be because of the period that we examined. Our study was the first to examine a period—2000 through 2002—in which information was readily available about the suspicion that second-generation antipsychotics—olanzapine and clozapine in particular, because they were the subject of some of the earliest reports—may be associated with diabetes. Thus clinicians may have deliberately avoided prescribing olanzapine to patients who would have otherwise been at higher risk of developing diabetes. We did observe that the monitoring rates for plasma glucose differed among the controls and that patients who received clozapine, olanzapine, or more than one second-generation antipsychotic had significantly higher rates of glucose testing than patients who received only first-generation antipsychotics. If clinicians altered their prescribing behavior, it may have attenuated the signal for clozapine and olanzapine and amplified the signal for the antipsychotics chosen instead, such as quetiapine or risperidone. However, although we observed an elevated OR for quetiapine that was statistically significant, we did not see this result for risperidone.

Gender may act as a moderator variable. Adjusted ORs were higher among men than women. This observed gender difference may have been due solely to chance, because the CIs for the men and the women overlap substantially for each drug. However, the differences could also be explained in other ways: antipsychotics may put men at greater risk of developing diabetes mellitus than women, and the effect of antipsychotics on developing diabetes may be harder to detect among women because women have a higher base rate of diabetes (35). In the population we studied, the prevalence of antidiabetic medication use among patients who received antipsychotics in 2000 through 2002 was 9.5 percent for men and 14.7 percent for women. This problem of detection of antipsychotic effect on diabetes mellitus has also been seen among older patients in other studies (5–7).

The study design was naturalistic. Treatment assignment was not randomized. Factors associated with the choice of medication and the risk of diabetes mellitus may have confounded our results. Our methodology shares this limitation with other large-scale pharmacoepidemiologic studies that have been previously published (18). Double-blind randomized clini-

cal trials avoid this limitation and may ultimately be needed to answer the question of how strong the association is between exposure to a second-generation antipsychotic and treatment-emergent diabetes mellitus.

Identification of cases was limited by using prescription of an antidiabetic agent as a proxy for the diagnosis of diabetes mellitus, with the rationale that the use of a pharmacologic intervention is indicative of severe disease that is readily identifiable. The Integrated Research Database does not consistently record medical diagnoses, nor does it contain information on care that is received outside the New York State psychiatric hospital system. However, hospital stays within the system can be very long. It is unknown what the prevalence of untreated or undiagnosed diabetes mellitus is in this population. Our procedure for case finding also missed patients who had a diagnosis of diabetes mellitus but who controlled their disorder by diet alone, which could have led to the inclusion of such patients as controls. As a consequence of these factors, we are probably underestimating the true number of patients with problems of glycemic dyscontrol. In addition, patients with elevated plasma glucose may have had their antipsychotic medications switched or stopped, which may have improved their hyperglycemic state. Not being able to include these patients as cases could also have resulted in an underestimation of risk.

Although we attempted to include only new cases by examining records in the Integrated Research Database back to January 1, 1994, and excluding patients who had received a prescription of an antidiabetic medication before January 1, 2000, it is possible that some patients received antidiabetic medication before January 1, 1994, or at any time in other health-care systems.

Another limitation of our study was the lack of information on weight and body mass index. It is known that obesity is a risk factor in the development of diabetes mellitus and that second-generation antipsychotics have a greater propensity for causing weight gain than first-generation antipsychotics (36). Other risk factors that were not controlled for include elevated insulin levels, family history of diabetes mellitus, lack of engagement in physical activity, and hepatitis C infection—all of which have been strongly associated with diabetes mellitus (37).

Although the risk of treatment-emergent diabetes with second-generation antipsychotics appears greater than with first-generation antipsychotics, the study design does not permit us to quantify differences between the second-generation antipsychotics in terms of risk for emergent diabetes. Generalizability of our results is limited to similar chronically mentally ill inpatient populations. Outpatient psychiatric populations may differ significantly on parameters such as diet, level of activity, and disease severity.

Conclusions

This study lends support to the hypothesis that an association exists between second-generation antipsychotic use and the development of diabetes mellitus. This association was demonstrated to be statistically significant for clozapine, quetiapine, and multiple second-generation antipsychotics. ORs were also elevated for olanzapine and risperidone, although the results were not statistically significant. Long-term prospective epidemiologic cohort studies, as well as randomized clinical trials, will be needed to ascertain whether or not there is a true cause-and-effect relationship between exposure to second-generation antipsychotics and diabetes mellitus. Future pharmacoepidemiologic studies need to be particularly mindful of the possibility of treatment assignment bias—that is, when physicians avoid prescribing agents that are believed to cause an increase in risk of diabetes among patients who are at a higher perceived baseline risk.

Actual incidence rates for emergent diabetes mellitus in this patient population appear small. However, given the long duration of illness, the prevalence of diabetes in this group of patients was not inconsiderable. At present, a reasonable clinical strategy would be to manage risk of onset of diabetes mellitus with careful medical monitoring, including baseline and regular monitoring of plasma glucose levels for all patients who are given antipsychotics, especially when risk factors such as weight gain, lack of physical activity, family history of diabetes, or advancing age are present. ♦

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ORIGINAL REPORT

Atypical antipsychotic drugs and diabetes mellitus in a large outpatient population: a retrospective cohort study†

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SUMMARY

Purpose Previous research has suggested an association between use of atypical antipsychotics and onset of diabetes mellitus. We sought to compare the incidence of new onset diabetes among patients receiving atypical antipsychotics, traditional antipsychotics or antidepressants.

Methods Retrospective cohort study of outpatients with claims for atypical antipsychotics ($n = 10\,265$) compared to controls with claims for traditional antipsychotics ($n = 4607$), antidepressants ($n = 60\,856$) or antibiotics ($n = 59\,878$) in the administrative claims database of a large pharmaceutical benefit manager between June 2000 and May 2002. Main outcome measures were adjusted and unadjusted incidence rates of diabetes (new cases per 1000 per year) in a 12-month period, as measured using new prescriptions for antidiabetic drugs after a 6-month lead-in period.

Results Annual unadjusted incidence rates of diabetes (new cases per 1000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics. In multivariable analyses, age, male sex and Chronic Disease Score were associated with greater odds of diabetes onset. There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups. Multivariable comparisons among specific agents showed increased odds of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone), but these comparisons did not reach statistical significance.

Conclusions In a large prescription claims database, outpatients taking atypical antipsychotics did not have higher rates of diabetes onset, compared to subjects taking traditional antipsychotics or antidepressants. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotic agents; cohort studies; diabetes mellitus; pharmaceutical services, insurance; pharmacoepidemiology; prescriptions, drug

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Use of atypical antipsychotic drugs has increased dramatically in the short time since the drugs were introduced. Although approved for the management of manifestations of psychotic illness, these drugs are prescribed for a variety of conditions.[1] Annual sales of atypical antipsychotics in the United States have reached approximately $3 billion.[2]

The primary advantage of atypical antipsychotics over traditional antipsychotics is their lower risk of extrapyramidal side effects.[3] However, atypical antipsychotics have been shown to stimulate appetite and induce weight gain.[4,5] A recent review of the Food and Drug Administration's MedWatch database found 384 reports of hyperglycemia among patients who were treated with clozapine.[6] Numerous case reports and some clinical and claims-based studies[7–26] suggest that atypical antipsychotics may increase the occurrence of diabetes mellitus and diabetic ketoacidosis, possibly through their tendency to induce weight gain. The proposed association has been reported in adolescents as well.[27] The exact mechanism for the association is unclear, and the putative latent period has varied from weeks to months.

Given the extensive and increasing use of atypical antipsychotics—and the seriousness of diabetes as a potential complication—further investigation of the presence and extent of an association is of considerable public health interest. We sought to compare the incidence of diabetes among patients receiving atypical antipsychotics, traditional antipsychotics, antidepressants (as a comparison group of patients receiving another type of psychotropic drug) or antibiotics (as a population comparison group).

METHODS

We accessed the outpatient prescription claims database of AdvancePCS (Irving, TX, and Scottsdale, AR), the largest pharmaceutical benefit manager in the United States. Health insurance carriers contract with AdvancePCS to manage their formularies and adjudicate their prescription drug claims. Advance PCS maintains a computerized pharmacy system that records data on each prescription drug dispensed to its beneficiaries, whether through a retail or mail-order pharmacy. More than 98% of the claims in the database are submitted and processed electronically at the time the prescriptions are filled (AW [awright@apclinical.com], e-mail, August 27, 2001).

We limited our analysis to subjects whose health plans or insurance carriers required AdvancePCS to track claims at the individual subject level. Subjects whose plans used the same identifier for multiple family members were excluded. The analysis dataset included all prescription drug claims adjudicated for 170 030 subjects who were continuously enrolled from June 2000 through May 2002 and who filed at least one prescription drug claim during that period. All claims relating to the same individual were linked using a unique beneficiary identifier that was encrypted to ensure confidentiality for this study. A total of 1171 health insurance carriers were represented in the data, covering all 50 states, as well as US territories. The institutional review board of Duke University Medical Center approved this study.

Study design

The study employed a retrospective cohort design. We used claims for prescriptions filled as a proxy for actual use of the exposure medications and of hypoglycemic agents. We considered the first 6 months of the study period to be the lead-in period and the ensuing 18 months to be the follow-up period. We excluded subjects with claims for insulin or oral hypoglycemic drugs during the lead-in period, as well as subjects for whom the claim for an antidiabetic drug predated the claim for an exposure drug. The main analysis included subjects for whom the first prescription for an exposure drug occurred after the lead-in period. Subjects whose first claim for an exposure drug occurred during the lead-in period were considered separately, but were excluded from the main analysis.

Exposure categories and covariates

The primary exposure group consisted of subjects who filled prescriptions for any of the five atypical antipsychotic agents (i.e. clozapine, olanzapine, quetiapine, risperidone, ziprasidone or a combination of two or more of these drugs) at any time during the follow-up period. These drugs were also considered individually. Inclusion in the primary exposure group required that claims for other psychotropic drugs were not filed during the study period.

The primary control group consisted of subjects who filled prescriptions for conventional antipsychotic agents (i.e. acetophenazine, chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, triflupromazine) during the follow-up period. Haloperidol and thioridazine were also considered individually. Inclusion in the control group required

that no prescriptions for other psychotropic drugs were filled during the study period.

A secondary comparison group consisted of a 10% simple random sample of subjects who filled prescriptions for antidepressants (i.e. amitriptyline, amoxapine, bupropion, chlordiazepoxide and amitriptyline combination, citalopram, clomipramine, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, perphenazine and amitriptyline combination, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine) at any time during the follow-up period. This group included only individuals who had not received any antipsychotic agents during the study period.

Finally, a 'general population' comparison group of a simple random sample of subjects who filled a prescription for an antibiotic but not for any psychotropic drug during the study period was followed for the same time period. A prescription for an antibiotic was not considered an 'exposure' *per se*, but was used as a criterion for inclusion in the control group.

We extracted several additional variables from the database, including age, sex, time of first and subsequent prescription claims, dosage and duration of the drugs in question.

We calculated a Chronic Disease Score according to the method outlined by von Korff[28] and later refined by Clark.[29] This pharmacy-based risk-adjustment score increases with the number of chronic diseases and the complexity of the treatment regimen.[30] The medications included in the scoring algorithm target diseases, not symptoms. Consequently, medications frequently used in the management of symptomatic conditions (e.g. analgesics, anti-inflammatory drugs, sedatives) are not included. None of the medications used to define exposure groups for this study are included in the Chronic Disease Score algorithm. For this analysis, the score was calculated on the basis of prescription claims filed during the lead-in period.

Outcome measures

The primary outcome was the prescription filled for any antidiabetic drug. We extracted the date of first and subsequent prescriptions for insulin or oral hypoglycemic drugs (i.e. tolbutamide, acarbose, tolazamide, repaglinide, glyburide, chlorpropamide, glipizide, metformin, acetohexamide, glimepiride, rosiglitazone). The time of first filled prescription for any of these medications served as a proxy for the time of onset of diabetes.

Data analysis

We compared the occurrence of diabetes (i.e. first prescription filled for insulin or an oral hypoglycemic drug) in the main exposure group to that in each of the three control groups. The primary comparison was between the atypical antipsychotic group and the traditional antipsychotic group. In separate analyses, individual atypical antipsychotics were compared to each other and to the traditional antipsychotic group.

The proportion of subjects in each exposure group who developed diabetes within 3 months, 6 months, 9 months and 1 year were compared to each other, and the annual incidence rate of diabetes was calculated for each exposure group and for individual atypical antipsychotics.

Multivariable analyses were performed using a logistic regression model of diabetes onset. We examined the effect of type, dosage and duration of antipsychotic drugs, adjusting for age, sex and Chronic Disease Score.

The primary ('pure') multivariable models included only subjects who belonged exclusively to one of the four exposure groups. Secondary multivariable models also included subjects with concurrent or sequential exposure to agents from different psychotropic drug classes. In these secondary models, the variable for exposure drug indicates exposure to a specific drug, but not to the exclusion of other exposure drugs.

RESULTS

Nearly 7 million subjects were enrolled for at least 12 months during the study period. Our analytical subset included 10 265 subjects who filled a new prescription for an atypical antipsychotic, 4607 subjects who filled a new prescription for a traditional antipsychotic and 60 586 subjects who filled a new prescription for an antidepressant. In addition, our analysis included 59 878 'population controls' who received antibiotics but no psychotropic drugs during the study period. In all, 170 030 subjects who filled new prescriptions for drugs in one or more of the four exposure categories during the study period were included in the analysis (Table 1).

Male subjects were more prevalent in the atypical antipsychotic and traditional antipsychotic groups, whereas female subjects were more prevalent in the antidepressant and antibiotic groups. Claims for atypical antipsychotics were filled by subjects in all age groups, with a relatively large number of prescriptions in the youngest age groups. Risperidone claims were most common in the youngest and oldest age groups. Traditional antipsychotics, especially

Table 1. Subject characteristics*

Characteristic	Cohort				
	Overall study population ($n = 170\,030$)	Atypical antipsychotics ($n = 10\,265$)†	Traditional antipsychotics ($n = 4607$)†	Antidepressants ($n = 60\,586$)†	Antibiotics ($n = 59\,878$)†
Male	64 796 (38.1)	5689 (55.4)	2396 (52.0)	18 217 (30.1)	24 507 (40.9)
Age, mean (SD), year	41.9 (21.5)	42.3 (27.5)	57.0 (21.2)	43.6 (16.5)	37.8 (23.5)
Age group					
0–19 year(s)	31 819 (18.7)	3148 (30.7)	279 (6.1)	4561 (7.5)	18 059 (30.1)
20–29 years	15 172 (8.9)	891 (8.7)	197 (4.3)	7091 (11.7)	3799 (6.3)
30–39 years	27 465 (16.2)	1162 (11.3)	456 (9.9)	12 949 (21.3)	7001 (11.7)
40–49 years	34 812 (20.5)	1229 (12.0)	750 (16.2)	15 750 (26.0)	10 092 (16.9)
50–59 years	26 596 (15.6)	780 (7.6)	803 (17.4)	10 895 (18.0)	9319 (15.6)
60–69 years	14 653 (8.6)	602 (5.9)	651 (14.1)	4820 (8.0)	5975 (10.0)
70–79 years	11 223 (6.6)	974 (9.5)	677 (14.7)	2896 (4.8)	3990 (6.7)
≥80 years	8290 (4.9)	1479 (14.4)	794 (17.2)	1624 (2.7)	1643 (2.7)
Chronic Disease Score					
Mean (SD)	3.1 (3.3)	3.0 (3.1)	3.5 (3.3)	2.7 (3.0)	2.8 (3.1)
0	57 778 (34.0)	3598 (35.1)	1240 (27.0)	22 898 (37.8)	22 065 (36.9)
1	12 284 (7.2)	511 (5.0)	320 (7.0)	5556 (9.2)	3955 (6.6)
2	11 244 (6.6)	590 (5.8)	218 (4.7)	4038 (6.7)	4644 (7.8)
3	29 641 (17.4)	2233 (21.8)	950 (2.6)	9703 (16.0)	10 027 (16.8)
4	12 364 (7.3)	720 (7.0)	391 (8.5)	4455 (7.4)	3970 (6.6)
≥5	46 719 (27.5)	2613 (25.5)	1488 (32.3)	13 936 (23.0)	15 217 (25.4)
Drug exposure groups‡					
Atypical antipsychotics	35 717 (21.0)				
Traditional antipsychotics	10 607 (6.2)				
Antidepressants	92 659 (54.5)				
Antibiotics	76 908 (47.8)				

*Values are expressed as number (percentage) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class.
‡Subjects may be included in more than one drug exposure group.

haloperidol, were more commonly used in older age groups. The mean ages of the subjects in each group were 42.3 years for atypical antipsychotics, 57.0 years for traditional antipsychotics, 43.6 years for antidepressants and 37.8 years for antibiotics.

Subjects who received quetiapine or multiple atypical antipsychotics had higher Chronic Disease Scores (i.e. poorer health) than those receiving other atypical antipsychotics, as did subjects who received traditional antipsychotics. Subjects who received antidepressants had slightly lower Chronic Disease Scores than those in the main exposure groups, while subjects in the antibiotic comparison group had the lowest scores.

Table 2 shows the occurrence of incident diabetes mellitus as measured by a first prescription for insulin or an oral hypoglycemic drug after a prescription for one of the exposure drugs. The overall numbers of new cases were low in all groups. The unadjusted rate among subjects in the traditional antipsychotic group (11.3 per 1000 per year) was somewhat higher than the rate in the atypical antipsychotic group (7.5 per 1000 per year), while the overall unadjusted rate was about the same in the antidepressant group (7.8 per 1000 per year) and lower in the antibiotic group (5.1 per 1000 per year).

With regard to individual atypical antipsychotics, the overall annual incidence rates of diabetes among subjects who received clozapine, olanzapine or ziprasidone were higher than among subjects who received quetiapine or risperidone. For traditional antipsychotics, incidence rates for subjects who received haloperidol and thioridazine were similar and somewhat higher than those of most atypical antipsychotics. No clear pattern emerged when we examined the duration from prescription for any exposure drug to the occurrence of diabetes.

Table 3 presents univariate and multivariable relationships between the onset of diabetes and the exposure groups. These models included only subjects who received prescriptions in a single drug class of interest during the study period. The univariate odds ratios were consistent with the rates presented in Table 2, with traditional antipsychotics, antidepressants, age and male sex significantly associated with onset of diabetes, and antibiotics inversely so. In the

Table 2. Occurrence of new prescriptions for insulin or oral hypoglycemic drugs by drug exposure group

Drug	Total exposed	Diabetes onset*				Unadjusted annual incidence†
		1–3 months	4–6 months	7–9 months	10–12 months	
Atypical antipsychotics	10 265	17 (0.2)	24 (0.2)	22 (0.2)	14 (0.2)	7.5
Clozapine	127	0	1 (0.8)	0	0	7.9
Olanzapine	3190	10 (0.3)	5 (0.2)	9 (0.3)	6 (0.2)	9.4
Quetiapine	1111	1 (0.1)	4 (0.4)	0	1 (0.1)	5.4
Risperidone	4859	4 (0.1)	10 (0.2)	12 (0.3)	3 (0.1)	6.0
Ziprasidone	69	1 (1.5)	0	0	0	14.5
Multiple drugs	909	1 (0.1)	4 (0.4)	1 (0.1)	4 (0.4)	11.0
Traditional antipsychotics	4607	10 (0.2)	16 (0.3)	15 (0.3)	11 (0.2)	11.3
Haloperidol	1766	3 (0.2)	6 (0.3)	5 (0.3)	4 (0.2)	10.2
Thioridazine	567	2 (0.4)	4 (0.7)	0	0	10.6
Other	2274	5 (0.2)	6 (0.3)	10 (0.4)	7 (0.3)	12.5
Antidepressants	60 586	114 (0.2)	121 (0.2)	147 (0.2)	91 (0.2)	7.8
Antibiotics	59 878					5.1

*Values represent the actual number of subjects who received a first diabetes-related prescription in the 3-month period. Values in parentheses represent percentages based on all subjects followed throughout the 3-month period.
†New cases per 1000 per year.

first multivariable model, in which users of any traditional antipsychotic constituted the reference group, atypical antipsychotics were associated with a lower risk of diabetes than were traditional antipsychotics. However, the effect was not statistically significant. Subjects in the antibiotic comparison group had the lowest risk estimate for diabetes, and the difference between the antibiotic and traditional antipsychotic groups was statistically significant. Age, male sex and Chronic Disease Score remained statistically significant predictors of diabetes.

The second multivariable model included only users of antipsychotic agents. The most frequently prescribed atypical antipsychotic, risperidone, was used as the reference category. Subjects who received clozapine, olanzapine or ziprasidone had an increased but not statistically significant risk of diabetes. Age and Chronic Disease Score had the same significant effects

Table 3. Characteristics associated with diabetes in the 'pure' exposure cohort*

	Model 1 ($n = 135\,336$)†		Model 2 ($n = 14\,872$)‡	
	Univariate	Multivariable	Univariate	Multivariable
Atypical antipsychotics				
Clozapine			0.91 (0.13–6.53)	1.13 (0.15–8.37)
Olanzapine			1.11 (0.74–1.67)	1.34 (0.83–2.15)
Quetiapine			0.60 (0.27–1.37)	0.66 (0.28–1.57)
Risperidone			0.60 (0.39–0.90)	1.00
Ziprasidone			1.69 (0.23–12.24)	2.64 (0.35–19.90)
Any	1.13 (0.89–1.43)	0.86 (0.60–1.23)		
Traditional antipsychotics				
Haloperidol			1.35 (0.85–2.15)	1.00 (0.57–1.74)
Thioridazine			1.46 (0.65–3.25)	1.27 (0.54–2.98)
Other			1.55 (1.06–2.25)	1.43 (0.89–2.31)
Any	1.73 (1.30–2.29)	1.00		
Antidepressants	1.34 (1.17–1.53)	1.08 (0.81–1.45)		
Antibiotics	0.69 (0.61–0.79)	0.68 (0.50–0.92)		
Age (per 10 years)	1.40 (1.36–1.46)	1.21 (1.17–1.26)	1.25 (1.16–1.34)	1.16 (1.06–1.26)
Male	1.13 (0.99–1.29)	1.26 (1.10–1.45)	0.68 (0.48–0.97)	0.89 (0.62–1.28)
Chronic Disease Score	1.27 (1.25–1.29)	1.23 (1.21–1.25)	1.23 (1.18–1.28)	1.19 (1.14–1.25)
Likelihood ratio		993.35		98.31
c-statistic		0.78		0.75

*Values are expressed as odds ratio (95% confidence interval) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class during the study period.
‡Subjects filled prescriptions for only one psychotropic drug during the study period.

Table 4. Characteristics associated with diabetes in the overall study population*

	Univariate ($n = 170\,030$)	Multivariable ($n = 170\,030$)
Drug†		
Atypical antipsychotic	2.49 (2.32–2.67)	1.70 (1.58–1.83)
Traditional antipsychotic	3.14 (2.86–3.45)	2.08 (1.88–2.30)
Antidepressant	2.28 (2.11–2.46)	2.12 (1.96–2.30)
Age	1.46 (1.44–1.49)	1.31 (1.22–1.41)
Male	1.15 (1.07–1.23)	1.24 (1.21–1.26)
Chronic Disease Score	1.34 (1.32–1.35)	1.28 (1.26–1.29)
Likelihood ratio		6033.92
c-statistic		0.85

*Values are expressed as odds ratio (95% confidence interval) unless otherwise indicated.
†Indicator variable indicating prescription of drug in this class (relative to no prescription of drug in this class).

as in the first model. An exploratory analysis (suggested by earlier studies[24,31]) that grouped clozapine and olanzapine together but maintained the same exposure and confounding variables used in the second model, suggested an increased but not statistically significant risk of diabetes for the combined group (odds ratio, 1.32; 95% confidence interval, 0.83–2.12).

We also performed analyses including subjects with a prevalent psychiatric disorder (i.e. subjects who received psychotropic drugs during the lead-in period), and the results were fully congruent with the models in Table 3 (data not shown). We constructed more complex models that included dosage and duration of exposure drugs, but these models showed no significant difference between the two antipsychotic groups or among individual atypical antipsychotics (data not shown).

Table 4 presents the multivariable models pertaining to the larger 'mixed' groups, wherein individuals could have been exposed to agents from one or more exposure groups. Where the 'reference category' consisted of subjects without exposure to psychotropic drugs, exposure to any of the three classes of psychotropic drugs was significantly associated with development of diabetes, as were age, male sex and Chronic Disease Score.

DISCUSSION

Using prescription claims data from a large national database, we found that the rate of incident diabetes was not significantly higher for subjects taking atypical antipsychotics as compared to subjects taking traditional antipsychotics. There was a trend toward higher incidence of diabetes in the combined olanzapine/clozapine group, when compared to rates for the other antipsychotics. Comparisons among specific drugs must be performed with caution, however, given the relatively limited number of outcome events in each group. Among users of atypical antipsychotics, rates of diabetes were not significantly higher than among users of antidepressants, but they were significantly higher than in our population reference group.

The analyses of the overall population, allowing exposure to more than one psychotropic drug, show that exposure to a drug from any one of the three classes considered is significantly related to the development of diabetes mellitus. In fact, the antidepressant group has the highest risk. It is difficult to disentangle effects among the subjects who received more than one drug, partly because this may be a special population of patients, and partly because there may be variable interactions among the drugs. We, therefore, consider the findings based on the 'pure' groups (Table 3) as stronger than those based on the overall group (Table 4).

Our findings complement results from several case reports and an increasing number of clinical and claims-based studies.[7–26,31,32] The mechanism for the proposed association between use of antipsychotics and diabetes remains unclear, but it is possible that antipsychotics may increase weight through their effect on insulin secretion and resistance.[23] In a clinical study of antipsychotics,[15] 14% of patients—mostly those receiving atypical antipsychotics—developed abnormally high glucose levels. Newcomer *et al.*[34] also found increased elevation of plasma glucose after glucose load in patients receiving olanzapine, but not among patients receiving risperidone or traditional antipsychotics. Weight gain and obesity may, therefore, link the use of these drugs to the development of diabetes. Our findings of little or no difference between the traditional and the atypical antipsychotics may point toward a causal pathway from schizophrenia *per se* to diabetes rather than a pathway involving the antipsychotic drugs. A possible association between schizophrenia and increased risk of diabetes has been documented previously.[31]

In previous claims-based studies, the presence and strength of the association between antipsychotics and diabetes have varied. A study in Quebec found that olanzapine was associated with an increased risk of diabetes compared to risperidone, especially during the first 3 months of treatment.[32] Gianfrancesco *et al.*[24] found that olanzapine, clozapine and traditional antipsychotics were associated with increased rates of diabetes, but that risperidone was not. Koro *et al.*[25] found that both olanzapine and risperidone were associated with increased rates of diabetes, but only the association with olanzapine was statistically

significant. In contrast, Wang *et al.*[33] found that exposure to clozapine was not related to development of diabetes, while other antipsychotics were. Differences in results among these studies may be due to differences in study populations, differences in outcome ascertainments and different lengths of follow-up.

A previous study based on prescription data from the same database as our study, but from an earlier time period,[26] concluded that users of both atypical and traditional antipsychotics had higher rates of prescription of oral hypoglycemic drugs and insulin than a control group, but the authors did not find a difference between the two groups taking antipsychotic agents. That study, based on a comparison with a reference group of subjects using a variety of medications, did not consider subjects on antidepressants as a separate comparison group, and the analyses were not adjusted for the presence of other chronic diseases. In spite of these differences, our results are consistent. Since the Chronic Disease Score is related to diabetes, the consistency between the studies is possibly due to the fact that the Chronic Disease Score is poorly related to the use of antipsychotics.

There are several strengths to our analyses. The primary analyses included only new users (i.e. an inception cohort). Thus, we eliminated the potential for bias caused by depletion of susceptibles, which can affect studies that include both new and continuing users. Other strengths include the large size and national representativeness of our dataset, the inclusion of only incident prescriptions for the exposure groups, the 6-month lead-in period to minimize confounding with prevalent diabetes, the ability to control for demographic factors and Chronic Disease Score, and comparison groups that included not only traditional antipsychotics, but also antidepressants and antibiotics as population controls.

Our study also has some limitations. Although prescription claims databases are considered to be reliable and valid for studying drug use,[35,36] they record only claims filed, not whether the drugs were actually taken. In addition, subjects may have had alternative sources of prescription drug coverage; such out-of-plan drug use would not be included in the analysis. Furthermore, the database likely underrepresents the elderly and persons with lower socioeconomic status, groups that are less likely to have private prescription drug insurance.

As with other claims-based studies, information regarding weight and other clinical variables were not directly available in our dataset. Thus, we were unable to explore potential interrelationships among underlying disease states, use of antipsychotics, weight gain, obesity and diabetes. However, we did control for age, sex and Chronic Disease Score. In the same way that clinical data would have been better for accurately identifying diabetes mellitus, clinical data would also have been better than the Chronic Disease Score for determining comorbidity.[37]

We also used claims filed for antidiabetic agents as an indicator of diabetes. Prescription claims data are well suited for studies in which diabetes is the outcome of interest, because prescriptions for insulin and oral hypoglycemic drugs are highly specific to diabetes. However, some subjects using antipsychotics may have developed impaired glucose tolerance and milder or transient forms of diabetes. These symptoms may have been reversed with discontinuation of the drug or successfully treated by dietary means. Therefore, our estimates of the occurrence of diabetes are likely underestimates, including only more severe forms of diabetes. Moreover, although earlier studies have indicated that the latent period from the start of atypical antipsychotic use until the development of diabetes may be only weeks or months, it is possible that cumulative exposures over a longer period than the follow-up period in our study could lead to higher rates of diabetes. In general, however, our annual diabetes incidence rates are comparable with national rates based on diagnosed diabetes. Estimates from the Centers for Disease Control and Prevention's diabetes surveillance system indicate an annual age-standardized incidence rate ranging from 2.5 to 3.5 per 1000 per year for the period 1990 through 1996.[38]

Our study demonstrates the potential for using pharmaceutical benefit manager data for postmarketing surveillance of approved and marketed drugs and for examining the 'near real-time' use of prescription drugs. In general, the availability of a large number of nationally representative, detailed, prescription-level data presents opportunities to examine how frequently individual drugs and drug combinations of interest are dispensed. Large pharmaceutical benefit manager datasets may also be useful for exploring the extent of associations observed in case reports.

In summary, we did not find a higher rate of antidiabetic drug prescriptions among subjects using atypical antipsychotics compared to subjects using traditional antipsychotics, although both groups had higher rates than the general population. Concern about a potential association remains, and continued vigilance combined with further clinical and epidemiological studies is required to further elucidate whether this effect is due to underlying illness, weight gain or the drugs themselves.

KEY POINTS

- We did not observe a higher rate of antidiabetic drug prescriptions among subjects using atypical antipsychotics, as compared to subjects using traditional antipsychotics.
- Subjects using antipsychotic drugs—either traditional or atypical—had higher rates of antidiabetic drug use than did subjects in the general population.
- Concern about a potential association between atypical antipsychotics and diabetes remains; therefore, continued vigilance and further research are required.
- Our study demonstrates the potential for using pharmaceutical benefit manager data for post-marketing surveillance of approved and marketed drugs and for examining the real-time use of prescription drugs.
- Large pharmaceutical benefit manager datasets may also be useful for exploring the extent of associations observed in case reports.

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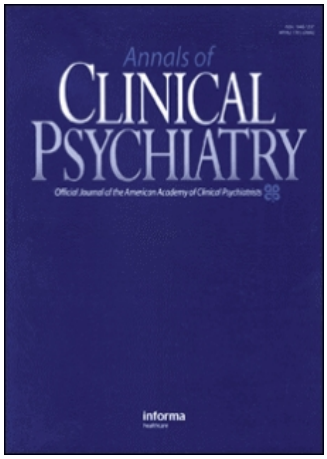

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A Regional Comparison of Developing Diabetes among VA Patients Exposed to Typical and Atypical Antipsychotics Relative to Corticosteroids and Proton Pump Inhibitors

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A Regional Comparison of Developing Diabetes among VA Patients Exposed to Typical and Atypical Antipsychotics Relative to Corticosteroids and Proton Pump Inhibitors

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Background. *Metabolic changes, including weight gain and onset of diabetes, have been associated with both systemic corticosteroid use and atypical antipsychotic drugs. The purpose of this study was to quantify and compare the risk of new-onset diabetes mellitus in a Veterans Affairs population receiving antipsychotics and corticosteroids, using persons taking proton pump inhibitors as a control group.*

Methods. *This study included data from subjects treated within Veterans Integrated Service Network 23 who had received an outpatient prescription in fiscal years (FY) 1999 or 2000 for a corticosteroid (CS), a proton pump inhibitor (PPI), a typical antipsychotic, or an atypical antipsychotic. Patients receiving prescriptions in more than one class were not excluded. Subjects were excluded if they had a documented diagnosis of diabetes either in the previous FY year (1998) or prior to their index prescription date.*

Results. *Thirteen percent of the population had a new diagnosis for diabetes during the two-year study. Cox-regression analysis using time dependent covariates determined a significantly higher risk of developing diabetes (RR = 1.21) in users of CS relative to PPIs. Demographic variables including age, race, gender, marital status, and VA financial classification as well as a marker for schizophrenia, were also included in the model. Comparison of both typical and atypical antipsychotics to PPIs found an increased but nonsignificant risk of developing diabetes (RR = 1.18 and RR = 1.19 respectively).*

Conclusions. *The diabetogenic risk associated with atypical antipsychotics was found to be less than that of corticosteroids when compared to controls. Periodic monitoring of blood glucose should be considered with chronic use of an agent from either class.*

Keywords Diabetes, Corticosteroid, Antipsychotic, Proton Pump Inhibitors

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INTRODUCTION

Atypical antipsychotics (AAP) agents are widely utilized in the treatment of schizophrenia as they have been shown to be

clinically effective while carrying a much lower risk of EPS than typical antipsychotic (TAP) agents (1). However, a growing body of evidence has implicated the role of treatment with certain AAP agents with an increased risk of DMII (23–67). Clinical trials and post-marketing surveillance of the use of AAP agents have elucidated substantial weight increases, particularly with clozapine and olanzapine (8). Weight gain secondary to AAP treatment is likely a mode by which metabolic changes, such as diabetes, hyperlipidemia and metabolic syndrome may occur. Continued study has focused on determining how treatment with AAP may impact pancreatic β-cell functioning, release of insulin, peripheral insulin sensitivity, as well as central hypothalamic regulation of glucose (9,10).

Atypical antipsychotics are not alone in their ability to precipitate diabetes. In fact, corticosteroids (CS), which are frequently used for maintenance or remission of a variety of respiratory, endocrinological, rheumatic, neoplastic, and autoimmune diseases, have long been associated with glucose dysregulation and development of DMII (11–14). Incidence rates of diabetes in patients on corticosteroid therapy have been reported to range from 1% to 46% (11). As with the antipsychotic agents, the exact pathophysiological mechanism by which corticosteroid therapy increases blood glucose levels is not certain. Similar to AAP, weight gain often accompanies extended corticosteroid therapy, and corticosteroids have been shown to promote gluconeogenesis and insulin resistance, and raise insulin levels (15–17).

Several studies have looked at the development of diabetes in patients exposed to AAPs relative to typical antipsychotics (TAPs); however clinical interpretation of these studies is often difficult. DMII has been shown to be more prevalent in patients with schizophrenia than the general population (18). Also, AP use is often coupled with weight gain, which makes it hard to separate possible metabolic liabilities of AP agents due to direct effects on cellular functioning. Further, only one study to date has examined the rate of diabetes associated with AAPs relative to CS and a control group; however this study was limited to an elderly Canadian population in a long-term care setting (19). The purpose of this study was to quantify and compare the risk of new-onset diabetes mellitus in a Veterans Affairs (VA) population receiving antipsychotics and corticosteroids, using persons taking proton pump inhibitors (PPIs) as a control group.

METHODS

Data Sources

The study utilized computerized patient information from three VA databases: the Pharmacy Benefits Management (PBM) database, maintained by the VA information Resource Center at the Hines VA Medical Center in Oak Brook, IL, and the Patient Treatment File (PTF) and the Outpatient Care File (OPC) databases maintained by the VA Automation Center in Austin, TX. The PBM contains patient-level information on all outpatient prescriptions filled in an outpatient VA pharmacy (20). The PTF and OPC are a set of linked databases that provide patient-level information on all outpatient and inpatient encounters from VA facilities and have been used extensively in health services research (21,22).

Data Elements

Data elements that were extracted from the PTF and OPC included: age, gender, race, marital status, social security number (to link PTF/OPC and PBM data); primary service facility; VA financial class; dates of admission and discharge for inpatient hospitalizations; dates of all outpatient visits; and all primary and secondary diagnoses captured on inpatient and outpatient encounters, as based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) taxonomy. VA financial class was categorized into three mutually exclusive groups: patients with chronic medical conditions attributable to military service (i.e., service-connected conditions) or patients who were financially indigent (based on VA income thresholds), and patients who were neither service-connected condition nor indigent. Data elements specifically captured from the PBM included the names, classes, and dates of all medications dispensed on an outpatient basis, from October 1, 1998 through September 30, 2000. VA medication names and classification are based upon nomenclature developed by the United States Pharmacopoeia.

Patients

The study population was drawn from a pool of 57,628 patients who received an outpatient prescription in fiscal years (FY) 1999 or 2000 from the VAMC. Of these patients, 17,887 received at least one prescription for either a CS, a PPI, a TAP, or an AAP; patients receiving prescriptions in more than one class were not excluded. PPIs were chosen as a control group because of their widespread use and the lack of an association with onset of diabetes.

The date of the first prescription for one of these four classes was assigned as the patient's index date. Next, we excluded 4,758 patients who were in a class, but did not receive at least a 30-day supply. Finally, we excluded 3,424 patients who had a primary or secondary (inpatient or outpatient) ICD-9-CM diagnosis code (250.xx) associated with diabetes either in the previous FY year (1998), or prior to their index date. These exclusions left a final analytical cohort of 9,705 patients.

Analytic Strategy

Patients were defined as developing diabetes if they had an inpatient or outpatient encounter with a primary or secondary

diabetes ICD-9-CM code (250.xx) after their index date. Diabetes was coded to a particular medication class (CS, PPI, TAP, AAP) if it occurred while the patient was on the medication, or within 60 days of discontinuation of a medication class. Comparisons between diabetic and non-diabetic patients were made using Chi-square tests for categorical variables and T-tests for continuous variables.

To examine the effect of medication class on the development of diabetes, we utilized a Cox-regression model using time dependent covariates. This approach is similar to the one developed by Fuller and colleagues to address the deficiencies of previous atypical antipsychotic and diabetes studies (3,23). Specifically, we sought to control for switching between classes of medication as well as the possibility of concomitant therapy within the four classes. This method allowed preservation of the patient's drug history while giving more weight to medication classes occurring closer in time to the development of diabetes. Because of this approach however, the interpretation of differences between medication groups becomes difficult. That is the classification by index group is counter intuitive because the importance of the index group decreases over time, while the reporting of all patients who were in a group results in non-independent observations.

Because of the importance of age in the development of diabetes, age was expressed as a continuous variable as well as one of thirteen indicator variables, which allowed for a better fitting model. Race and gender were expressed using an indicator variable, as was marital status, and VA financial category. As schizophrenia has been implicated as an independent risk factor for diabetes (25), an indicator variable for schizophrenia was included in the model if the patient had a diagnosis (ICD-9-CM codes of 295.00–295.90) during the study period. Coefficients associated with medication classes were used to determine relative risks. In Cox regression analyses, patients not developing diabetes were censored. The proportional hazards model met the assumption that the hazard was similar over time and the assumption that diabetes and censoring were independent events (26). Finally, to determine whether the results were consistent for each of the individual agents within the AAP class, follow up analyses were performed separating the four AAP (clozapine, olanzapine, quetiapine, and risperidone) agents and running a final Cox regression model. All analyses were conducted using SAS for Windows, Version 8.1 (SAS Institute; Cary, NC).

RESULTS

The mean age of the 9,975 study patients was 63 years. Ninty-six percent of patients were male and a similar proportion were white (Table 1). Slightly under two-thirds of the patients were married, while nearly one-third of the patients had a service-connected medical condition and nearly one-half were indigent. We found that 13% (N = 1,283) of our study population had a new diagnosis for diabetes during our two-year study. The percentage of patients in our sample having a least a 30 day exposure to corticosteroids was 18% (N = 1,839), PPIs 73% (N = 7,292), while exposure to typical and atypical antipsychotic was 8% (N = 883) and 12% (N = 1,201), respectively.

Table 1 Baseline Characteristics of Regional VAMC Patients Receiving Corticosteroids, Proton Pump Inhibitors, Typical Antipsychotics or Atypical Antipsychotics (n = 9,975)

Mean Age ± SD (years)	62.7 ± 13.5
Male, number, (%)	9,536 (95.6%)
White, number, (%)	9,625 (96.5%)
Married, number, (%)	6,121 (61.4%)
Schizophrenia diagnosis	996 (9.9%)
VA Classification	
Indigent, number, (%)	4,780 (47.9%)
Service Connected, number, (%)	3,026 (30.3%)
Other, number, (%)	2,169 (21.7%)
Diabetes encounter, number, (%) (At least one during follow up period)	1,283 (12.9%)
Medication Classes (numbers add up to more than 9,975 because patients may have received more than one class during the follow up period)	
Corticosteroids, number, (%)	1,839 (18.4%)
Proton Pump Inhibitors, number, (%)	7,292 (73.1%)
Typical Antipsychotics, number, (%)	833 (8.2%)
Atypical Antipsychotics, number, (%)	1,201 (12.0%)

Patient characteristics for patients who were in each of the four medication classes are shown in Table 2, although it should be stressed that these groups are not independent, because a single patient may be in one, two, three, or all four groups depending on their medication history over the two year time period. Patients receiving antipsychotics, both typical and atypical, were noticeably younger than patients in the corticosteroid and PPI groups. Patients receiving antipsychotics were also less likely to be married and were more likely to have a service-connected condition. As expected, a diagnosis of schizophrenia was much higher in the antipsychotic groups. Incidence of diabetes was relatively consistent across the groups. Classification of patients into mutually exclusive categories by index medication group resulted in similar findings (results not shown).

As mentioned previously, 1,283 (12.9%) patients developed a diagnosis for diabetes, as defined as having a new encounter for diabetes care, after their index prescription date. Differences in patient characteristics for those with and without new diabetes encounters are shown in Table 3. The mean time until diagnosis was 415 days and the median time was 384 days. In the multivariate Cox regression model using time dependent covariates and controlling for the previously mentioned factors, only corticosteroids relative to PPIs were associated with a significantly higher risk of developing diabetes (RR = 1.21; 95% CI, 1.09 – 1.33; P = .03), (Table 4). We also found a higher, although non-significant, increased risk of developing diabetes for both typical and atypical antipsychotics relative to PPIs (RR = 1.18; 95% CI, 0.80 – 1.62; P = .52 RR = 1.19; 95% CI, 0.90 – 1.49; P = .66,

Table 2 Differences in Characteristics Between Patients Receiving: Corticosteroids, Proton Pump Inhibitors, Typical Antipsychotics, or Atypical Antipsychotics

	Corticosteroids (n = 1,839)	Proton Pump Inhibitors (n = 7,292)	Typical Antipsychotics (n = 833)	Atypical Antipsychotics (n = 1,201)
Mean Age ± SD (years)	66.3 ± 12.5	63.8 ± 13.0	54.2 ± 12.8	51.4 ± 13.0
Male, number, (%)	1,764 (95.9%)	7,000 (96.0%)	775 (93.0%)	1,115 (92.8%)
White, number, (%)	1,780 (96.8%)	7,089 (97.2%)	770 (92.4%)	1,096 (91.3%)
Married, number, (%)	1,251 (68.0%)	4,821 (66.1%)	225 (27.0%)	379 (31.6%)
Schizophrenia diagnosis	26 (1.4%)	172 (2.4%)	549 (65.9%)	665 (55.4%)
VA Classification				
Indigent, number, (%)	885 (48.1%)	3,518 (48.2%)	380 (45.6%)	582 (48.5%)
Service Connected, number, (%)	488 (26.5%)	2,097 (28.8%)	381 (45.7%)	528 (44.0%)
Other, number, (%)	466 (25.3%)	1,677 (23.0%)	72 (8.6%)	91 (7.6%)
Diabetes encounter, number, % (At least one during follow up period)	279 (15.2%)	933 (12.8%)	124 (14.2%)	160 (13.3%)

Table 3 Differences in Characteristics between Patients Not Developing Diabetes and Those Developing Diabetes

	No Diabetes Encounter (n = 8,692)	At Least One Diabetes Encounter (n = 1,283)	P Value
Mean Age ± SD (years)	62.4 ± 13.7	64.3 ± 12.6	<.001
Male, number, (%)	8,310 (95.6%)	1,226 (95.6%)	=.93
White, number, (%)	8,392 (96.5%)	1,233 (96.1%)	=.67
Married, number, (%)	5,324 (61.3%)	797 (62.1%)	=.71
Schizophrenia diagnosis	846 (9.7%)	150 (11.7%)	=.02
VA Classification			<.001
Indigent, number, (%)	4,173 (48.0%)	607 (47.3%)	
Service Connected, number, (%)	2,525 (29.1%)	501 (39.1%)	
Other, number, (%)	1,994 (22.9%)	175 (13.6%)	

Table 4 Relative Risk of Developing Diabetes in Users According to Exposure of Medication Groups Using a Time Dependent Covariant and Adjusting for Age, Schizophrenia, Gender, Race, Marital Status and VA Service Connection

	Relative Risk	95% CI	P Value
Corticosteroids vs. PPIs	1.21	1.09 – 1.33	=.03
Antipsychotics vs. PPIs	1.18	0.87 – 1.52	=.52
Typical Antipsychotics vs. PPIs	1.18	0.80 – 1.62	=.43
Atypical Antipsychotics vs. PPIs	1.19	0.90 – 1.49	=.66
Typical Antipsychotics vs. Corticosteroids	0.90	0.62 – 1.20	=.88
Atypical Antipsychotics vs. Corticosteroids	0.94	0.61 – 1.27	=.91
Atypical Antipsychotics vs. Typical Antipsychotics	1.03	0.77 –1.28	=.89

Table 5 Relative Risk of Developing Diabetes in Atypical Antipsychotic Users According to Individual Agents Using a Time Dependent Covariant and Adjusting for Age, Schizophrenia, Gender, Race, Marital Status and VA Service Connection

	Relative Risk	95% CI	P Value
Atypical Antipsychotics vs. PPIs			
Olanzapine vs. PPIs	1.17	0.93 – 1.41	=.33
Risperidone vs. PPIs	1.10	0.81 – 1.38	=.51
Clozapine vs. PPIs	1.63	0.49 – 2.77	=.34
Quetiapine vs. PPIs	1.04	0.11 – 1.97	=.94
Atypical Antipsychotics vs. Corticosteroids			
Olanzapine vs. Corticosteroids	0.96	0.54 – 1.35	=.69
Risperidone vs. Corticosteroids	0.90	0.56 – 1.22	=.42
Clozapine vs. Corticosteroids	1.32	0.13 – 2.51	=.67
Quetiapine vs. Corticosteroids	0.86	0.21 – 1.55	=.72
Atypical Antipsychotics vs. Typical Antipsychotics			
Olanzapine vs. Typical Antipsychotics	1.03	0.75 – 1.31	=.95
Risperidone vs. Typical Antipsychotics	0.96	0.47 – 1.45	=.81
Clozapine vs. Typical Antipsychotics	1.42	0.04 – 2.82	=.50
Quetiapine vs. Typical Antipsychotics	0.92	0.12 – 1.73	=.85

respectively). However, we found a decreased risk of diabetes when comparing typical and atypical antipsychotics to corticosteroids, (RR = 0.90; 95% CI, 0.62 – 1.20; P = .88, RR = 0.94; 95% CI, 0.61 – 1.27; P = .91, respectively). Further, we found almost no increase in risk when examining atypical antipsychotics relative to typical antipsychotics relative to typical antipsychotics (RR = 1.03; 95% CI, 0.77 – 1.28; P = .89)

As mentioned earlier, we sought to disentangle the association of diabetes among the specific atypical agents. However, because of the relatively few number of clozapine (N = 44) and quetiapine (N = 107) encounters relative to olanzapine (N = 681) and risperidone (N = 910), only results for the later two agents are discussed. Specifically, we found a higher, but non-significant, increase in risk for diabetes among both olanzapine and risperidone agents relative to PPIs (RR = 1.17; 95% CI, 0.93 – 1.41; P = .33, RR = 1.10; 95% CI, 0.81 – 1.38; P = .51, respectively) (Table 5). We also found a slight decrease in risk for both agents relative to corticosteroids (RR = 0.96; 95% CI, 0.54 – 1.35; P = .69, RR = 0.90; 95% CI, 0.56 – 1.22; P = .42, olanzapine and risperidone, respectively). Finally, we observed almost no difference between the individual atypicals relative to typical agents (RR = 1.03; 95% CI, 0.75 – 1.31; P = .95, RR = 0.96; 95% CI, 0.47 – 1.45; P = .81, olanzapine and risperidone, respectively).

DISCUSSION

The current study represents the first direct comparisons of typical and atypical antipsychotic medications relative to a widely used class of medications known to be associated with diabetes, corticosteroids, as well as a widely used class of medications with no known relationship to diabetes, proton pump inhibitors. We found patients receiving antipsychotics to be younger, less likely to be married, more likely to have a diagnosis of schizophrenia, and more likely to have a service-connected classification compared to patients receiving corticosteroids and PPIs. Patients were relatively similar in other measures, that is, gender, race, and incidence of diabetes. Among patients acquiring a diagnosis of diabetes, we found these to be slightly older and more likely to have a service-connected condition and more likely to have a diagnosis of schizophrenia relative to non-diabetes, but similar in regards to other measures. Using a multivariate Cox-regression to analyze VAMC claims over a two-year period for an entire region, we found that VA patients with exposure to typical antipsychotics as a whole, had higher, although nonsignificant ($P < .05$), increased risk of developing diabetes relative to PPIs; but a lower, nonsignificant risk, relative to corticosteroids. When analyzing the two major atypical antipsychotics (olanzapine and risperidone) separately, we found consistently higher risks for olanzapine compared to risperidone, relative to PPIs, corticosteroids, and typical antipsychotics, although again, all results were nonsignificant.

Several studies have directly examined the correlation between diabetes and antipsychotic use; however the study designs have differed considerably with regards to exclusion and inclusion criteria, basis of comparison, length of follow-up. Using a nationwide VA sample, Sernyak and colleagues compared patients with a diagnosis of schizophrenia who had received either AAPs or TAPs (7). Using TAPs as the comparison group, the authors found that patients whose last prescription was written for an atypical antipsychotic were 9% more likely to have diabetes than those who received typical antipsychotics. Also, the prevalence of diabetes was increased for those persons receiving clozapine, olanzapine, and quetiapine, but not risperidone. However, this analysis was limited by the fact that pre-existing diabetes was not excluded when determining the prevalence of diabetes.

A second study used a nested case control design to assess the risk of diabetes among schizophrenic patients taking olanzapine and risperidone (6). Patients on conventional antipsychotic therapies, as well as patients that were non-users of antipsychotics served as comparators. Subjects with a previous diagnosis of diabetes were excluded and the mean follow-up period was 5.2 years. Compared with conventional antipsychotic use, olanzapine was associated with a significantly increased risk of diabetes (OR = 4.2, p = 0.008), while risperidone was not (OR = 1.2, p = 0.290). Compared to those with no antipsychotic use, significant increased risk of diabetes was found with both olanzapine (OR = 5.8, p = 0.001) and conventional agents (OR = 1.4, p = 0.004).

Similarly, increased rates of diabetes with olanzapine and clozapine use have been reported in other studies (2,3,4,24). Caro and colleagues compared relative risk of diabetes among patients with one prescription for either risperidone or olanzapine (2). Follow-up continued for a period up to three years, and persons with a previous diabetes diagnosis were excluded. The authors reported a 20% increased risk of diabetes with olanzapine relative to risperidone ($P = 0.05$) after adjustments were made for potential confounders.

Increased odds of diabetes were also found when considering an exposure period of 12 months in patients with psychosis treated with olanzapine, clozapine, and high and low potency typical agents, when compared to untreated patients (24). No significant increase in risk was found with risperidone use. However, in a separate analysis, using a more stringent criteria for evidence of diabetes, only olanzapine remained as having a significant increase in odds for diabetes (OR = 1.42, 95% CI = 1.05 – 2.0).

A recent study examining only atypical antipsychotics found that among a large group of VA patients on stable monotherapy, that clozapine and olanzapine patients had a greater risk of developing diabetes relative to quetiapine and risperidone. However the authors estimated that the overall risk of diabetes with the atypicals was minimal, ranging from 0.05% for risperidone to 2.3% for clozapine (27).

Similar to our study design, Fuller and colleagues utilized Veterans Affairs databases to assess risk of developing diabetes in patients taking APs, particularly olanzapine, risperidone, haloperidol, and fluphenazine (3). Additionally, they incorporated antipsychotic therapy as a time dependent covariate to account for switching to or concomitant treatment. A diagnosis of diabetes was noted by either the presence of ICD-9 codes or claims for hypoglycemic therapy. Persons with a previous diagnosis of diabetes were excluded. One important difference in their analysis was the use of the risperidone cohort as the basis for comparison, while our methods involved comparisons to CS's and PPI's. The overall rate of developing diabetes was 6.3%, which is significantly lower than we report here (12.9%). Fuller and colleagues also reported a 37% increased risk of developing diabetes compared to risperidone ($p = 0.016$), while no differences were found when comparing either fluphenazine or haloperidol to risperidone.

The increased risk of diabetes associated with AAPs that we report is slightly higher than what was reported in a similar study Caro and colleagues, and may reflect differences in study design and ability to measure and adjust for potential confounders (2). In addition, our study may more closely reflect real world conditions in which patients are exposed to a wide range of medications over time, and may more closely estimate the true risk of exposure.

In interpreting our findings, it is important to consider several potential limitations. First, the study involved a single regional VA network. The generalizability to VA hospitals serving other markets is uncertain, as is the generalizability to the larger population of all patients receiving these classes of medications.

Second, as we did not attempt to adjust for comorbidity in the study population. Our results may be confounded by unmeasured comorbidity, as previous studies have shown that VA patients have more comorbid conditions than the general population (28,29).

Third, while diagnosis-based methods have been found to explain a large proportion of resource utilization, such methods are dependent on the accuracy of capturing diagnosis codes from patient encoutners and may be subject to systematic variations between practitioners and facilities (30,31). We also had no clinical data to monitor serum glucose levels, weight gain or other potential markers for diabetes. A measure such as weight or BMI would have allowed us to adjust or stratify based on these potential risk factors.

Fourth, pharmacy data has its own set of potential limitations. Specifically, automated pharmacy databases require significant human effort to maintain congruence with medications that patients are actually taking. Patients may have obtained medications from providers and pharmacies outside the VA. Indeed, a recent analysis of the agreement between VA computerized medication lists obtained from a detailed history by a clinical pharmacist found complete agreement for less than 5% of patients (32).

Also, another important limitation of our analysis is the potential for dual utilization of care in the private sector by Veterans who use VA services (33,34). Thus, our estimates of diabetes are likely underestimates and may introduce systematic bias, as private sector utilization is likely to vary according to specific factors, including the availability of private health insurance. Finally, our study sample size may have limited our ability to detect statistically significant differences in our Cox regression analyses that may have been of clinical significance.

Nonetheless, if generalizable, our findings suggest that previous studies may have over estimated the true risk of diabetes associated with antipsychotics, particularly with regards to the atypical agents olanzapine and risperidone. While some clinicians have suggested more stringent guidelines and monitoring with atypical antipsychotics, we are not aware of any such calls for similar measures associated with corticosteroids, a class of medications which are clearly linked to the development of diabetes. Moreover, in the absence of long-term follow-up data, our results highlight the potential bias that can be introduced by an artificial assignment to medication classes, and the need to use analytical methods that consider the duration of patient observation and control for the time of exposure.

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Brief Report

Incidence of Newly Diagnosed Diabetes Attributable to Atypical Antipsychotic Medications

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Objective: The purpose of the study was to determine the proportion of patients with schizophrenia with a stable regimen of antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis.

Method: Patients with schizophrenia for whom a stable regimen of antipsychotic monotherapy was consistently prescribed during any 3-month period between June 1999 and September 2000 and who had no diabetes were followed through September 2001 by using administrative data from the Department of Veterans Affairs. Cox proportional hazards models were developed to identify the characteristics associated with newly diagnosed diabetes and ketoacidosis.

Results: Of the 56,849 patients identified, 4,132 (7.3%) developed diabetes and 88 (0.2%) were hospitalized for ketoacidosis. Diabetes risk was highest for clozapine (hazard ratio=1.57) and olanzapine (hazard ratio=1.15); the diabetes risks for quetiapine (hazard ratio=1.20) and risperidone (hazard ratio=1.01) were not significantly different from that for conventional antipsychotics. The attributable risks of diabetes mellitus associated with atypical antipsychotics were small, ranging from 0.05% (risperidone) to 2.03% (clozapine).

Conclusions: Although clozapine and olanzapine have greater diabetes risk, the attributable risk of diabetes mellitus with atypical antipsychotics is small.

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There is some evidence to suggest that atypical antipsychotics can cause weight gain and increased risk of diabetes mellitus (1–5). Other studies have suggested that there might be a link between atypical antipsychotics and diabetic ketoacidosis (6, 7). However, few published studies have examined diabetes mellitus prevalence (8) or risk of new-onset diabetes mellitus or diabetic ketoacidosis for patients treated with antipsychotics (6, 9), and, to our knowledge, no studies have reported diabetes mellitus incidence rates in this population.

The goals of this study were to determine the proportion of patients with schizophrenia with a stable regimen of antipsychotic monotherapy who developed diabetes mellitus or were hospitalized for diabetic ketoacidosis and to identify patient demographic, clinical, and pharmacological characteristics associated with these adverse events.

Method

We identified 73,946 patients with schizophrenia in the Department of Veterans Affairs (VA) for whom a stable regimen of antipsychotic monotherapy was consistently prescribed during any 3-month period between June 1999 and September 30, 2000. We defined five groups of antipsychotic medications: clozapine, risperidone, olanzapine, quetiapine, and all conventional antipsychotics. Ziprasidone and aripiprazole were not included in the study because they had only recently been approved for use.

Patients with any outpatient claims for diabetes mellitus (N=11,069) or less than two medical primary care visits (N=6,028) in the previous 6 months were excluded from the sample. Stably medicated patients with no diabetes mellitus were followed through September 30, 2001. Patients who received a diagnosis of diabetes mellitus or who were hospitalized for diabetic ketoacidosis during that period were identified.

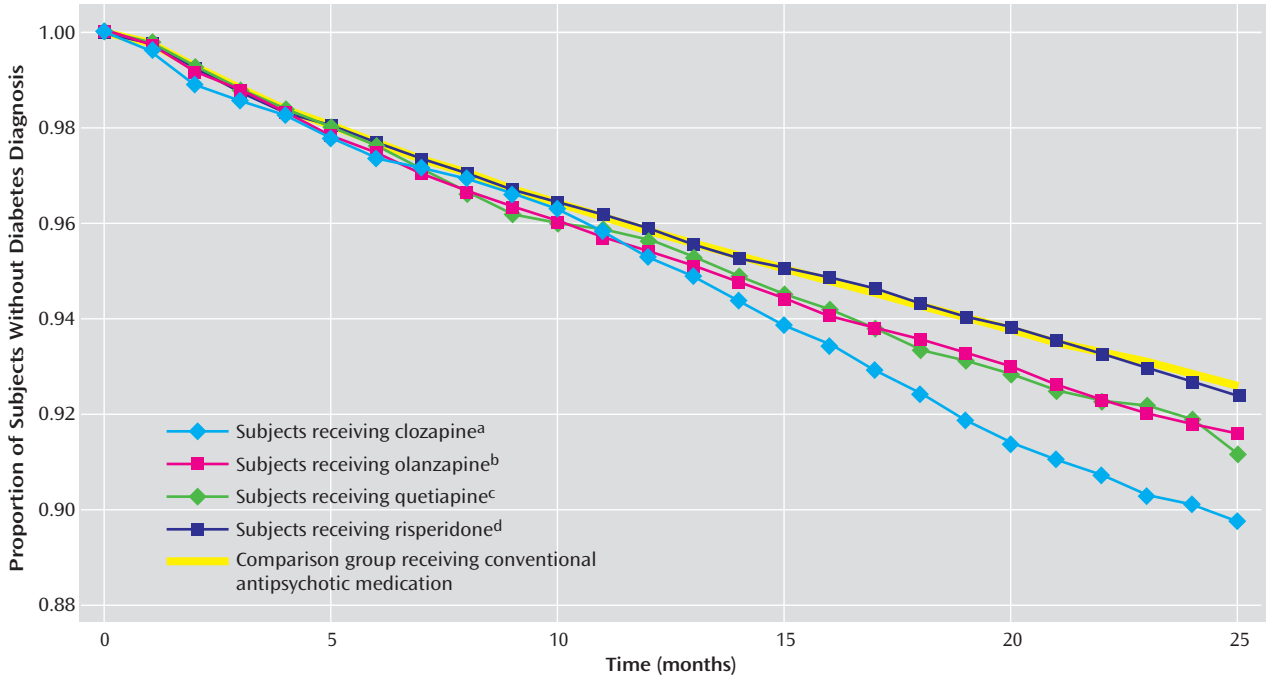
Cox proportional hazards models were used to model the time to diabetes mellitus diagnosis and time to diabetic ketoacidosis hospitalization. Independent variables included in the models were antipsychotic agent prescribed during the stable period, date of the end of the stable period, age, gender, race, income, comorbid mental health diagnoses, levels of service use during the stable period, and the degree of VA service-connected disability. We also calculated the attributable risk of diabetes mellitus and diabetic ketoacidosis associated with each atypical antipsychotic, which is the estimated proportion of patients taking each drug who would not have received a diagnosis of diabetes mellitus or diabetic ketoacidosis if they had been taking a conventional antipsychotic (10, p. 38).

Results

Of the 56,849 patients in the sample, 4,132 patients (7.3%) received a diagnosis of diabetes mellitus during the follow-up period, representing an annual incidence rate of 4.4%. Only 88 patients (0.2%) were hospitalized for diabetic ketoacidosis. Figure 1 shows the fitted survival functions associated with each medication group from the model predicting diabetes mellitus diagnosis. The attributable risk associated with these medications was highest for clozapine (2.03%), followed by quetiapine (0.80%), olanzapine (0.63%), and risperidone (0.05%).

In the diabetic ketoacidosis model, hazard ratios associated with atypical antipsychotics were larger than in the diabetes mellitus model, but the attributable risks were much smaller (ranging from 0.004% for risperidone to 0.071% for clozapine). In the entire sample, hazard ratios for diabetic ketoacidosis were significant only for clozapine (hazard ratio=3.75, 95% confidence interval [CI]=1.39–10.09) and olanzapine (hazard ratio=1.77, 95% CI=1.05–2.98). None of the hazard ratios for diabetic ketoaci-

FIGURE 1. Fitted Survival Functions From the Cox Proportional Hazards Model Predicting Time to Diabetes Mellitus Onset Among Outpatients With Schizophrenia For Whom a Stable Regimen of Antipsychotic Monotherapy Was Prescribed



[a] Hazard ratio=1.57, 95% confidence interval (CI)=1.31–1.89
[b] Hazard ratio=1.15, 95% CI=1.07–1.24
[c] Hazard ratio=1.20, 95% CI=0.99–1.44
[d] Hazard ratio=1.01, 95% CI=0.93–1.10

dosis were statistically significant when the analysis was limited to diabetes mellitus patients.

Discussion

The incidence of diabetes mellitus in this population was relatively high, even among patients for whom a stable regimen of a conventional antipsychotic was prescribed. The overall annual diabetes mellitus incidence rate of 4.4% in this study is considerably higher than the estimated rate of 6.3 cases per 1,000 in the general U.S. population (11). It is unclear how much of the increased diabetes mellitus incidence in the sample was due to the use of antipsychotic medications (conventional or atypical antipsychotics), the underlying disease of schizophrenia, or other factors such as poorer overall physical health, less healthy lifestyles, or poorer access to health care services.

Differences in diabetes mellitus risk across antipsychotic medications did not become apparent until 14 months after the end of the stable period (Figure 1). Hence, the additional diabetes mellitus risk associated with clozapine and olanzapine took more than a year to develop. This interval should offer ample time for clinicians to identify weight gain and/or elevated diabetes mellitus risk and perhaps to change the antipsychotic regimen accordingly.

Our results do not support the claim that weight gain and elevated risk of diabetes mellitus are a "class effect" of all atypical antipsychotic medications. In addition, the attributable risks of diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics were small. However, diabetes mellitus and diabetic ketoacidosis are severe, life-threatening disorders, and while these attributable risks are small, they may still be of concern.

Several limitations of the study deserve comment. First, we examined the incidence of diabetes mellitus diagnosed in the VA system among patients with schizophrenia for whom a stable regimen of an antipsychotic medication was prescribed. Hence, our results may not be generalizable to other populations or health care systems. In addition, there may have been cases of diabetes mellitus that were undiagnosed or diagnosed outside of the VA. Although we were unable to identify undiagnosed diabetes mellitus cases, we have no reason to believe that the likelihood of failure to diagnose diabetes mellitus would be different across groups of patients for whom different antipsychotic medications were prescribed. Finally, our analysis attributed all of the diabetes mellitus risk to the atypical antipsychotic that was consistently prescribed for the patient during a 3-month window. Different medications may have been prescribed either before or after the medication identified in our study, and the increased risk of diabetes mellitus might be partially attributable to these other medications. Data were not available to identify medications taken earlier, and the proportions of patients whose drugs were switched during the follow-up

period were small (17% overall) and were similar across medication groups.

Despite these limitations, the results offer insight into the risk of diabetes mellitus and diabetic ketoacidosis in an older, predominantly male population with schizophrenia for whom antipsychotic medications are prescribed.

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Original Article

Rate of New-Onset Diabetes Among Patients Treated With Atypical or Conventional Antipsychotic Medications for Schizophrenia

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Abstract and Introduction

Abstract

Context: Understanding the association between use of antipsychotics and onset of diabetes.

Objective: To compare the rates of new-onset diabetes mellitus (DM) between patients treated for schizophrenia with atypical or conventional antipsychotics.

Design: Retrospective analysis of medical and pharmacy claims data.

Setting: 61 US health plans.

Patients: Patients with schizophrenia who were treated with atypical or conventional antipsychotics between September 1996 and June 2001 and were enrolled for 12 or more months before and 3 or more months after therapy initiation.

Main Outcome Measures: New-onset DM was defined based on 2 or more claims with a diabetes diagnosis or initiation of antidiabetic therapy during follow-up. Rates of DM were compared between patients receiving atypical and conventional antipsychotics, and among 4 subgroups of patients receiving atypical antipsychotics (olanzapine, clozapine, risperidone, quetiapine). Statistical analyses employed logistic regression and Cox proportional hazards models.

Results: Patients treated with atypical antipsychotics (N = 1826) were younger, had a lower rate of diagnosed hypertension, and longer duration of therapy than those receiving conventional antipsychotics (N = 617). The crude incidence of DM did not differ (2.46% vs 2.76% for atypical antipsychotics and conventional antipsychotics, *P* = .525). In Cox proportional hazards models, patients treated with atypical antipsychotics had a statistically significant, moderately increased risk of DM relative to conventional antipsychotics (hazard ratio [HR] = 1.17, 95% confidence interval [CI] = 1.06, 1.30); no significant differences in risk were observed when atypical antipsychotic cohorts were compared. In logistic regression models, no significant differences in DM risk were observed.

Conclusions: Patients with schizophrenia treated with atypical antipsychotics had a moderately increased risk of DM relative to those treated with conventional antipsychotics, as measured by Cox proportional hazards models; such risk was not significantly different among patients treated with individual atypical medications.

Introduction

Schizophrenia is a disabling condition characterized by profound disruption in cognition and emotion, affecting language, thought, perception, affect, and sense of self. The array of symptoms, while substantially varied among patients, frequently includes psychotic manifestations such as hallucinations and delusions.[1] Prior research has documented that in addition to psychiatric difficulties, patients with schizophrenia are also at greater risk than the general population of concurrent medical conditions such as vision and dental problems, high blood pressure, diabetes, and sexually transmitted diseases.[2,3]

Beginning in 1990, a new generation of antipsychotic medication was introduced. These "atypical" antipsychotic medications, in comparison with first-generation (or "conventional") antipsychotics, have been associated with improved efficacy in treating both positive and negative symptoms of schizophrenia, and have exhibited a superior safety profile in regard to adverse events such as extrapyramidal symptoms.[4,5] In the past decade, atypical antipsychotics such as risperidone, olanzapine, and quetiapine have become first-line treatment options for patients with schizophrenia.

Although atypical antipsychotics have greatly improved the treatment of schizophrenia, weight gain, increased serum prolactin levels, and QTc prolongation have been reported during treatment with some atypical antipsychotics.[6-9] More recently, the results of several case reviews and database studies have examined a potential association between atypical antipsychotic use and increased insulin resistance or risk of developing overt DM.[9-23] These studies have varied greatly, however, in their study populations, methods, results, magnitude of identified risk, and implication of specific atypical medications over others. For example, using logistic regression techniques, Gianfrancesco and colleagues[20] found DM risk for risperidone users to be similar to that among untreated subjects, while excess risk was observed among olanzapine, clozapine, and selected conventional drugs. In contrast, findings from survival-based research on 2 databases by Sowell and colleagues[19] indicated that risperidone and olanzapine had similar effects on DM risk; in fact, a significantly greater risk was attributed to risperidone in one of these analyses.

While all of these methodologic factors may contribute to discrepant findings, choice of methodology is an actionable variable that may have a significant effect on study conclusions. Although fixed follow-up techniques are widely accepted, the introduction of accrued person-time (ie, allowing all candidate populations to contribute observation times of varying duration) provides an alternative that may better reflect the nature of usual psychiatric practice for patients with schizophrenia in the United States. Specifically, antipsychotic therapy is often sporadic, and patients may be lost to follow-up for a variety of reasons (eg, changes in healthcare coverage, death, confinement, or imprisonment).

The present study examined the rate of new-onset DM in a large, geographically diverse, commercially insured population treated with atypical or conventional antipsychotics. We present findings using both fixed follow-up and accrued person-time techniques to examine the effects of choice of methodology on these results.

Methods

Data Source

Data were obtained from the PharMetrics Patient-Centric Database, which is composed of medical and pharmaceutical claims for approximately 36 million unique patients from 61 health plans across the United States. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats), as well as both standard and mail order prescription records; available data on prescription records include the NDC code as well as days supplied and quantity dispensed. All medical and pharmaceutical claims include dates of service. Additional data elements include demographic variables (age, gender, geographic region), health plan type (eg, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

Because all pertinent patient information in the database is encrypted and privacy-protected, no informed consent or approval by institutional review boards was required.[24]

Sample Selection

The sample included patients with 1 or more medical claims with a listed diagnosis of schizophrenia (ICD-9-CM code 295.XX) as well as 1 or more paid pharmacy claims for an antipsychotic medication (generic product index

class code 2816080000) between September 30, 1996 and June 30, 2001. All medical and pharmacy claims were then compiled for these patients for the period September 30, 1995-September 30, 2001. The first observed antipsychotic pharmacy claim was deemed the "index date"; a pretreatment period of 12 months' duration was compiled in relation to this date. Patients with prescriptions for more than 1 antipsychotic on the same date were excluded from the sample (this constituted less than 1% of the candidates for inclusion in the study). All patients also were required to have a minimum of 3 months of follow-up; follow-up was allowed to vary, as techniques to account for right-censored data were employed in primary data analyses.

Patients were grouped by type of antipsychotic received on the index date -- atypical (ie, clozapine, risperidone, quetiapine, or olanzapine) or conventional (eg, haloperidol or fluphenazine) antipsychotics. A list of antipsychotics included can be found in Table 1. Ziprasidone, sertindole, and aripiprazole were not included in the atypical antipsychotic group, as they are newer atypical medications, and the timeframe used for this study did not allow for creation of sufficiently sized samples of patients receiving these medications. In addition, prochlorperazine was excluded from consideration as a conventional antipsychotic, as its use is primarily nonpsychiatric (eg, antiemesis). All patients who had evidence of use of an atypical or conventional antipsychotic in the 6 months prior to the index date were excluded from the study sample, as were those who had evidence of DM (based on medical claims or prescriptions for DM medications) throughout the entire 12-month pretreatment period. In addition, all members of health plan contributors to the PharMetrics database that "carve out" mental health services (6 of the 61 plans) were excluded from the sample because complete utilization data were not available for these patients. Finally, patients who were not continuously eligible for health and drug benefits throughout the pretreatment and follow-up periods were excluded.

A total of 1826 patients receiving atypical antipsychotics (n = 937, 690, 164, and 35 for olanzapine, risperidone, quetiapine, and clozapine, respectively) and 617 patients receiving conventional medications were selected for analysis.

Measures

The primary measure of interest in this analysis was the incidence of new-onset DM at any time during the year after initiation of antipsychotic therapy. Patients were deemed to have been diagnosed with DM if they had 1 or more paid pharmacy claims for an oral DM medication, insulin, or insulin syringes, or if they had 2 or more claims with a listed DM-related diagnosis (ICD-9-CM 250.XX, 362.01, 362.02), on or after the index date.

A variety of demographic and clinical characteristics also were examined for the study sample, including age, gender, health plan type (eg, HMO, PPO), geographic region (Northeast, Midwest, South, and West), calendar year of drug initiation, number of DM screening tests (CPT-4 codes 80048-80050, 80054, 80069, 81000-81005, 82947-82954), number of laboratory tests overall, and other psychiatric diagnoses (ie, other than schizophrenia) recorded in the pretreatment or follow-up periods (ie, bipolar disorder [ICD-9-CM 296.0-296.1, 296.4-296.9], and/or depression [296.2-296.3; 300.4]) as well as other medical diagnoses known to be risk factors or concomitant conditions with DM -- specifically, hypertension (ICD-9-CM 401.XX-405.XX), cardiovascular disease (ICD-9-CM 410.XX-414.XX, 420.XX-429.XX, 433.XX-436.XX, 437.0, 437.1, 440.XX-442.XX), obesity (278.0X), and impaired glucose tolerance (790.2). The total duration of therapy (calculated based on the period of time between the last fill and first fill dates for the index medication) also was calculated, as was the number of prescriptions for the index medication.

Measures were examined comparing the atypical and conventional antipsychotic cohorts on an overall basis as well as among the individual atypical antipsychotic cohorts (ie, risperidone, olanzapine, clozapine, and quetiapine).

Analyses

Primary analyses were conducted on an intent-to-treat basis; all patients with at least 1 prescription for an index medication of interest were therefore included in these analyses. Findings were presented as group means and percentages, along with appropriate measures of precision (ie, standard deviations, 95% confidence intervals).

Demographic and clinical characteristics of the study sample as well as the incidence of new-onset DM were reported for patients receiving atypical and conventional antipsychotics. Analyses were replicated for patients receiving atypical antipsychotics, and compared between the 4 cohorts available for analysis (olanzapine, risperidone, quetiapine, and clozapine). In all such analyses, comparisons of categorical variables were performed using an overall chi-square test or Fisher's Exact Test (ie, for cell sizes less than 5); comparisons of mean age were

performed using a t-test.

In addition to unadjusted comparisons, 2 modeling techniques were employed to compare the rate of new-onset DM between cohorts. In the overall cohorts, Cox proportional hazards models were employed to estimate DM rates in the setting of variable follow-up. In the subgroup of patients with 12 months of continuous enrollment subsequent to the index date, logistic regression techniques were used to examine DM rates. Explanatory variables in both base models included the demographic and clinical variables described above. Model specifications and HRs or odds ratios (ORs) (along with corresponding 95% CIs) were set forth for the overall population as well as the comparisons performed among atypical medications. For these risk estimates, a *P* value < .05 was considered statistically significant.

All analyses were conducted using Statistical Analysis Software (SAS®), version 8.2.

Results

A total of 18,134 patients were initially identified for analysis. After application of study enrollment criteria, a total of 12,368 remained. Finally, exclusion of patients without a schizophrenia diagnosis in their claims history yielded a total of 2443 patients remaining (n = 1826 and 617 for atypical and conventional users, respectively) (Table 2). The mean duration of follow-up was 435 days and was significantly longer among patients in the conventional group (485.0 vs 418.8 days for atypicals, *P* < .0001). Patients receiving atypical medications were significantly younger (mean [± SD] age: 38.0 [± 12.4] vs 42.4 [± 11.7] years for conventional antipsychotics, *P* < .0001). The mean duration of therapy was approximately 9 months in both groups while the mean number of prescriptions was significantly higher in the atypical group (8.5 vs 6.6; *P* < .0001). Distribution of calendar year of therapy initiation was significantly different between patients receiving atypicals and conventionals (*P* = .0003). Patients receiving atypical medications were also significantly more likely to have additional psychiatric diagnoses, but significantly less likely to have a pretreatment diagnosis of hypertension (12.5% vs 17.2% for conventional medications, *P* = .0033). Slightly more than half of selected patients had sufficient follow-up for logistic regression analyses (n = 953 and 363 for atypical and conventional antipsychotics, respectively). For these analyses, demographic and clinical characteristics, as well as differences between atypical and conventional antipsychotic cohorts, were essentially identical to those with variable follow-up.

A total of 45 patients in the atypical medication group and 17 patients in the conventional group were identified as having developed DM during follow-up; given the shorter duration of follow-up in the atypical group, its crude DM incidence rate was nonsignificantly lower than that of the typical group (2.46% vs 2.76% for atypical and conventional medications, respectively, *P* = .5252). The mean time to event across both groups was 62.2 (± 35.8) days.

Among atypical antipsychotic users, nearly all patients had an index medication of olanzapine (n = 937) or risperidone (n = 690); the totals were 164 and 35 for quetiapine and clozapine, respectively (Table 3). Patients in the 4 groups were similar with respect to age, duration of follow-up, and duration of use of index medication. Significant differences were observed, however, with respect to distribution by health plan type, geographic region, number of prescriptions for index therapy, and calendar year of initiation. Risperidone users were more frequently observed in more stringently managed (ie, HMO) settings and Southern health plans, while olanzapine was seen more frequently in Western plans. Clozapine users had a higher number of prescriptions on average as compared with the other atypical groups. A larger proportion of patients receiving olanzapine began therapy in 2001 and fewer began therapy in the previous years as compared with patients receiving risperidone, clozapine, and quetiapine. Olanzapine, risperidone, and quetiapine users were significantly more likely to have psychiatric comorbidities than clozapine users, although these results should be interpreted with caution due to small sample sizes in the latter group.

Of the 45 cases of new-onset DM during follow-up for patients receiving atypical antipsychotics, 23 (2.45%), 16 (2.32%), 2 (5.71%), and 4 (2.44%) were among olanzapine, risperidone, clozapine, and quetiapine users, respectively. These differences were not statistically significant (*P* = .9363).

The results of Cox proportional hazards analyses are presented in Table 4. When the overall atypical and conventional antipsychotic cohorts were compared, atypical antipsychotic use was temporally associated with a moderately increased risk of DM at 1 year after therapy initiation relative to conventional antipsychotics (HR = 1.172, 95% CI = 1.061, 1.300; *P* = .0063). Among other variables in the model, age, number of DM and other laboratory tests, and the presence of a bipolar disorder diagnosis all conferred moderately protective effects with respect to DM

risk. Each increase in calendar year of therapy initiation, however, was associated with a more than threefold increase in DM risk independent of therapeutic choice (HR = 3.581, 95% CI = 3.492, 3.659; *P* < .0001).

When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset DM (HR = 1.049, 95% CI = 0.930, 1.168, *P* = .4308; HR = 1.170, 95% CI = 0.967, 1.372, *P* = .1291; and HR = 1.467, 95% CI = 0.967, 1.968, *P* =.1332 for olanzapine vs risperidone, quetiapine, and clozapine, respectively). Findings with respect to covariates were similar to those observed in overall comparisons of patients treated with atypical vs conventional medications.

In logistic regression comparisons among those enrolled for at least 12 months after index date, follow-up constraints necessitated collapse of the quetiapine and clozapine cohorts into a single "other" category. In these models, a similar magnitude of difference in risk between the atypical and conventional antipsychotic cohorts was observed, although this was not statistically significant (OR = 1.193 for atypical antipsychotics vs conventional medications, 95% CI = 0.505, 2.820; *P* = .6871) (Table 5). Among other explanatory variables included in this model, no statistically significant differences were observed. DM risk also did not significantly differ among the 3 atypical medication cohorts available in this analysis.

Discussion

To assess, under conditions of general practice, the rate of new-onset DM in schizophrenic patients treated with atypical vs conventional antipsychotics, we retrospectively examined patient data from a US-based, patient-level database of integrated medical and pharmacy claims. The rate of new-onset DM was studied during the first year after therapy initiation, and was examined on a crude and adjusted basis. We found that, in a managed-care population, patients receiving atypical antipsychotic medications for schizophrenia had a statistically significant, moderately increased risk of new-onset DM relative to patients treated with conventional medications. Results were similar in a subset of these patients followed for 12 months or more after therapy initiation. However, in contrast to findings from other studies that have implicated selected atypical medications,[10,20] our results do not suggest any material differences among the patients treated with major atypical medications in use during the study period, regardless of the analytic paradigm employed (ie, fixed follow-up or accrued person-time). It is worth noting that we were able to follow patients for 15 months after therapy initiation on average, a duration of follow-up that exceeds that available in other database studies on this topic.[18,20] While it is premature to conclude that differences among patients treated with various atypical medications in terms of DM risk do not exist, further study is needed to evaluate whether risk differences highlighted after relatively short drug exposure converge over time.

Of note, the variable most predictive, by far, of new-onset DM was calendar year of therapy initiation, which imparted nearly a fourfold increased risk of DM with *each* successive year between 1996 and 2001. This finding may be correlated to the amount of research focused on this topic, suggesting that increased awareness of DM risk may be leading to a heightened amount of scrutiny for DM symptoms in antipsychotic-treated patients. If screening intensity is found to differ by class of antipsychotic or type of atypical medication, however, significant biases may be inherent in any retrospective study of this phenomenon; the true answer may only be determined through the conduct of prospective studies in which DM screening is controlled and unbiased.

The findings of this study also indicate that patients treated for schizophrenia are at higher risk of developing DM than those in the general population. Rates of DM in this study ranged from 1% to 2.5% over 1 year of follow-up, which is 2-10 times the age-adjusted annual rate for US residents as a whole.[25-27] Other published database studies have also found that patients treated with atypical or conventional antipsychotics have an increased risk of developing DM as compared with the general population.[18,19]

Our results are similar to those of other retrospective studies that have relied on automated administrative data. In an analysis of medical and pharmacy claims among patients with schizophrenia enrolled in the Iowa Medicaid program, Lund and colleagues[11] found that the incidence of DM did not materially differ between patients receiving clozapine and those receiving conventional medications over approximately 2 years of follow-up. While a significantly greater risk was noted among clozapine patients aged 20-34 years, this study design did not feature a "washout" period (ie, a period during which prior mental health or DM claims could not have been observed). Findings may have therefore been confounded by experience prior to Medicaid enrollment.

Similarly, in a large study (n = 38,632) of workload data at Veteran's Administration outpatient facilities, the prevalence of DM was essentially identical (approximately 19%) in patients receiving atypical and conventional antipsychotics.[12] The same age-related phenomenon noted in the Lund study was observed here; in addition,

patients treated with clozapine, olanzapine, and quetiapine, but not risperidone, had a significantly increased prevalence of DM in logistic regression analyses. However, systematic differences were noted in the 2 populations, including a higher propensity for hospitalization among atypical users (which may have resulted in opportunistic case finding).

In contrast, Koro and colleagues[10] conducted a nested case-control study using a database of physician records in the United Kingdom, in which use of olanzapine was associated with a fourfold increased risk of diabetes relative to conventional antipsychotics, whereas no such association was observed among patients receiving risperidone. Findings from this study may be limited, however, by the following: (a) data are only included in this database when certain research standards are met (reducing the availability of historical data) and only three quarters of specialist interactions are captured electronically; and (b) the confidence interval around DM risk was quite large among users of atypical medications (which was likely due in part to a very small number of incident events in this group). This phenomenon was not observed in the much larger group with conventional medication exposure, suggesting that a different analytic paradigm with a larger representation of medications in the atypical class (as we feel our study represents) may yield different results.

While our sample included patients diagnosed with schizophrenia who were newly started on antipsychotic medications, it is likely that many of these patients were not newly diagnosed. Patients may have ceased antipsychotic therapy more than 6 months before our defined index date and were therefore retained in our sample, or may have been hospitalized during much of the preindex period. Indeed, the fact that the average age of our sample was older than typical for a cohort of newly diagnosed schizophrenics supports the notion that patients in our sample were a mix of the newly diagnosed and "restarted." While it could be argued that ICD-9-CM coding of mental health disorders is neither highly sensitive nor specific, we allowed medication use to be the final arbiter of sample inclusion, as most of the other studies on this topic have done.

We note some important limitations of our analysis. First, the data sources for the PharMetrics database consist of processed healthcare claims from managed care organizations; as such, we could not control for certain clinical or other differences between treatment groups (eg, baseline body mass index, lipid levels, family history) that may have confounded our findings. Also, privacy regulations prohibit the capture of race or ethnicity in the database, a well-documented confounding variable when assessing DM incidence.

In addition, as with all quasi-experimental research using retrospective data, we cannot rule out the possibility that selection bias may have influenced our findings; nevertheless, our results were unchanged when we controlled for differences in those demographic and clinical variables that were available to us in this database.

We also note that antipsychotic exposure was estimated based on prescription filling behavior as a proxy for actual consumption. If patients receiving atypical medications are in fact more or less likely to comply with prescribed treatment regimens than those receiving conventional agents, a bias may be introduced to our study. In this sample, however, *persistence* (as measured by duration of therapy) was quite similar across these cohorts while number of prescriptions was significantly higher in the atypical group, suggesting that they were behaviorally similar in persistence while atypical patients may have been more compliant with therapy.

Given the above discussion, this sample is likely to be fundamentally different from the US schizophrenic population, many of whom are insured by public sources or uninsured. Still, the large number of data sources that feed into this database speaks to the study's internal validity. In addition, the biologic effects of antipsychotic medication on DM incidence should not be subject to great variability across cohorts, even given the potential differences in risk factor profiles across groups.

Despite these limitations, the results of our study suggest that attribution of an increased risk of diabetes to a particular brand of antipsychotic may represent a premature conclusion. Patients treated with atypical antipsychotics appear to have a moderately increased risk of diabetes relative to patients treated with older medications. However, further rigorously controlled, long-term, prospective studies are needed.

Tables

Table 1. Conventional and Atypical Antipsychotic Medications Included in Analyses

Conventional	Atypical
Acetophenazine	Clozapine
Chlorpromazine	Olanzapine
Chlorpromazine HCL	Quetiapine
Chlorprothixene	Risperidone
Fluphenazine	
Fluphenazine decanoate	
Fluphenazine enanthate	
Fluphenazine HCL	
Haloperidol	
Haloperidol decanoate	
Haloperidol lactate	
Loxapine	
Loxapine HCL	
Loxapine succinate	
Mesoridazine besylate	
Molindone HCL	
Perphenazine	
Pimozide	
Promazine	
Promazine HCL	
Thioridazine	
Thioridazine HCL	
Thiothixene	
Thiothixene HCL	
Trifluoperazine	
Triflupromazine	

Table 2. Demographic and Clinical Characteristics as Well as Diabetes Incidence Among Schizophrenia Patients, by Antipsychotic Treatment Group

Characteristic	Atypical (N = 1826)		Conventional (N = 617)		P Value
"Age in years (mean, SD)"	38.0	12.4	42.4	11.7	< .0001
Gender (% male)	877	48.0%	300	48.6%	0.8272
"Duration of follow-up (mean, SD)"	418.8	247.2	485.0	285.7	< .0001
"Index medication use (mean, SD):"					

Total duration of therapy	260.8	247.6	252.4	273.5	0.4889
Number of prescriptions	8.5	9.6	6.6	7.6	< .0001
Year of therapy initiation:					0.0003
1996	9	0.5%	7	1.1%	
1997	16	0.9%	13	2.1%	
1998	274	15.0%	130	21.1%	
1999	693	38.0%	220	35.7%	
2000	645	35.3%	188	30.5%	
2001	189	10.4%	59	9.6%	
Plan type:					0.535
HMO	879	48.1%	309	50.1%	
PPO	259	14.2%	96	15.6%	
POS	201	11.0%	57	9.2%	
Indemnity	117	6.4%	41	6.6%	
Other	370	20.3%	114	18.5%	
Geographic region:					0.276
Northeast	297	16.3%	98	15.9%	
South	554	30.3%	212	34.4%	
Midwest	591	32.4%	179	29.0%	
West	384	21.0%	128	20.7%	
Psychiatric diagnosis:					
Bipolar disorder	796	43.6%	193	31.3%	< .0001
Depression	972	53.2%	232	37.6%	< .0001
Medical diagnosis:					
Hypertension	228	12.5%	106	17.2%	0.0033
Cardiovascular disease	188	10.3%	50	8.1%	0.1068
Obesity	69	3.8%	24	3.9%	0.8952
Impaired glucose tolerance	2	0.1%	1	0.2%	0.7463
"Laboratory tests (mean, SD):"					
Diabetes screening	1.0	1.9	1.1	2.1	0.1098
All other	5.8	11.5	5.9	13.2	0.8428
Incidence of diabetes at one year (%)	45	2.46%	17	2.76%	0.5252

Table 3. Demographic and Clinical Characteristics and Diabetes Incidence Among Schizophrenia Patients, by Atypical Antipsychotic Group

	Olanzapine	**Risperidone**	**Clozapine**	**Quetiapine**	***P***

Characteristics	(N = 937)		(N = 690)		(N = 35)		(N = 164)		Value
Age (mean SD)	38.4	12.4	37.2	12.3	36.8	9.5	39.7	11.1	0.0695
Gender (% male)	469	50.1%	334	48.4%	16	45.7%	58	35.4%	0.0039
Duration of follow-up (mean SD):	415.4	236.8	429.4	257.3	388.9	263.0	399.8	234.3	0.1295
Index medication use (mean SD):									
Total duration of therapy	261.4	236.6	260.5	256.6	329.5	260.5	244.1	238.0	0.237
Number of prescriptions	8.3	8.4	7.5	7.0	32.0	26.8	9.0	11.1	< .0001
Year of therapy initiation:									< .0001
1996	0	0.0%	9	1.3%	0	0.0%	0	0.0%	
1997	9	1.0%	6	0.9%	1	2.9%	0	0.0%	
1998	160	17.1%	101	14.6%	3	8.6%	10	6.1%	
1999	379	40.4%	243	35.2%	14	40.0%	57	34.8%	
2000	297	31.7%	266	38.6%	11	31.4%	71	43.3%	
2001	92	9.8%	65	9.4%	6	17.1%	26	15.9%	
Plan type:									0.0001
HMO	449	47.9%	345	50.0%	13	37.1%	72	43.9%	
PPO	117	12.5%	99	14.3%	4	11.4%	39	23.8%	
POS	104	11.1%	74	10.7%	7	20.0%	16	9.8%	
Indemnity	55	5.9%	38	5.5%	7	20.0%	17	10.4%	
Other	212	22.6%	134	19.4%	4	11.4%	20	12.2%	
Geographic region:									< .0001
Northeast	153	16.3%	114	16.5%	4	11.4%	26	15.9%	
South	244	26.0%	240	34.8%	5	14.3%	65	39.6%	
Midwest	309	33.0%	212	30.7%	20	57.1%	50	30.5%	
West	231	24.7%	124	18.0%	6	17.1%	23	14.0%	
Psychiatric diagnosis:									
Bipolar disorder	407	43.4%	293	42.5%	7	20.0%	89	54.3%	0.003
Depression	481	51.3%	375	54.3%	12	34.3%	104	63.4%	0.0071
Medical diagnosis:									
Hypertension	118	12.6%	81	11.7%	2	5.7%	27	16.5%	0.3264
Cardiovascular disease	97	10.4%	70	10.1%	2	5.7%	19	11.6%	0.5879
Obesity	31	3.3%	25	3.6%	2	5.7%	11	6.7%	0.2903
Impaired glucose tolerance	1	0.1%	0	0	1	2.9%	0	0	< .0001
Lab tests (mean SD):									
Diabetes screening tests	1.0	2.1	0.9	1.8	0.7	1.7	1.1	1.7	0.705
All other general lab tests	5.4	10.0	5.8	11.6	15.7	27.5	6.2	11.4	< .0001
Incidence of diabetes (%)	23	2.45%	16	2.32%	2	5.71%	4	2.44%	0.9363

Table 4. Results of Cox Proportional Hazards Model of Risk of Diabetes at 1 Year Post-Index Among Schizophrenia Patients, by Comparison Cohort

Variable	Coefficient	Standard Error	Chi-Square	P Value	Hazard Rate	95% CI Lower	95% CI Upper
Atypical vs Conventional	0.1608	0.059	7.4044	0.0063	1.172	1.061	1.30
Olanzapine vs:							
Risperidone	0.0477	0.0606	0.6206	0.4308	1.049	0.930	1.168
Quetiapine	0.1566	0.1032	2.3035	0.1291	1.170	0.967	1.372
Clozapine	0.3834	0.2553	2.2549	0.1332	1.467	0.967	1.968

Table 5. Results of Logistic Regression Model of Risk of Diabetes Among Schizophrenia Patients Followed for 12 Months Post-Index, by Comparison Cohort

Variable	Coefficient	Standard Error	Chi-Square	*P* Value	Odds Ratio	95% CI Lower	95% CI Upper
Atypical vs Conventional	0.0884	0.2194	0.1623	0.6871	1.193	0.505	2.82
Olanzapine vs:							
Risperidone	-0.1481	0.4521	0.1073	0.7433	0.521	0.182	1.490
Other	-0.1481	0.4521	0.1073	0.7433	1.232	0.138	11.001

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A Comprehensive Retrospective Study of Associations Between Diabetes and Treatment with Risperidone, Olanzapine, Quetiapine, and Conventional Antipsychotics

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Abstract

Background: Retrospective studies using large patient databases have had conflicting findings regarding diabetes risks associated with antipsychotics. Sensitivity of findings to study design was assessed.

Methods: Claims data were analyzed for thousands of patients with psychoses both treated and untreated with antipsychotics. Screening for pre-existing diabetes, identification of diabetes with prescription claims only, and antipsychotic monotherapy provide better control for confounding influences and represent a stronger study design. Diabetes odds ratios for patients treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics versus untreated patients were estimated varying the above criteria. This was done for all patients and patients stratified by low, medium, and high dose levels. Logistic regression controlled for patient age, sex, type of psychosis, length of observation/treatment, pre-existing excess weight, and use of other drugs with potential diabetogenic effects.

Results: Under a weaker study design, all of the antipsychotics were associated with significantly higher odds of diabetes relative to patients untreated with antipsychotics. Differences among the antipsychotics were relatively small; odds ratios with 12 months of treatment were: risperidone 1.388 (CI: 1.276-1.509), olanzapine 1.331 (CI: 1.224-1.446); quetiapine 1.394 (CI: 1.247-1.559), and conventionals 1.365 (CI: 1.238-1.503). Under a stronger study design, relative odds for quetiapine became statistically insignificant and declined sharply,1.087(CI: .742-1.612), while those for olanzapine and conventional antipsychotics remained significant and increased, 1.858 (CI: 1.549-2.238) and 1.755 (CI: 1.381-2.221) . Risperidone's overall odds ratio also declined and became nonsignificant, 1.224 (CI: .962-1.562). When stratified by dose, quetiapine alone showed a lack of statistical significance at all dose levels. For conventionals antipsychotics odds of diabetes were significantly higher than untreated patients at all dose levels, for olanzapine at medium and high doses, and for risperidone at high dose only. Regardless of statistical significance, however, all three atypicals showed an increasing relationship between estimated odds of diabetes and dose level. Absence of this association for

conventional antipsychotics may be explained by the aggregate nature of this category.

Conclusion: In large database studies, estimated risks of diabetes among antipsychotics are affected by study design. With a more reliable design, the estimated risks associated with quetiapine and risperidone are lower than those associated with olanzapine and conventional antipsychotics.

Introduction

A growing number of case reports and studies suggest that some antipsychotic medications impose a higher risk of diabetes mellitus than others.[1-18] Case findings, prospective trials and chart reviews have strongly implicated olanzapine and clozapine,[1-9] but are limited by small numbers. Restrospective studies based on claims and similar patient records[10-18] often have the advantage of large numbers, but have had more varied results, which may be attributed to differences in study design. For example, some studies have used less precise methods for associating diabetes with specific antipsychotics[10,11,13,15] while this study and earlier studies identified antipsychotic treatment episodes to match the time of diabetes onset with the time of specific antipsychotic use.[14,16,17,18] Because of real world practices of switching antipsychotics and prolonged periods of non-antipsychotic use (possibly characterized by use of other psychotropic drugs), less timing-sensitive methods have a greater likelihood of wrongly associating diabetes cases.

Findings of diabetes risk can also be affected by other aspects of study design including decisions to screen or not screen patients for preexisting diabetes and to identify diabetes using medical or prescription claims versus prescription claims only. Screening for pre-existing diabetes is particularly important if antipsychotics are subject to selection bias. Patients with pre-existing diabetes may be more likely to be initiated on or switched to antipsychotics that are perceived to be safer. The presence of prescription claims for antidiabetics or insulin is a definite indicator of diabetes, while medical claims showing diabetes ICD-CM-9 codes may simply reflect testing for diabetes including tests with negative results. Precautionary testing for diabetes among patients treated with antipsychotics may have become more common with increasing awareness of this adverse effect. Also, mild cases of glucose elevation not requiring treatment should be distinguished from more serious cases requiring antidiabetics or insulin.

Building on our earlier work,[18] this retrospective claims-based study represents a more rigorous assessment of associations of risperidone, olanzapine, quetiapine, and conventional antipsychotics with diabetes mellitus. Estimates of diabetes risk were generated using both a weaker and a stronger study design to demonstrate why retrospective studies have come up with conflicting findings..

Methods

The study was based on claims data for tens of thousands of patients with schizophrenia, bipolar disorder, and major depression obtained from several commercial health plans totaling 33 million lives. The data covered the period 1999 through April 2002.

Methods are similar to those of our earlier studies in that defined treatment episodes were used to associate diabetes cases. A main deviation from earlier work is the focus on all diabetes mellitus rather than just type 2. Type 2 or non-insulin-dependent diabetes mellitus, also known as adult onset diabetes, is distinguished from type 1 or insulin-dependent diabetes mellitus, which usually emerges early in life and is due to a genetic defect that causes the pancreas to under-produce insulin or to produce none at all.[21] Known effects of antipsychotics on weight gain[22,23] and suspected effects of reducing glucose transporters and decreasing pancreatic β-cell responsiveness, resulting in impairment of glucose metabolism,[1,2,19,20] make type 2 diabetes the obvious concern. Case reports have largely focused on type 2 diabetes.[3] Nevertheless,exclusion of type 1 cases now seems inappropriate. First, some researchers have identified reduced insulin secretion (type 1) as being very likely in some antipsychotic-related diabetes cases, particularly those involving diabetic ketoacidosis.[20] Second, in claims data reporting of diabetes type is likely inaccurate. For example, in about 40% of patients it was found that diabetes type was not specified or that both type 1 and type 2 were reported. The latter may reflect a tendency to indicate type 1 if a type 2 patient is prescribed insulin.

By and large, commercially insured patients with psychoses do not have continuous use of antipsychotics. This is not surprising among individuals with bipolar disorder or major depression where other psychotropic medications such as mood stabilizers and antidepressants have been the principal forms of therapy. (Though off-label use is widespread, antipsychotics, with the exception of olanzapine, have FDA indications for schizophrenia only.) A treatment episode represents continuous or fairly continuous use of an antipsychotic. Antipsychotic use was most continuous for patients with schizophrenia and least continuous for patients with major depression. Prescriptions with fill dates separated by ninety days or less were judged to be part of same treatment episode. For determining the beginning of a treatment episode, it was required that a prescription for a given antipsychotic not be preceded by an earlier prescription for that antipsychotic for at least 120 days. The vast majority of prescriptions were for 30 days supply. Also, to ensure an adequate amount of antipsychotic exposure

and that patients were in fact compliant, only those patients who had at least two consecutive prescriptions (60 days) of an antipsychotic were included. Generally, an antipsyhotic treatment episode was measured from the fill date of the first prescription to the end date of treatment, which was determined by adding the last prescription's days supply to its fill date. A patient's disenrollment date or the end date of the data replaced this calculated date if it came first. These methods are similar those used in three publications on this subject[14,17,18] and are also discussed in a methods publication.[24]

Treatment episodes, rather than patients per se, were the sampling units for which diabetes risk was measured. Use of the patient rather than the antipsychotic treatment episode as the unit of analysis is incompatible with how antipsychotics are used in real world settings. Many patients had multiple treatment episodes with different antipsychotics or even the same antipsychotic. The fact that antipsychotic treatment durations vary considerablyadds to the complexity of using the patient as the ampling unit.. Picking a uniform duration, and therefore observation period, not only limits sample size, but also precludes important information on the relationship between treatment duration and diabetes risk. Making the observation period uniform, while allowing treatment duration to vary also makes little sense. For example, if the observation period were set at 12 months for all patients, a large number of patients would have treatment durations that were far shorter, meaning that diabetes that became manifest long after the treatment ended would be assigned to the antipsychotic. These and related issues were discussed in an earlier publication.[14]

The control population consisted of psychosis patients who were not treated with antipsychotics for extended periods of time. Because diabetes may be associated with schizophrenia, bipolar disorder, and major depression independently of antipsychotic use,[25-29] an untreated psychosis population is more suitable than the general population for measuring the incremental diabetogenic effects of antipsychotics. To avoid confounding the presence or absence of treatment with the length of observation, observation periods for controls were made to vary in length as did antipsychotic treatment episodes. .

Statistical methods

As in earlier published studies,[11,14,15, 17,18] logistic regression was used to estimate diabetes risk associated with specific antipsychotics.The risk of acquiring diabetes was related to the length of time

that an individual was treated with an antipsychotic. Some antipsychotics may not pose a risk and, therefore, there would be no relation with treatment duration. Others may pose a more accelerated risk, while yet others may pose a more gradual risk. In earlier studies[14,17,18] treatment duration was measured as a continuous variable. The effect of each antipsychotic on diabetes risk was related to the number of months that an individual was treated with that antipsychotic. Zero values for all of the antiposychotics specified in the models indicated a control patient. The estimated odds ratio for each antipsychotic indicated the proportion by which one month of treatment with that antipsychotic increased the risk of diabetes relative to an untreated psychosis patient. With continuous variables in logistic regression, the correct procedure for determining the effects of multiple units, months of treatment in this case, is to raise the estimated odds ratio to a power equivalent to the desired number of units (months).[30] For example, if the estimated (one-month) odds ratio for an antipsychotic is 1.05, the odds ratio for twelve months of treatment is $(1.05)^{12} = 1.80$. This means that twelve months of treatment with the antipsychotic increases the risk of diabetes by 80 percent over that of an untreated patient.

Antipsychotic dose levels may also affect the risk of diabetes. To assess differences in diabetes risk associated with antipsychotic dose, patients were grouped into low, medium and high daily dose cohorts with these gradations determined separately for 4 subgroups of patients stratified by: 1) male or female; and 2) child (<18) or adult. Age and gender are correlated with bodyweight, which may influence the effective dose of an antipsychotic. Low, medium, and high dose correspond to the bottom, middle, and top third of the daily dose range for each antipsychotic and patient subgroup Because conventional antipsychotics were grouped into one category and because of concurrent use of antipsychotics, dose was measured in risperidone-equivalent milligrams. For each antipsychotic, the mean daily milligrams for patients falling in the highest and lowest 10 percent of the range were calculated. These were then averaged. Averages of the other antipsychotics were divided into that of risperidone to create conversion factors. Overall means were not used to calculate conversion factors because they are more sensitive to case mix differences among the antipsychotics and may have also reflect prevailing dosing practices.

Diabetes frequencies and logistically estimated odds ratios for treated versus untreated patients were generated irrespective of antipsychotic dose levels as well as separately for patients treated with low, medium, and high doses. To demonstrate the sensitivity of results to study design, comparisons were

made under two extreme designs reflecting weaker and stronger controls for confounding influences. Under the weaker design, patients were not screened for preexisting diabetes, diabetes was identified with medical or prescription claims, and concurrent use of different antipsychotics was allowed. Under the stronger design, patients were screened for preexisting diabetes at eight months prior to observation/treatment, diabetes was identified with prescription claims only, and antipsychotic monotherapy was required.

Identification and removal of preexisting diabetes cases may be necessary to accurately measure antipsychotic-induced diabetes. This is particularly so where selection bias is a likely factor. A growing number of case reports and studies have already made some antipsychotics more suspect than others. Reports and studies on associations between antipsychotics and excessive weight gain, a major risk factor for type 2 diabetes, may have also affected practitioner perceptions regarding certain antipsychotics. Consequently, in more recent years, there may have been a tendency to prescribe "safer" antipsychotics to patients with diabetes or patients perceived to be at greater risk. Therefore, an analysis performed on a patient population not screened for preexisting diabetes would likely be biased. The historical tendency of practitioners to prescribe quetiapine as a second-line antipsychotic may have made it more susceptible to selection bias. In some instances quetiapine may have been switched to because of the preceding antipsychotic's side effects, including effects on patient glucose levels and weight.

In our first two studies,[14,17] we counted as diabetes cases all patients reporting this condition on one or more medical claims or having one or more prescription claims for antidiabetes products. In our third study[18] we took a more conservative approach requiring for proof of its presence treatment of diabetes as evidenced by prescription claims.. The problem with the earlier, more liberal approach is that a medical claim showing an ICD-9-CM code for diabetes does not necessarily mean that the patient tested positively for this condition. (Claims are payment instruments and not medical records.) Also, testing for diabetes may not even be indicative of a "potential" problem with the new therapy. It may reflect concerns over a problem, say excessive weight gain, caused by a prior therapy. The likelihood of carry-over concerns with prior therapies is greater for quetiapine, which historically was more likely than risperidone and olanzapine to have been used as a second-line antipsychotic. While more accurate,

reliance on prescription claims only, excludes cases of modest glucose elevation and thereby tends to favor antipsychotics with relatively mild diabetogenic effects.

The data for this and earlier studies reveal that a considerable proportion of psychosis patients use two or more antipsychotics concurrently. While this is largely explained by a recommended overlap when transitioning from one antipsychotic to another,[31] there were many cases of prolonged concurrent use. In our earlier diabetes studies, the confounding effects of concurrent use were dealt with in two ways. First, a variable was specified in the models that indicated the presence and degree of concurrent treatment with another or other antipsychotics. Second, because treatment episodes overlapped where there was concurrent use, diabetes manifesting during the overlap was assigned to both antipsychotics. Nevertheless, these remedies may be inadequate. Where there are overlaps, there is no way of avoiding assignment of diabetes to antipsychotics that in actuality have no or weaker diabetogenic effects, since this cannot be known a priori.

The following measures were specified as control variables in the logistic models.

Age	The risk of type 2 diabetes, also known as adult-onset diabetes, increases with age. Patient age was specified as a continuous variable.
Gender	Patient gender was specified as a categorical (1,0) variable. Case reports and some patient record reviews have revealed a higher proportion of males with antipsychotic associated diabetes.[3,32] This finding, however, is contradicted by other findings that show a higher proportion of females with antipsychotic associated diabetes[12] or suggest that the higher proportion of males reflects the higher proportions treated with specific antipsychotics.[2]
Other drugs w/ diab. Effect.	Categorical variables were specified to indicate patient use of each of the following drugs known or suspected of having diabetogenic effects: 1) thiazide diuretics; 2) beta-blockers; 3) protease inhibitors; 4) SSRI's; 5) valproate sodium; and 6) lithium.[33-36] In

	addition, the total amount spent on these prescriptions per patient per month was specified to capture intensity of use.
Prior excess weight problem	A categorical variable was specified to indicate if a patient had a prior (i.e. prior to observation) excess weight problem, as indicated by prior prescriptions for diet medications or medical claims for this condition.
Substance abuse/dependence	Type 2 diabetes can result from excessive use of alcohol or drugs. A categorical variable was specified to indicate if a patient had present or past evidence of alcohol or drug abuse or dependence. This will be evidenced by medical claims with the appropriate ICD-9-CM codes (292.xx, 293.xx, 304.xx, 304.xx).
Switch from other antipsychotic	A categorical variable was specified to indicate whether the patient initiated on risperidone, olanzapine, quetiapine, or a conventional switched from another antipsychotic. Switches were defined as treatment episodes showing another antipsychotic prescription within 60 days prior to their begin dates.
Concurrent use of oth antipsych	This was measured with a continuous variable which is the ratio of the concurrent antipsychotic's total days supply to the index antipsychotic's total days supply within the index antipsychotic's treatment episode. This variable was used only in the scenario not restricted to monotherapy.
Type of psychosis	Risk of diabetes mellitus may be psychosis-related,[22-26] and because of their different pathogeneses, the different forms of psychosis may pose different risks. Type of psychosis was indicated by two categorical variables representing bipolar disorder and schizophrenia, with zeros for both of these representing major depression. Where more than one of the three types of psychosis was reported on a patient's medical claims, classification was based on the most recent because this was judged to be the more accurate (being based on more patient history).

Length of observation	For psychosis patients treated with antipsychotics, observation periods, which correspond to treatment episodes, vary in length. Observation periods for untreated patients were also be made to vary in length to avoid confounding. Since the likelihood of observing diabetes (or most any illness) in an individual increases with time of observation, it is necessary to control for these differences.
Type of insurance coverage	Because of differing emphases on preventive care, type of coverage may affect risk of diabetes. It may also affect access to care and, therefore, diagnosis of diabetes. Four categorical variables captured the four main types of insurance coverage represented in the database: HMO, preferred provider, point of service, and indemnity. Zero values for all of these represent other lesser types of coverage.

Although it was done in other studies,[11] the inclusion of other mental disorder comorbidities is questionable in that the direction of causality is uncertain. For example, depression and anxiety may result from diabetes.[37]

Results

Sample and Patient Characteristics

There were a total of 37,318 treatment episodes with risperidone, olanzapine, quetiapine or conventional antipsychotics that were initiated within the period 1999 through 2001 and had at least 60 consecutive days of the defining antipsychotic. The number of unique patients represented by these treatment episodes was somewhat smaller because some patients were counted more than once, being treated at different times with the same or a different antipsychotic. The control group consisted of 33,272 psychosis patients who were not treated with antipsychotics or not treated for long periods. Treated and untreated psychosis patients consisted mainly of persons with major depressive disorder (46% and 56%) followed by bipolar disorder.(34% and 39%). The number of schizophrenia patients was relatively small in both groups (20% and 4%), particularly the untreated group.

Characteristics of untreated psychosis patients and patients treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics are shown in Table 1. These characteristics correspond to the control variables specified in the logistic regression models. Patients treated with conventionals were considerably older than those treated with the atypicals, particularly risperidone. Untreated patients fell in between. Females were generally more prevalent than males among both treated and untreated patients. Risperidone and olanzapine-treated patients had relatively higher proportions males. Major depression and bipolar disorder were the dominant psychosis types among both treated and untreated patients, with schizophrenia patients being relatively few particularly in the untreated group. Observation periods, which are equal to treatment durations for treated patients, averaged the longest for the untreated group and the shortest for olanzapine. Median observation periods/treatment durations, however, were more similar. Among treated patients, antipsychotic daily dose, measured in risperidone-equivalent milligrams, averaged highest for conventionals. This is consistent with the fact that conventional-treated patients by far had the highest proportion of schizophrenia. Median daily doses show the same ranking but are less disparate.

Other medications with suspected diabetogenic effects were generally more widely used by treated than untreated patients, as reflected in the percentages as well as in the per capita expenditures per patient per month. SSRIs were the most widely used of these drugs followed by lithium. Risperidone-treated patients had the highest use of SSRIs while conventional-treated patients had the highest use of beta-blockers, consistent with their older age. Substance dependence/abuse was most prevalent among olanzapine-treated patients followed by quetiapine. Quetiapine-treated patients had the highest proportion with prior excess weight problems followed by conventionals, while untreated patients had the smallest proportion. Conventional-treated patients had the smallest proportion on antipsychotic monotherapy followed by quetiapine. A considerably higher proportion of quetiapine-treated patients were switched from another antipsychotic, which is consistent with the greater prevalence of prior excess weight problems within this group. The mix of insurance coverage did not differ greatly between groups, with HMO generally being the dominant type.

Comparisons of Diabetes Frequencies

In Table 2 diabetes frequencies of patients treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics are compared to each other and to those of psychosis patients untreated with antipsychotics. This is done under both a weaker and stronger study design. Patients are stratified by antipsychotic treatment duration or length of observation. Treated patients are also stratified by low, medium, and high antipsychotic dose. Under both designs relative frequencies generally increase with treatment duration. There is also a general tendency for relative frequencies to increase with dose among all of the antipsychotics except conventionals

Under the weaker study design – no pre-screening, diabetes identified with medical or prescription claims, and monotherapy not required– diabetes relative frequencies for treated patients are higher than those for patients untreated with antipsychotics for every observation/treatment length and for every dose level. Among treated patients, conventionals had the highest relative frequencies irrespective of dose level while risperidone had the lowest followed closely by quetiapine. This ranking is also apparent when frequencies are stratified by dose. Generally, differences among the three atypicals are not large.

Under the stronger study design –pre-screening at 8 months, diabetes identified with prescription claims only, and monotherapy required - differences in diabetes frequencies between untreated patients and quetiapine-treated patients became relatively small. If fact, patients treated with low doses of quetiapine had lower diabetes frequencies than untreated patients . In addition, diabetes frequencies for quetiapine are lowest among the antipsychotics followed closely by risperidone. Frequencies for olanzapine and conventionals are much higher overall and in each of the three dose levels and exceed those of untreated patients by considerable margins. Among all three of the atypical antipsychotics , there was a clear tendency for diabetes frequencies to increase with dose level. The absence of this relationship for conventional antipsychotics may be explained by the aggregate nature of this category.

Odds ratios estimated with logistic regression

Odds ratios reflecting 12 months of treatment with risperidone, olanzapine, quetiapine, or conventionals versus psychosis patients untreated with antipsychotics are reported in Table 3. These were estimated

irrespective of dosage level and separately for patients grouped into low, medium and high dose cohorts. Ratios under the weaker and stronger study designs were estimated with logistic regression and reflect control for patient differences reported in Table 1. Under the weaker study design, odds ratios measured over all dose levels were statistically significant and similar for all antipsychotic categories, ranging from 1.331 for olanzapine to 1.394 for quetiapine. With the exception of low-dose risperidone, odds of diabetes were significantly higher than untreated patients among all of the antipsychotics at all three dose levels. Odds ratios generally increased with antipsychotic dose, with this tendency being notably weaker for conventionals. .

Large differences among the antipsychotics emerged when a stronger study design was applied.. Over all dose levels, olanzapine and conventionals alone had odds of diabetes that were significantly higher than untreated patients (OR=1.858 and OR=1.755, respectively). Overall odds ratios for quetiapine (1.087) and risperidone (1.224) were statistically insignificant and much lower than those for olanzapine and conventionals. When patients were separated by dose level, conventionals had significantly higher odds of diabetes than untreated patients at all dose levels (p=.0007, .0009, and .0425 for low, medium, and high dose). Olanzapine had significantly higher odds at medium (p<.0001) and high (p<.0001) dose levels while risperidone had significantly higher odds at the high dose level only (p=.0249). Quetiapine's odds ratios were not statistically significant at any dose levels (p = .3452, .3552, and .1596 for low, medium and high dose). Despite the lack of significance, quetiapine's odds ratios increased with dose as did olanzapine's and risperidone's and this ~~in itself may suggest~~ relationship of some diabetogenic effect. The absence of an increasing relationship between diabetes odds and dose for conventional antipsychotics seems counterintuitive. This result, however, may be explained by the aggregate nature of this category (over 20 conventionals are represented). The mix of conventional antipsychotics may have changed considerably from one dose level to the next.

Among the control variables, patient age, a diagnosis of schizophrenia, a preexisting excessweight problem, and use of beta-blockers were consistently significant and positively associated with diabetes risk. Each additional year of age increased diabetes risk by 4-6% depending on study design and dose cohort. Patients with schizophrenia had a 40-100% greater risk of diabetes than patients with major depression and about a 30-70% greater risk than patients with bipolar disorder. Patients with a prior weight problem had about a150% greater risk of diabetes. Use of beta-blockers increased diabetes risk

by 75-90%. Male gender, use of thiazide diuretics and SSRIs, and switching from another antipsychotic also had significant positive associations with diabetes risk, but were less consistent.

Discussion

Evidence from case reports, prospective studies, and chart reviews generally support the conclusion that olanzapine and clozapine have stronger diabetogenic effects than other atypical antipsychotics.[1-9] Retrospective studies based on claims orsimilar patient data, and involving much larger numbers, have had more mixed results. These studies have compared the atypicals to one another, to conventionals, and to persons untreated with antipsychotics. The studies have varied considerably in research design including decisions to screen (e.g., Koro et al., 2002,[12] and Gianfrancesco et al., 2002 [14]) or not screen (e.g. Sernyak, 2002,[11] and Lee et al., 2003[15]) for pre-existing diabetes; to use medical or prescription claims (e.g., Gianfrancesco et al., 2002[14]) versus prescription claims only (Gianfrancesco et al., 2003,[18] and Buse et al., 2003[16]) to identify diabetes; to restrict (e.g. Buse et al.,2003[16]) or not restrict (e.g., Caro et al.,2002[13]) comparisions to antipsychotic monotherapy; and to use more (e.g.,Gianfrancesco et al., 2002,[14] and Buse et al.,2003[16]) or less (e.g., Hendenmalm et al., 2002,[10] and Sernyak et al., 2002,[11]) precision in relating time of diabetes onset to time of specific antipsychotic use. A main goal of the present study has been to assess the sensitivity of findings to study design and, through this exercise, arrive at a more definite determination of the relative diabetes risks associated with the various antipsychotics.

Failure to screen for pre-existing diabetes can bias comparisons if prescribing behavior is sensitive to the perceived risks associated with antipsychotics. For example, mounting evidence regarding antipsychotic effects on glucose levels and body weight may have created a tendency to prescribe "safer" products to patients with diabetes or at greater risk for this condition. Use of medical claims to identify diabetes may also bias comparisons in a manner unfavorable to safer products. Medical claims showing diabetes codes but unaccompanied by prescription claims for anti-diabetics do not necessarily establish the presence of this condition. They may reflect tests with negative results, and growing concerns over antipsychotic-induced diabetes may have made precautionary testing more widespread. Even where tests are positive, glucose elevations may be insufficient to warrant medical intervention. Prescription claims are more definite indicators of significant diabetogenic effects. Lastly, comparing situations where different antipsychotics are used concurrently can further bias comparisons against safer products. Since

diabetes emerging where two antipsychotics overlap must be attributed to both, the safer product is placed at a disadvantage. Comparing only situations of antipsychotic monotherapy avoids this sort of bias.

Consistent with the above arguments, this study has shown that estimates of relative diabetes risk are highly sensitive to screening for preexisting diabetes, to how diabetes is identified and to whether or not comparisons are restricted to situations of antipsychotic monotherapy. Differences among the antipsychotic categories were relatively small under a study design without pre-screening, not restricted to antipsychotic monotherapy, and where diabetes was identified using medical or prescription claims rather than prescription claims only. Under this weaker approach, all of the antipsychotic categories were found to be associated with a significantly higher risk of diabetes than psychosis patients untreated with antipsychotics.

Quetiapine's, and to a lesser extent risperidone's, relative position improved when comparisons were restricted to monotherapy, diabetes was identified with prescription claims only, and with 8 months pre-screening. Under this stronger study design odds of diabetes for quetiapine-treated patients, at all dose levels, were not significantly different from those of psychosis patients untreated with antipsychotics. In contrast, odds for olanzapine-treated patients were significantly higher at medium and high dose levels and those for conventionally-treated patients, at all dose levels. Risperidone showed significantly higher odds at the high dose level only. Patients treated with medium and high doses of olanzapine appear to face twice the risk of diabetes than psychosis patients untreated with antipsychotics. Patients treated with conventional antipsychoticss appear to face 60% more to twice the risk. Regardless of statistical significance, however, estimated odds ratios for all three atypicals increased with dose, which ~~in itself may suggest the presence of~~ a diabetogenic effect. Conventionals did not show an increasing relationship between odds of diabetes and dose, a result that is likely explained by the aggregate nature of this category. For example, the mix of conventional antipsychotics (about 20 different products) may differ in the low, medium, and high dose ranges.

In comparison to the other antipsychotics, results for quetiapine are more sensitive to screening for pre-existing diabetes, the method used to identify diabetes, and to whether comparisons are restricted to antipsychotic monotherapy. Sensitivity to pre-screening and to how diabetes is identified is perhaps

associated with the fact that historically quetiapine was more likely to have been used as a second-line therapy. As reported in Table 1, 35.3% of patients initiated on quetiapine were switched from another antipsychotic versus 17.4% for risperidone and 20.6% for olanzapine, which is also consistent with the fact that a higher percentage of quetiapine-treated patients had prior excess weight problems (3.5% versus 2.6% for risperidone and 2.4% for olanzapine). A medical claim for diabetes does not necessarily mean that a patient has this condition. It may simply reflect testing and testing may have been induced by circumstances, such as excess weight gain, brought on by a prior antipsychotic. Furthermore, even if medical claims are associated with elevated glucose, the absence of prescription claims for antidiabetic medications or insulin suggest that the elevation is not serious. In comparison with the other antipsychotics, particularly olanzapine and conventionals, quetiapine is associated with relatively few diabetes cases requiring medical intervention. The improvement in quetiapine results with monotherapy further attests to its weaker diabetogenic effects. Estimates based on monotherapy more clearly indicate the diabetes risks imposed by each of the antipsychotics, both with respect to each other and with respect to untreated patients.

Effects of study design on estimates of diabetes risk are revealed in other studies. Consider, for example, the study by Sernyak et al (2002)[11] in which a large Veterans Affairs database was used to perform a retrospective comparison of schizophrenia patients treated with typical and atypical antipsychotics. Diabetes was identified with medical claims (ICD-CM-9 codes), there was no screening for preexisting diabetes, and comparisons were not strictly confined to monotherapy. In addition, treatment episodes were not defined, which prevented control for treatment duration and reduced assurance that diabetes onset coincided with the time of specific antipsychotic use. Not surprising, the study found that quetiapine in conjunction with olanzapine and clozapine had significantly higher odds of diabetes than conventional antipsychotics; in fact, quetiapine's estimated odds ratio was the highest. Similarly, a more recent and yet unpublished study by Cunningham et al (2003),[38] also focusing on schizophrenia patients in a large Veterans Affairs database, found quetiapine, olanzapine, and risperidone, but not clozapine, to have significantly higher risks for diabetes in comparison to conventionals. Also, estimated hazard ratios for risperidone and quetiapine were larger than that for olanzapine. While the study controlled for pre-existing diabetes, medical claims were used to identify diabetes and it does not appear, from the limited details available, that comparisons were restricted to monotherapy and that antipsychotic treatment durations were measured and used to refine the analysis.

The above studies' findings with respect to quetiapine are not only at odds with this study, but also conflict with a study involving chart reviews, a clinical trial, and another retrospective study using a very large database. In an examination of medical charts for several hundred patients treated with typical and atypical antipsychotics, Wirsching et al (2002)[9] found significant glucose elevations from baseline for clozapine, olanzapine, and haloperidol, but not for quetiapine and risperidone. In a clinical trial involving 65 schizophrenia patients who were initiated on clozapine and then switched to a clozapine-quetiapine combination, Reinstein et al. (1999)[6] found that glucose levels improved in patients who had developed this condition under clozapine monotherapy. A recent study by Buse et al (2003)[16] exemplifies what we have defined as a "stonger study design": prescription claims only were used to identify diabetes; comparisons were restricted to antipsychotic monotherapy; patients were screened for pre-existing diabetes at 12 months; and antipsychotic treatment duration was measured to ensure that diabetes onset coincided with time of antipsychotic use. Quetiapine was found to have a relatively low diabetes risk in comparison to patients treated with other atypicals and conventionals.

While all of the antipsychotics were associated with significantly higher risks than the general population, this may in part have been due to the underlying psychoses in the treated population.

Lastly, findings from this and other more recent database studies may be affected by a growing practitioner awareness of the potential diabetogenic effects associtiated with specific antipsychotics. There may be an increasing tendency to avoid products that are perceived to be less safe. Since evidence from case reports and past studies has been more negative with respect to olanzapine and clozapine, it is not unreasonable to assume that use of these products is declining among patients at greater risk for diabetes. This tendency would bias more recent database findings against "safer" products such as risperidone and quetiapine.

Conclusion

This study has demonstrated that, in retrospective analyses using claims or other such data, findings of diabetes risk may be strongly influenced by study design. Specifically, because there has been historically a greater tendency to use quetiapine as a second-line antipsychotic, findings relating to its potential diabetogenic effects are highly sensitive to screening for preexisting diabetes, to whether diabetes is identified solely with the more definite indicator, prescription claims, and to whether comparisons are restricted to antipsychotic monotherapy. With an approach incorporating these refinements, quetiapine was found to have the weakest diabetogenic effects, particularly in relation to olanzapine and conventionals.

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Table 1. Profile of Study Population

	Without antipsychotic Treatment	Risperidone	Olanzapine	Quetiapine	Conventionals
Maximum N	33272	12427	12572	6476	5843
Age					
Mean (SD)	35.7 (14)	33.1 (17.2)	36.1 (15)	34.7 (14.6)	41 (13.7)
Median	37	35	38	37	42
Sex (percent)					
Female	65.9	57.1	56.5	67.4	64.8
Male	34.1	42.9	43.5	32.6	35.2
Diagnosis (percent)					
Schizophrenia	4.2	16.3	18.7	14.9	33
Bipolar and Manic	39.5	33.2	38.2	36	27.4
Major Depression	56.3	50.5	43.1	49.1	39.6
Observation Period/antipsych treat duration (months)					
Mean (SD)	10.7 (7.3)	7.7 (6.4)	7.4 (6.3)	7.5 (6.2)	8.1 (6.9)
Median	5	5.5	5.2	5.5	5.7
Antipsychotic Dose (risp equiv mgs)					
Mean (SD)	NA	2.7 (4.2)	3 (3.8)	2.8 (3.2)	3.8 (7.1)
Median	NA	2	2.4	2.1	2.6
Use of Other Drugs with Diab risk					
Valproate sodium (pct of patients)	.29	.64	.83	.57	.87
Lithium (pct of patients)	10.4	13.5	15.2	15.1	15.6
SSRIs (pct of patients)	32.8	40.1	36.8	35.2	32.3
Beta-blockers (pct of patients)	6.1	7.5	8.3	9.6	11.6
Thiazide diuretics (pct of patients)	2.1	2.8	2.9	3.1	4.1
Protease inhibitors (pct of patients)	.09	.08	.15	.05	.29
Mean (SD) dollars of above drugs per patient per month	23.8 (48.4)	42.2 (92.6)	40.1 (152.2)	41.2 (112.9)	37.4 (75.9)
Substance abuse/depend (percent)	3.5	5.0	6.1	5.4	4.9
Prior weight gain problem (percent)	1.9	2.6	2.4	3.5	3
Antipsych monotherapy (percent)	NA	80.4	78.3	73.4	66.3

Switch from other antipsych (percent)	NA	17.4	20.6	35.3	26.6
Type of insurance coverage (percent)					
HMO	47.7	51.9	50.4	47.4	50.9
Preferred provider	25.4	21.2	21.8	25.3	21.1
Point of service	16.9	13	13.3	14.8	12.5
Indemnity	5.1	4	4.4	5.4	5.4
Other	4.9	9.9	10.1	7.1	10.1

NA means "not applicable."

Table 2. Frequency of Diabetes Among Antipsychotic Categories by Treatment Duration and Dose – Weaker Versus Stronger Study Designs

Group	Weaker study design: no screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required		Stronger study design: screening for preexisting diabetes at 8 months prior to observation/treatment, diabetes identified with prescription claims only, and monotherapy required	
	N	Pct diab.	N	Pct diab.
Without antipsychotic treatment				
≤4 months observation	3124	3.14	664	0.00
>4≤8 months observation	13578	4.40	11351	.45
>8≤12 months observation	9078	5.56	8789	.79
>12≤20 months observation	4325	7.49	4165	1.49
> 20 montha observation	3158	7.19	3075	2.15
Average		5.56		.98
		All Dose	**Levels**	
Risperidone				
≤4 months observation/duration	4453	6.15	2868	.66
>4≤8 months observation/duration	3730	7.86	2326	.82
>8≤12 months observation/duration	1857	7.92	1143	1.22
>12≤20 months observation/duration	1602	9.99	940	1.70
> 20 montha observation/duration	785	12.61	356	2.25
Average		8.91		1.33
Olanzapine				
≤4 months observation/duration	4809	5.51	3119	.51
>4≤8 months observation/duration	3757	7.00	2313	1.17
>8≤12 months observation/duration	1744	9.12	1040	2.12
>12≤20 months observation/duration	1496	11.70	815	3.44
> 20 montha observation/duration	766	13.84	344	6.10
Average		9.43		2.67
Quetiapine				
≤4 months observation/duration	2336	5.91	1453	.62
>4≤8 months observation/duration	1994	8.48	1171	.51

>8≤12 months observation/duration	979	8.17	575	.70
>12≤20 months observation/duration	791	9.99	436	1.61
> 20 montha observation/duration	376	12.23	168	1.79
Average		8.96		1.05
Conventionals				
≤4 months observation/duration	2085	7.43	1065	.94
>4≤8 months observation/duration	1639	10.49	783	.89
>8≤12 months observation/duration	857	12.49	386	3.37
>12≤20 months observation/duration	794	16.37	331	3.02
> 20 montha observation/duration	468	14.32	161	8.70
Average		10.82		3.38
		Low	**Dose**	
Risperidone				
≤4 months observation/duration	1314	5.86	985	.91
>4≤8 months observation/duration	1476	6.91	1045	1.05
>8≤12 months observation/duration	773	6.99	531	.75
>12≤20 months observation/duration	633	7.74	421	1.66
> 20 montha observation/duration	248	9.68	135	1.48
Average		7.44		1.17
Olanzapine				
≤4 months observation/duration	1038	5.30	773	.39
>4≤8 months observation/duration	1228	6.84	895	1.45
>8≤12 months observation/duration	548	8.39	390	1.79
>12≤20 months observation/duration	449	10.25	278	1.80
> 20 montha observation/duration	201	9.95	116	3.45
Average		8.15		1.78
Quetiapine				
≤4 months observation/duration	705	5.25	525	.76
>4≤8 months observation/duration	813	8.12	586	.85
>8≤12 months observation/duration	402	6.97	291	.69
>12≤20 months observation/duration	289	10.03	197	.51
> 20 montha observation/duration	118	11.02	88	0.00
Average		8.28		.56

Conventionals				
≤4 months observation/duration	470	7.66	323	1.24
>4≤8 months observation/duration	553	8.14	357	.56
>8≤12 months observation/duration	339	10.62	199	2.01
>12≤20 months observation/duration	323	15.79	173	3.47
> 20 montha observation/duration	192	16.67	81	8.64
Average		11.78		3.18
		Medium	**Dose**	
Risperidone				
≤4 months observation/duration	1530	6.14	1083	.37
>4≤8 months observation/duration	1331	7.96	869	.69
>8≤12 months observation/duration	666	7.81	442	1.81
>12≤20 months observation/duration	561	9.45	365	1.64
> 20 montha observation/duration	309	14.89	155	1.29
Average		7.85		1.16
Olanzapine				
≤4 months observation/duration	1716	5.77	1241	.81
>4≤8 months observation/duration	1444	6.65	942	.74
>8≤12 months observation/duration	681	7.78	431	3.02
>12≤20 months observation/duration	531	10.92	333	3.60
> 20 montha observation/duration	306	12.75	148	6.08
Average		8.77		2.85
Quetiapine				
≤4 months observation/duration	712	6.46	521	.58
>4≤8 months observation/duration	605	6.12	393	0.00
>8≤12 months observation/duration	298	8.05	183	1.09
>12≤20 months observation/duration	236	7.63	151	1.99
> 20 montha observation/duration	1.36	11.03	76	2.63
Average		7.86		1.26
Conventionals				
≤4 months observation/duration	424	7.31	262	1.53
>4≤8 months observation/duration	422	10.66	231	1.30
>8≤12 months observation/duration	220	13.18	101	4.95

>12≤20 months observation/duration	185	14.05	92	3.26
> 20 montha observation/duration	108	12.96	36	8.33
Average		11.63		3.87
		High	**Dose**	
Risperidone				
≤4 months observation/duration	1609	6.40	800	.75
>4≤8 months observation/duration	923	9.21	412	.49
>8≤12 months observation/duration	418	9.81	170	1.18
>12≤20 months observation/duration	408	14.22	154	1.95
> 20 montha observation/duration	228	12.72	66	6.06
Average		10.47		2.09
Olanzapine				
≤4 months observation/duration	2055	5.40	1105	.27
>4≤8 months observation/duration	1085	7.65	476	1.47
>8≤12 months observation/duration	515	11.65	219	.91
>12≤20 months observation/duration	516	13.76	204	5.39
> 20 montha observation/duration	259	18.15	80	10.00
Average		11.32		3.61
Quetiapine				
≤4 months observation/duration	919	5.98	407	.49
>4≤8 months observation/duration	576	11.46	192	.52
>8≤12 months observation/duration	279	10.04	101	0.00
>12≤20 months observation/duration	266	12.03	88	3.41
> 20 montha observation/duration	122	14.75	24	4.17
Average		10.85		1.72
Conventionals				
≤4 months observation/duration	1191	7.39	480	.42
>4≤8 months observation/duration	664	12.35	195	1.03
>8≤12 months observation/duration	298	14.09	86	4.65
>12≤20 months observation/duration	236	18.53	66	1.52
> 20 montha observation/duration	168	12.50	44	9.09
Average		12.97		3.34

Table 3. Odds Ratios for 12 Months of Treatment with Risperidone, Olanzapine, Quetiapine, or Conventionals Versus Psychosis Patients Untreated with Antipsychotics , Overall and Stratified by Dose - Weaker Versus Stronger Study Design

Group	Weaker study design: No screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required*	Stronger study design: screening for preexisting diabetes at 8 months prior to observation/treatment, diabetes identified with prescription claims only, and monotherapy required*
Risperidone		
All dose levels	1.388 (1.276-1.509)	1.224 (.962-1.562)
Low dose	1.134 (.985-1.307)	1.132 (.766-1.762)
Medium dose	1.502 (1.331-1.695)	1.140 (.784-1.657)
High dose	1.568 (1.363-1.805)	1.683 (1.069-2.645)
Olanzapine		
All dose levels	1.331 (1.224-1.446)	1.858 (1.549-2.238)
Low dose	1.207 (1.041-1.401)	1.394 (.987-1.970)
Medium dose	1.262 (1.111-1.434)	1.996 (1.541-2.586)
High dose	1.511 (1.334-1.712)	2.283 (1.658-3.144)
Quetiapine		
All dose levels	1.394 (1.247-1.559)	1.087 (.742-1.612)
Low dose	1.404 (1.171-1.684)	.667 (.288-1.545)
Medium dose	1.276 (1.049-1.552)	1.279 (.760-2.151)
High dose	1.561 (1.193-1.621)	1.677 (.817-3.445)
Conventionals		
All dose levels	1.365 (1.238-1.503)	1.755 (1.381-2.221)
Low dose	1.340 (1.162-1.545)	1.753 (1.267-2.426)
Medium dose	1.353 (1.128-1.623)	2.013 (1.331-3.045)
High dose	1.391 (1.193-1.621)	1.620 (1.017-2.581)

*12 month Odds ratios with 95 percent confidence intervals.

NOTES: Logistic regressions controlled for patient age, sex, type of psychosis (schizophrenia, bipolar disorder, major depression), observation period length, use of other drugs having potential diabetogenic effects, prior excess weight problem, substance abuse/dependence, switch from other antipsychotic, and type of insurance coverage. Age, schizophrenia, observation period length, use of beta-blockers and thiazide, and prior excess weight problem were consistently significant and associated with higher odds of diabetes.

Frequency of New-Onset Diabetes Mellitus and Use of Antipsychotic Drugs Among Central Texas Veterans

Jamie C. Barner, Ph.D., Jason Worchel, M.D., and Min Yang, M.S.

Study Objectives. To determine whether the frequency of new-onset diabetes mellitus differs between patients taking atypical antipsychotic agents and those taking typical agents, whether the frequency of new-onset diabetes differs among those taking the atypical antipsychotic agents, and what clinical and demographic factors influence the occurrence of new-onset diabetes.

Design. Retrospective analysis.

Setting. Central Texas Veterans Health Care System.

Patients. Continuously enrolled adult (≥ 18 yrs) patients with no previous (6 mo) antipsychotic use and no history (previous 1 yr) of diabetes.

Measurements and Main Results. Data from the Central Texas Veterans Health Care System were extracted from September 1995–November 2002. Clinical and demographic factors used in the analysis were antipsychotic agent taken, body mass index, diabetes-related risk factors, type of mental health comorbidity, age, sex, and race. Among those who met the inclusion criteria (3469 patients), χ^2 analyses revealed no significant difference in the frequency of diabetes between the typical and atypical groups (p=0.5553) or among those taking atypical agents (p=0.6520). Multivariate logistic regression (1587 patients) revealed that increasing age (odds ratio [OR] 1.213, 95% confidence interval [CI] 1.016–1.447, p=0.0324), nonwhite race (OR 1.761, 95% CI 1.174–2.640, p=0.0062), and hyperlipidemia (OR 1.606, 95% CI 1.064–2.425, p=0.0242) were significantly related to new-onset diabetes.

Conclusions. Among veterans taking antipsychotic agents, no difference was noted in the frequency of diabetes between patients who took typical agents and those who took atypical agents. After controlling for demographic and clinical variables, still no significant difference was noted among the agents. The main factors (increasing age, nonwhite race, and hyperlipidemia) related to new-onset diabetes were those that are typically associated with the disease.

Key Words: antipsychotics, diabetes mellitus, risk factors.

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Atypical antipsychotic agents have been well received because of their increased efficacy and decreased rate of extrapyramidal symptoms compared with those of typical antipsychotics. Although the atypical agents have some distinct advantages, they also have some disadvantages. Some of the most recently noted issues involve weight gain,[1–6] elevation in triglyceride and cholesterol levels,[7–10] and new-onset diabetes mellitus and diabetes-related complications.[11–34]

The literature surrounding the issue of new-onset diabetes and its association with antipsychotic therapy is primarily populated with case reports[11–30] that date back to 1994 and a few small clinical trials.[31–34] Of the atypical antipsychotic agents, olanzapine and clozapine have

been mentioned more times regarding new-onset diabetes or diabetes-related problems compared with risperidone and quetiapine. Most of the case reports were in men and in people of African-American descent. Most of the case reports did not indicate a family or personal history of diabetes, although it is not clear if these variables were validly assessed. Some reports involved diabetic ketoacidosis, and other cases reported that discontinuation of the atypical antipsychotic resulted in normalization of blood glucose levels.

A number of researchers have conducted several large-scale studies in the last few years to substantiate the claims of treatment-emergent diabetes or exacerbation of preexistent diabetes in patients newly prescribed a particular antipsychotic.[35–46] However, the results from these large-scale studies are far from conclusive.

The mechanism for the potential link between antipsychotic agents and diabetes is not well understood. It has been proposed that the increase in weight gain through stimulation of serotonin, histamine, dopamine, prolactin, and leptin receptors could potentiate glucose dysregulation and subsequently promote new-onset diabetes mellitus.[5, 30] Another mechanism could involve the relationship among triglyceride levels, antipsychotic agents, and diabetes.[32, 33]

In one study, the authors assessed whether patients who switched to ziprasidone experienced significant changes in body mass index (BMI) and glucose, cholesterol, and triglyceride levels.[31] The study showed no significant changes in BMI or glucose level, but a significant improvement in cholesterol and triglyceride levels.

Another group conducted a retrospective study to assess differences in weight, glucose level, cholesterol level, and blood pressure in patients who received olanzapine and haloperidol.[32] Significant weight increases were found in patients receiving olanzapine compared with those receiving haloperidol. Although the olanzapine group had significantly higher glucose and cholesterol levels (when compared with those of the haloperidol group), no significant differences were noted in the frequency of increased glucose level, cholesterol level, or blood pressure.

Another group of investigators assessed the frequency of new-onset diabetes among patients treated with clozapine.[33] Diabetes mellitus was diagnosed in more than one third (36.6%) of the patients. The development of diabetes was significantly associated with increased triglyceride levels. The study also found that there was a significant increase in weight and that the weight gain was significantly associated with increased serum cholesterol and triglyceride levels.

Results of two of the above studies[32, 33] suggest that weight gain may not be the direct link to new-onset diabetes. In a Swedish study, the authors assessed the prevalence of diabetes and impaired glucose tolerance in patients taking clozapine versus those taking depot neuroleptics.[34] Although the study found that the prevalence of diabetes mellitus or impaired glucose tolerance was not statistically significant between the two groups, the percentages of patients who developed diabetes mellitus and impaired glucose tolerance were higher in the clozapine group (12% clozapine vs 6% depot neuroleptics and 10% clozapine vs 3% depot neuroleptics, respectively).

A brief review of the literature shows that the issue of new-onset diabetes among patients taking antipsychotic agents is not well understood. Interpretation of the numerous case reports is difficult because of the lack of a rigorous method to systematically combine the data from the cases. Many of the clinical trials were conducted with small sample sizes and primarily focused on one agent or comparisons of two agents. Most of the large database studies did not control for known factors related to diabetes such as weight gain, hypertension, or hyperlipidemia. In our study, we incorporated these covariates, as well as others, in a multi-variate analysis to determine the relationship between antipsychotic therapy and new-onset diabetes.

The following three objectives were the focus of this study: to determine whether the frequency of new-onset diabetes differed between those

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taking atypical agents and those taking typical agents; to determine whether the frequency of new-onset diabetes differed among those taking the atypical antipsychotic agents; and to determine what factors (e.g., antipsychotic agent used, BMI, diabetes-related risk factors, and demographics) influenced the occurrence of new-onset diabetes.

Methods

Data Source

We used data from the Central Texas Veterans Health Care System (CTVHCS). One distinct aspect of CTVHCS is the computerized patient record system, which electronically captures most patient and clinical information from the medical chart.

Inclusion Criteria

Individual patient level claims records were extracted and analyzed for patients who were aged 18 years or older; had not received a prescription for an atypical or typical antipsychotic agent 6 months before the dispensing of an atypical or typical antipsychotic agent; had no previous use of an antidiabetic drug or diagnosis of diabetes for 1 year before a prescription for a typical or atypical antipsychotic; and were continuously enrolled for 12 months before and after the date of receiving an atypical or typical antipsychotic agent.

Study Variables

The dependent variable for all analyses was whether or not the subject developed diabetes. This was operationalized by a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision* [ICD-9] code 250.xx), blood glucose levels greater than 200 mg/dl, and/or use of an antidiabetic drug between 8 and 365 days after the index date (i.e., the date of the first prescription for an antipsychotic agent).

The primary independent variable was the type of antipsychotic agent that the patient was taking initially—typical agents or the individual atypical agents. The atypical agents were olanzapine, quetiapine, risperidone, clozapine, and ziprasidone.

The control independent variables (and possible answers) were the following: diabetes-related risk factors (yes or no), which included change to higher BMI category, previous hyperlipidemia, and change in hypertension status; persistence (total number of days without a 15-day gap); type of mental health comorbidity (yes or no), which included bipolar disorder, depression, schizophrenia, and substance abuse; age group (18–39 yrs, 40–49 yrs, 50–59 yrs, 60–69 yrs, or 70 yrs or older); sex (male or female); and race (white or nonwhite).

The BMI was calculated for the weight closest (within a 6-mo time frame) to the first use of the antipsychotic agent and for the weight closest (within a 6-mo time frame) to the last use of an antipsychotic agent. Based on their BMI, subjects were assigned to one of six BMI categories established by the National Heart, Lung, and Blood Institute.[47] A dichotomous variable was used to indicate whether or not the subject moved to a higher BMI category status from the first to the last use of the antipsychotic agent.

Previous hyperlipidemia was defined as a cholesterol level of 200 mg/dl or above, a low-density lipoprotein cholesterol level of 130 mg/dl or above, or a triglyceride level of 150 mg/dl or above within 6 months before the first antipsychotic used. Because of limited data within the study time frame, lipid level changes could not be calculated.

Blood pressure measurements were extracted closest to the first and last use of the antipsychotic within a 6-month window. Subjects were categorized into one of six blood pressure groups established by the National Heart, Lung, and Blood Institute.[48] A dichotomous variable was used to indicate whether or not the subject moved to a higher blood pressure category.

Persistence was calculated by summing the total number of continuous days the patient took an antipsychotic agent without a gap (i.e., a 15-day lapse in therapy).

The study received institutional review board approval from both the CTVHCS and the University of Texas.

Data Collection and Analysis

Data from the CTVHCS record system was extracted for the time frame of September 30, 1995–November 1, 2002. The follow-up time period was 1 year after the index date. To compare the frequency of diabetes between patients who received atypical agents and those who received typical agents, χ^2 analyses were used. To compare the frequency of new-onset diabetes among patients receiving atypical antipsychotic agents while controlling for clinical and patient-related variables, a logistic regression

analysis was used. An a priori significance level of 0.05 was used for all analyses.

Results

A total of 6735 patients were identified as taking antipsychotics in the CTVHCS database. One was excluded for being younger than 18 years, 1999 were excluded because of previous antipsychotic use, 819 were excluded because of previous diabetes, and 447 were excluded owing to a less than 12-month enrollment period after antipsychotic use. This resulted in a total of 3469 subjects meeting the inclusion criteria. Most of the sample was male (94.3%) and white (69.9%). Mean ± SD age was 59.4 ± 14.5 years, with subjects aged 50–59 years and those aged 70 years or older constituting 34% and 28% of the sample, respectively.

By using any of the three criteria mentioned in Methods for defining the dependent variable new-onset diabetes, the frequency of new-onset diabetes was 7.1%. When using single categories of elevated blood glucose levels, ICD-9 diagnosis, or antidiabetic drug as the criterion for diabetes, the frequency rates were 4.1%, 3.0%, and 2.1%, respectively. The time to diabetes onset was approximately 5 months (mean ± SD 151.9 ± 105.6 days).

More than 40% (44.3%) of the subjects were taking atypical agents, with olanzapine (23.0%) being prescribed most often, followed by risperidone (16.2%). Among the typical agents, haloperidol (20.0%) was most often prescribed. For the atypical agents, the mean number of persistent days ranged from 117–167 days (3.9–5.6 mo), and for the typical agents the range was 141–220 days (4.7–7.3 mo).

The subjects had various mental health and other comorbidities. Of the 3469 subjects, 1461 (42.1%) did not have ICD-9 data. Of the 2008 subjects with documented ICD-9 data, the diagnoses were substance abuse in 841 (41.9%) patients, depression in 715 (35.6%), and bipolar disorder in 689 (34.3%). Schizophrenia was diagnosed in 681 (33.9%) subjects. On average, the subjects had three (mean ± SD 2.5 ± 1.4) mental health comorbidities.

Subjects were categorized into one of six BMI groups established by the National Heart, Lung, and Blood Institute.[47] Changes in BMI categories from the first to the last use of an antipsychotic agent were assessed. Approximately 36% and 34% (first BMI and last BMI, respectively) of the subjects were considered to be of normal weight, and approximately 38% (both first BMI and last BMI) were categorized as overweight. Approximately 23% and 26% (first BMI and last BMI, respectively) of the patients were categorized as obese. Therefore, 61% and 64% (first BMI and last BMI, respectively) of the patients were either overweight or obese. Most subjects (88%) did not change to a higher BMI category from first to last antipsychotic use.

Thirty percent of the subjects met the criteria for previous hyperlipidemia (cholesterol level ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 130 mg/dl, or triglyceride level ≥ 150 mg/dl 6 mo before taking the first antipsychotic) when using any of the three lipid level categories.[49] Subjects were categorized into one of six hypertension groups established by the National Heart, Lung, and Blood Institute.[48] According to the guidelines, 36% and 34% (first blood pressure and last blood pressure, respectively) of the subjects had hypertension. In most subjects (72%), the hypertension status category did not change.

Table 1. Frequency of New-Onset Diabetes Mellitus in the Atypical and Typical Agent Groups

	No. (%) of Patients	
Variable	Atypical Group (n=1537)	Typical Group (n=1932)
Diabetes	105 (6.8)[a]	142 (7.3)[a]
No diabetes	1432 (93.2)	1790 (92.7)

Intent-to-treat methodology was used.
[a]χ^2=0.3479, p=0.5553.

Table 2. Frequency of New-Onset Diabetes Mellitus Among the Atypical, Typical, and Both Agents Groups

	No. (%) of Patients		
Variable	Atypical Group (n=1390)	Typical Group (n=992)	Both[a] Groups (n=1087)
Diabetes	94 (6.8)[b]	69 (7.0)[b]	84 (7.7)[b]
No diabetes	1296 (93.2)	923 (93.0)	1003 (92.3)

[a]Indicates concomitant use of both atypical and typical agents or switching between the two.
[b]χ^2=0.9160, p=0.6325.

Study Objectives

Tables 1–3 address our first objective, which was to determine whether the frequency of new-onset diabetes differed between those taking typical agents and those taking atypical agents.

Table 3. Frequency of New-Onset Diabetes Mellitus Among the Atypical+ and Typical Agent Groups

Variable	No. (%) of Patients: Atypical+[a] Group (n=2477)	No. (%) of Patients: Typical Group (n=992)
Diabetes	178 (7.2)[b]	69 (7.0)[b]
No diabetes	2299 (92.8)	923 (93.0)

[a]Includes patients taking atypical agents only, as well as those taking both atypical and typical agents.
[b]χ^2=0.0569, p=0.8115.

Table 4. Frequency of New-Onset Diabetes Mellitus Among Patients Taking Atypical Agents

Atypical Agent[a]	No. (%) of Patients: Diabetes	No. (%) of Patients: No Diabetes
Risperidone	42 (7.5)[b]	520 (92.5)
Quetiapine	9 (5.8)[b]	147 (94.2)
Olanzapine	51 (6.4)[b]	745 (93.6)

[a]Ziprasidone (2 patients) and clozapine (21 patients) were not included because of the small sample sizes.
[b]χ^2=0.8554, p=0.6520.

Table 5. Logistic Regression Analysis of Factors Related to New-Onset Diabetes Mellitus in 1587 Patients

Variable[a]	Odds Ratio	95% Confidence Interval	Wald χ^2 Value[b]	p Value
Olanzapine	0.976	0.594–1.605	0.0411	0.8394
Quetiapine	1.149	0.531–2.485	0.2330	0.6293
Risperidone	0.926	0.544–1.579	0.2283	0.6328
Increasing age	1.213	1.016–1.447	4.5773	0.0324[c]
Nonwhite	1.761	1.174–2.640	7.4881	0.0062[c]
Female	0.718	0.277–1.857	0.4679	0.4940
Persistent days	1.001	0.999–1.002	1.4273	0.2322
Comorbidity				
Depression	1.305	0.850–2.002	1.4837	0.2232
Substance abuse	0.869	0.561–1.345	0.3983	0.5280
Bipolar disorder	1.192	0.772–1.840	0.6262	0.4288
Schizophrenia	1.117	0.678–1.570	0.0215	0.8834
Body mass index	1.032	0.477–1.581	0.2137	0.6439
Hypertension	0.759	0.415–1.388	0.7994	0.3713
Previous hyperlipidemia	1.606	1.064–2.425	5.0804	0.0242[c]

[a]Reference categories for the atypical agents, nonwhite, and female variables were the typical agents, white, and male, respectively.
[b]Model χ^2=20.00, p=0.1302.
[c]Significance at p<0.05.

The results show that the frequency of new-onset diabetes was not significantly different (p=0.5553) between the atypical group (6.8%) and the typical group (7.3%).

Two additional analyses were performed to further investigate this issue. Because of the concomitant use of atypical and typical agents, the analysis was run separating the data into three groups: atypical, typical, and both. Table 2 shows that the results were similar to those of the previous analysis: no significant difference in new-onset diabetes among the three groups. The third analysis (Table 3) collapses the atypical and both categories into one group (atypical+). Once again, the results show that the frequency of new-onset diabetes was not significantly different between the typical and atypical groups.

Table 4 addresses our second objective, which was to determine whether the frequency of new-onset diabetes differed among those taking the atypical antipsychotic agents (note that clozapine and ziprasidone were dropped from the analyses due to small sample sizes). The χ^2 results show that there was no significant difference in frequency of new-onset diabetes among the atypical agents.

Tables 5 and 6 address our third objective, which was to determine what factors—antipsychotic agent used, BMI category increase, previous hyperlipidemia, increase in hypertension status category, persistence, type of mental health comorbidity, age, sex, and race—influence the occurrence of new-onset diabetes. Table 5 shows that increasing age, minority race, and previous hyperlipidemia were the only variables significantly related to new-onset diabetes. To increase power, another logistic regression analysis was run to include only

Table 6. Logistic Regression Analysis of Factors Related to New-Onset Diabetes Mellitus That Included Only Demographics and Comorbidities in 3170 Patients

Variable[a]	Odds Ratio	95% Confidence Interval	Wald χ^2 Value[b]	p Value
Olanzapine	0.941	0.639–1.384	0.0901	0.7641
Quetiapine	1.034	0.508–2.106	0.0370	0.8474
Risperidone	0.963	0.641–1.447	0.0190	0.8903
Increasing age	1.274	1.130–1.435	15.7806	<0.0001[c]
Nonwhite	1.689	1.274–2.239	13.2741	0.0003[c]
Female	0.797	0.395–1.605	0.4025	0.5258
Comorbidity				
Depression	1.302	0.895–1.893	1.9060	0.1674
Substance abuse	0.929	0.641–1.346	0.1505	0.5981
Bipolar disorder	1.321	0.907–1.925	2.1033	0.1470
Schizophrenia	0.953	0.670–1.355	0.0722	0.7881

[a]Reference categories for the atypical agents, nonwhite, and female variables were the typical agents, white, and male, respectively.
[b]Model χ^2=29.57, p=.0010.
[c]Significance at p<0.05.

demographics (age, race, and sex) and mental health comorbidities. This analysis increased the sample size from 1587 to 3170 subjects. Table 6 shows that once again, increasing age and minority race were significantly related to new-onset diabetes.

Discussion

Our study showed that among central Texas veterans who used antipsychotics, the overall frequency of diabetes was 7.1%. These results compare with those of another study that found that the frequency of diabetes was 6.3% among Ohio veterans.[38] Our study may have had a higher rate because we used a more inclusive definition of diabetes, that is to include not only ICD-9 diagnoses and antidiabetic drugs, but also elevated glucose levels. In addition, our sample population was composed of approximately 30% minorities, which may be higher than some of the other populations studied. Diabetes is more prevalent among minorities than nonminorities.

Another group found that the diabetes incidence rate for all of the patients with schizophrenia who were taking antipsychotics was 4.4/1000 person-years.[42] In another study, the incidence rates in the general population, in patients taking typical antipsychotics, and in patients taking atypical antipsychotics were 15.7, 84, and 67/1000 patient-years, respectively.[35]

Our study showed no difference in the frequency of diabetes between the atypical and typical agent groups or among those taking atypical agents in both the unadjusted and adjusted analyses. One group of authors reported that the overall diabetes rates among patients with schizophrenia who were treated with clozapine versus typical antipsychotics were 4.0% and 3.4%, respectively, which were not statistically significantly different.[43] Another group found no increased risk of diabetes when comparing clozapine with typical agents in a Medicaid population.[45] In another study, the authors found no difference in incident diabetes between the atypical and typical antipsychotic cohorts, but both groups were significantly associated with increased risk of diabetes when compared with the general population.[35] Another group found no difference in the frequency of diabetes between atypical and typical agents.[46]

In contrast to these study results, other large database studies[36, 39, 40, 42, 44] have found significant differences in the frequency of new-onset diabetes between atypical agents and typical agents and/or among atypical agents. However, one study found atypical agents to have a significant increased risk of diabetes compared with typical agents, but no difference was noted in new-onset diabetes among the atypical agents.[37] In other studies comparing the atypical agents, olanzapine was most often associated with the increased risk of diabetes,[36, 39, 40, 42, 44] whereas risperidone was associated with new-onset diabetes in two studies.[35, 46] In one of those studies, the authors compared haloperidol use to individual atypical antipsychotics and found risperidone to have a significantly increased risk of diabetes.[35] In the other study, the authors compared the occurrence of diabetes among

Table 7. Comparison of Methodologies of Retrospective Database Studies Examining Antipsychotic Use and New-Onset Diabetes Mellitus

Setting or Database	Study Time Frame	Sample Population	Study Design	Sample Size	Drugs	Clinical Covariates	Demographic Covariates
Managed care[35]	1998–2000	All AP users and general population	RC	58,751 (AP users) 5,816,473 (general population)	All APs	AP exposure duration, AP dosage	Age, sex
Quebec public health plan[36]	1997–1999	All risperidone and olanzapine users	RC	33,946	Risperidone, olanzapine	AP exposure duration, concomitant haloperidol, psychiatric diagnosis	Age, sex
VA[37]	1999–2001	Schizophrenic patients	RC, CC	12,235	All APs	Use of drugs associated with glucose intolerance	Age, sex, race, VA facility, marital status
Ohio VA (men only)[38]	1997–2000	All AP users	RC	5837	Risperidone, olanzapine, haloperidol, fluphenazine	AP exposure duration, psychiatric diagnoses, use of lithium and valproic acid, concomitant AP use	Age, race
Managed care[39]	1996–1997	Psychiatric patients	RC	7933	All APs	AP exposure duration, concurrent AP use, AP dosage, psychotropic use, psychiatric diagnoses	Age, sex, health care coverage
Managed care[40]	1997–2000	Psychiatric patients	RC	10,296	All APs	AP exposure duration, concurrent AP use, β-blocker use, prior weight gain treatment, psychotropic use, psychiatric diagnoses	Age, sex, health care coverage
United Kingdom General Practice Research[41]	1994–1998	All AP users	CC	1946 (424 cases, 1522 controls)	All APs	AP exposure duration, concurrent AP use, body mass index, smoking, use of drugs associated with glucose intolerance, alcoholism, cardiovascular history, psychiatric diagnoses	Age, sex, practice setting
United Kingdom General Practice Research[42]	1987–2000	Schizophrenic AP users	CC	3147 (451 cases, 2696 controls)	All APs	AP exposure duration, use of drugs associated with glucose intolerance	Age, sex
Iowa Medicaid[43]	1990–1994	Schizophrenic patients	RC	3013	Clozapine, typical APs	AP exposure duration	Age, sex
VA[44]	1998–1999	Schizophrenic AP users	RPC	38,632	All APs	Previous hospitalization, psychiatric diagnoses, comorbidities	Age, sex, race, income, distance to hospital, VA compensation

patients with schizophrenia and found those taking risperidone to have a higher risk compared with those taking typical agents or olanzapine.[46]

Other authors found that both olanzapine and clozapine, as well as selected typical antipsychotic agents, were associated with an increased risk of

Table 7. Comparison of Methodologies of Retrospective Database Studies Examining Antipsychotic Use and New-Onset Diabetes Mellitus (continued)

Setting or Database	Study Time Frame	Sample Population	Study Design	Sample Size	Drugs	Clinical Covariates	Demographic Covariates
New Jersey Medicaid and Medicare, Pharmaceutical Assistance to Aged and Disabled[45]	1990–1995	Psychiatric patients	CC	14,007 (7227 cases, 6780 controls)	Clozapine vs nonclozapine	Psychiatric diagnoses, psychotropic use, clozapine duration, clozapine dosage, comorbidity score, use of drugs associated with glucose intolerance	Age, sex, race, socio-economic status
Managed care[46]	1996-1998	Schizophrenic AP users	RC	815	All APs	AP exposure duration, general health comorbidities, psychiatric diagnoses	Age, sex region, enrollment status

AP = antipsychotics; RC = retrospective cohort; VA = Veterans Administration; CC = case-control; RPC = retrospective (prevalent cases).

diabetes when compared with no treatment for psychoses.[39] In a later study by the same authors, only olanzapine was associated with an increased risk of diabetes.[40] Another group compared olanzapine and risperidone and found that olanzapine was significantly associated with incident diabetes.[36] In a study that compared typical with atypical agents, the authors found that atypicals (with the exception of risperidone) were associated with increased diabetes in a large Veterans Affairs study.[44] In the younger age groups (< 40 yrs), all atypical agents were associated with increased diabetes. This discussion shows that the literature is far from conclusive regarding the relationship between antipsychotic agents and incident diabetes.

Several factors could explain differences in the results. Table 7 shows a comparison of the study methodologies. Several of the large database studies were conducted in various settings: in veterans[37, 38, 44]; in Medicaid populations[43, 45]; at managed care organizations[35, 39, 40, 46]; and outside the United States.[36, 41, 42] Comparison of results across each of the settings may have inherent biases. Also, the study designs differed in terms of inclusion criteria: all patients taking antipsychotic agents[35, 36, 38, 41] versus persons with psychiatric diagnoses.[37, 39, 40, 42–46] The studies differed in terms of comparison groups (typical vs atypicals)[35, 37, 38, 41–46]; among atypicals[36, 38, 46]; antipsychotic use versus no antipsychotic use among persons with psychoses[39, 40]; and antipsychotic use versus no antipsychotic use among the general population.[35]

Another factor that differed across the studies was the covariates used. Most studies controlled for demographics such as age[35–46] and sex,[35–37, 39–46] whereas fewer studies controlled for race.[37, 38, 44, 45] As mentioned previously, race is an important risk factor for diabetes, with minorities more likely to develop diabetes compared with nonminorities. Regarding clinical variables, several studies controlled for psychoses treatment–specific issues such as other antipsychotic use,[36, 38–41, 45] psychiatric diagnoses,[36, 38–41, 44–46] and treatment exposure duration,[35, 36, 38–43, 45, 46] and three studies controlled for dosage.[35, 39, 45] Several studies controlled for use of other drugs that may cause diabetes, such as steroids, β-blockers, anticonvulsants,[37, 38, 40–42, 45] whereas only a few captured other factors associated with diabetes such as BMI[41] and weight gain,[40] hypertension,[41, 45, 46] and dyslipidemia.[46]

One distinct aspect of our study is the use of elevated glucose levels as a proxy for incident diabetes, in addition to drug therapies and diagnoses. Another distinct aspect of our study was the inclusion of clinical covariates in the analysis. Blood pressure changes, previous hyperlipidemia, and BMI changes were incorporated into the multivariate analysis to control for known factors related to diabetes. The results showed that even after controlling for these comorbid conditions, increasing age and minority race were consistently related to new-onset diabetes. In a separate multivariate analysis, previous hyperlipidemia was also associated with new-onset diabetes. Other studies have also found age to be a significant factor in incident diabetes. One group[43] found occurrence to be more prevalent in the younger age group (20–34 yrs), whereas other studies

found increasing age to be related to incident diabetes.[35, 39, 40, 46]

In September 2003, the U.S. Food and Drug Administration issued a request for manufacturers of atypical antipsychotic agents to modify their labeling to include the risk of glucose abnormalities. They also recommended regular monitoring for hyperglycemia in patients with diabetes and those at risk for diabetes. Although our study results show no difference in new-onset diabetes between patients taking typical agents and those taking atypical agents, the overall frequency in this population was 7.1%, which is higher than the 6.3% prevalence in the general population.[50] Thus, it is important that all patients taking antipsychotic agents be monitored for symptoms of diabetes.

Limitations

Our results should be interpreted with caution. Although retrospective database studies can capture effectiveness among a large patient group, causality cannot be established. The database used in this study involved veterans in central Texas and more than 90% of the study subjects were male; thus, differences in outcomes regarding sex and other regions cannot be fully assessed. It is possible that subjects could have obtained drugs from outside the Veterans Affairs system; however, internal resources indicate that veterans tended to use the Veterans Affairs resources exclusively since they were free during the time of this study. We used an intent-to-treat analysis; this does not account for switching and concomitant use of antipsychotics, which routinely occur in practice.[38] However, in our unadjusted analyses comparing typical and atypical antipsychotic agents, we tried to overcome this limitation by performing analyses to incorporate switching and concomitant use.

We found no differences in the frequency of diabetes between the typical and atypical groups when using this method. Studies have shown that primary care, in terms of routine screening for diabetes, for the mentally ill may be suboptimal and thus, new cases of diabetes may go undetected.[51] Although we used a very inclusive definition (ICD-9, antidiabetic drugs, and elevated glucose levels) to identify new-onset diabetes, it is likely that this may have been underestimated since the American Diabetes Association reports that in nearly one third of persons with diabetes is undetected.[50] Also, we did not control for antipsychotic dosage or other nonantipsychotic drugs (e.g., lithium, steroids, thiazide diuretics) that may have been related to new-onset diabetes.

Conclusion

This study found that the frequency of new-onset diabetes mellitus among a population of veterans in central Texas was 7.1%. No significant difference was noted in the frequency of new-onset diabetes between patients taking typical agents and those taking atypical antipsychotic agents or among those taking atypical antipsychotic agents. In addition, a multivariate logistic regression analysis revealed that when controlling for demographic and clinical variables, no significant difference was noted among the antipsychotics. The analysis revealed that new-onset diabetes was significantly related to increasing age and minority race. Nevertheless, patients who are taking antipsychotic agents and have diabetes or are at risk for diabetes should be monitored for any adverse effects related to diabetes.

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Incidence of New-Onset Diabetes Mellitus Among Patients Receiving Atypical Neuroleptics in the Treatment of Mental Illness

Evidence From a Privately Insured Population

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Abstract: The purpose of this study is to determine sociodemographic, clinical, and pharmacotherapeutic characteristics, especially use of atypical antipsychotics, associated with incident diabetes mellitus in a population of privately insured patients with mental health diagnoses. Patients with a mental health diagnosis stably medicated for a 3-month period during January 1999 through October 2000 and having no diabetes were followed through December 2000. Cox proportional hazards models were developed to identify antipsychotic medications associated with newly diagnosed diabetes. Of the 7381 patients identified, 339 developed diabetes, representing an annual incidence rate of 4.7%. Diabetes risk among the entire sample was lowest for risperidone (hazard ratio [HR] = 0.69; $p < 0.05$), while quetiapine (HR = 0.74), olanzapine (HR = 0.95), and clozapine (HR = 1.22) were not significantly different from first-generation antipsychotics. Diabetes risk was significantly lower among males receiving risperidone (HR = 0.49; $p < 0.01$) or quetiapine (HR = 0.50; $p < 0.10$), while diabetes risk among females did not differ significantly from first-generation antipsychotics for any atypical examined. These findings are substantially different from other reports.

Key Words: Antipsychotic agents, psychopharmacology, diabetes mellitus, risk factors, comparative study.

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Pharmacotherapy is the foundation of effective treatment of schizophrenia. Atypical antipsychotic medications, including clozapine (Kane et al., 1988), olanzapine (Tollefson et al., 1997), quetiapine (Small et al., 1997), risperidone (Marder and Meibach, 1994), ziprasidone (Goff et al., 1998), and aripiprazole (Kane et al., 2002) have been found to be as effective as first-generation antipsychotics, with substantially fewer extrapyramidal side effects (Stahl, 1999). However, there is some evidence to suggest that these medications have other side effects, such as weight gain and increased risk of diabetes mellitus (DM), which have been associated with the use of clozapine (Bustillo et al., 1996; Cohen et al., 1990; Gianfrancesco et al., 2002; Henderson et al., 2000; Lamberti et al., 1992), olanzapine (Allison et al., 1999; Fertig et al., 1998; Koro et al., 2002; Ober et al., 1999; Wirshing et al., 1998), and quetiapine (Sobel et al., 1999). Other studies suggest that there might be a link between atypical antipsychotics and diabetic ketoacidosis (Jin et al., 2002; Lafayette et al., 2003; Ragucci and Wells, 2001; Straker et al., 2002; Tavakoli and Arguisola, 2003; Wheeler, 2003; Wilson et al., 2003). There is also some concern that weight gain and increased risk of DM may be a class effect of all atypical antipsychotics (Burton, 2003; Goode, 2003), which led the Food and Drug Administration to update the labeling requirements for these medications to include information about the potential for hyperglycemia and its related symptoms (Rosack, 2003). However, there is little evidence to link risperidone with DM (Feldman, 2003; Fuller et al., 2004; Gianfrancesco et al., 2002; Koro et al., 2002), and the newer atypical drugs, ziprasidone and aripiprazole, appear not to cause significant weight gain (Keck and McElroy, 2003; Marder et al., 2003; Potkin et al., 2003; Taylor and McAskill, 2000). Much of the evidence linking clozapine, olanzapine, and quetiapine to weight gain and DM consists of case reports and studies involving relatively small samples (Allison et al., 1999; Bustillo et al., 1996; Cohen et al., 1990; Fertig et al., 1998; Gianfrancesco et al., 2002; Henderson et al., 2000;

Koro et al., 2002; Lamberti et al., 1992; Ober et al., 1999; Sobel et al., 1999; Wirshing et al., 1998), although a few studies using large sample sizes have recently been published (Leslie and Rosenheck, 2004; Sernyak et al., 2002).

While few published studies have examined DM prevalence among patients with schizophrenia (Wheeler, 2003) or risk of new-onset DM or DKA (Gianfrancesco et al., 2003; Wilson et al., 2003), only one study has reported the DM incidence rates in this population (Leslie and Rosenheck, 2004). Using administrative data from the Department of Veterans Affairs (VA), in particular, this recent study found that 7.3% of patients with schizophrenia initially stable on an antipsychotic medication were diagnosed with DM during follow-up, for an annual incidence rate of 4.4%. Whereas patients on clozapine (hazard ratio [HR] = 1.57) and olanzapine (HR = 1.15; $p < 0.05$ for both) exhibited significantly higher risk of developing diabetes than patients on first-generation antipsychotics, patients on quetiapine (HR = 1.20) and risperidone (HR = 1.01) were not significantly different. The attributable risk of DM associated with atypicals was small, however, ranging from 0.05% (risperidone) to 2.03% (clozapine).

In an effort to understand better the risks of new-onset DM among patients prescribed antipsychotic medications, we sought to replicate this VA study in a privately insured population. Comparing the results of similar studies across public sector and privately insured populations is instructive given differences in financing, service delivery, and the populations served (Leslie and Rosenheck, 2000). To examine whether the use of atypical antipsychotics increases the risk of new-onset DM among privately insured patients as they did with VA patients, the goals of the present study were (1) to determine the proportion of privately insured patients with a mental health diagnosis initially stable on an antipsychotic medication who developed DM, and (2) to identify patient demographic, clinical, and pharmacological characteristics associated with these adverse events. In light of considerable off-label use of antipsychotic medications for psychiatric illnesses other than schizophrenia (Rosenheck et al., 2001), we expand the sample in this study to include any mental health patient receiving an antipsychotic.

METHODS

Data for this study come from MEDSTAT's MarketScan database, which compiles claims information for individuals nationwide who are privately-insured through the benefit plans of large employers. The covered individuals include employees, their dependents, and early retirees of companies who participate in the database. MEDSTAT collects the claims data, standardizes and combines them, and then reports back to the firms who participate. The database contains information for over 2.5 million covered lives between 1999 and 2000. These claims data are collected from over 200 different insurance companies, including Blue Cross and Blue Shield plans and third-party administrators.

We identified patients with a mental health diagnosis who were stable on an antipsychotic regimen for any 3-month period between January 1999 and October 2000 following the first prescription for an antipsychotic medication. Patients were identified as stable on an antipsychotic regimen if they received at least 30 days' worth of prescriptions for the same agent during the 3-month period, although the dose could change. Patients could be stable in any 3-month interval during January 1999 to October 2000.

Patients were defined as having a mental health diagnosis if they had any claims with an ICD-9 code in the range of 290.00 to 312.99 or 331.00 to 331.99, excluding 305.1 (tobacco use disorder). Any claim with a diagnosis within this range of ICD-9 values was considered a mental health claim, regardless of whether care was received in an inpatient or outpatient setting. Like the VA study, we had initially considered focusing exclusively on patients diagnosed with schizophrenia. Because we could identify fewer than 1000 individuals with schizophrenia who were stable on an antipsychotic regimen, we chose to expand our criteria to include individuals with other mental health diagnoses. If we had limited our study to patients with schizophrenia, we would have excluded most individuals receiving antipsychotic medications during the period studied.

We defined five groups of antipsychotic medications: clozapine, risperidone, olanzapine, quetiapine, and all first-generation antipsychotics. Ziprasidone and aripiprazole were not included in the study because they were only recently approved for use, and very few patients received these drugs during the study period. First-generation antipsychotics were lumped together as a group because years of experience with these medications have shown that they are not significantly different from each other in their risk of DM, and to be consistent with the VA study (Leslie and Rosenheck, 2004). Although some patients in the sample received prescriptions for multiple antipsychotic medications in the 3 months following first prescription of an antipsychotic (polypharmacy), they were not considered to be stable on a medication regimen and were excluded from the analysis.

Outpatient and inpatient claims were checked for existing DM in all visits back to January 1, 1999, preceding the 3-month stable period. Patients with any claims for DM (ICD-9 codes 250.00–250.99) were also excluded from the sample. Stable patients with no history of DM were followed through December 31, 2000. Patients with a diagnosis of DM during the follow-up period were identified, along with the date of the first diagnosis of DM.

Cox proportional hazards models were used to model the time to DM diagnosis. Independent variables included in the models were antipsychotic agent prescribed during the stable period, age, gender, mental health diagnoses, and

clinical comorbidity. Mental health diagnoses were based on ICD-9 diagnostic codes and included the following: adjustment reaction, anxiety disorder, dementia or Alzheimer disease, bipolar disorder, dysthymia, major depression, psychosis other than schizophrenia, posttraumatic stress disorder, personality disorder, schizophrenia, substance abuse, and other mental health disorders. Clinical comorbidity is measured using a weighted index developed by Charlson et al. (1987) and adapted for use with ICD-9 administrative databases by Deyo et al. (1992).

RESULTS

We identified 7381 patients who were stable on an antipsychotic medication. Characteristics of these patients are presented in Table 1. The average age of patients in the sample was 40.4 years, and 43% were male. The most common medication on which patients were stable was risperidone (35%), followed by first-generation antipsychotics and olanzapine (27% each), quetiapine (10%), and clozapine (1%). Particular agents received by patients on first-generation antipsychotics were perphenazine (25.6%), haloperidol (15.5%), thioridazine (14.2%), prochlorperazine (12.6%), thiothixene (9.4%), trifluoperazine (7.5%), chlorpromazine (6.4%), fluphenazine (3.7%), loxapine (2.5%), mesoridazine (1.3%), and molindone (1.1%). The most common mental health diagnoses were major depression (47%), dysthymia (36%), bipolar disorder (28%), and anxiety disorder (25%). Only 17% were diagnosed with schizophrenia. Patients exhibited little clinical comorbidity, as indicated by an average score of 0.5 on the index used.

Overall, 339 patients (4.6%) contracted diabetes during the follow-up period, representing an annual incidence rate of 4.7%. Table 1 reports comparisons of patient characteristics according to whether the patient eventually contracted DM. Patients who developed new-onset DM were significantly older ($p < 0.0001$) and were more often prescribed a first-generation antipsychotic ($p < 0.0001$) and less often prescribed risperidone ($p < 0.0001$) and quetiapine ($p = 0.04$).

TABLE 1. Characteristics of the Sample

Variable	Overall (N = 7381)		Patients who eventually were diagnosed with diabetes (N = 339)		Patients who did not contract diabetes (N = 7042)		t statistic or χ^2 statistic	df	p
	N	%	N	%	N	%			
Age[a]	40.4	16.8	51.5	10.9	39.9	16.8	−18.54	420	<0.0001
Male gender	3176	43%	130	38.3%	3046	43.3%	3.1764	1	0.0747
Stable medication									
First generation	1981	27%	145	42.8%	1836	26.1%	45.9413	1	<0.0001
Clozapine	84	1%	7	2.1%	77	1.1%	2.7129	1	0.0995
Olanzapine	1986	27%	93	27.4%	1893	26.9%	0.0501	1	0.8229
Quetiapine	775	10%	24	7.1%	751	10.7%	4.4232	1	0.0355
Risperidone	2555	35%	70	20.6%	2485	35.3%	30.6248	1	<0.0001
Mental health diagnoses									
Adjustment reaction	878	12%	38	11.2%	840	11.9%	0.1595	1	0.6896
Anxiety disorder	1836	25%	78	23.0%	1758	25.0%	0.6619	1	0.4159
Alzheimer disease/dementia	568	8%	35	10.3%	533	7.6%	3.4575	1	0.0630
Bipolar disorder	2084	28%	110	32.4%	1974	28.0%	3.1135	1	0.0776
Dysthymia	2623	36%	97	28.6%	2526	35.9%	7.4352	1	0.0064
Major depression	3467	47%	158	46.6%	3309	47.0%	0.0189	1	0.8906
Other psychosis	858	12%	22	6.5%	836	11.9%	9.1192	1	0.0025
PTSD	291	4%	17	5.0%	274	3.9%	1.0786	1	0.2990
Personality disorder	297	4%	13	3.8%	284	4.0%	0.0329	1	0.8561
Substance abuse	613	8%	26	7.7%	587	8.3%	0.1884	1	0.6642
Schizophrenia	954	13%	76	22.4%	878	12.5%	28.4559	1	<0.0001
Other mental health disorders	1253	17%	48	14.2%	1205	17.1%	2.0002	1	0.1573
Clinical comorbidity[a]	0.5	1.3	1.1	1.9	0.5	1.3	−5.83	354	<0.0001

[a]Statistics presented for these variables are mean and *SD* instead of *N* and %.

Patients who contracted DM were more often diagnosed with schizophrenia ($p = <0.0001$), had more comorbid medical conditions ($p < 0.0001$), and were less often diagnosed with dysthymia ($p = 0.0064$) and psychoses other than schizophrenia ($p = 0.0025$).

Table 2 reports the results from the Cox proportional hazards model predicting time to DM onset. With respect to the effect of antipsychotic medication, the lowest risk of new-onset DM was associated with risperidone (HR =0.69; CI= 0.51, 0.93). Quetiapine had the second lowest risk (HR = 0.74), although it did not reach statistical significance (CI = 0.48, 1.15). The reduced risk associated with olanzapine was small (HR = 0.95) and not statistically significant (CI = 0.73, 1.24). Though the risk associated with clozapine was greater than first-generation antipsychotics (HR = 1.22), it did not achieve statistical significance either (CI = 0.73, 1.24). Diabetes risk was also higher for individuals diagnosed with schizophrenia (HR = 1.62; CI = 1.23, 2.13), bipolar disorder (HR = 1.36; CI = 1.07, 1.71), and PTSD (HR = 1.69; CI = 1.02, 2.81), and lower for individuals with other psychoses (HR = .60; CI = 0.39, 0.93).

Fitted survival functions associated with each stable medication from the Cox proportional hazards model predicting time to DM onset are illustrated in Figure 1. The survival functions are very close together until approximately 5 months (150 days) past the end of the stable period, when the curve for first-generation antipsychotics starts to fall faster than the others. The olanzapine and quetiapine curves start to fall faster at about 7 months (200 days) and remain close together until about the eighth month (240 days), after which the olanzapine curve begins to fall more quickly. The clozapine curve drops suddenly at 8.5 months (260 days), most likely as a result of the unique characteristics of the small number of patients prescribed that drug. The risperidone curve hovers above the other curves for the duration of the follow-up period.

A second Cox proportional hazards model that included interaction terms between stable atypical regimen and gender

TABLE 2. Results of the Cox Proportional Hazards Model of New-Onset Diabetes (Total Population, Males, and Females)

	Total population (N = 7881)			Males (N = 3176)			Females (N = 4205)		
		95% Confidence limits			95% Confidence limits			95% Confidence limits	
Variable	Hazard ratio	Lower	Upper	Hazard ratio	Lower	Upper	Hazard ratio	Lower	Upper
Age	1.047***	1.037	1.057	1.069***	1.052	1.086	1.030***	1.017	1.042
Male gender	1.194	0.954	1.495	—	—	—	—	—	—
Stable medication[a]									
Clozapine	1.222	0.563	2.652	1.051	0.320	3.453	1.435	0.517	3.983
Olanzapine	0.947	0.726	1.236	0.790	0.516	1.209	1.079	0.766	1.520
Quetiapine	0.740	0.477	1.146	0.499	0.224	1.108	0.929	0.546	1.580
Risperidone	0.690*	0.514	0.925	0.485**	0.298	0.789	0.849	0.587	1.226
Mental health diagnoses									
Adjustment reaction	1.294	0.915	1.830	1.204	0.675	2.149	1.352	0.874	2.092
Anxiety disorder	1.111	0.856	1.443	1.419	0.946	2.129	0.940	0.668	1.324
Alzheimer disease/dementia	0.960	0.664	1.387	0.829	0.478	1.438	1.129	0.689	1.848
Bipolar disorder	1.355*	1.073	1.711	1.474*	1.015	2.141	1.213	0.896	1.643
Dysthymia	0.831	0.651	1.060	0.817	0.546	1.222	0.819	0.602	1.114
Major depression	1.065	0.850	1.335	1.400	0.968	2.025	0.891	0.666	1.192
Other psychosis	0.602*	0.389	0.931	0.587	0.295	1.169	0.585	0.331	1.034
PTSD	1.691*	1.019	2.806	2.012	0.712	5.688	1.591	0.885	2.862
Personality disorder	1.002	0.570	1.762	1.509	0.549	4.148	0.870	0.440	1.718
Substance abuse	1.051	0.696	1.588	0.850	0.456	1.585	1.142	0.651	2.001
Schizophrenia	1.622***	1.233	2.132	1.811**	1.158	2.832	1.541*	1.085	2.189
Other mental health disorders	1.058	0.775	1.445	1.327	0.832	2.115	0.905	0.592	1.385
Clinical comorbidity	1.154***	1.095	1.216	1.164***	1.075	1.260	1.141***	1.063	1.224

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.
[a]First-generation antipsychotics were the omitted reference group.

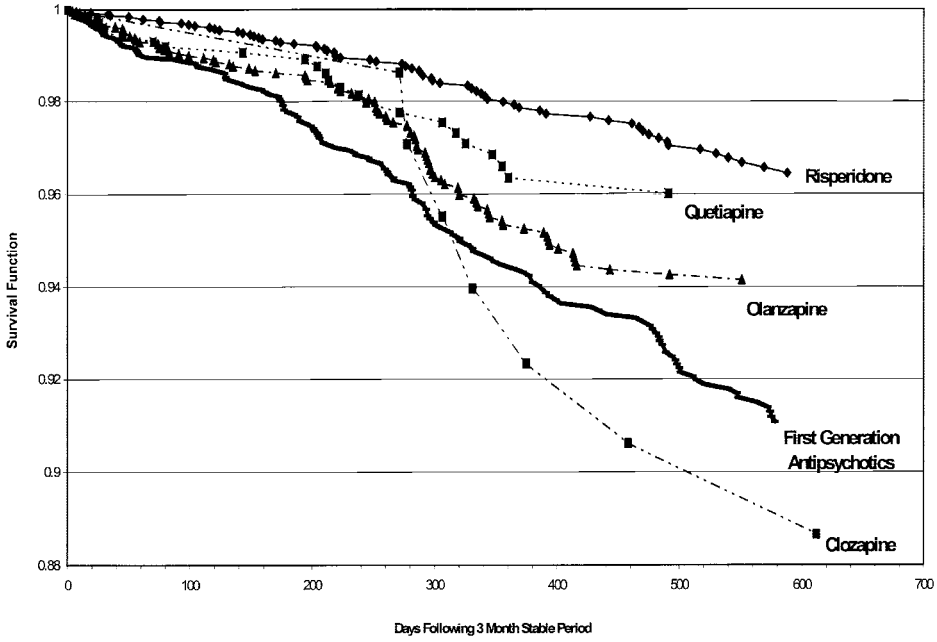

FIGURE 1. Fitted survival functions from the Cox proportional hazards model predicting time to DM onset among privately insured patients with a mental health diagnosis.

revealed a significant interaction between male gender and risperidone (HR = 0.53; p = 0.0345; CI = 0.29, 0.95). To further explore the relationship between gender and time to new DM onset, therefore, separate Cox models were estimated for male and female enrollees. The lowest risk of new-onset DM among males was associated with risperidone (HR = 0.49; CI = 0.30, 0.79) and quetiapine (HR = 0.50; CI = 0.22, 1.11), although the latter was only statistically significant at the .01 level. The reduced risk associated with olanzapine was smaller (HR = 0.79) and not statistically significant (CI = 0.52, 1.23), nor was the slightly greater risk associated with clozapine (HR = 1.05; CI = 0.32, 3.45). Though the relative ordering of atypicals with respect to DM risk was the same for females as for males, diabetes risk among females did not differ significantly from first-generation antipsychotics for any of the atypical drugs.

DISCUSSION

This study estimated the annual incidence of new-onset DM between 1999 and 2000 in a sample of privately insured patients with a mental health diagnosis who were stable on an antipsychotic medication. We found that the annual incidence rates in this population were high, averaging 4.7 new cases per 100 patient-years across the entire sample. Patients initially stable on risperidone were at significantly lower risk for DM than patients initially stable on a first-generation antipsychotic; patients initially stable on quetiapine, clozapine, and olanzapine were no more likely to develop new-onset DM than those on first-generation antipsychotics. Gender-specific analyses indicate that while males initially stable on risperidone were significantly less likely to develop diabetes, females were no more likely to develop diabetes regardless of which atypical antipsychotic they were on.

The incidence of DM in this population was relatively high, even among patients initially stable on first generation antipsychotics. Although the overall DM incidence rate of 4.7% per year is considerably higher than the estimated rate of 2.7 cases per 1000 in the general US population (Kenny et al., 1995), it is nearly identical to the rate of 4.4% found in the VA study, which examined the incidence of diabetes among patients with schizophrenia initially stable on an antipsychotic (Leslie and Rosenheck, 2004). We are not aware of other studies estimating DM incidence rates in VA populations or among patients with schizophrenia or other mental illness; however, DM prevalence rates have been shown to be higher among patients with schizophrenia than among the general population (Dixon et al., 2000; Mukherjee et al., 1996). It is unclear how much of the increased DM incidence rates in the privately insured and VA samples examined here were due to the use of antipsychotic medications (whether first-generation or atypical), to the underlying mental illness, or to other factors such as poorer overall physical health or less healthy lifestyles. However, it is noteworthy that these two very different populations exhibited essentially the same rate of DM incidence. Whereas the entire VA sample population was diagnosed with schizophrenia, only 13% of the privately insured sample was so diagnosed. In addition, the average age of the VA sample was 52.2 years, and it was mostly male (94.3%), while the average age of the privately insured sample was 40.4 years, the majority of whom were female (57%). Because individuals eligible for VA mental health services are poor and frequently homeless (Rosenheck

and Seibyl, 1998) and unemployed (Rosenheck and DiLella, 1999), they are likely to be sicker on average than a group of employed individuals, retirees, and their families with private insurance. That both VA and privately insured populations initially stable on an antipsychotic should exhibit similar rates of DM incidence suggests that the risk of diabetes may extend beyond factors associated with schizophrenia to factors associated with mental illness more generally, possibly including treatment with certain antipsychotic medications.

Independent of how they compare with first-generation antipsychotics, the relative ordering of atypicals with respect to the risk of DM in our study matched that found in the VA study, with risperidone exhibiting the lowest risk of new-onset diabetes, followed by quetiapine, olanzapine, and clozapine. Contrary to the findings of the VA study, however, as well as other prior research and case reports, our results do not support the claim that atypical antipsychotics are associated with elevated risk of DM relative to first-generation antipsychotics. In fact, risperidone was associated with a substantial (HR = 0.69) and statistically significant lower risk of new-onset DM when compared with first generation antipsychotics ($p < 0.05$). The reduced risk of DM associated with quetiapine was also substantial (HR = 0.74), but did not reach the level of statistical significance ($p = 0.18$) in part due to the relatively small number of patients initially stable on this drug (775). This is in contrast to the reduced risk of DM associated with olanzapine, which was small (HR = 0.95) and not statistically significant despite a large number of initially stable patients (1986). However, the protective effects of olanzapine (HR = 0.79) along with risperidone (HR = 0.49) and quetiapine (HR = 0.50) all grew when analyses were limited to male enrollees only. Together with published reports that suggest that the newer atypical drugs (ziprasidone and aripiprazole) do not cause significant weight gain or increase the risk of DM (Keck and McElroy, 2003; Marder et al., 2003; Potkin et al., 2003; Sernyak et al., 2002), results of this study suggest that atypicals fare well where the risk of new-onset diabetes is concerned when compared with first-generation antipsychotics in some populations.

At approximately 5 months, differences in DM risk across antipsychotic medications became apparent, soon after the end of the stable period. As such, the additional DM risk associated with first-generation antipsychotics took less than half a year to develop. In the VA study, differences in DM risk took almost three times as long to become apparent (14 months; Leslie and Rosenheck, 2004). Although elevated DM risk associated with use of certain antipsychotic medications manifested itself more quickly in our study, the 8 months constituted by the stable period and follow-up should still provide clinicians with enough time to identify elevated DM risk and perhaps change antipsychotic regimen accordingly.

The most common medication on which patients were stable was risperidone (35%), followed by first-generation antipsychotics and olanzapine (27% each), quetiapine (10%), and clozapine (1%). In the VA study, however, the most common medication on which patients were stable was first-generation antipsychotics (41.9%), followed by olanzapine (28.3%), risperidone (24.6%), quetiapine (3.0%), and clozapine (2.2%) (Leslie and Rosenheck, 2004). Focusing on the relatively few patients with schizophrenia in the private sector sample, however, reveals prescription patterns that better approximate what was found in the VA, with the most common medication being first-generation antipsychotics (32.6%), followed by risperidone (27.6%), olanzapine (26.5%), quetiapine (7.1%), and clozapine (6.2%). Thus, although prescription patterns vary between patients diagnosed with mental illness other than schizophrenia, there appears to be a certain degree of uniformity in the patterns of prescriptions provided to both public sector and privately insured populations with schizophrenia (Leslie and Rosenheck, 2000).

The fact that patients with schizophrenia are more likely to develop diabetes than other patients, and are more likely to be prescribed a first-generation antipsychotic, may explain why patients on first-generation antipsychotics were more likely to develop diabetes than patients on three of the four atypicals examined. To assess this possibility, we repeated our analyses for the 954 patients in our sample with a diagnosis of schizophrenia. Although none are significant, coefficients on each of the atypicals—risperidone (HR = 0.89), quetiapine (HR = 0.64), olanzapine (HR = 0.73), and clozapine (HR = 0.82)—still indicate that even among patients with schizophrenia in this sample, atypicals are associated with a lower risk of new-onset diabetes when compared with first-generation antipsychotics, although due to the small sample, these results were not statistically significant.

Another possible reason why patients prescribed first-generation antipsychotics were more likely to develop diabetes than patients prescribed risperidone, quetiapine, and olanzapine is that that patients prescribed first-generation antipsychotics may have been on those medications longer. To assess this possibility, we compared average duration between first prescription for a stable medication and last prescription for that medication before diabetes diagnosis across the antipsychotics examined. Although results fail to reveal significant differences in duration before diabetes onset between patients prescribed first-generation antipsychotics (251 days) and patients prescribed olanzapine (235 days; $p = 0.48$) and risperidone (284 days; $p = 0.23$), they indicate that patients prescribed first-generation antipsychotics tended to be on those drugs significantly longer than patients prescribed quetiapine (170 days; $p = 0.04$). We also compared average duration between first prescription for a stable medication and last prescription before the end of our follow-up period for those who did not develop diabetes. Results indicate not only that average duration was significantly longer

for first-generation antipsychotics (321 days) when compared with quetiapine (226 days; $p = <0.0001$) but also that average duration was significantly longer for first-generation antipsychotics when compared with risperidone (247 days; $p < 0.0001$) and olanzapine (242 days; $p < 0.0001$). Consequently, one reason why patients on first-generation antipsychotics may have been more likely to develop diabetes is that they may have had more cumulative exposure to neuroleptic drugs than patients receiving atypical antipsychotics.

Whereas VA patients treated with clozapine and olanzapine exhibited a significantly higher risk of diabetes than patients treated with first-generation antipsychotics, privately insured patients treated with risperidone exhibited a significantly lower risk of diabetes. One possible explanation for the discrepancy in these findings is that VA patients may have been prescribed atypical antipsychotics earlier in the course of the disease than privately insured patients, providing more time for the cumulative effects of these drugs on the likelihood of developing diabetes to build up. Because the VA study focused on patients with schizophrenia, it examined the risk of DM in a sicker population than the present study, which examined the risk of DM in a privately insured population with a variety of mental health diagnoses. Consequently, privately insured patients in our study may have been treated with atypical antipsychotics later in the course of their illness. This may true because privately insured patients receiving atypical antipsychotics (not all of whom have schizophrenia) may be less seriously ill than VA patients treated primarily for schizophrenia. In addition, privately insured patients may have been treated with atypical antipsychotics later because it takes longer for drugs to diffuse to off-label use (e.g. for major depression rather than schizophrenia as originally intended). Because the VA study did not collect data on when patients initiated treatment, however, we were unable to assess whether patients in our study did in fact initiate treatment later.

Another possible explanation for the discrepancy between the two studies may have been differences in the average daily doses prescribed to VA patients with schizophrenia as compared with privately insured patients with other mental health diagnoses. While patients in the VA study were prescribed daily doses for first-generation antipsychotics that were 80% higher, on average, than those prescribed privately insured patients in our study (628.00 mg vs. 346.44 mg), they were prescribed daily doses that were, on average, only 37% higher for clozapine (583.44 mg vs. 434.47 mg), 31% higher for olanzapine (14.23 mg vs. 10.83 mg), and 56% higher for both quetiapine (330.03 mg vs. 211.93 mg) and risperidone (4.13 mg vs. 2.65 mg). Not surprisingly, VA patients with schizophrenia were prescribed higher doses for each of the antipsychotics examined than privately insured patients with a variety of mental health diagnoses. Greater differences in average daily dose were exhibited with first-generation antipsychotics than with atypicals, however. Lower doses of atypicals may explain why, in contrast to other studies, we did not find any greater risk of DM with atypical than first-generation antipsychotics, but it does not explain why we found significantly lower risk of DM for males on risperidone or quetiapine relative to first-generation drugs.

There are several limitations that we would like to address. First, we examined the incidence of DM in the private sector among patients with a mental health diagnosis stable on an antipsychotic medication. There may have been cases of DM that were not diagnosed or that were diagnosed outside of the health insurance plans included in the MarketScan database. Because we had access only to claims records and not detailed clinical data, we were unable to identify undiagnosed DM cases. However, we have no reason to believe that there were differences across our medication groups in the number of undiagnosed DM cases, so we suspect any bias resulting from this limitation to be minimal.

More likely is the possibility that all patients with a mental health diagnosis were not identified. Given limited mental health benefits among most private health insurance plans, patients who were more severely ill may have exhausted their plan benefits. Consequently, our claims database may not have captured services used by those patients after their claims were no longer paid. This is a limitation of all analyses that rely on private sector claims. Furthermore, patients in the private sector must follow very specific rules in order for insurance companies to consider their claims valid. Some claims may not be reimbursed and therefore would not have been included in our database (Leslie and Rosenheck, 2000). Because our sample involved only patients with a mental health diagnosis who were covered by health plans participating in MarketScan, our results may not be generalizable to other populations or health care systems.

In addition, our analysis attributed all of the DM risk to the atypical antipsychotic medication on which a patient was stable during a 3-month window. In fact, patients may have been stable on a different medication either before or after the medication identified in our study, and the increased DM risk might be partially attributable to these other medications. Data were not available to identify earlier stable medications, but the proportion of patients who switched drugs during the follow-up period was small (13.3% overall) and was similar across medication groups. Finally, there are limitations associated with all types of administrative data. For example, diagnoses may not be as accurate as in detailed clinical data.

CONCLUSION

Despite limitations posed by our data, results presented here offer important insight into the risk of DM in a privately insured mentally ill population who were prescribed antipsychotics. We found that the risk of diabetes varied across the

atypical antipsychotics examined. Unlike previous research, we found that patients treated with certain atypical antipsychotics exhibited a lower risk of new-onset diabetes than patients treated with first-generation antipsychotics. Furthermore, these effects were limited to male enrollees only. This latter finding is reflected in a recent study suggesting that the risk of DM associated with risperidone may be limited to elderly pharmacy plan enrollees 75 and older (Feldman, et al., 2004).

The association between DM and atypical antipsychotics may also be more of a problem for certain subgroups of the population—for example, VA patients with schizophrenia versus privately insured patients with general mental illness. Although the Food and Drug Administration recently concluded that increased risk of diabetes, hyperglycemia, and related symptoms is an adverse effect associated with atypical antipsychotics as a general class of medications, additional research is needed to determine the true association between the risk of DM and use of atypicals and variation in this risk across subgroups. Health care providers should be aware of this potential association, however, and monitor patients appropriately, in addition to educating them to look for signs and symptoms of DM when using these agents.

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GLUCOSE REGULATION

Diabetes and Insulin Resistance in the Neuropsychiatric Population

Samuel Dagogo-Jack, MD

Incidence of diabetes in the general population has increased dramatically in recent years. In only 9 states is the current prevalence of diabetes below 6%. Persons with mental illness are at higher risk for diabetes because of a variety of factors; incidence of diabetes in schizophrenic persons is estimated at about 10%. Insulin resistance can precede the development of diabetes by several years. Mental health professionals as well as primary care physicians should screen patients with mental illness for signs of insulin resistance and diabetes before starting therapy with antipsychotic medications. Patients receiving antipsychotic medications should also have their blood glucose levels monitored regularly so that any metabolic disturbances that may arise can be evaluated and treated promptly

Key words: Antipsychotic agents • Diabetes mellitus • Insulin resistance

Diabetes is epidemic not only in the United States but around the world. In 1990, when the CDC first began tracking diabetes incidence, there were just 4 states in which the prevalence of diabetes was 6% or higher (Figure 1A).[1] By 2000, in only 9 states was the prevalence below 6% (Figure 1B).[2] This shift has occurred in just 1 decade.

The population of persons with diabetes continues to expand, and with 40% of cases of diabetes undiagnosed, these estimated prevalence rates are vastly understated.

Projections are that, if the national trends of poor dietary habits, weight gain, and abhorrence of exercise continue unabated, the incidence of diabetes will approach the current prevalence rate of diabetes in the schizophrenic population, which is estimated at about 10%.[3]

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PATHOPHYSIOLOGY

Although the incidence of type 1 diabetes is also increasing, 90% to 99% of the diabetes burden in the United States is attributable to type 2 diabetes.[1] Unlike type 1 diabetes, the cause or causes of type 2 diabetes are not as clearly understood, and there appear to be multiple contributing factors. Onset of type 2 disease is gradual. Several years before type 2 diabetes is diagnosed, tissues have altered behavior in response to insulin.

Type 2 diabetes used to be called adult-onset or maturity-onset diabetes because it seemed that a person needed to grow old enough or attain a certain body proportion to manifest this condition. Everyone who became diabetic by age 45 presumably was healthy at age 18, but something changed in their bodies, which we have termed "insulin resistance." Persons with type 2 diabetes can have adequate, sometimes even elevated, amounts of insulin in their blood, yet blood glucose levels remain high because the insulin is not working as it

should. With the development of insulin resistance, the pancreas is called upon to increase its production of insulin. If this is successful, glucose is forced through whatever is impeding its transport, and blood glucose levels are normalized.

The development of insulin resistance is necessary but not sufficient for type 2 diabetes to develop. There must also be inadequate compensation by the pancreas when blood glucose levels rise.

Recent research has shown that the liver also plays a role in the development of insulin resistance syndrome.[4] The liver makes a finite amount of glucose to feed the brain during sleep. In persons with type 2 diabetes, the liver makes proportionately more insulin and less glucose. Thus, a person may be having problems getting glucose from the bloodstream because he or she is insulin resistant and not making enough insulin. Yet, at the same time, this person's liver is producing glucose at a higher rate than normal, which is paradoxic.

Insulin resistance can precede the diagnosis of diabetes by several years. Abnormal function of pancreatic β cells also occurs early during the transition from normal metabolism to diabetes.[5] The earliest defect seen in the pancreas is the loss of first-phase insulin secretion. This first phase normally prevents the excessive rise of blood glucose levels after eating and

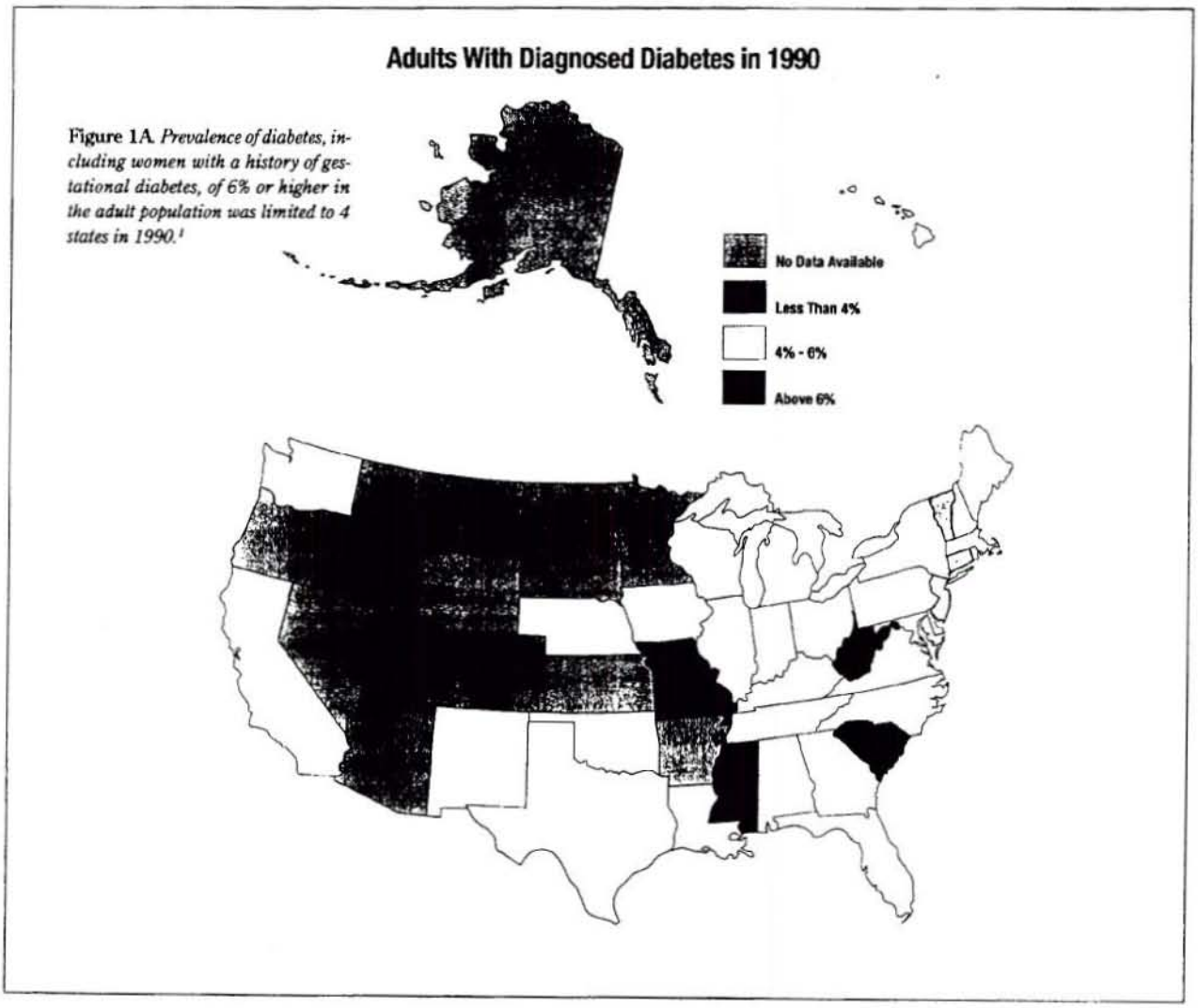

Figure 1A. *Prevalence of diabetes, including women with a history of gestational diabetes, of 6% or higher in the adult population was limited to 4 states in 1990.*[1]

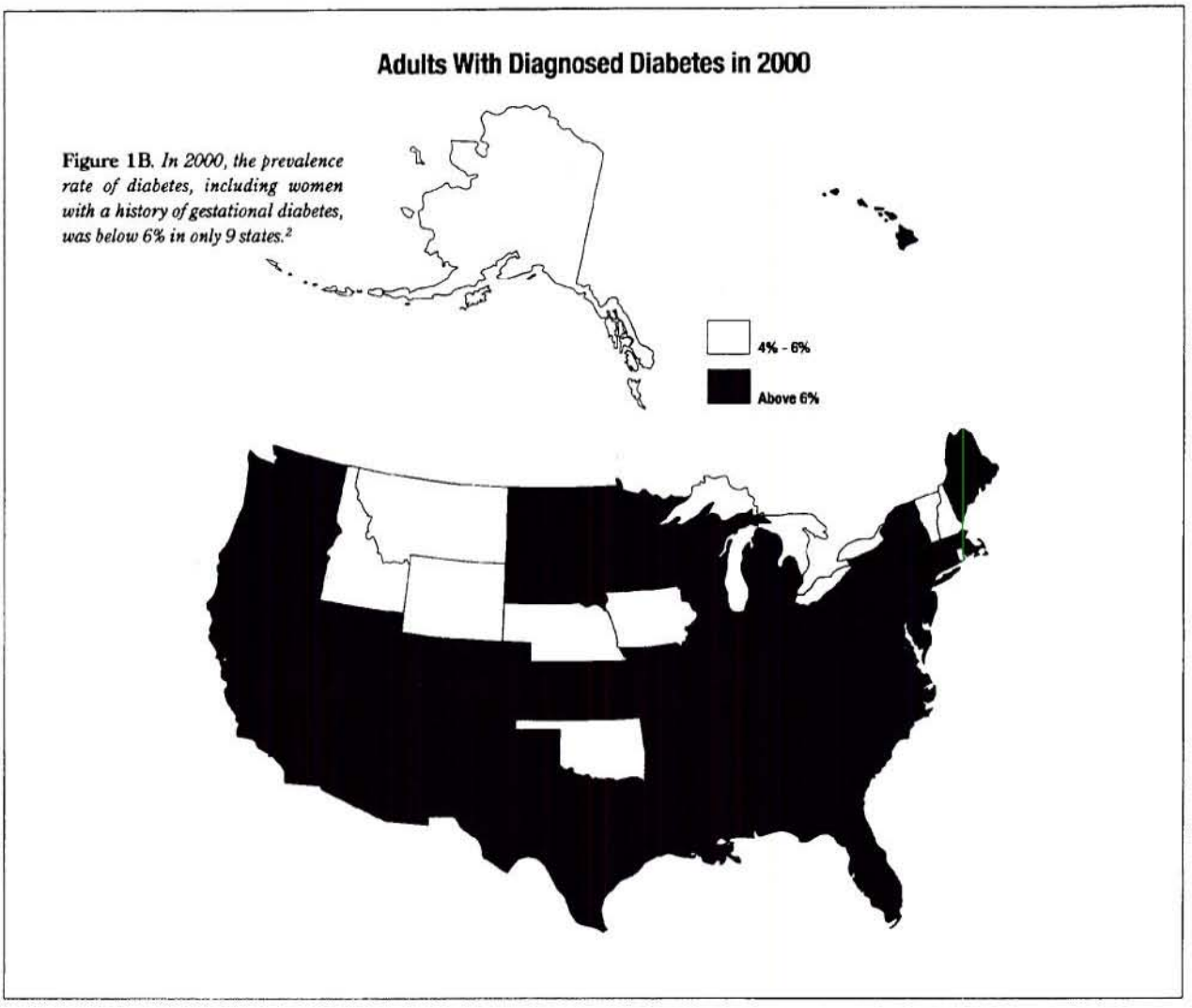

Figure 1B. *In 2000, the prevalence rate of diabetes, including women with a history of gestational diabetes, was below 6% in only 9 states.*[2]

is the first defense against postprandial hyperglycemia.

Preformed insulin granules stored within the islet cells of the pancreas are released with the stimulation of eating or drinking. A study by Pfeifer and associates[6] demonstrates how this process occurs in persons who do not have diabetes. In healthy volunteers, 20 g of glucose was infused as an intravenous bolus. From another venous line, blood was drawn at frequent intervals to track insulin secretion. At baseline, these test subjects had insulin levels around 10 µU/mL. Within 3 to 8 minutes of glucose administration, the insulin secretion increased 10-fold to more than 100 µU/mL. In contrast, patients with type 2 diabetes are unable to produce first-phase insulin secretion in response to the same stimulus.

Such acute insulin secretory failure, a sine qua non of type 2 diabetes, can be demonstrated years before type 2 diabetes is evident. Development of type 2 diabetes is not an overnight phenomenon. Persons progress to it from documented stages of lesser impairment, an important consideration when diabetes and insulin resistance are discussed in the psychiatric population.

Researchers have observed for several decades that there is a 2- to 4-fold increased prevalence of type 2 diabetes in psychiatric patients compared with the general population.[7-10] These studies evaluated patients with

depression,[11] bipolar disorder,[10-12] Alzheimer disease,[13-15] and schizophrenia.[8,9,16-18] Among the earliest reports was that of Braceland and colleagues[16] in 1945, noting increased incidence of diabetes in persons with mental health conditions and severe mental illness compared with persons who are mentally healthy.

RISK FACTORS

What risk factors in the general population might be operating disproportionately in the psychiatric population to trigger this increased prevalence of diabetes?

- *Demographics.* The US population is aging, and there is a strong correlation between age and the development of diabetes and glucose intolerance. By the age of 70 in the United States, 1 in 3 persons is at risk for diabetes.
- *Genetic and familial factors.* Persons with a family history of diabetes in a first-degree relative are at higher risk for diabetes than are persons without such a family history.
- *Weight gain and obesity.* (See "Mechanisms affecting glucose regulation.")
- *Physical inactivity.* Patients who are manic might be overactive, but in general, the psychiatric population tends to be socially withdrawn, and these individuals are not spending time at fitness centers working out on exercise machines.
- *Intrinsic stress and the activated hypothalamic-pituitary-adrenal axis.* The end product of this activation is the production of cortisol, an anti-insulin and diabetogenic hormone. Cortisol causes release of free fatty acids that the liver uses to make more glucose. So increased stress can contribute to increased incidence of diabetes. A study conducted by Eaton and colleagues[19] demonstrated that depression can precede the onset of diabetes, and another study by Lustman and associates[20] showed that managing depression can improve glucose control in patients with established diabetes.
- *Medications.* Can diabetes be drug-induced, such as with atypical antipsychotics? Use of typical antipsychotics has been reported to either worsen diabetes[21] or trigger new-onset diabetes.[22] In a 1968 study by Thonnard-Neumann[23] of patients being treated with chlorpromazine versus controls, investigators found a 4-fold increase in the incidence of diabetes.

With the atypical antipsychotics being more widely used, there are reports of metabolic abnormalities reminiscent of the old literature. These agents have been associated with exacerbation of preexisting diabetes, new-onset diabetes, and even ketoacidosis. Virtually all available agents in the class, including clozapine,[24-27] olanzapine,[28-31] risperidone,[26,32,33] and quetiapine,[33,34] have been associated with hyperglycemia. The newer drug, ziprasidone,[35] which has been less widely used, has so far not been implicated in metabolic perturbation. Nonetheless, based on available data, there is no discernible hierarchy of antipsychotic drugs with regard to their propensity for inducing glucose dysregulation.

MECHANISMS AFFECTING GLUCOSE REGULATION

In patients who are receiving antipsychotic medications, a variety of mechanisms can affect glucose regulation. These include weight gain, insulin resistance, serotonergic mechanisms, β-cell function, pancreatitis, prolactin levels, and drug interactions. Weight gain is well known to increase diabetes risk, as seen in the Nurses' Health Study.[36] Weight gain up to a body mass index (BMI) of about 40 kg/m^2 led to a 60-fold increase in the risk of diabetes. Weight gain is certainly an issue, but is it the smoking gun?

Insulin resistance is a precursor to type 2 diabetes. Indeed, type 2 diabetes does not develop without evident insulin resistance and defective β-cell insulin secretory response.

There have been anecdotal reports of pancreatitis in persons receiving atypical antipsychotics, but causality is unproven. In any case, pancreatic exocrine damage is an unlikely mechanism for a major increase in diabetes risk, because the islets of Langerhans are usually spared.

Weight gain in patients receiving antipsychotic medications is seen across all drug classes, more so in some than in others. The relationship of weight changes to use of atypical antipsychotic agents was examined by Allison and coworkers.[37] Patients receiving haloperidol or ziprasidone were found to be at low risk for weight gain, while those receiving clozapine were at the highest risk for weight gain. In 1 study, significant weight gain (up to 8%) was seen in patients being treated with clozapine.[38] In a longitudinal study (160 weeks) comparing weight gain in patients receiving haloperidol or olanzapine, patients receiving olanzapine gained more weight than those receiving haloperidol. Of note, however, is the fact that the weight gain with olanzapine was not continuous and plateaued at 39 weeks.[39]

Weight gain, though, is not synonymous with use of atypical antipsychotics. In fact, up to a quarter of individuals lost weight while receiving olanzapine therapy. In addition, the individual's baseline BMI can play a role

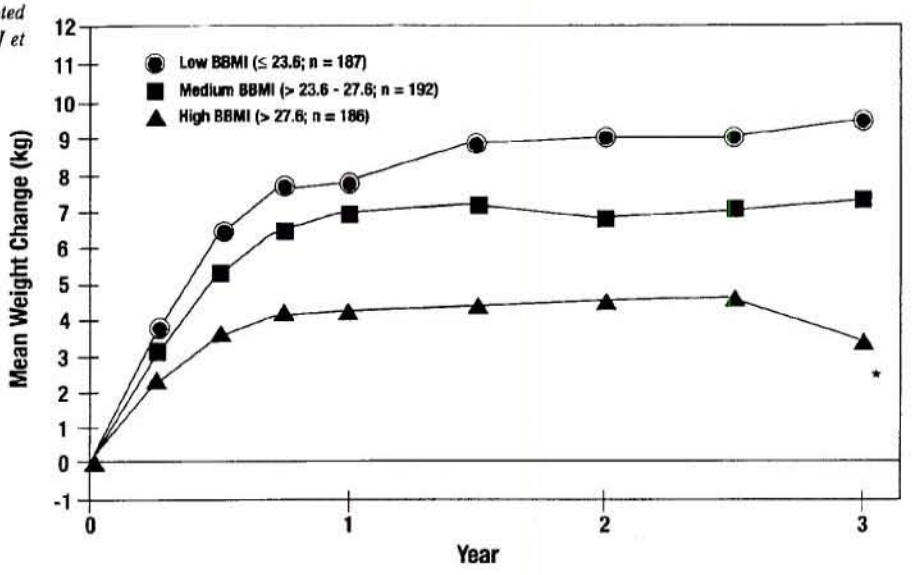

Figure 2. *In patients receiving olanzapine, weight gain is related to the individual's BMI and plateaus across all weight levels. (Adapted with permission from Kinon BJ et al.* J Clin Psychiatry. *2001.[39])*

in the amount and rapidity of weight gain.[39] When comparing persons who are underweight, of moderate weight, or overweight, those who are overweight at baseline appear to gain less weight than those who are underweight. In a study of patients receiving olanzapine,[39] the mean weight change was 3 to 9 kg, but there was a 3-fold difference in the amount of weight gain in persons with a low baseline BMI than in those with a high baseline BMI (Figure 2).

The characteristic plateau point across all weight classes and the noncontinuity of the weight gain effect argue against a fundamental cause-and-effect relationship. A more complex metabolic interaction exists, demonstrated by the leveling of weight gain over time. Furthermore, the available data do not indicate a linear or significant relationship between the amount of weight gain and alterations in blood glucose levels.[39] Of 571 patients receiving olanzapine in the 2.5-year study, nearly one quarter did not gain weight, 1 patient gained 40 to 50 kg, and most patients were in the category of gaining 10 kg or less. There was no statistically significant correlation between the amount of weight gained and change in blood glucose levels.

ATYPICAL VERSUS TYPICAL ANTIPSYCHOTICS

Based on clinical reports from the field of mental health, the advent of the atypical antipsychotic agents has been a major therapeutic advance in terms of efficacy, safety, and tolerability. Notably, adverse effects, such as tardive dyskinesia and other extrapyramidal symptoms, occur at much lower frequency with the atypical agents as compared with the older drugs. Arguably, the burden of side effects of glucose alteration or weight gain seems to be a fair price to pay for the benefits that these agents provide.

According to the 2003 recommendations issued by the American Diabetes Association (ADA),[40] all Americans aged 45 years and older are eligible for diabetes screening. The screening should be done every year or every 3 years, if results of the first year's test are normal and there are no risk factors. Patients with risk factors, such as a family history of diabetes, habitual inactivity, certain ethnic heritage (African American, Asian American, Hispanic, Native Ameri-

can), or diagnosis of hypertension or vascular disease, should be tested at a younger age and more frequently.

What is missing in the new ADA recommendations is the specific listing of the mental health population in the high-risk group. The data support such a listing. In fact, data concerning the risk of diabetes among persons with mental illness have been available for a long time.

Mental health professionals as well as primary care physicians should be encouraged to monitor their patients with mental illness for signs of diabetes and insulin resistance before and during therapy with agents that may cause a metabolic disturbance. Timely education and dietary modification as well as physical activity should reduce the diabetes risk. If diabetes is diagnosed during screening, appropriate therapy can be initiated promptly. If caught early and treated, diabetes does not pose the degree of risk caused by severe mental illness and the possibility of suicide.

For example, in a diabetes prevention program, patients were encouraged to increase their physical activity and modify their diets. Walking was a favorite activity for the majority of subjects; the results, after approximately 3 years of study, showed a 60% reduction in the risk of type 2 diabetes developing. Patients who are physically active can improve their insulin sensitivity independent of weight loss. ●

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A 24-WEEK, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY TO COMPARE CHANGES IN GLUCOSE METABOLISM IN PATIENTS WITH SCHIZOPHRENIA RECEIVING TREATMENT WITH OLANZAPINE, QUETIAPINE AND RISPERIDONE

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Poster presented at the Annual Meeting of the American Psychiatric Association, San Diego, CA, USA, 19-24 May 2007.

Poster presented at the American Diabetes Association, Chicago, IL, USA, 22-26 June 2007.

Abstract

Objective: This randomized, 24-week, flexible-dose study compared changes in glucose metabolism in patients with schizophrenia receiving initial exposure to olanzapine, quetiapine, or risperidone.

Methods: Primary endpoint was change (baseline to Week 24) in area under the curve (AUC) 0-2h plasma glucose during oral glucose tolerance test (OGTT); primary analysis: olanzapine versus quetiapine. Secondary endpoints included change in AUC 0-2h plasma insulin, insulin sensitivity index (ISI), and fasting lipids.

Results: Mean weight change over 24 weeks was +3.65 kg (quetiapine), +4.58 kg (olanzapine), and +3.57 kg (risperidone). Based on data from 395 patients (quetiapine n=115 [mean 607.0 mg/day], olanzapine n=146 [15.2 mg/day], and risperidone n=134 [5.2 mg/day]), change in AUC 0-2h glucose (mg/dL×h) at Week 24 was significantly lower for quetiapine versus olanzapine (t=1.98; DF=377; p=0.048). Increases in AUC 0-2h glucose were statistically significant with olanzapine (+21.9 mg/dL, 95% CI 11.5, 32.4) and risperidone (+18.8, CI 8.1, 29.4), but not quetiapine (+9.1, CI -2.3, 20.5). AUC 0-2h insulin increased statistically significantly with olanzapine, but not quetiapine or risperidone. Reductions in ISI were statistically significant with olanzapine and risperidone, but not quetiapine. Total cholesterol and LDL increased statistically significantly with olanzapine and quetiapine, but not risperidone. Statistically significant increases in triglycerides, cholesterol/HDL, and triglyceride/HDL ratios were observed with olanzapine only.

Conclusion: The results indicate a significant difference in the change in glucose tolerance during 6 months' treatment with olanzapine versus quetiapine, with

significant reductions on olanzapine and risperidone, but not quetiapine; these differential changes were largely explained by changes in insulin sensitivity.

Word count: 250/250

Keywords: glucose, insulin, lipids, olanzapine, quetiapine, risperidone, schizophrenia.

Introduction

Schizophrenia is a chronic, debilitating, and multidimensional illness that can adversely impact on quality of life and significantly reduce lifespan, largely related to premature cardiovascular disease.[1;2] Patients with schizophrenia have an increased prevalence of modifiable cardiometabolic risk factors (obesity, hyperglycemia, smoking, hypertension, lipid abnormalities), compared with that found in the general population.[3-5] Contributions to the increased prevalence of these risk factors are multifactorial, including poverty, poor nutrition, lack of exercise and restricted access to healthcare, and relative underutilization of primary and secondary prevention approaches in this population.[3;6;7]

In addition, there is increasing interest in the effects of antipsychotic treatment on the development or worsening of metabolic disturbances, based on evidence that treatment with specific antipsychotics is associated with changes in weight, plasma lipids, insulin resistance, and glucose tolerance.[7-10]

The American Diabetes Association (ADA), as well as the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, sponsored a consensus statement summarizing differences in the risk of weight gain, diabetes and dyslipidemia associated with different atypical antipsychotics, based on evidence available at the time. The consensus statement recommended that patients undergo baseline screening and follow-up monitoring of weight, plasma glucose, and plasma lipids.[11]

A variety of approaches have been used to study medication-specific risk for adverse effects on glucose and lipid metabolism during antipsychotic treatment. Prospective,

randomized, controlled clinical trials provide the gold standard approach for hypothesis testing in this area. A recent, well-publicized example is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[10] Although the trial was designed primarily to compare the time to treatment discontinuation between olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine in patients with schizophrenia, secondary endpoints included several metabolic indicators (e.g. body weight, plasma glucose, lipids and glycosylated hemoglobin). The results suggested differences between medications with regard to changes in weight, glucose and lipids, relevant to the prediction of cardiovascular and diabetes risk parameters.[10] However, interpretation of the metabolic findings in the CATIE study are limited by unconfirmed fasting conditions, the confounding effect of variable prior treatments preceding the study, and a lack of sensitive metabolic indicators.[12] Similarly, the interpretation of many other studies evaluating the metabolic effects of antipsychotics are limited by methodological concerns that include use of less sensitive measures, such as unconfirmed fasting plasma glucose measurements at single timepoints, lack of needed comparator groups, and lack of adequate controls for potentially confounding factors such as underlying medical conditions.[8]

This report provides results from a large-scale, multicenter study evaluating differential changes in glucose tolerance, as well as insulin sensitivity, weight, plasma lipids, and other relevant parameters, in patients with schizophrenia randomized to 24 weeks of treatment with olanzapine, quetiapine, or risperidone. Key design strengths include sensitive primary and secondary measures of glucose metabolism, confirmed fasting conditions, rigorous screening methods, and a patient sample not previously exposed for at least 90 days to any of the agents under testing.

Methods

Study design

This was a multicenter, randomized, 24-week, open-label, flexible-dose, parallel-group study (study number D1441C00125) that compared differential changes in glucose metabolism, plasma lipids, and weight-related measures in patients with schizophrenia receiving olanzapine, quetiapine, or risperidone. The first patient enrolled on 29 April 2004 and the last patient completed the study on 24 October 2005.

This study was conducted in 58 participating centers from 9 countries: Bulgaria (8 centers), the Czech Republic (8 centers), Germany (6 centers), Hungary (7 centers), Norway (1 center), Romania (7 centers), Slovakia (12 centers), South Africa (8 centers), and the United Kingdom (1 center). The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). Patients provided written informed consent before the start of any study-related procedures.

Patients

Male and female patients aged 18-65 years were included in this study if they fulfilled the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Patients were eligible if they had not received previous antipsychotic treatment or had shown an inadequate response or poor tolerance to previous treatment, and could benefit from a change in treatment. Key exclusion criteria included: previous treatment with one of the study

medications (quetiapine, olanzapine, or risperidone), clozapine, or chlorpromazine within three months and/or valproic acid, lithium, or antidepressants within one month; treatment with insulin or oral antidiabetic agents; patients who had recently started treatment with agents known to affect insulin sensitivity; patients with a known diagnosis of diabetes; and pregnancy. Patients were also excluded if they had a history of nonadherence, a diagnosis of any other Axis I disorder, any clinically relevant disease (e.g. liver, renal, or heart disease), or had received treatment with a depot antipsychotic within one dosing interval.

A small number of patients whose blood glucose rating was in the diabetic range as defined by the ADA (≥126 mg/dL for fasting glucose and/or ≥200 mg/dL for 2-h post-load glucose) at baseline were incorrectly randomized for participation in the study, despite the fact that they fulfilled exclusion criteria, due to a programming failure in the central laboratory. This affected 20 patients in the primary analysis population (PAP) [3 patients in the quetiapine group, 10 in the olanzapine group, and 7 in the risperidone group] and 26 patients in the safety population (n=5, 11, and 10, respectively); these patients were excluded from the per-protocol (PP) population. Following randomization, no patients were excluded due to development of diabetes during the study.

Treatment

Patients were randomized sequentially, with an equal probability of receiving olanzapine, quetiapine, or risperidone. Patients were stratified according to body mass index (BMI) in four groups (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2) and according to age in two groups (≤50 years, >50 to ≤65 years). Randomization was performed using a validated computer-based system and an interactive voice

recording system, which provided the assigned treatment and a randomization code for each patient, after all relevant information was entered by the investigator. Serum glucose and HbA_{1c} values at screening were required to determine patient eligibility. These values were not blinded, and treatment assignment was open.

Patients entered a five-day crossover period during which any previous antipsychotic was tapered off and study medication was escalated to the target dose (quetiapine 600 mg/day, olanzapine 15 mg/day, risperidone 6 mg/day). This was followed by a 23-week, flexible-dose, open-label period during which quetiapine was administered in the range 400-800 mg/day, olanzapine 10-20 mg/day, and risperidone 4-8 mg/day. Quetiapine was administered twice daily, olanzapine once daily, and risperidone once or twice daily, depending on local prescribing information.

No other psychoactive medications were allowed during the study. All previous anticholinergic medication had to be withdrawn during the first week of treatment, by which time any residual extrapyramidal symptoms (EPS) from previous medication should have resolved. Benztropine mesylate (≤6 mg/day), trihexyphenidyl (≤6 mg/day), biperiden (≤6 mg/day), or procyclidine (≤30 mg/day) could be used to treat any new emerging EPS-related adverse events (AEs); prophylactic use was prohibited. Benzodiazepines (lorazepam ≤4 mg/day, oxazepam ≤60 mg/day**,** or alprazolam ≤2 mg/day) and sleep medication (zolpidem tartrate ≤10 mg/day, chloral hydrate ≤2mg/day, zaleplon ≤20 mg/day, or zopiclone ≤7.5 mg/day) were permitted during the study. Medications considered to potentially affect glucose metabolism and insulin sensitivity (e.g. some antihypertensives) were restricted during the study.

Assessments

AUC 0-2 h plasma glucose during an oral glucose tolerance test

The primary objective of the study was to compare the safety/tolerability effect profile of olanzapine versus quetiapine on glucose metabolism. The primary outcome variable was the change from baseline to Week 24 in area under the curve (AUC) for plasma glucose from 0-2 h (AUC 0-2 h), during an oral glucose tolerance test (OGTT).[13] A secondary objective was to compare the safety/tolerability of quetiapine and risperidone on glucose metabolism, by evaluating the change from baseline to Week 24 in AUC 0-2 h of plasma glucose values during the OGTT.

Patients were hospitalized overnight to ensure 8-14 h fasting conditions prior to OGTT.[13] A blood sample was taken prior to the test to determine fasting levels of variables related to glucose and lipid metabolism. The test commenced with the patient drinking 75 g of anhydrous glucose in 250-300 mL of water over 5 min. Blood samples were collected at 30, 60, 90, and 120 min by venous catheter.

Measures of insulin sensitivity and secretion

Other secondary objectives of the study were to compare the changes from randomization to Week 24 in: plasma insulin AUC 0-2 h during OGTT; insulin sensitivity index (ISI) derived from OGTT,[14] fasting insulin; and homeostasis model assessment (HOMA-IR).[15] The change in plasma C-peptide levels was an exploratory measure, and mean relative changes in the insulinogenic index (IGI)[16] were estimated in a post hoc descriptive analysis.

ISI was calculated as the 10,000/square root of ([fasting glucose (mg/dL) × fasting insulin (μIU/mL)] × [mean glucose (mg/dL) × mean insulin (μIU/mL) during OGTT]). HOMA-IR was calculated as: fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L)/22.5. IGI was calculated as the ratio between simultaneous increments in plasma insulin and glucose from 0 to 30 min after glucose load (change in insulin at 30 min [μIU/mL] / change in glucose at 30 min [mg/dL]).

Additional glucose parameters

Other secondary objectives of the study were to compare: the changes from randomization to Week 24 for fasting and 2-h post-load glucose; incidences of patients with hyperglycemia (fasting plasma glucose ≥126 mg/dL and/or 2-h glucose ≥200 mg/dL); incidences of patients with impaired fasting glucose (IFG, defined as fasting plasma glucose ≥100 and <126 mg/dL) or impaired glucose tolerance (IGT, defined as 2-h glucose ≥140 and <200 mg/dL); and the change from randomization to Week 24 in HbA_{1c} levels. The proportion of patients with HbA_{1c} ≥6.05% was an exploratory measure.

Lipid parameters

Additional secondary objectives of the study were to compare the safety/tolerability of quetiapine, olanzapine and risperidone on blood lipid levels by evaluating fasting plasma lipid levels (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides). The change in ratios between total cholesterol and HDL, and triglyceride and HDL levels, as proposed predictors of cardiovascular risk,[17;18] was also estimated as a post hoc analysis.

Bodyweight

Changes from randomization to Week 24 were assessed for bodyweight, BMI, (calculated as weight in kg/height in m^2), and waist circumference.

All of the above assessments were made at the following intervals: baseline (randomization), Week 12, and Week 24 (±4 weeks). Key laboratory values, including glucose metabolic variables and lipids, were blinded throughout the study.

Other safety and tolerability objectives

In order to compare changes in prolactin levels, the change from baseline to Week 24 in plasma prolactin (μg/L) was determined. The safety/tolerability profile of quetiapine, olanzapine, and risperidone on EPS and other AEs was also examined, by recording the following: change from baseline to Week 24 in Simpson-Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) total score; incidence of AEs; sitting and standing systolic and diastolic blood pressure and pulse rate; changes in electrocardiogram (ECG); and the proportion of patients using anticholinergic medication.

Efficacy measures

The efficacy of quetiapine, olanzapine, and risperidone was assessed by evaluation of clinical symptoms, using the following outcome variables: the proportion of patients with a Clinical Global Impression-Improvement (CGI-I) rating of "very much improved" or "much improved" at the final assessment (last observation carried forward, [LOCF]), and the proportion of patients with a Clinical Global Impression Severity of Illness rating scale (CGI-S) score less than or equal to 3 at Week 24.

Statistical analyses and patient populations

The power calculation for the sample size determination was based on weight change, due to its anticipated correlation with changes in plasma glucose levels, and because there is a lack of published data on the variance of the primary variable. Calculations were based on information from previous long-term trials of quetiapine,[19] as well as on published olanzapine data.[20] The within-patient variability of the change from baseline for weight was assumed to be 6.4 kg. The sample size was calculated as the number of patients needed to find a change of 3 kg in mean weight from baseline to Week 24 between the quetiapine and olanzapine groups. It was estimated that 95 patients per group (285 in total) would be required to provide 90% power for a two-sided test at the 5% alpha level. After allowing for withdrawals and protocol violations, approximately 500 patients had to be randomized in order to get 285 evaluable patients at Week 24.

Primary and secondary endpoints were analyzed using the PAP, which consisted of all randomized patients who were given study treatment and had baseline and Week 24 (±4 weeks) assessments. Primary and secondary measures were analyzed using analysis of covariance (ANCOVA) with baseline AUC 0-2 h glucose, BMI group, age group, and treatment as independent variables. Least squares means (LSMs) and 95% confidence intervals (CIs) were calculated. For the primary analysis, a p-value was derived. For insulin and insulin sensitivity indices, log-transformed values were analyzed with the ANCOVA model. LSMs and CIs were exponentially back-transformed. As the protocol stated that only descriptive analyses would be presented for secondary endpoints, post hoc analyses were performed to evaluate between-group differences and changes from baseline within groups, with statistical significance

based on CI coverage of zero; no adjustments were made for multiplicity. A post hoc analysis was also carried out to assess the change in ratios between total cholesterol and HDL, and triglyceride and HDL levels, as validated predictors of cardiovascular risk.[17;18] Pearson correlation coefficients were calculated to explore possible correlations between change in weight and change in AUC 0-2 h glucose, and between change in weight and change in log-transformed ISI.

The per-protocol (PP) population excluded patients with significant protocol violations or deviations, or patients considered to be nonadherent to treatment, i.e., who took <70% or >120% of the tablets. One patient randomized to the olanzapine group actually received treatment with quetiapine; this patient was excluded from the PP population and was not included in the PAP population because of discontinuation before Week 20. Only the primary analysis was repeated on the PP sample to test for homogeneity of the treatment changes. AE data and any other safety analyses that were not the focus of the study objectives were analyzed on the safety population, which consisted of all randomized patients who were given study treatment (i.e. who took at least one dose of medication), classified according to the treatment actually received. Efficacy data were analyzed for the intent-to-treat (ITT) population, which included all randomized patients who were given study treatment, classified according to randomized treatment.

Results

Patients

A total of 574 patients were enrolled, and 510 were randomized: quetiapine n=168, olanzapine n=169, and risperidone n=173. Details of patient disposition and baseline

demographics are given in Figure 1 and Table 1, respectively. Overall, the treatment groups were well matched for baseline demographic and glucose metabolism characteristics (Table 1). Most patients were male, had paranoid schizophrenia, and were receiving antipsychotic medication at time of randomization. A total of 395 patients (quetiapine n=115, olanzapine n=146, risperidone n=134) had data at baseline and at ≥20 weeks, and were included in the PAP. The PP population consisted of 330 patients (quetiapine n=98, olanzapine n=126, risperidone n=106), the safety population included 509 patients (quetiapine n=169, olanzapine n=168, risperidone n=172), and the ITT population comprised 509 patients (quetiapine n=168, olanzapine n=169, risperidone n=172). Unless otherwise stated, results from the PAP are presented.

Treatment

Following randomization, mean (SD) doses at Week 24 were: quetiapine, 607.0 (128.3) mg/day; olanzapine, 15.2 (2.7) mg/day; and risperidone, 5.2 (1.0) mg/day. The corresponding dose ranges were: quetiapine 338-785 mg/day, olanzapine 10-20 mg/day, and risperidone 3-8 mg/day.

Use of concomitant medication during the study was similar across the treatment groups. Total use of concomitant benzodiazepines at any time during the study was 17.4% in the quetiapine group, 13.0% in the olanzapine group, and 18.7% in the risperidone group. The use of sleep medication was 16.5% in the quetiapine group, 17.1% in the olanzapine group, and 23.1% in the risperidone group.

Bodyweight

At Week 24, mean weight change from baseline was +3.65 kg (95% CI 2.43, 4.87) for quetiapine, +4.58 kg (95% CI, 3.46, 5.71) for olanzapine, and +3.57 kg (95% CI 2.42, 4.73) for risperidone. These changes from baseline were statistically significant for all groups. Between-treatment differences were not statistically significant.

The change from baseline in mean BMI (kg/m^2) was: +1.29 (95% CI 0.87, 1.72) for quetiapine, +1.64 (95% CI 1.25, 2.03) for olanzapine, and +1.28 (95% CI 0.88, 1.68) for risperidone. The mean change from baseline in waist circumference (cm) was +3.24 (95% CI 1.87, 4.60) in the quetiapine group, +4.37 (95% CI 3.11, 5.63) in the olanzapine group, and +2.99 (95% CI 1.71, 4.27) in the risperidone group. Pairwise comparisons showed that there were no significant differences in change from baseline in BMI or waist circumference between the treatment groups.

AUC 0-2 h plasma glucose during OGTT

Mean change from baseline to Week 24 in AUC plasma glucose (mg/dL × h) was +9.1 (95% CI -2.3, 20.5) with quetiapine (not statistically significant based on CI coverage of zero) and +21.9 (95% CI 11.5, 32.4) with olanzapine (statistically significant based on CI non-coverage of zero). The primary analysis results indicated that the difference in mean change from baseline in AUC 0-2 h plasma glucose was significantly different between quetiapine and olanzapine (-12.8 mg/dL × h; 95% CI -25.5, -0.11) (t=1.98; DF=377; p=0.048) [Figure 2]. The mean change from baseline in AUC plasma glucose with risperidone was +18.8 mg/dL (95% CI 8.1, 29.4) (statistically significant based on CI non-coverage of zero) at Week 24. The secondary analysis results indicated that the difference in mean change from baseline

in AUC plasma glucose for quetiapine compared with risperidone was -9.6 mg/dL × h; 95% CI -22.7, 3.4 (not statistically significant based on CI coverage of zero) [Figure 2]. The change from baseline to Week 24 in mean plasma glucose values over time (0-120-min post-glucose load) for the three treatment groups is shown in Figure 3.

In the PP population, the mean change from baseline to Week 24 in AUC 0-2 h plasma glucose (mg/dL × h) was +11.24 (95% CI -0.08, 22.56) in the quetiapine group and +26.2 (95% CI 15.49, 36.92) in the olanzapine group. The difference between quetiapine and olanzapine was statistically significant (t=2.34; DF=322; p=0.0199), confirming the results in the PAP. Mean change from baseline to Week 24 in the PP population was +20.97 (95% CI 10.25, 31.68) in the risperidone group.

Examination of the within-treatment correlation between change in weight and change in AUC 0-2 h glucose indicated relatively weak associations for quetiapine, olanzapine, and risperidone (Pearson correlation coefficient 0.25, 0.14, and -0.10, respectively).

Measures of insulin sensitivity and secretion

Relative increases from baseline in AUC 0-2 h plasma insulin during OGTT were not statistically significant with quetiapine (+13.15%; 95% CI, -0.14, 28.22) or risperidone (+10.74%; CI, -1.2, 24.13), but were with olanzapine (+24.45%; CI, 11.46, 38.96). Analysis of insulin sensitivity, as assessed by ISI, showed that decreases from baseline were not statistically significant with quetiapine (-10.8%, 95% CI -21.9, 1.85), but were statistically significant with olanzapine (-19.1%, CI -27.9, -9.33) and risperidone (-15.8%, CI -25.1, -5.41) [Figure 4]. Within-treatment

correlations between change in weight and change in ISI also indicated relatively weak associations (Pearson correlation coefficient -0.31, -0.45, -0.15 for quetiapine, olanzapine, and risperidone, respectively).

To further explore insulin secretion, the IGI, i.e. the early insulin response to oral glucose stimulation during the first 30 min of the OGTT, was estimated. The median relative change in IGI from baseline to Week 24 was -0.20% (lower quartile [LQ] -41.73, upper quartile [UQ] 40.49) in the quetiapine group, -9.15% (LQ -45.28, UQ 32.23) in the olanzapine group, and -3.27% (LQ -35.17, UQ 50.16) in the risperidone group.

Mean changes (95% CIs) in fasting insulin from baseline to Week 24 were 3.324% (-9.2, 17.58) for quetiapine, 8.475% (-3.33, 21.73) for olanzapine, and 11.9% (-0.2, 25.47) for risperidone.

For HOMA-IR, a measure of insulin resistance, increases of 6.44% (CI -7.63, 22.65) and 10.97% (CI -2.22, 25.94) from baseline to Week 24 were seen for quetiapine and olanzapine, respectively, but were not statistically significant. A statistically significant difference from baseline to Week 24 occurred with risperidone (16.75%; 95% CI 2.95, 32.41).

Change from baseline to Week 24 in plasma C-peptide levels was 0.36 ng/mL (95% CI, 0.11, 0.62) for quetiapine, 0.43 (CI 0.20, 0.67) for olanzapine, and 0.42 (CI 0.19, 0.66) for risperidone. These increases from baseline were statistically significant for all three treatment groups.

Pairwise comparisons of the treatment groups at Week 24 did not show any statistically significant difference in terms of mean change from baseline for AUC 0-2 h plasma insulin, ISI, fasting insulin, HOMA-IR, or C-peptide.

Additional glucose parameters

At Week 24, small changes from baseline in fasting glucose were seen in all treatment groups: 3.18 mg/dL (95% CI 0.24, 6.12) for quetiapine; 2.33 (CI -0.40, 5.06) for olanzapine; 4.40 (CI 1.62, 7.18) for risperidone (statistically significant for quetiapine and risperidone). All mean changes were within the normal range, and there were no statistically significant differences between the treatment groups.

For 2-h post-load glucose (mg/dL), the mean change from baseline was not statistically significant for quetiapine (-1.88, 95% CI -10.01, 6.26), but was statistically significant for olanzapine (+9.77, 95% CI 2.37, 17.17) and risperidone (+10.58, 95% CI 2.91, 18.24) [Figure 3]. The differences between quetiapine and olanzapine and between quetiapine and risperidone were statistically significant.

The proportion of patients in the PAP with a blood glucose value in the diabetic range (fasting plasma glucose $\geq$126 mg/dL and/or 2-h glucose $\geq$200 mg/dL) at baseline was 2.6% for quetiapine, 6.9% for olanzapine, and 5.2% for risperidone. At Week 24, the corresponding values were 4.3%, 6.8%, and 6.8%. Of the 20 patients in the PAP who had high glucose values at baseline (diabetic levels), 6 patients similarly had a high glucose measurement recorded at their following visit. The number (%) of patients with fasting glucose ≥126 mg/dL at baseline was 2 (1.8%), 3 (2.1%), and 3 (2.2%) and at Week 24 was 3 (2.6%), 5 (3.4%), and 4 (3.0%) for quetiapine, olanzapine, and risperidone, respectively. In total, 8 patients had glucose values below the diabetic

range at randomization but then at least 2 consecutive post-randomization values of fasting glucose ≥126 mg/dL and/or 2-h glucose ≥200 mg/dL. Of these 8 patients, 2 patients received quetiapine, 2 received olanzapine, and 4 received risperidone. At baseline, 26.3% of patients receiving quetiapine, 20.0% receiving olanzapine, and 32.1% receiving risperidone were defined as having IFG (defined as fasting plasma glucose ≥100 and <126 mg/dL) and/or IGT (defined as 2-h glucose ≥140 and <200 mg/dL). At Week 24, the corresponding values were 32.2%, 29.5%, and 40.6%. Pairwise comparisons between the treatment groups showed no significant differences between treatments with respect to the frequency of glucose measurements at the IFG, IGT, or diabetic levels.

Small increases in HbA_{1c} from baseline were seen in each treatment group: quetiapine 0.12% (95% CI 0.05, 0.19), olanzapine 0.05% (CI -0.01, 0.11), risperidone 0.07% (CI 0.00, 0.13); these changes were statistically significant for quetiapine and risperidone, but were within the normal range and not clinically significant. The proportion of patients with HbA_{1c} ≥6.05% at baseline was 4.5% for quetiapine, 4.2% for olanzapine, and 6.8% for risperidone. At Week 24, the corresponding values were 5.5%, 3.5%, and 4.7%. There were no statistically significant differences between treatments in HbA_{1c} levels or in the proportion of patients with HbA_{1c} ≥6.05% at Week 24.

Lipid parameters

Changes from baseline to Week 24 in total cholesterol, HDL, LDL, and triglycerides are shown in Table 2. Statistically significant increases from baseline in mean total cholesterol and LDL, but not triglycerides, were seen for quetiapine. Increases from baseline in mean total cholesterol, LDL, and triglycerides were statistically significant

for olanzapine. No significant increases in total cholesterol, LDL, or triglycerides were observed with risperidone. Olanzapine showed a statistically significantly greater increase in mean total cholesterol and LDL compared with risperidone. No other between-group comparisons were statistically significant.

A post hoc analysis of triglyceride/HDL and total cholesterol/HDL ratios indicated that changes from baseline to Week 24 were statistically significant with olanzapine only (Table 2). There were no statistically significant differences between treatments for triglyceride/HDL ratios. Olanzapine was associated with a statistically significantly greater change in total cholesterol/HDL ratio compared with risperidone, but not quetiapine.

Other safety and tolerability endpoints

Mean (SD) plasma prolactin levels at baseline were: 36.5 (40.9) μg/L in the quetiapine group, 57.2 (82.1) μg/L in the olanzapine group, and 44.7 (49.9) μg/L in the risperidone group. At Week 24, LSM change in prolactin was -32.1 μg/L (95% CI -42.2, -22.0) and -22.4 μg/L (CI -31.7, -13.1) in the quetiapine and olanzapine treatment groups, respectively. In the risperidone group, prolactin levels increased by +11.7 μg/L (95% CI 2.1, 21.3). A between-group analysis showed that the increase in prolactin levels with risperidone was statistically significant compared with quetiapine and olanzapine.

AEs during the treatment and follow-up period are presented in Table 3. No patients died during the treatment period. Two deaths occurred in the follow-up period in the risperidone group; however, these were not considered treatment related. No

unexpected AEs were reported; the pattern of the most frequently reported AEs conformed to what was expected from the pharmacological profiles of each drug.

Treatment-related EPS, as measured by BARS and SAS scores, showed statistically significant improvements in all treatment groups. LSM change at Week 24 in BARS scores was: -0.5 (95% CI -0.61, -0.39) with quetiapine; -0.48 (95% CI -0.58, -0.38) with olanzapine; and -0.21 (95% CI -0.31, -0.11) with risperidone. LSM change in SAS scores was: -2.89 (95% CI -3.27, -2.5) with quetiapine; -2.63 (95% CI -2.99, -2.28) with olanzapine; and -1.84 (95% CI -2.2, -1.48) with risperidone. The improvements were statistically significantly greater in the quetiapine and olanzapine groups, compared with the risperidone group. During the study, anticholinergic medication was used by 4.2% of patients in the quetiapine group, 5.9% in the olanzapine group, and 25.6% in the risperidone group.

The baseline values for sitting or standing pulse, and systolic or diastolic blood pressure, were comparable across the treatment groups. At Week 24, there were no significant increases from baseline in any of these variables in the PAP, apart from sitting pulse rate (bpm), which showed a significant increase with quetiapine (+3.12; 95% CI 1.13, 5.10) compared with olanzapine (+0.62, 95% CI -1.19, 2.44) and risperidone (+0.60, 95% CI -1.27, 2.46). These changes were not considered to be clinically significant. ECG abnormalities at Week 24 were reported for 12 (7.7%) patients in the quetiapine group, 13 (8.3%) in the olanzapine group, and 12 (7.3%) in the risperidone group. None of these were considered clinically significant or led to discontinuation of treatment.

Efficacy

Efficacy was assessed by CGI-S and CGI-I scores in the ITT population. The proportion of patients with CGI- S score ≤3 at baseline was: 28.0% in the quetiapine group, 28.4% in the olanzapine group, and 25.6% in the risperidone group. At Week 24, the vast majority of patients showed improvements, i.e. the proportion of patients with a CGI-S score ≤3 was 70.2% in the quetiapine group, 75.7% in the olanzapine group, and 74.3% in the risperidone group. Furthermore, the proportion of patients with CGI-I score of "very much improved" or "much improved" at Week 24 was 57.7% for quetiapine, 63.9% for olanzapine, and 55.6% for risperidone.

Discussion

Addressing growing interest in individual antipsychotic medication changes on risk for diabetes,[11] this large-scale, multicenter, randomized clinical trial offers the first report to our knowledge of a study using sensitively assessed differential changes in glucose tolerance observed during treatment with various atypical antipsychotics as the primary endpoint. Measuring mean change from baseline in AUC 0-2 h plasma glucose during 24 weeks of treatment with quetiapine, olanzapine, or risperidone, the primary analysis indicates a significant difference between quetiapine and olanzapine in the change from baseline to Week 24 in glucose tolerance, explained by a significant reduction in glucose tolerance during treatment with olanzapine but not quetiapine. Although a statistically significant reduction in glucose tolerance from baseline to Week 24 was also observed during treatment with risperidone, the reduction was smaller in magnitude than that observed with olanzapine, and the difference between risperidone and quetiapine in the change in glucose tolerance – although the study was not powered for this comparison – was not significant.

Secondary analysis of additional metabolic indices, including changes from baseline to Week 24 in AUC 0-2 h plasma insulin, insulin sensitivity (ISI), and a calculated measure of insulin secretion (IGI), strongly suggest that the changes in glucose tolerance observed in this study were largely related to changes in insulin sensitivity rather than insulin secretion.

While other studies have contributed to a growing understanding of differential antipsychotic medication changes in metabolic parameters, this study offers several advantages over previous reports. Key strengths include sensitive primary and secondary measures focused on glucose metabolism, confirmed fasting conditions, and timely sample collection ensured by overnight hospitalization, rigorous screening methods, and a patient sample not previously exposed for at least 90 days to any of the agents under testing. In particular, the modified 2-h OGTT method used in this study provided sensitive measures of glucose metabolism, such as AUC 0-2 h plasma glucose and insulin, which permit a calculation of insulin sensitivity previously validated against the euglycemic-hyperinsulinemic clamp, a reference methodology.[9;13;14]

Small increases in HbA_{1c} and fasting glucose were observed in all three treatment groups; however, these changes remained within the normal range, and there were no statistically significant between-group differences. Results from the CATIE study suggest that HbA_{1c} might be sensitive to differential medication changes under some conditions, but while patients in the CATIE study were instructed to fast, there was limited certainty that fasting was consistently achieved and no statistically significant effects of treatment group were observed on plasma glucose.[10] However, HbA_{1c} is not generally recommended as a screening tool because of limited sensitivity to early

change, and even confirmed fasting plasma glucose values are recognized as less sensitive than post-load glucose as a screening method, with clinical practice guidelines recommending post-load glucose as the ideal screening tool in higher risk patients[21] and several guidelines recognizing schizophrenia as a risk state.[22;23]

In this study, there were statistically significant changes in weight for all treatment groups, with the largest change from baseline in the olanzapine group. Whole body or abdominal adiposity, measured directly or estimated by BMI/weight or waist circumference, is an established predictor or correlate of insulin sensitivity in a variety of human populations, including treated patients with schizophrenia,[24] leading to the expectation that treatment-induced weight gain would explain substantial variance in treatment-induced changes in insulin sensitivity or glucose tolerance. However, previous evidence indicates that certain antipsychotic medications can produce adiposity-independent changes in glucose metabolism or insulin sensitivity.[25-27] In this study, the correlation between change in weight and change in insulin resistance or glucose tolerance was relatively weak, which is in part explained by the increased error/residual effect observed in correlations of change scores in comparison to correlations of single timepoint values. Despite the known effect of adiposity on insulin sensitivity and glucose metabolism, it remains possible that adiposity-independent mechanisms may be of importance in explaining some portion of the observed treatment-induced changes in insulin sensitivity or glucose tolerance. Such adiposity-independent effects, and/or underlying changes in regional adiposity not captured by observed changes in weight, could contribute to the explanation of differential results for risperidone and quetiapine on baseline to endpoint change in insulin sensitivity and glucose tolerance.

Measurement of plasma lipid changes in this study indicated that olanzapine treatment was associated with significant increases in total cholesterol, LDL, and triglyceride, quetiapine treatment was associated with numerically smaller but still statistically significant increases in total cholesterol and LDL, but not triglyceride, and risperidone treatment produced no significant changes in plasma lipid levels. Notably, the quetiapine-related changes in LDL and total cholesterol occurred in the setting of changes in AUC 0-2 h plasma insulin, ISI, weight, BMI and waist circumference that were less than or similar to risperidone treatment. Risperidone treatment, however, did not increase plasma lipids, suggesting that the changes in lipid profile observed during treatment with quetiapine can be influenced by mechanisms other than changes in adiposity and insulin sensitivity. With regard to lipid ratios that can be used to predict cardiovascular risk,[17;18] triglyceride/HDL and total cholesterol/HDL ratios increased significantly from baseline in patients treated with olanzapine.

Although this study was highly controlled, some of its methodological limitations warrant discussion. For instance, there was no placebo control group, which may restrict the interpretation of the absolute value of changes from baseline. In addition, the patient population was largely European. Moreover, the findings of this study may or may not be generalizable beyond 24 weeks. Despite these limitations, this study represents an advance from previously reported trials measuring the observed changes with antipsychotic medications on glucose metabolism, providing further evidence of differential changes with individual medication on the primary endpoint that are largely explained by treatment-related changes in insulin sensitivity.

Conclusions

This large-scale, randomized, 24-week clinical trial evaluated differential changes in glucose metabolism, insulin sensitivity, and lipid parameters in non-diabetic patients with schizophrenia treated with quetiapine, olanzapine, or risperidone. At clinically relevant doses, a significant difference was observed in the change in glucose tolerance during 6 months of treatment with olanzapine versus quetiapine, with significant reductions in glucose tolerance on olanzapine and risperidone, but not quetiapine. The observed treatment-related changes on glucose tolerance were largely explained by changes in insulin sensitivity.

Clinical trials registration: ClinicalTrials.gov identifier NCT00214578

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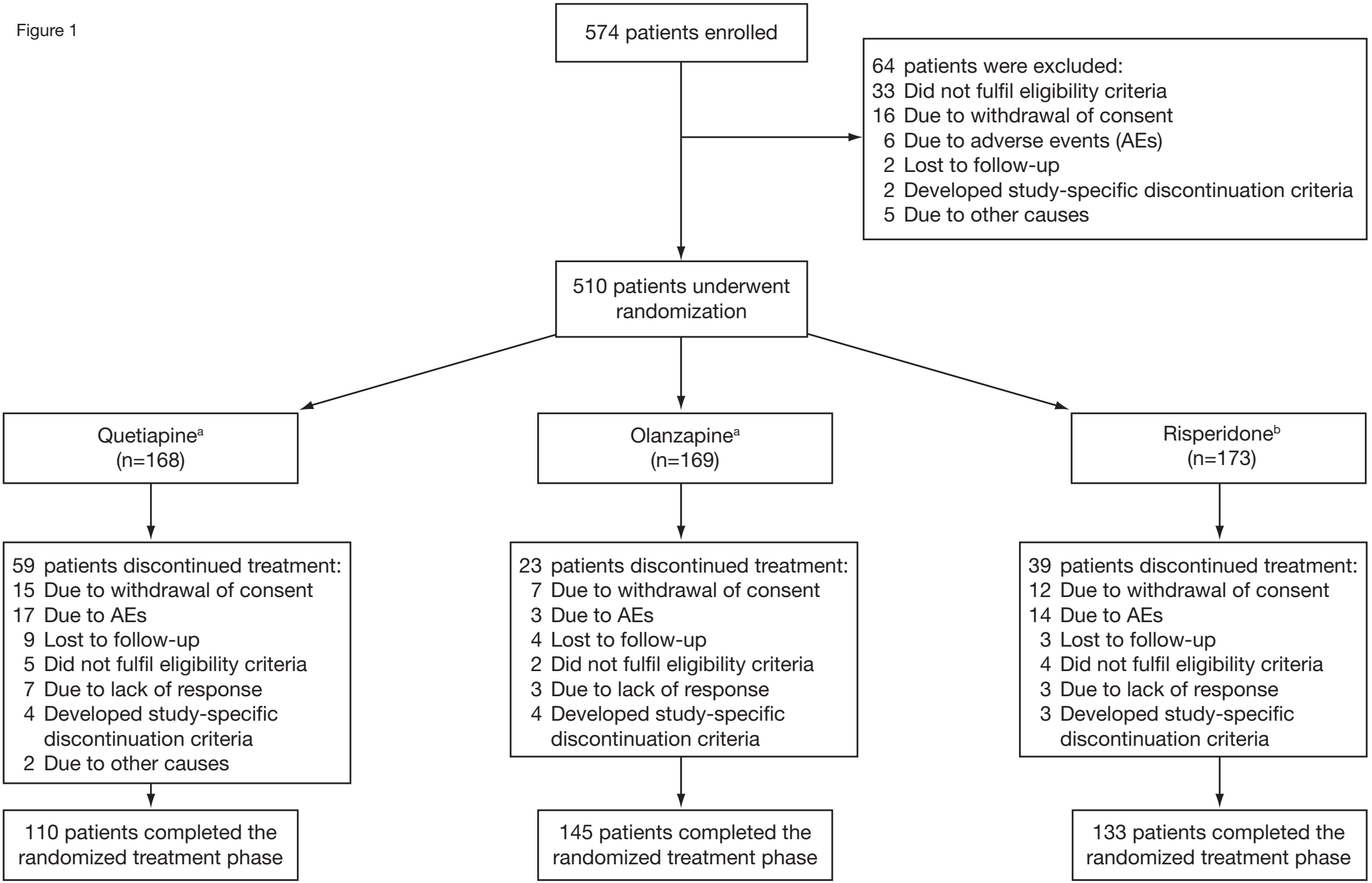
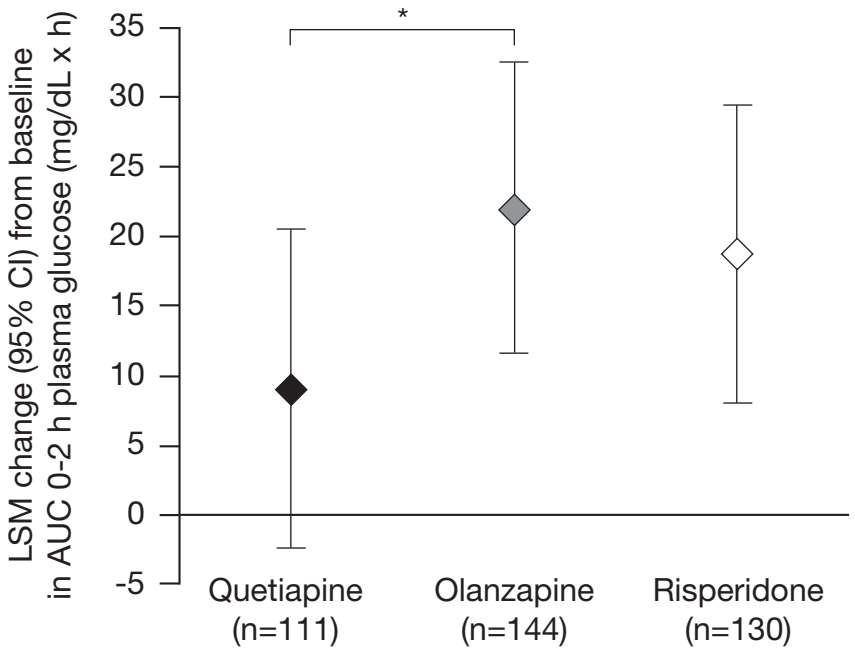
Figure 1



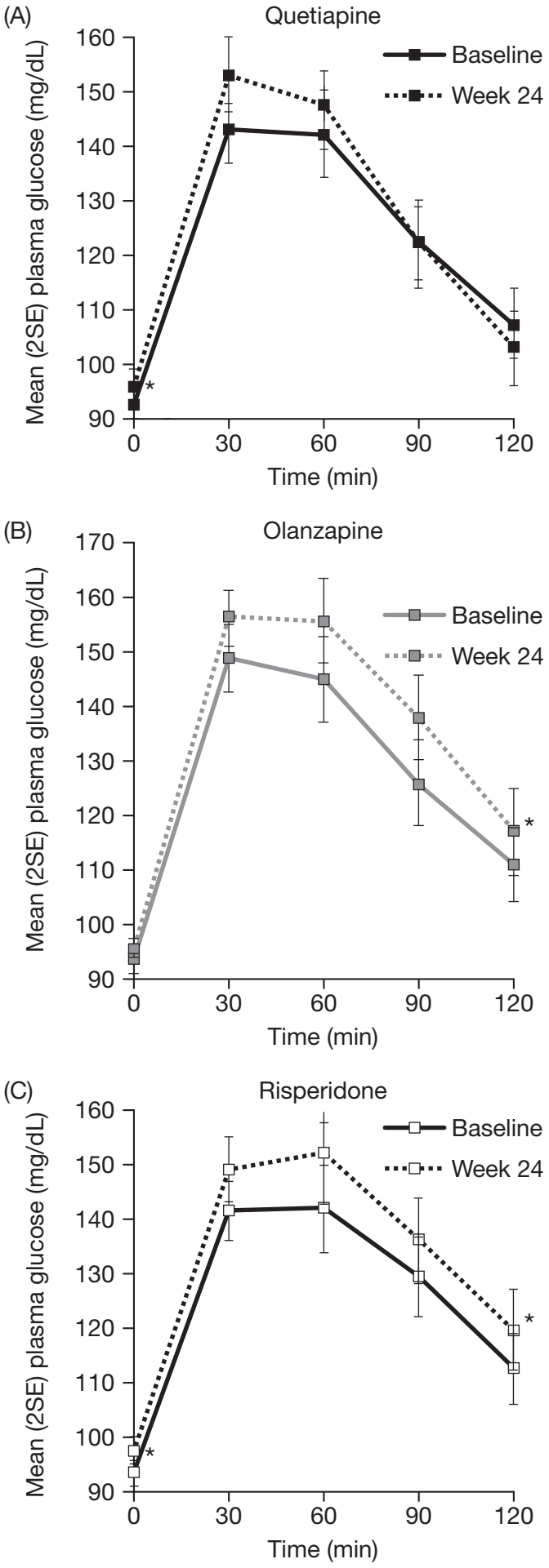
[a]1 patient randomized to olanzapine actually received quetiapine
[b]1 patient did not receive treatment

Figure 2



*p=0.048 vs olanzapine

Figure 3



*Significant change from baseline to Week 24.
Values at 30, 60, and 90 min were not tested for significance.
Change from baseline to Week 24 in AUC 0-2 h plasma glucose:
p=0.048 quetiapine vs olanzapine

Figure 4

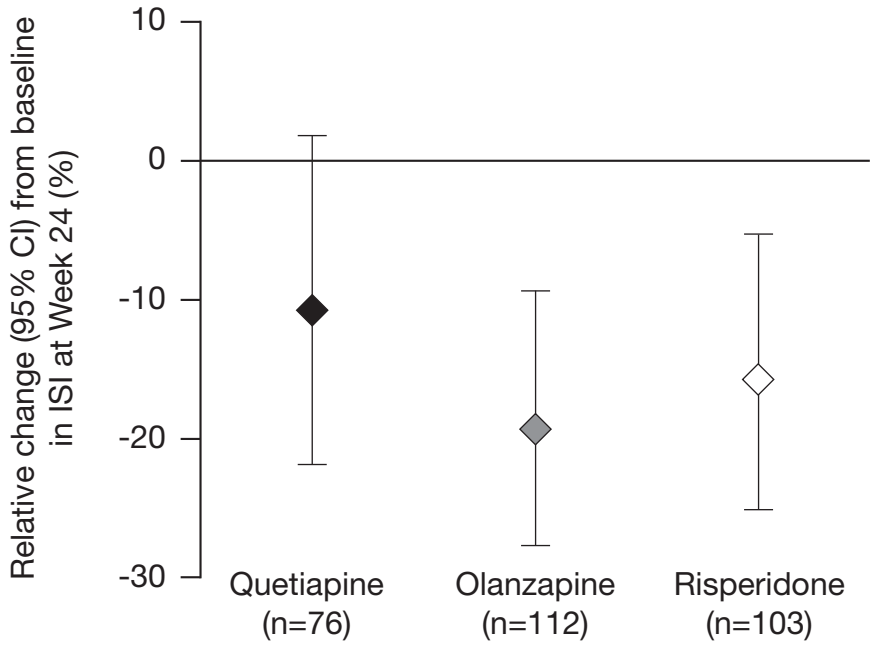

Relative change (95% CI) from baseline in ISI at Week 24 (%)
10
0
-10
-20
-30
Quetiapine (n=76)
Olanzapine (n=112)
Risperidone (n=103)

Table 1. Key demographic and glucose metabolism characteristics at baseline (PAP).

	Quetiapine (N=115)	**Olanzapine (N=146)**	**Risperidone (N=134)**
Mean (SD) age, years	39.4 (11.1)	40.5 (10.4)	38.3 (11.1)
Male:female, %	66:34	66:34	65:35
Caucasian, %	90.4	91.8	86.6
Mean (SD) weight, kg	73.6 (15.4)	71.9 (14.6)	72.1 (15.8)
LSM BMI (SE), kg/m^2	24.6 (0.36)	24.8 (0.36)	24.6 (0.36)
BMI, %			
<18.5	7.0	6.8	6.7
18.5 to <25	47.0	49.3	52.2
25 to <30	32.2	29.5	26.1
≥30	13.9	14.4	14.9
Schizophrenia subtype, %			
Paranoid	79.1	71.9	72.4
Residual	10.4	17.1	14.9
Undifferentiated	7.0	6.8	11.9
Disorganized	3.5	3.4	0.7
Catatonic	0.0	0.7	0.0

Years since diagnosis, mean (SD)	11.1 (10.2)	12.6 (10.5)	10.2 (9.7)
Antipsychotic medication at randomization, n (%)	82 (71.3)	104 (71.2)	97 (72.4)
Smoking, n (%)	67 (58.3)	86 (58.9)	86 (64.2)
Glucose metabolism characteristics, mean (SD)			
AUC glucose, mg/dL × h	255.11 (54.43)	260.89 (69.08)	259.34 (65.44)
Fasting glucose, mg/dL	92.59 (12.12)	93.65 (17.78)	93.73 (11.93)
2-h glucose, mg/dL	106.90 (33.59)	111.03 (42.05)	112.87 (38.29)
HbA_{1c}, %	5.33 (0.43)	5.32 (0.39)	5.33 (0.49)
Fasting plasma insulin, µIU/mL[a]	5.21 (79.9)	5.36 (63.7)	5.44 (52.50)
AUC insulin (OGTT) [µIU/mL × h][a]	80.28 (64.9)	71.26 (68.7)	67.58 (56.90)
Fasting C-peptide, ng/mL	2.27 (1.11)	2.23 (0.91)	2.25 (1.05)

[a]Geometric mean (coefficient of variation).

AUC = area under the curve; BMI = body mass index; LSM = least squares means; OGTT = oral glucose tolerance test; PAP = primary analysis population; SD = standard deviation; SE = standard error.

Table 2. Mean change from baseline to Week 24 in fasting lipid levels (PAP), and lipid ratios.

	Quetiapine	**Olanzapine**	**Risperidone**
Total cholesterol, mg/dL			
n[a]	107	142	124
Baseline	193.05	192.41	195.05
Change at Week 24	13.11	21.09	4.82
95% CI	4.29, 21.93	13.02, 29.17	-3.54, 13.18
HDL, mg/dL			
n[a]	89	116	106
Baseline	41.83	43.38	44.68
Change at Week 24	0.98	0.11	1.07
95% CI	-1.36, 3.32	-2.04, 2.26	-1.12, 3.27
LDL, mg/dL			
n[a]	108	142	125
Baseline	117.42	121.42	121.13
Change at Week 24	13.29	20.47	5.07
95% CI	6.05, 20.53	13.82, 27.12	-1.78, 11.93
Triglycerides, mg/dL			
n[a]	104	142	123
Baseline	166.24	146.12	154.20

Change at Week 24	17.61	30.93	11.66
95% CI	-4.57, 39.79	10.86, 51.00	-9.19, 32.51
Total cholesterol/HDL ratio			
n[a]	86	116	104
Baseline	4.86	4.59	4.62
Change at Week 24	0.23	0.48	0.06
95% CI	(-0.12, 0.58)	(0.16, 0.79)	(-0.27, 0.38)
Triglycerides/HDL-ratio			
n[a]	86	116	104
Baseline	1.80	1.59	1.72
Change at Week 24	0.24	0.32	0.18
95% CI	(-0.11, 0.58)	(0.01, 0.63)	(-0.14, 0.50)

[a]Number of patients with non-missing value.

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAP = primary analysis population.

Table 3. Adverse events (AEs) during the treatment and follow-up period (safety population).

Category of AE	**Quetiapine N=169**		**Olanzapine N=168**		**Risperidone N=172**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
AEs[a]	101	(59.8)	79	(47.0)	116	(67.4)
Serious AEs[a]	17	(10.1)	4	(2.4)	13	(7.6)
Drug-related AEs[a,b]	57	(33.7)	36	(21.4)	87	(50.6)
AEs leading to discontinuation[a]	17	(10.1)	3	(1.8)	14	(8.1)
Common AEs[c] (MedDRA term)						
Extrapyramidal disorder	3	(1.8)	3	(1.8)	42	(24.4)
Insomnia	11	(6.5)	7	(4.2)	25	(14.5)
Somnolence	17	(10.1)	6	(3.6)	8	(4.7)
Akathisia	2	(1.2)	3	(1.8)	22	(12.8)
Schizophrenia	12	(7.1)	2	(1.2)	8	(4.7)
Sedation	11	(6.5)	5	(3.0)	5	(2.9)
Dizziness	9	(5.3)	0	(0.0)	6	(3.5)

[a]Patients with multiple events in the same category are counted only once. Patients with events in more than one category are counted once in each category.

[b]As judged by the investigator.

[c]Any AE occurring at an incidence of ≥5% in any randomized treatment group.

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QUETIAPINE-ASSOCIATED HYPERGLYCEMIA AND HYPERTRIGLYCERIDEMIA

[Letters To The Editor]

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See the Instructions for Authors for information about the preparation and submission of Letters to the Editor.

To the Editor:

Several reports in the adult literature have linked the atypical antipsychotics clozapine, olanzapine, and quetiapine with hyperglycemia, weight gain, and hypertriglyceridemia (Meyer, 2001;Nguyen and Murphy, 2001;Procyshyn et al., 2000;Sobel et al., 1999;Wirshing et al., 2000). Almost all cases of atypical antipsychotic–associated hyperglycemia or hypertriglyceridemia reported to date have been in adults older than age 30. We wish to report such a case associated with quetiapine use in a 17-year-old African-American female.

The patient presented with paranoia, assaultive behavior, and homicidal ideation. Her diagnoses included bipolar disorder, conduct disorder, and mild mental retardation. She had been in state custody since age 3, and her family medical history was unknown. Psychotropic medications at the time of presentation included divalproex 1,500 mg/day (for more than 8 months), quetiapine 600 mg/day (for more than 3 months), and paroxetine 20 mg/day (for 1 day). Between 2 and 3 months prior to presentation, reportedly after the initiation of quetiapine, type II diabetes mellitus was diagnosed; her serum glucose levels approached 300 mg/dL. She was started on a 2,000-calorie diet and on metformin 1,000 mg twice per day. She had not experienced significant weight gain during the 3 months of quetiapine therapy.

Admission laboratory studies were unremarkable except for a serum glucose level of 144 mg/dL, serum cholesterol level of 235 mg/dL, and serum triglyceride level of 456 mg/dL (all fasting). She was slightly overweight; height and weight were 165 cm and 75.5 kg, respectively (body mass index 27.7 kg/m^2). Her valproic acid level at the time of admission was 84 mg/L.

Quetiapine was tapered over 1 week and discontinued because she had not responded as robustly as hoped and because her hyperglycemia and hypertriglyceridemia apparently developed after the initiation of quetiapine. Risperidone was initiated and titrated to 4 mg/day. The divalproex was increased to 2,000 mg/day, resulting in a serum level of 104 mg/L. Paroxetine was

continued at 20 mg/day. Her paranoia and behavior stabilized over the subsequent weeks on these medications.

For 1 week after quetiapine was discontinued, while the patient was receiving metformin and a 2,000-calorie diet, her fasting glucose levels were consistently below 120 mg/dL. Metformin was decreased to 1,000 mg in the evening and was discontinued after 1 week of normal fasting glucose levels. Fasting serum glucose levels, checked three times per week, ranged between 99 and 170 mg/dL over the next month, averaging 128 mg/dL. Serum cholesterol and triglyceride levels within a week of the discontinuation of quetiapine were 196 and 167 mg/dL, respectively, and 6 weeks later (4 weeks after the discontinuation of metformin) were 226 and 163 mg/dL, respectively. Her weight remained between 73.6 and 75.5 kg over this period of time. While she may have developed diabetes at some point without quetiapine, she did demonstrate improved serum glucose control after it was discontinued.

The mechanisms remain unclear, but there has been much speculation about the possible causes of glucose and lipid abnormalities and weight gain observed with some atypical antipsychotics. We offer no more definitive explanation of these observations, but the proposal that hyperglycemia and hypertriglyceridemia are simply secondary to weight gain does not seem sufficient to explain our case or several others in the literature. Perhaps the unique neurotransmitter profiles of these medications play a role, through the disruption of normal metabolic processes.

We hope this report adds to the growing body of evidence regarding these adverse effects and alerts clinicians to the possibility of abnormal glucose and lipid regulation with atypical antipsychotic use in the pediatric population.

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[illegible] amnesia, fugue, dissociative identity disorder, or depersonalization. Rather, they seem to be [illegible] of [illegible] and delusions. In addition, our data, albeit preliminary, do not show a significant difference in scores on the Dissociative Experiences Scale between patients with and without psychotic symptoms.

With regard to DSM-IV categories, the patients in our study did not meet diagnostic criteria for schizophrenia, and only a minority met criteria for comorbid schizoaffective disorder or major depression with psychotic features. We believe that the diagnosis that best fits these symptoms in the majority of the subjects is psychosis not otherwise specified. Perhaps a subtype of PTSD with psychotic features, similar to what exists for major depression, should be considered for future DSM editions.

We share the concerns regarding inappropriate use of neuroleptic medications for PTSD patients. However, the benefits of conventional pharmacologic treatments for the severely affected subpopulation represented in our paper appear to be limited. Given the improved safety profile of atypical neuroleptics over traditional neuroleptics and a recent positive report of open-label treatment with an atypical antipsychotic,[3] we feel that further evaluation of the use of atypical antipsychotics in severe and chronic PTSD is warranted.

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Patient's Coping Skills and Environmental Stress Important to Understanding Recurrence During Antidepressant Maintenance

Sir: Recently, Byrne and Rothschild[1] reported on possible mechanisms for loss of antidepressant efficacy during maintenance therapy. Although I would agree with the theoretical mechanisms cited by the authors, there is a glaring oversight in their thinking about this important issue: specifically, the role of new psychosocial stresses encountered by the patient during the maintenance period, the cumulative effect of ongoing chronic psychosocial stress in the patient's life, and ongoing coping deficits. Psychosocial stress that the patient cannot manage could overwhelm all or part of a previously positive biological antidepressant response. Byrne and Rothschild's thinking makes several problematic assumptions: (1) all patients have the same level of psychosocial stress in their lives; (2) all patients have the same level of skill at handling stresses when they encounter them; (3) the level of psychosocial stress remains a constant for patients throughout the acute, continuation, and maintenance phases of antidepressant treatment; and/or (4) life events and ability to cope with them are trivial in relation to the course of affective disorders. These assumptions lead to the position that the effect of the medication is the only important independent variable to be considered during the maintenance period.

The "biological disease" of depression cannot be separated from the environmental context of the patient or the coping skills of the patient. For example, people with personality disorders or with detrimental personality traits are both less likely to cope well with certain environmental stresses when they occur and more likely to create frequent or painful psychosocial stresses in their lives. The ongoing grinding stress of poverty or abusive relationships is depressogenic, presumably especially in people with a biological diathesis for affective disorder. A divorce, job loss, poor job evaluation, etc., during the maintenance period may precipitate the relapse or recurrence of a full affective syndrome in susceptible individuals. Possibilities of important factors other than biological medication effect are numerous.

I am not arguing the reverse extreme point of view, that only psychological and environmental factors cause depression or affective disorders. However, psychiatric literature frequently ignores obvious and salient psychosocial factors impacting the disorders it studies. The quality of our science suffers because of our biological tunnel vision.

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New-Onset Diabetes Mellitus Associated With the Initiation of Quetiapine Treatment

Sir: Quetiapine is a novel antipsychotic that antagonizes both serotonergic (5-HT_{1A} and 5-HT_2) and dopaminergic (D_1 and D_2) receptors. The manufacturer describes hypoglycemia, hyperglycemia, and diabetes mellitus as infrequent side effects (0.1%–1.0%).[1] The following is a case report of possible quetiapine-induced onset of diabetes mellitus.

Case report. Mr. A, a 42-year-old white man with a history of bipolar disorder, type I, was seen by the psychiatry consultation service after admission for new-onset diabetes mellitus. Mr. A had no prior history of glucose intolerance or hyperglycemia, and, 4 months before his admission to the hospital, the results of random blood glucose tests were 126 and 107 mg/dL. He did have hypertriglyceridemia, which had been noted for more than a year prior to this admission. His family history was negative for diabetes. His bipolar disorder had been managed with a combination of lithium carbonate, 900 mg daily; gabapentin, 2000 mg daily; clonazepam, 1 mg at night; and venlafaxine, 37.5 mg daily. Quetiapine had been added to his regimen 1 month before his admission to the hospital and titrated to 200 mg at night.

Mr. A was admitted to the medicine ward after several days of nausea, vomiting, polyuria, and confusion. At the time of admission, he was noted to have a blood glucose level of 607 mg/dL and was started on intravenous fluids and a sliding-scale insulin regimen. He was eventually discharged from the hospital on a regimen of 17 units regular and 33 units NPH insulin in the morning and 6 units regular and 10 units NPH insulin in the

evening. He was also started on gemfibrozil treatment for hypertriglyceridemia at the time of discharge.

After discharge, he was seen in follow-up in the psychiatry and medicine clinics. His quetiapine dosage was reduced and then discontinued over the course of 9 days. Since the discontinuation of quetiapine, Mr. A's insulin requirements have decreased markedly. His insulin was eventually discontinued [illegible] months after his admission.

Clearly, there is no absolute proof in this case report that this patient's apparently first episode of diabetes was caused by the quetiapine. However, we are reasonably sure that other explanations were ruled out. Although there have been case reports of clozapine associated hyperglycemia and diabetes mellitus,[2-4] a MEDLINE search does not reveal any case reports of this association with quetiapine. There have been no reports of any adverse interactions between quetiapine and the patient's other medications. Clinicians should be aware of this possible adverse effect and should use caution when prescribing quetiapine to patients with known glucose intolerance or frank diabetes mellitus.

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Valproate-Induced Hyperammonemia in the Psychiatric Setting: 2 Cases

Sir: Although several case reports have described valproate-induced reversible elevation of serum ammonia levels, this problem may not be recognized quickly owing to lack of sufficient awareness. A high level of suspicion will enable the busy clinician to identify and intervene promptly in this clinical setting. This is particularly relevant in today's clinical psychiatric practice owing to the current widespread use of valproate in the acute and maintenance treatment of psychiatric disorders. Also, hyperammonemia manifests as mental status change, which is likely to be attributed to a worsening of psychosis or mania. Furthermore, the typical absence of abnormalities in routine liver function testing makes the clinician who relies on these tests likely to overlook this interesting and relatively infrequent adverse effect.

Case 1. Ms. A, a [illegible]-year-old single white woman with a long-standing diagnosis of bipolar disorder type I and alcohol dependence, was admitted to the inpatient psychiatric and substance abuse treatment unit for treatment of mania with psychotic features, detoxification, and early phase rehabilitation of [illegible] emergency service by the police after she was found by staff of a local hotel to be aggressive, argumentative, and demonstrating a delusional belief that she was the personal assistant to a famous songwriter who was staying at the same hotel. Other symptoms included decreased sleep, increased goal-directed behavior, and intermittent auditory hallucinations of grandiose [illegible] been drinking 6 to 10 beers [illegible] weeks prior to presentation. [illegible] tion, Ms. A had taken no psychotropic medication [illegible] no psychiatric follow-up.

Results of laboratory studies upon admission [illegible] normal limits, including complete blood [illegible] aminotransferase, and alanine [illegible] phatase, and bilirubin levels. She successfully completed alcohol detoxification in [illegible] days and was given [illegible] divalproex sodium, 500 mg p.o. t.i.d. [illegible] peridol, 5 mg p.o. b.i.d., and lorazepam, [illegible] also started to treat the acute psychotic symptoms. [illegible] ter she started valproate treatment, irritability and [illegible] ness began to decrease, and her serum valproic acid level was 74 µg/mL. Several days later, the dose of divalproex was increased by 250 mg/day to a total daily dose of 1750 mg, and over the next 5 days mania further improved and psychosis began to resolve.

However, over the next few days, Ms. A began to complain of feeling very lethargic, wandered into other patients' rooms, had intermittently illogical speech, and would often be found to be napping in the day room. Valproic acid level was 107 µg/mL and all liver function indices were well within normal limits. A serum ammonia level was obtained and found to be [illegible] µmol/L (normal range, 11–35 µmol/L). The dose of valproate was decreased by over one half to 250 mg p.o. t.i.d., and lithium was started at 300 mg p.o. b.i.d. in an effort to prevent reemergence of mania. Serum ammonia level dropped to 54 µmol/L [illegible] days later, and within 3 days of the reduction in dose of valproate, sensorium returned to normal with no evidence of mania. One week after the dose of valproate was decreased, serum ammonia level was 30 µmol/L, and valproic acid level was 43 µg/mL with no further mental status change. Ms. A was discharged a few days later.

Case 2. Mr. B, a 23-year-old single white man with a diagnosis of schizoaffective disorder and mania, was admitted to the inpatient psychiatric and substance abuse treatment unit for treatment of a progressively worsening bizarre thought disorder and mania. He also had a long history of alcohol dependence and crack cocaine abuse. He had drunk up to a 6-pack of beer per day for the last several years and smoked crack cocaine intermittently. His last use of alcohol and cocaine was over [illegible] weeks before admission, and detoxification was not necessary. He was started on treatment with olanzapine, 10 mg p.o. q.d., and divalproex, 500 mg p.o. t.i.d. Initial laboratory values, including liver function test results, were all within normal limits. Valproic acid levels during the first 10 days of hospitalization were therapeutic in the 70- to 80-µg/mL range.

By the end of the second week of hospitalization, Mr. B appeared to be lethargic during the day and more bizarre in his speech, which was initially attributed to exacerbation of psychosis. Serum ammonia level was 54 µmol/L, and liver function values were normal. Over the next week, he became more confused, and a repeat serum ammonia level was [illegible] µmol/L. Liver function and metabolic profiles were normal. Valproate was discontinued promptly, and Mr. B was given lactulose for several days. Lithium, 300 mg p.o. b.i.d., was started for prophylaxis of mania. Within the next [illegible] days, Mr. B's sensorium fully cleared, and his ammonia level decreased to [illegible] µmol/L. There was no emergence of mania, and Mr. B resumed his treatment [illegible]

Quetiapine-induced diabetes with metabolic acidosis

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Medication adherence with antipsychotics is adversely impacted by the burden of untoward adverse effects. In particular, sexual side-effects may interfere with compliance, but are often underreported by patients. Sexual dysfunction related to hyperprolactinemia is commonly described, but ejaculatory disturbance due to potent alpha1 adrenergic antagonism may also occur, and has been reported frequently with certain typical antipsychotics such as thioridazine, but rarely with atypical antipsychotics. Presented here is the case of a 51 year old male with schizophrenia who developed retrograde ejaculation on high dose risperidone therapy (8 mg/day) with prompt resolution of symptoms upon dose reduction. The absence of decreased libido or erectile dysfunction indicates that alpha1 adrenergic antagonism and not low serum testosterone due to hyperprolactinemia is the etiology for this side-effect. This case illustrates another mechanism for sexual adverse effects, and the need for routine inquiry into sexual dysfunction during atypical antipsychotic therapy. *Int Clin Psychopharmacol* 19:169–171 © 2004 Lippincott Williams & Wilkins.

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Keywords: Antipsychotic, risperidone, sexual side effect, retrograde ejaculation

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Introduction

There is increasing concern about the short- and long-term metabolic consequences of antipsychotic therapy in schizophrenic patients (Meyer, 2003). In part, this is traceable to such patients having twice the mortality rate from cardiovascular disease (CVD) as a group compared to the general population. Although smoking, hypertension and lipid abnormalities are recognized as traditional contributing risk factors for CVD, the third revision of the national cholesterol monitoring guidelines (ATP III) identified diabetes mellitus as being equivalent in risk for a major coronary event over 10 years to those diagnosed formally with coronary artery disease (Expert Panel on Detection and Adults, 2001).

Although US regulatory authorities are recommending labelling changes to suggest monitoring for hyperglycemia and diabetes in all patients on atypical antipsychotics, an abundance of data generated by biological and epidemiological studies over the past 5 years has generally indicated that clozapine and olanzapine are associated with higher risk for new-onset diabetes mellitus, glucose intolerance or diabetic ketoacidosis, whereas there are fewer studies implicating risperidone and ziprasidone with metabolic adverse effects (Gianfrancesco *et al.*, 2002; Jin *et al.*, 2002; Atmaca *et al.*, 2003; Cohen *et al.*, 2003; Gianfrancesco *et al.*, 2003; Koller *et al.*, 2003; Lindenmayer *et al.*, 2003; McIntyre, 2003; Taylor, 2003; Weiden *et al.*, 2003). Quetiapine is a dibenzothiazepine, which is structurally similar to the dibenzodiazepines olanzapine and clozapine and appears to share their propensity for induction of hypertriglyceridemia, but with a lesser degree of weight gain (Meyer, 2001a,b). Although the Japan Ministry of Health, Labour and Welfare, Safety Division, Pharmaceutical and Medical Safety Bureau has issued a warning regarding the use of quetiapine in patients with a history of diabetes, and required changes to the package insert, there is a paucity of data regarding the association between quetiapine and hyperglycemia or new onset diabetes mellitus, aside from a small number of case reports and retrospective case series (Sobel *et al.*, 1999; Domon and Cargile, 2002; Jin *et al.*, 2002; Sernyak *et al.*, 2002; Wirshing *et al.*, 2002; Sneed and Gonzalez, 2003; Wilson *et al.*, 2003), and one published large database study suggesting that quetiapine may also have a predilection towards induction of glucose intolerance (Sernyak *et al.*, 2002). Given this limited data, new cases where a strong causal association is indicated between the use of quetiapine and hyperglycemia help to reinforce the concept that this agent may possess similar metabolic risks as the structurally related compounds clozapine and olanzapine.

Case report

The patient was a 48-year-old, non-Hispanic, White male with a long-standing psychotic disorder variably

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Table 1 Patient treatment

Date	Weight (lb)	BMI (kg/m^2)	Serum glucose (mg/dl)	Comments
16 May 2001	162	22.03	101 (fasting)	Meds: Haloperidol 20 mg h.s.
16 October 2001	173.7	23.62	112 (fasting)	Meds: Haloperidol 20 mg h.s.
November 2002 to 5 March 2003 unmedicated				
5 March 2003 hospital admission	139	19.90	113 (fasting)	Meds: Quetiapine and haloperidol started, but refused until court petition approved 3/11/03
31 March 2003	147	19.99		Meds: Haloperidol 5 mg b.i.d. Quetiapine titrated to 400 mg b.i.d. by 3/24/03
5 April 2003	139.8	19.01		Meds: Haloperidol 5 mg b.i.d Quetiapine 400 mg b.i.d
9 April 2003			859 (random) Hb A_{1c} 12.1%	
14 June 2003	156	21.22	138 (fasting) Hb A_{1c} 7.3%	Meds: Risperidone 6 mg h.s. Lithium 1500 mg h.s. Metformin 500 mg a.m., 1000 mg h.s. (plus sliding scale insulin)

BMI, Body mass index; Hb A_{1c} glycosylated haemoglobin

diagnosed as schizophrenia or schizoaffective disorder bipolar type, with a history of poor medication adherence resulting in frequent hospitalization. This patient was quite delusional about his medications and insisted on taking haloperidol, although he achieved only modest therapeutic benefit. In 2001, during active treatment with haloperidol (Table 1) at an average dose of 20 mg/day, this patient gained nearly 12 lb and developed impaired fasting glucose (fasting glucose 112 mg/dl). He was admitted under court order on 31 October 2001 to a locked facility because of poor medication adherence resulting in repeated hospitalization, but was lost to follow-up late in November 2002 after discharge from the locked facility, and did not come to clinical attention until early March 2003 after being out of treatment and, by his own admission, homeless for several months. The patient was grossly psychotic on presentation to the hospital, had lost substantial weight (35 lb), and initially refused medication until a court petition for medication was granted on 11 March 2003. Despite the weight loss, there was evidence of impaired fasting glucose on admission laboratory evaluation (fasting glucose 113 mg/dl). In the hospital environment, the patient rapidly gained weight on the combination of haloperidol 5 mg b.i.d., and quetiapine, titrated to a dose of 400 mg bid, with an increase of 8 lb over the next 2 weeks. Despite good oral intake, the patient started losing weight and, by week 4, was back at his admission weight. Four days later, he was noted to be confused and lethargic, and laboratory investigation revealed a random glucose of 859 mg/dl, a glycosylated haemoglobin of 12.1%, and serum chemistries suggestive of metabolic acidosis (sodium 126, chloride 86). The patient was emergently admitted to the intensive care unit and treated with aggressive intravenous hydration and insulin. On his return to the psychiatric inpatient unit, the treatment team decided to discontinue quetiapine and haloperidol in favour of haloperidol monotherapy initially, and then over time opted for risperidone combined with lithium to help manage mood lability and other manic-like symptoms. Although the patient regained the weight lost during the period of presumed uncontrolled diabetes mellitus (31 March to 9 April 2003), the requirement for insulin rapidly diminished over the next 2 months. By the time of discharge in mid-June, the patient's glucose intolerance was primarily managed with an oral agent alone, metformin, with sliding-scale insulin used only to cover the patient's frequent dietary indiscretions.

Discussion

The reversibility, or improvement in, new-onset diabetes related to clozapine and olanzapine treatment has been noted in 78% of patients who are switched in to a less offending agent (Koller *et al.*, 2001; Koller and Doraiswamy, 2002; Wilson *et al.*, 2003), and the same appeared to be true in our present case where haloperidol and, later, risperidone were substituted for the quetiapine/haloperidol combination. Haloperidol is typically assumed to be a metabolically neutral medication, but our patient had already demonstrated a predilection towards glucose intolerance even when on that medication. The addition of high-dose quetiapine in our patient resulted in the rapid development of uncontrolled diabetes with metabolic acidosis, which, fortunately, occurred in a hospital setting where it was promptly treated.

The hospital course of our patient illustrates two important points regarding the development of diabetes mellitus associated with atypical antipsychotics. The patient's weight at the time his diabetes was diagnosed was identical to that at which time he entered treatment, a finding described in multiple cases (Jin *et al.*, 2002). However, in our patient, the availability of multiple weights demonstrates that he actually gained a significant amount of weight, and then abruptly began losing weight, most likely due to polyuria and catabolic effects from uncontrolled hyperglycemia. Thus, the development of rapid weight loss, perhaps more so than weight gain, is an important clinical clue that a patient may have developed

hyperglycemia and requires acute intervention. Second, despite regaining a substantial amount of weight on the risperidone and lithium combination beyond that experienced on quetiapine, his glycemic control continued to improve to the extent that routine insulin therapy was no longer required, thereby illustrating the concept that certain atypical agents may have a greater direct impact on glucose tolerance independent of the effects on weight gain. Cases such as this thereby reinforce the need for vigilance in monitoring of serum glucose during antipsychotic therapy, particularly when higher risk agents for hyperglycemia are employed, and the necessity of routine inquiry on each visit of the clinical signs of diabetes including excessive thirst, frequent urination, fatigue and unexplained weight loss.

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MECHANISTIC CONNECTIONS BETWEEN GLUCOSE/LIPID DISTURBANCES AND WEIGHT GAIN INDUCED BY ANTIPSYCHOTIC DRUGS

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Antipsychotic drugs produce an array of metabolic side effects including elevated serum lipids (especially triglycerides), hyperglycemia, significant weight gain and even diabetes in some patients. This review will focus on possible molecular mechanisms by which the drugs affect metabolic function. There appears to be a connection between the drug-induced lipid and glucose disturbances and weight gain in patients. The relationship between these metabolic effects stems from operation of the glucose-fatty acid cycle and the cooperative regulation of energy metabolism at the level of signaling pathways, including Akt and AMPK, which converge on forkhead and C/EBP transcription factors. Genetic studies have provided some insight into the possible pharmacological basis for drug-induced weight gain with apparent contributions by histamine H1 and serotonergic (5-HT2C) receptors. However, additional targets of the drugs must be involved in the induction of the metabolic syndrome. These targets may include

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glucose transporters, cytochrome P450 enzymes, aryl hydrocarbon receptors, K^+ channels, and glucose-sensing systems in general. Additional clues have emerged from animal models. Antipsychotic drugs produce hyperglycemia and weight gain in mice and rats. Moreover, the drugs stimulate lipid accumulation in the nematode, *Caenorhaditis elegans*, a valuable genetic tool for elucidation of molecular targets involved in diverse biological responses. A better understanding of the drug-induced side effects may ultimately allow identification of risk factors in patients and prevention of weight gain and glucose disturbances with adjunctive approaches. Finally, knowledge of the molecular basis of these emergent syndromes may inspire the development of the next generation of antipsychotic drugs with minimal metabolic liability.

I. Introduction

Over the past 10 years, there has been a growing appreciation of the adverse metabolic effects produced in patients by the second-generation antipsychotic drugs (Allison *et al.*, 1999; Baptista *et al.*, 2002; Dwyer *et al.*, 2001; Henderson *et al.*, 2000; Haupt and Newcomer, 2001; Lindenmayer *et al.*, 2003; Wetterling and Muessigbrodt, 1999; Wirshing *et al.*, 2002). The clinical importance of these metabolic side effects was highlighted in the recent decision (in 2003) by the Food and Drug Administration (FDA, to require warning labels on second-generation drugs concerning the possibility of drug-induced diabetes, including diabetic ketoacidosis. This move was followed in 2004 by joint recommendations formulated by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity for monitoring weight gain, glucose intolerance, and hypertension in patients treated with second-generation antipsychotics (American Diabetes Association, Consensus Statement, 2004). However, the adverse metabolic effects of antipsychotics are by no means limited to the newer second-generation drugs. Disturbances in glucose regulation and weight gain were noted for some of the older drugs, especially chlorpromazine and loxapine (Arneson, 1964; Hiles, 1956; Kalucy, 1980; Tollefson and Lesar, 1983). With the conventional antipsychotics, the focus was instead on drug-induced movement disorders—the extrapyramidal symptoms, including tardive dyskinesia (Faurbye, 1970). The clinical implications of the metabolic disturbances associated with antipsychotic treatment are discussed in some detail in this chapter and are the main subject of recent excellent reviews (Baptista *et al.*, 2002; Casey, 2004; Newcomer, 2004; Wirshing, 2004).

It has been known for some time that various drugs induce weight gain and even diabetes in patients. In general, the connection between weight gain and the second-generation antipsychotics is well accepted. However, the role of these drugs in the induction of diabetes is more controversial. There are older reports of an increased incidence of diabetes in schizophrenic patients compared to the general population (Simon and Garvey, 1951; Waitzkin, 1966), and relative insulin resistance among psychotic patients was observed during trials of insulin shock therapy for psychosis prior to the introduction of antipsychotic drugs (Sakel, 1938). Irrespective of the baseline risk of diabetes in schizophrenia, case reports describe patients who developed hyperglycemia shortly after the start of antipsychotic drug treatment and resolution of the hyperglycemia on discontinuation of drug; reappearance of elevated glucose levels has also been observed with reinstitution of drug (Koller and Doraiswamy, 2002; Koller *et al.*, 2001; McIntyre *et al.*, 2001). In further support of the contribution of drugs to emerging glucose dysregulation, Arranz *et al.* (2004) recently reported normal glucose metabolic parameters in antipsychotic-naive patients in comparison to controls, whereas previously-medicated patients exhibited a significant increase in insulin resistance. The mechanisms involved in the drug-induced metabolic effects of antipsychotic drugs are still unknown. Therefore, our goal is to provide a thorough analysis of possible mechanisms of action that might contribute to the metabolic disturbances in patients. It is our general thesis that the metabolic side effects are not adequately explained by the established pharmacology of the antipsychotic drugs; additional mechanisms must be involved. Moreover, we explore the possibility of mechanistic connections between drug-induced glucose and lipid disturbances that frequently emerge as diabetes or weight gain depending on patient susceptibility. We believe it is unlikely that glucose and lipid disturbances, including weight gain, are brought about through separate, unrelated pathways. Furthermore, many other drug classes are noted for their ability to induce glucose abnormalities and weight gain. Each drug class could produce these metabolic effects via unique pathways; however, we favor the possibility that common mechanisms are involved.

Regrettably, we are unable to cite all of the literature related to the topic of this chapter. Of necessity, our focus is somewhat restricted; therefore readers are referred to recent reviews for additional references and in-depth discussion (Baptista *et al.*, 2002; Casey, 2004; Newcomer, 2004; Wirshing, 2004).

II. Metabolic Effects: Glucose Disturbances and Diabetes

The incidence of diabetes in the general population is currently estimated to be about 5–6% (International Diabetes Federation Consensus Workshop, 2004; Diabetes in Children and Adolescents Work Group, 2004). By contrast, various

groups have reported that the incidence of diabetes in schizophrenic patients treated with antipsychotic drugs is in the range of 10–35% (Baptista *et al.*, 2002; Hagg *et al.*,1998; Henderson *et al.*, 2000). Additional patients may have impaired glucose regulation without frank diabetes. If we accept the idea that the drugs produce glucose abnormalities in at least a subset of patients, the question then becomes how do the drugs interfere with normal glucose regulation? From a theoretical perspective, normal glucose metabolism could be adversely affected by antipsychotic drugs via (1) a decrease in insulin production, (2) reduced insulin sensitivity, (3) alterations in other glucoregulatory hormones and factors, (4) altered energy metabolism (i.e., a reduction in glucose utilization), (5) increased gluconeogenesis, and (6) defective glucose sensing. In relation to points 1 and 2, there is little evidence to support a decrease in insulin secretion as the major factor involved in drug-induced hyperglycemia (Sowell *et al.*, 2002). In fact, most studies report hyperinsulinemia (Melkersson *et al.*, 2000; Newcomer *et al.*, 2002; Yazici *et al.*, 1998), and studies of insulin sensitivity in patients have revealed conflicting findings. Newcomer *et al.* (2002) and Henderson and Ettinger (2002) reported a decrease in insulin sensitivity in patients treated with second-generation antipsychotic drugs, whereas Sowell *et al.* (2002) found no significant change in the insulin response of normal subjects treated acutely with olanzapine and risperidone. Differences in the treatment conditions (chronic vs. acute) and study populations (patients vs. normal volunteers) may explain the discrepancies in these studies. Of course, the drugs may also induce a combination of deficits to produce diabetes such as a reduction in insulin sensitivity concomitant with an increase in gluconeogenesis. Regardless of the precise path toward a disturbance in glucose regulation, these processes outlined lie downstream of the ultimate target of the antipsychotic drugs. Some of the likely targets are considered here.

A. Direct Effect of Drugs on Glucose Transport

Previously we showed that high concentrations of certain antipsychotic drugs inhibited glucose transport into neuronal cells and other cell types (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999a,b). The drugs were noncompetitive inhibitors of transport and competed with cytochalasin B (a selective inhibitor and photoaffinity label for the glucose transporter [GLUT]) for binding to the GLUT protein (Ardizzone and Dwyer, 2002; Dwyer *et al.*, 2002). We speculated that interference with glucose transport may, at some level, contribute to the observed hyperglycemia in patients. The effects of antipsychotic drugs on glucose transport have recently been reviewed in an earlier volume of this series (Dwyer *et al.*, 2002); readers are referred there for a more detailed account of these findings. In addition to these *in vitro* studies, we showed that administration of antipsychotic

drugs to mice induced acute hyperglycemia in relation to the effects of the drugs on glucose transport (Dwyer and Donohoe, 2003), that is, drugs that potently inhibited glucose transport *in vitro* produced the highest blood glucose concentrations in mice. Nevertheless, there are certain limitations in extrapolating from the *in vitro* data. The concentrations of drug that block glucose transport in cell lines (2–40 μM) are higher than serum concentrations under steady-state conditions in patients, which are in the range of 0.02–1 μM depending on the drug (Olesen, 1998; Olesen and Linnet, 1999; Robertson and McMullin, 2000 Ulrich *et al.*, 1998). Furthermore, inhibition of glucose transport by the antipsychotics is diminished in high glucose conditions, suggesting that under normal circumstances the drugs may produce limited interference with glucose transport in many tissues.

Several findings support the possibility that interference with glucose transport by the antipsychotic drugs may contribute to the metabolic effects in patients with normal dosing. First, antipsychotic drugs are accumulated 25- to 30-fold in tissues such as fat and brain (Aravagiri *et al.*, 1995; Baldessarini *et al.*, 1993; Cohen *et al.*, 1992; Kornhuber *et al.*, 1999; Weigmann *et al.*, 1999), which means that ambient concentrations may reach the levels needed to affect glucose transport. Second, certain metabolites of the antipsychotic drugs are far more potent than the parent compound at inhibiting glucose transport (Ardizzone *et al.*, 2001). Thus, the concentrations and nature of drug metabolites may be significant factors. Third, clozapine at clinically relevant doses produced significant hyperglycemia in mice (Dwyer and Donohoe, 2003). Cytochalasin B at the same dose as clozapine induced comparable hyperglycemia and the only known relevant action of this compound is to inhibit glucose transport by direct blockade of GLUTs (Dwyer and Donohoe, 2003; Dwyer *et al.*, 2002). Therefore, direct actions of the drugs on glucose transport cannot be ruled out as a contributing factor to the emergence of hyperglycemia in patients.

B. Interference with Glucose Sensing

Various cells in the body have evolved as specialized sensors of glucose concentrations that respond by regulating aspects of glucose metabolism. In particular, cells in the pancreas, gut, and brain monitor glucose and mount responses when glucose levels rise or fall beyond certain thresholds. These cells control the secretion of insulin, gut hormones (including incretins), and regulate feeding and adaptive responses (Schuit *et al.*, 2001). The glucose-sensing mechanisms are best understood in β cells of the pancreas and hypothalamic neurons in the brain (Efrat *et al.*, 1994; Levin *et al.*, 2002; Matschinsky and Collins, 1997). At a minimum, the sensor is composed of glucokinase, which phosphorylates incoming glucose; the high-Km transporter, GLUT2; and adenosine triphosphate

(ATP)/sulfonylurea–sensitive K^+ channels (Bell *et al.*, 1996; Efrat *et al.*, 1994; Matschinsky and Collins, 1997). This system appears to have largely evolved to govern the secretion of insulin by cells and neurotransmitter in glucose-sensing neurons.

Interference with glucose sensing, directly or indirectly, has a significant impact on energy metabolism in man. For example, inhibition of glucose transport in glucose-sensing cells by an antipsychotic drug would falsely lead those cells to perceive a state of glucose deprivation. Consequently, the systems regulated by those cells may respond by decreasing glucose utilization, stimulating glycogen breakdown and perhaps gluconeogenesis, altering lipid metabolism, and mobilizing alternative fuel supplies. The end result would be an acute hyperglycemic response with the emergence of glucose intolerance in susceptible individuals over time. Similarly, if an antipsychotic drug reduced the efficiency of glucose utilization in glucose-sensing cells via direct mitochondrial effects, these cells may incorrectly perceive a shortfall in available energy and stimulate mobilization of glucose reserves and production. Again, hyperglycemia might result because there are actually normal levels of glucose in circulation, and glycogen breakdown and gluconeogenesis would add yet more glucose to the system. Finally, the antipsychotic drugs may interfere with other signaling in the glucose-sensing pathway. It is known that clozapine and other antipsychotics inhibit K^+ channels (Kobayashi *et al.*, 2000; Muller *et al.*, 1991; Wu *et al.*, 2000). Perhaps the drugs that cause hyperglycemia in patients inhibit the ATP-sensitive K^+ channels, leading to insulin secretion over the short term but impairing insulin production with chronic drug treatment. Several groups have reported elevated insulin concentrations in patients treated with second-generation antipsychotics (Melkersson *et al.*, 2000; Newcomer *et al.*, 2002; Yazici *et al.*, 1998), which would be consistent with this proposed mechanism.

A number of different neurons distributed over several major brain regions are involved in the monitoring and control of systemic glucose concentrations. In the context of schizophrenia, one such circuit involves GABAergic (gamma aminobutyric acid) neurons in the striatum and glucose-sensitive dopaminergic neurons in the substantia nigra (Levin *et al.*, 2002). Functional activity of these dopaminergic neurons is modulated by glucose and antipsychotic drugs. This might explain the observation that movement disorders, especially tardive dyskinesia, are observed more frequently in diabetic patients or patients with high blood glucose levels who are treated with antipsychotic medications (Mukherjee *et al.*, 1985). As mentioned previously, there is some evidence that schizophrenics have a higher rate of diabetes than normal individuals. Perhaps there is a connection between the two that stems from defective glucose-sensitive circuits in the brain that include dopaminergic and GABAergic neurons in the nigro–striatal pathway.

C. Effects on Signaling Pathways: Phospholnositide 3-Kinase/Akt

Recently our group showed that several second-generation antipsychotic drugs stimulate phosphorylation (activation) of kinase-signaling pathways that include Akt and the mitogen-activated protein kinases (MAPK), ERK1/2 (Lu *et al.*, 2004). Akt and ERK regulate a variety of downstream targets involved in cell growth, differentiation, maintenance of cell size, and anabolic processes (Hajduch *et al.*, 2001; Kyosseva, 2004; Lawlor and Alessi, 2001). Notably, Akt is a major effector of insulin-mediated signaling by enhancing the recruitment of GLUTs to the cell surface and increasing expression of glucose-6-phosphate dehydrogenase (G6PDH), the major rate-limiting step of the pentose phosphate pathway (PPP). Upstream of Akt is phosphphatidylinositol 3-kinase (PI3K). Activation of PI3K is required for the phosphorylation of Akt induced by antipsychotic drugs (Lu *et al.*, 2004). Interestingly, phosphatiylinositol kinases regulate the ATP/sulfonylurea–sensitive K^+ channel via production of phosphatidylinositol phosphates that affect channel opening (Baukrowitz and Fakler, 2000). Consequently, secretion of insulin is affected by PI3K and by input from glucose-sensing neurons. Thus, antipsychotic drugs, by activating PI3K, may disturb glucose sensing in various tissues and directly affect insulin secretion by the pancreatic β cells.

Additional outcomes may result from drug-induced activation of Akt. A major role of Akt in insulin-responsive tissues is regulation of glucose metabolism, including glucose uptake via GLUTs in the plasma membrane and utilization via the PPP. Recent data from our laboratory suggest that antipsychotic drugs interfere with Akt activation in response to insulin. For these studies, 3T3-L1 preadipocytes were incubated in the absence or presence of olanzapine for 18 hours prior to addition of insulin. Normally, insulin elicits rapid (within 10 minutes) phosphorylation of Akt (Fig. 1A). However, after an 18-hour exposure to antipsychotic drug, there was a greatly diminished response to insulin. Quantification of phosphorylated Akt by enzyme-linked immunosorbent assay (ELISA) revealed a significant reduction in Akt activation by insulin subsequent to the 18-hour preincubation period with olanzapine (Fig. 1B). We have observed a similar reduction in the response to nerve growth factor in PC12 cells incubated with antipsychotic drugs (unpublished observations). One possible scenario is that activation of Akt by drugs produces desensitization or other down-modulation of the Akt pathway with long-term exposure. Chronic treatments that lead to phosphorylation of Akt on Ser473 are associated with inactivation of signaling via the insulin receptor–subunit and insulin resistance (Morisco *et al.*, 2005). If this occurred in human patients, the end result would be a decrease in insulin sensitivity, a condition associated with the development of diabetes. It will be important in future studies to explore possible mechanisms involved in the cross-regulation between drug and insulin signaling via Akt. Moreover, these

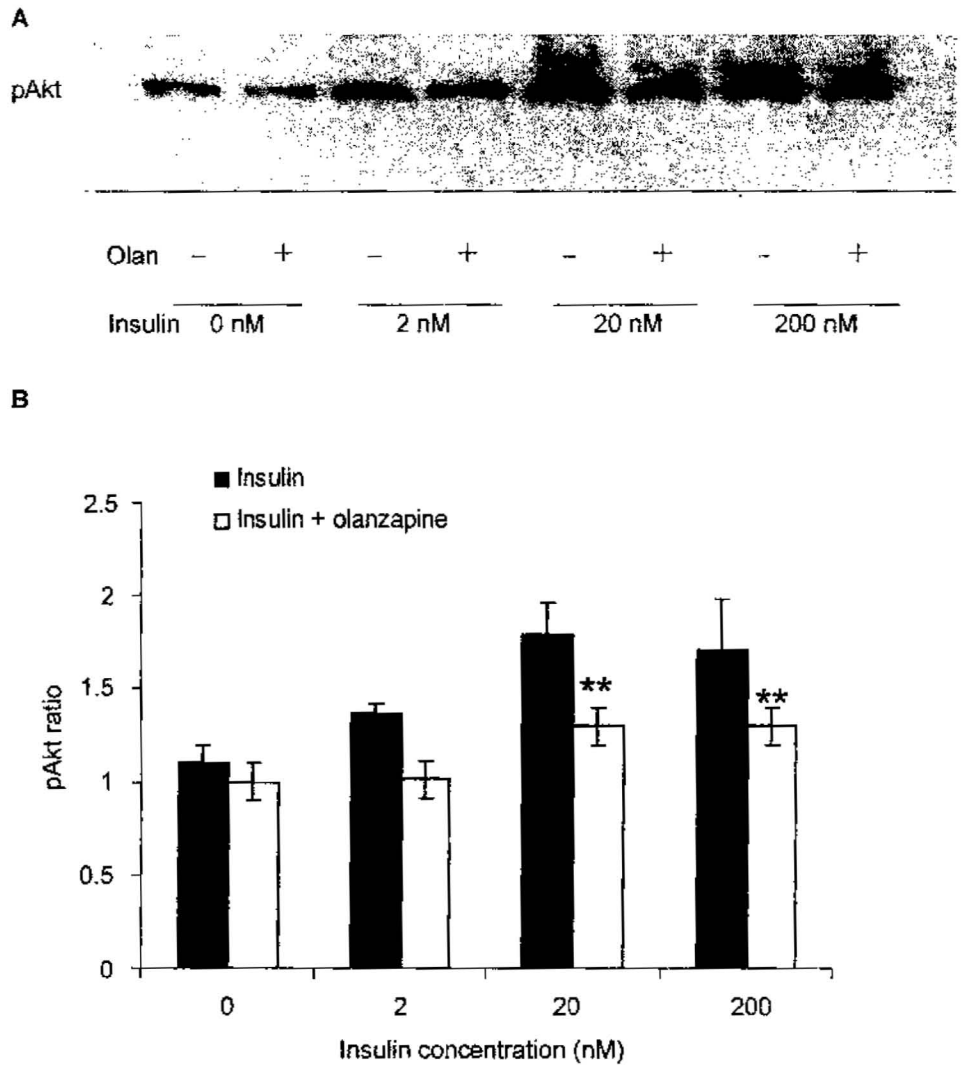

FIG. 1. Effect of olanzapine on the insulin response. 3T3-L1 cells were exposed to vehicle (solid bars) or olanzapine (50 μM; open bars) as described in the text and cell extracts were then prepared 10 minutes after the addition of insulin to the cultures. Phosphorylated Akt (Ser473) was detected with specific antibodies (Cell Signaling Technology; Beverly, MA) by western blot analysis (A) or with an ELISA kit (BioSource; Camarillo, CA) (B). The data in (B) were first normalized on the basis of total protein and are expressed in relation to the values of control samples from cells cultured in the absence of olanzapine or insulin. The asterisks indicate significant differences from the cells incubated with insulin alone (**$p < 0.01$; N = 3 experiments).

observations may have clinical relevance in that there may be an interaction between the timing of drug dose relative to meals such that prior exposure to peak levels of drug reduces the sensitivity of tissues to insulin that is induced after a meal some hours later.

D. Regulatory Balance Between Akt and AMP Kinase

In addition to insulin/PI3K/Akt, another pathway regulates glucose transport, especially in response to exercise and hypoxia, namely, the 5′-adenosine monophosphate (AMP)-activated kinase (AMPK; Hardie *et al.*, 2003; Rutter *et al.*, 2003). AMPK is itself activated by phosphorylation in response to a decrease in the ratio of cellular ATP/AMP and other signals (Hardie *et al.*, 2003; Lizcano *et al.*, 2004). AMPK appears to act as a fuel gauge whose major purpose is to increase the level of ATP in the cell via regulation of energy metabolism. Although AMPK stimulates glucose transport, which is similar to Akt, in most respects AMPK opposes the actions of Akt in cells and is involved in energy conservation and ATP production. Thus, AMPK inhibits lipid and cholesterol biosynthesis, glycogen formation, protein synthesis, and lipolysis, while it stimulates glycolysis and fatty acid oxidation and enhances insulin sensitivity (Carling, 2004; Hardie *et al.*, 2003; Rutter *et al.*, 2003). Therefore, a reduction in AMPK activity would be expected to produce a decrease in insulin sensitivity and an increase in fatty acid synthesis, which are two features of the metabolic syndrome induced by antipsychotic drugs. AMPKα2 knockout mice exhibit high glucose levels after feeding or glucose challenge and significant elevation of free fatty acids in both the fasted and fed states (Viollet *et al.*, 2003). It was suggested that hyperglycemia develops in these mice as a consequence of increased activity of the sympathetic nervous system, which controls various aspects of glucose metabolism including the insulin response (Nonogaki, 2000). Interestingly, expression of constitutively active AMPK in the medial hypothalamus of mice with recombinant adenoviruses significantly increased food intake and body weight (Minokoshi *et al.*, 2004), which is consistent with central nervous system (CNS)-regulatory mechanisms related to metabolic control that sense a shift in the ATP/AMP ratio.

Preliminary data from our laboratory suggest that olanzapine treatment for 30 minutes stimulates phosphorylation of AMPK in PC12 cells (data not shown). The activation of AMPK by olanzapine was comparable or superior to that produced by 5-aminoimidazole-4-carboxamide riboside (AICAR), a well-established pharmacological activator of this pathway (Corton *et al.*, 1995). If similar activation by olanzapine occurred in glucose-sensing neurons in the hypothalamus, this might lead to an increase in food consumption, weight gain, and sympathetic stimulation of glucose mobilization by peripheral tissues. Finally, AMPK is an attractive candidate to explain some of the observed metabolic disturbances because it is positioned to regulate both glucose and fat metabolism, which are both abnormal in many patients treated with second-generation antipsychotic drugs.

III. Metabolic Effects: Lipid Disturbances and Weight Gain

In addition to their effects on glucose metabolism, antipsychotic drugs produce abnormalities in triglyceride and cholesterol levels and significant weight gain in some patients. It seems likely that there is a connection between the lipid–weight gain effects of the antipsychotic drugs and their adverse effects on glucose regulation. The existence of a glucose–fatty acid cycle was established more than 40 years ago (Randle *et al.*, 1963). This cycle refers to the interrelationship between glucose metabolism and fatty acid levels in man. According to this scheme, uptake of glucose by cells regulates the release of fatty acids for use as fuel. Conversely, elevated concentrations of free fatty acids and ketone bodies in blood inhibit glucose metabolism and alter insulin sensitivity in various tissues. The glucose–fatty acid cycle is considered a rudimentary system for the regulation of fuel utilization that functions independently of hormonal control (Randle *et al.*, 1963). The effects of an antipsychotic drug on one aspect of this cycle will necessarily affect regulation of the other metabolic component. Interestingly, Melkersson *et al.* (2000) reported a close correlation between blood glucose levels and triglyceride and cholesterol levels in patients treated with olanzapine. Furthermore, the fact that the amount of visceral fat correlates with glucose intolerance and insulin responsiveness provides support for the interdependence of glucose and fat metabolism (Despres *et al.*, 1989). The balancing act between the use of glucose and fat for energy takes place in the larger context of a balance between anabolic and catabolic processes related to energy homeostasis. Schwartz *et al.* (2003) recently suggested that overall the system is tilted toward weight gain, which is consistent with earlier notions of "thrifty" genes that promote efficient storage of energy to withstand periods of food deprivation (Neel, 1962). However, in the face of high-fat Western diets, these thrifty genes and the anabolic bias in the system encourage weight gain and impair glucose regulation. Therefore, it is not surprising that many drugs induce significant weight gain and metabolic disturbances in patients because the inherent bias means that a small change in this same direction (induced by drugs) is sufficient to produce large cumulative effects over time.

The coordinated regulation of glucose and fatty acid metabolism is accomplished through several major mechanisms. Elevated glucose levels in blood normally lead to insulin secretion, a decrease in lipolysis, and an increase in the synthesis of fatty acids and triglycerides. A subsequent rise in fatty acids and triglycerides shifts metabolism in muscle and other responsive tissues to fatty acid oxidation (Randle, 1995; Randle *et al.*, 1963). This is accompanied by an increase in ATP and citrate, which are allosteric modulators of phosphofructokinase, a limiting enzyme of glycolysis (Randle, 1980). At the same time, an increase in the acetyl CoA/CoA ratio inhibits pyruvate dehydrogenase through both direct and indirect actions (Randle, 1980). The net effect is a decrease in glycolysis and

further glucose metabolism. Moreover, the increase in fatty acid oxidation is associated with inhibition of glucose uptake into muscle and relative insulin insensitivity. This situation reverses as lipid stores are utilized and with a rise in blood glucose levels after the next meal.

One additional connection between glucose and lipid metabolism is noteworthy: the dependence of fatty acid synthesis on the PPP. The PPP uses glucose to provide precursors for nucleotide synthesis and in the process generates NADPH, which is essential for various cell functions including fatty acid synthesis (Baquer *et al.*, 1988; Wood, 1986). Consequently, there is tight linkage between glucose metabolism via the PPP and the rate of lipogenesis in adipocytes (Kather *et al.*, 1972). From this perspective, the metabolic effects of antipsychotic drugs could be viewed as drug-induced hyperglycemia driving lipid synthesis (especially triglycerides) or alternatively as drug-induced upregulation of lipid synthesis, which mobilizes glucose to sustain the PPP. In view of the interrelationships between glucose and lipid metabolism outlined here, this is ultimately a dubious distinction.

Regardless of the precise mechanisms involved in the metabolic effects of the antipsychotic drugs, weight gain results from a person ingesting on a consistent basis more calories than he or she burns. This leads to an accumulation of fat and body mass over time. Theoretically, an imbalance between intake and consumption in response to drug treatment may arise from one of two conditions: there is an increase in caloric intake or a decrease in energy expenditure. There is little evidence that either of these situations dominates in the case of antipsychotic-induced weight gain. Therefore, we presume that both processes play a role in the metabolic effects of these drugs.

A. Clinial Observations and Scope of the Problem

Case reports of weight gain induced by the second-generation antipsychotic drug, clozapine, appeared shortly after introduction of this drug into clinical practice (Cohen *et al.*, 1990; Leadbetter *et al.*, 1992; Povlsen *et al.*, 1985). Although the problem of weight gain is typically associated with the second-generation drugs, conventional first-generation medications, including chlorpromazine and thioridazine, were also reported to cause significant weight gain in some patients (Allison *et al.*, 1999; Brady, 1989; Kalucy, 1980). Data from meta-analysis by several groups indicated that the prevalence of weight gain in patients treated with antipsychotic drugs ranged from 10–90% for those drugs with weight gain liability (Allison *et al.*, 1999; Russell and Mackell, 2001; Zimmermann *et al.*, 2003). Among the second-generation atypical antipsychotic drugs, clozapine and olanzapine produced the greatest weight gain with around 40% of patients adding more than 7% of their initial body weight. Risperidone and quetiapine produced significant weight gain in smaller percentages of patients, estimated in the range of 10–30%, whereas the newest drugs, ziprasidone and aripiprazole, stimulated weight gain in

~7–10% of patients (Russell and Mackell, 2001; Wirshing, 2004). The latter two drugs were considered weight neutral (American Diabetes Association, Consensus Statement, 2004; Russell and Mackell, 2001; Wirshing, 2004). Among the older conventional drugs, thioridazine, chlorpromazine, and thiothixine induced the greatest weight gain, whereas molindone has been reported to produce weight loss in patients (Allison *et al.*, 1999; Brady, 1989; Kalucy, 1980). Haloperidol was found to produce minimal weight gain in the meta-analysis of Allison *et al.* (1999). It is possible that some of the weight gain observed in these studies was secondary to an improvement in symptoms and the return of a healthy appetite. We favor this explanation for the instances of weight gain in patients taking the weight-neutral drugs, including ziprasidone, aripiprazole, and haloperidol.

There is some evidence that weight gain induced by antipsychotic drugs is more pronounced in younger patients, especially adolescents (Kelly *et al.*, 1998; Theisen *et al.*, 2001). However, this may, in part, be due to the lower baseline weight and greater potential for growth in this population. Most of the weight gain with antipsychotic drugs occurs in the first 4 months of therapy with a plateau observed thereafter for some medications (Umbricht *et al.*, 1994; Wetterling and Muessigbrodt, 1999). Clozapine and olanzapine appear to produce more prolonged and steady weight gain in patients (Henderson *et al.*, 2000; Wirshing, 2004). It is not uncommon for patients to add as much as 10–15 pounds over the course of treatment, although weight gain >10% of initial body mass is less frequent. Nevertheless, even modest weight gain is associated with an increased risk of cardiovascular disease, diabetes, stroke, and other serious complications (Almeras *et al.*, 2004; Fontaine *et al.*, 2001).

In addition to weight gain, the antipsychotic drugs produce a significant disturbance in lipid metabolism, most frequently hypertriglyceridemia (Casey, 2004; Meyer and Koro, 2004). Dufresne and colleagues were the first to report elevation of triglycerides in patients treated with clozapine and olanzapine (Ghaeli and Dufresne, 1995, 1996; Gaulin *et al.*, 1999; Osser *et al.*, 1999). Since those initial reports, many studies have found elevated levels of triglycerides in patients treated with second-generation antipsychotics (Henderson *et al.*, 2000; Koro *et al.*, 2002; Melkersson *et al.*, 2000; Meyer, 2001; Sheitman *et al.*, 1999); some groups reported elevated cholesterol levels as well (Baymiller *et al.*, 2002; Melkersson *et al.*, 2000; Meyer, 2002). The incidence of hypertriglyceridemia in patients treated with second-generation drugs ranges from 20–50% depending on the drug with the rank ordering: clozapine > olanzapine > quetiapine > risperidone (Saari *et al.*, 2004; Wirshing *et al.*, 2002). Ziprasidone and aripiprazole produce little or no elevation of triglycerides or cholesterol in patients (Casey, 2004; Meyer and Koro, 2004). The findings with antipsychotic drugs are significant because moderately elevated levels of triglycerides are associated with an increased risk of heart disease, including myocardial infarction (Gotto, 2002; Jonkers *et al.*, 2001), whereas high levels may cause pancreatitis

(Miller, 2000; Toskes, 1990). Hypertriglyceridemia has also been implicated in insulin-resistance, exacerbation of diabetes, and metabolic syndrome (Grundy, 1998; Krentz, 2003). As might be expected, there is generally a good correlation between the lipid disturbances and drug-induced weight gain in patients (Atmaca *et al.*, 2003; Baymiller *et al.*, 2002; Henderson *et al.*, 2000; Osser *et al.*, 1999), although this is not a universal finding (Meyer, 2001).

The weight gain and hyperlipidemia observed in patients taking antipsychotics are clearly related to the medication regimen. The disturbances appear within weeks of initiation of treatment and discontinuation of drug is accompanied by a decrease in lipid levels and loss of weight (Casey, 2004; Ghaeli and Dufresne, 1995; McIntyre *et al.*, 2001). In addition, switching a patient from a drug with high weight gain/lipid liability to a drug with a safer metabolic profile is typically associated with normalization of lipid levels and weight.

Interestingly, a number of studies have found an association between weight gain and clinical improvement. Early clinical practice with chlorpromazine revealed weight gain associated with treatment response (Planansky, 1958), although others did not observe this relationship (Gordon and Groth, 1964). With the newer second-generation drugs, a correlation between weight gain and clinical improvement has been reported in patients treated with clozapine and olanzapine (Czobor *et al.*, 2002; Gupta *et al.*, 1999; Leadbetter *et al.*, 1992; Meltzer *et al.*, 2003). One study failed to find this relationship for clozapine (Umbricht *et al.*, 1994), whereas another study confirmed the association for total BPRS (Brief Psychiatric Rating Scale) scores, but not for SANS (Scale for the Assessment of Negative Symptoms) scores (Bustillo *et al.*, 1996). To explain these observations, two main schools of thought have emerged. The first posits that the biological processes affected by the drugs to produce weight gain also contribute to the normalization of brain function. The second school of thought suggests that patients whose psychotic symptoms improve are more likely to regain their appetite for food and subsequently put on more weight than unresponsive patients. Anecdotal reports of carbohydrate craving in patients treated with antipsychotic drugs tend to support the latter interpretation. Nevertheless, more thorough investigation is needed to resolve some of these issues. For example, studies exploring the mechanisms of drug-induced weight gain would benefit from knowledge that similar biochemical and/or signaling pathways are affected in the brain during the course of treatment.

B. Genetic Studies

Several excellent reviews on the relationship between genetic factors and drug-induced weight gain have recently been published; readers are referred to these articles for a more detailed account of this topic (Basile *et al.*, 2001; Correll

(−2548G/A) and weight gain. Patients with the homozygous −2548A/A genotype gained more weight while taking chlorpromazine and risperidone than patients with the G allele. This same group found increased levels of leptin in the serum of patients who gained weight while taking antipsychotics (Zhang *et al.*, 2004), as have others (Atmaca *et al.*, 2003; Melkersson and Hulting, 2001). However, Haupt *et al.* (2005) have argued convincingly against a role for leptin in the weight disturbances seen in patients treated with antipsychotics. Genetic analysis of additional patient populations treated with drugs such as clozapine and olanzapine with greater weight gain liability may help to clarify the contribution of leptin to weight gain.

Several genes have shown a trend for involvement in antipsychotic-induced weight gain: the β_3- and α_1-adrenergic receptors and TNF-α (Basile *et al.*, 2001). In the case of the β_3 adrenergic receptor, arginine substitution at amino acid 64 was associated with greater weight gain in patients treated with clozapine (Basile *et al.*, 2001). This same polymorphism was associated with metabolic disturbances, including insulin resistance and weight gain, in untreated patients (Clement *et al.*, 1995; Widen *et al.*, 1995). On the other hand, patients homozygous for cysteine at position 347 of the α_1-adrenergic receptor showed a tendency for less weight gain with clozapine (Basile *et al.*, 2001). The TNF-α gene shows an SNP at position 308G/A. Patients treated with clozapine who were homozygous for the A variant gained about twice as much weight as patients who lacked this genotype (Basile *et al.*, 2001). Although central actions of antipsychotic drugs on these receptor systems are a possibility, it is interesting to note that all three genes are expressed in adipocytes and directly affect fat cell biology. As discussed in the following text, we believe that the weight gain liability attributable to these genes is likely expressed at the level of adipocytes rather than neuronal cells. Polymorphisms in a variety of other genes have been examined, including histamine receptors, dopamine receptors, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_6 receptors, and serotonin transporters (Basile *et al.*, 2001; Hong *et al.*, 2001, 2002; Rietschel *et al.*, 1997), however, none have shown a significant association to drug-induced weight gain thus far.

C. Animal Model Systems

1. *Rats and Mice*

Information from animal studies may help to identify some of the mechanisms by which antipsychotic drugs produce weight gain and metabolic disturbances in patients. Knockout mice have already provided significant clues that are being followed up in patient studies. Mice with a functional deletion of the 5-HT_{2C} receptor are overweight due to hyperphagia with hyperinsulinemia at later stages of development (Tecott *et al.*, 1995). The mice are also prone to potentially

fatal seizures. Perhaps surprisingly, there was no hyperlipidemia and no elevation of triglycerides even when the mice were fed a high-fat diet and despite significant weight gain. These studies revealed a role for the 5-HT_{2C} receptor in the CNS regulation of appetite and suggested that knockout mice do not suffer from a general metabolic disturbance, but rather impaired sensation of satiety. By contrast, histamine H_1-receptor knockout mice develop normally at first, although with advancing age their response to leptin (suppression of food intake) is attenuated and they become hyperphagic and obese (Masaki *et al.*, 2001, 2004). Histamine H_3-receptor knockout mice have a mild obese phenotype with an increase in food intake and adiposity (Takahashi *et al.*, 2002), although another group failed to observe significant weight gain in null mice (Toyota et a., 2002). Weight gain may result from the observed decrease in locomotory behavior and reduced energy expenditure (Toyota *et al.*, 2002). Thus, histamine receptor knockout mice provide only a partial model of the metabolic abnormalities observed in patients taking antipsychotic drugs. On the other hand, mice with a deletion of the gene coding for histidine decarboxylase, the enzyme responsible for histamine synthesis, exhibit a phenotype that more closely resembles the metabolic syndrome in patients (i.e., increased visceral adiposity, glucose intolerance, and hyperleptinemia) (Fulop *et al.*, 2003). β_3-Adrenergic receptor knockout mice have a slight increase in body fat but show few metabolic abnormalities otherwise (Susulic *et al.*, 1995). If anything, free fatty acid and glucose levels in blood are lower in the β_3-receptor $-/-$ mice than wild-type controls. While tantalizing in many respects, studies of knockout mice have also been disappointing. These studies have so far failed to mimic the situation observed in patients taking antipsychotic drugs—weight gain, lipid disturbances (especially hypertriglyceridemia), and glucose intolerance—by knocking out single relevant neurotransmitter receptors.

In parallel efforts, several groups have sought to establish animal models of antipsychotic drug-induced weight gain in order to learn more about the possible mechanisms involved. The studies can be generally categorized into one of two types: (1) those that characterize acute effects of antipsychotic drugs on appetite and feeding behavior in rats or mice, and (2) studies of weight gain with longer-term drug treatment. In an early study of feeding behavior, Benvenga and Leander (1997) reported that clozapine, but not olanzapine, increased food intake in rats with acute administration, which is curious because both drugs produce significant weight gain in patients. Kaur and Kulkarni (2002) studied feeding behavior of female mice 30 minutes after injection of either conventional or second-generation antipsychotic drugs. Chlorpromazine, haloperidol, clozapine, olanzapine, and risperidone all produced significant hyperphagia in the mice, and clozapine induced significant weight gain over a 2-week treatment period; it was the only drug tested for weight gain liability. By contrast, Hartfield *et al.* (2003a) found that administration of clozapine and olanzapine 30 minutes

prior to testing increased fat intake (ingestion of a lipid-rich liquid emulsion), whereas haloperidol did not. In a follow-up study, this group reported that stimulation of fat intake by antipsychotic drugs was not mimicked by pharmacological antagonism of histamine H_1 receptors or 5-$HT_{1/2}$ receptors alone or in combination (Hartfield *et al.*, 2003b). Finally, Kirk *et al.* (2004) showed that ziprasidone suppressed the increase in food intake brought about by administration of olanzapine, despite the fact that ziprasidone is a potent inhibitor of both 5-HT_{2C} and H_1 receptors.

A more relevant model to study the actions of the antipsychotic drugs may be the induction of weight gain in rodents with chronic drug treatment. Baptista *et al.* (1987) reported that long-term administration (21 days) of certain antipsychotic drugs in rats was associated with weight gain. Haloperidol and sulpiride produced significant weight gain in female, but not male rats. In addition, chlorpromazine caused weight loss in male rats and was weight neutral in female rats. These results are opposite to what might be expected based on clinical observations, that is, chlorpromazine is associated with weight gain in patients, whereas haloperidol has modest weight gain liability. Pouzet *et al.* (2003) confirmed that haloperidol produced significant weight gain over 3 weeks of treatment in female rats, but not male rats. Olanzapine produced a similar overall response in the rats. Pouzet *et al.* (2003) concluded that Wistar rats do not offer a relevant model for the study of antipsychotic-induced weight gain. By contrast, Arjona *et al.* (2004) observed significant weight gain in female Sprague–Dawley rats after 10 days of treatment with olanzapine but not haloperidol. However, the dose of haloperidol that was used was much lower than in previous studies. Weight gain in the olanzapine group appeared to be due to an increase in food intake and a decrease in motor activity. Differences in the dosing regimens or the strain of rats may explain some of the discrepancies in these studies. Nevertheless, it appears that rats may be of limited value in the study of the metabolic effects of antipsychotic drugs (Norman and Hiestand, 1955).

Our group has observed significant weight gain in male C57Bl/6 mice treated every other day with clozapine (Dwyer and Donohoe, 2003). The data from this study are shown in Table I. Compared with control mice injected with vehicle, the clozapine-treated mice gain an additional 1.8 g over a 2-week treatment period. Although acute administration of clozapine produced significant hyperglycemia in the mice (Dwyer and Donohoe, 2003), chronic treatment with drug did not lead to sustained hyperglycemia (Table I). A recent study by Zarate *et al.* (2004) is very informative. This group treated male mice from two different strains (A/J and C57Bl/6) daily with clozapine and measured weight gain and behavioral parameters at early (3–4 days) and late (21–22 days) time points. Intriguingly, they observed weight loss over the first 5 days of treatment, whereas the behavioral effects of the drug were maximal at this same time period. Significant weight gain was observed in both strains of mice at 3 weeks, although

TABLE 1
WEIGHT GAIN IN MICE AFTER TREATMENT WITH CLOZAPINE FOR 2 WEEKS[a]

Treatment group	Weight (g ± SD)	Acute serum glucose (mg/dl ± SD)	Chronic serum glucose (mg/dl ± SD)
Control	22.3 ± 0.9	99.2 ± 17.0	120.6 ± 16.0
Clozapine (10 mg/kg)	24.1 ± 0.7[b]	196.1 ± 39.2[b]	113.3 ± 22.4

[a]Male C57Bl/6 mice (12-weeks old) were injected with clozapine every other day for 2 weeks. Twenty-four hours after the last injection, the mice were weighed and serum was obtained for determination of blood glucose concentrations (Chronic Serum Glucose). Acute Serum Glucose levels were obtained at the start of the experiment from blood samples drawn 3 hours after the first injection of drug. All drug injections were intraperitoneal and control mice were injected with vehicle alone.

[b]Significant differences from the control group ($p < 0.01$; $N = 8$).

the effects on behavioral measures had returned to baseline levels. Thus, the antipsychotic drugs may produce acute effects on behavior (perhaps including feeding) that are related to their established pharmacology, whereas their longer-term effects on weight gain and glucose metabolism may result from desensitization of the initial pharmacological response or from mobilization of additional biological pathways. These two possibilities are not mutually exclusive. In future studies, it will be important to distinguish between the contributions of acute effects of the drugs on appetitive behaviors and chronic effects on appetite regulation (CNS control) versus fundamental metabolic processes in peripheral tissues.

a. Caenorhabditis Elegans. Recent studies in the soil nematode, *C. elegans*, suggest that this model organism may prove quite useful for research on obesity. Ashrafi *et al.* (2003) and McKay *et al.* (2003) have pioneered the use of *C. elegans* to study the regulation of fat storage at the genetic level. Ashrafi *et al.* (2003) used the fluorescent, lipid-sensitive dye Nile red to visualize fat storage in *C. elegans* and RNA interference (RNAi) to characterize the role of more than 16,500 genes on the lipid storage phenotype. They identified 305 gene inactivations associated with reduced fat storage and 112 gene inactivations that caused increased fat accumulation. Some prominent examples include inactivation of dopamine receptors and fatty acid synthesis enzymes, which are associated with reduced fat storage, and inactivations of the aryl hydrocarbon receptor, PI3K, and a glucose transporter, which produce a "fat" phenotype in the animals. McKay *et al.* (2003) inactivated two transcription factors known to regulate formation of fat in mammals and showed that *C. elegans* lacking these factors displayed a lipid-depleted phenotype or *lpd*. By reverse genetic screens (RNAi induction of *lpd*), they identified additional genes that regulated fat accumulation.

Importantly, they showed that 7 out of 8 of these genes are expressed in mammals and have similar functional roles across species.

Based on the success of these groups, we sought to determine whether *C. elegans* would respond to antipsychotic drugs with an increase in lipid accumulation in fat-storing cells. If so, the relative ease of genetic manipulation in this system may allow identification of the biological pathways involved. For these studies, animals at the first larval stage (L1) were transferred to culture plates seeded with bacteria and containing either antipsychotic drug or solvent (dimethyl sulfoxide [DMSO], control). After 2 days, the animals were rinsed off the plates, washed, fixed in 1% paraformaldehyde, and subjected to two freeze-thaw cycles. They were then stained with the lipophilic dye, Sudan black, washed several times with M9 buffer, and observed under the light microscope. The photomicrographs in Fig. 2 show that treatment with both clozapine and olanzapine produced greater staining with Sudan black than the control conditions, which indicates a relative increase in lipid stores. We wished to confirm these observations by examining the effects of olanzapine on the accumulation of Nile red in lipid deposits in *C. elegans*. For these experiments, L1 animals were cultured on seeded plates that contained agar with Nile red (0.05 μg/ml) in the absence or

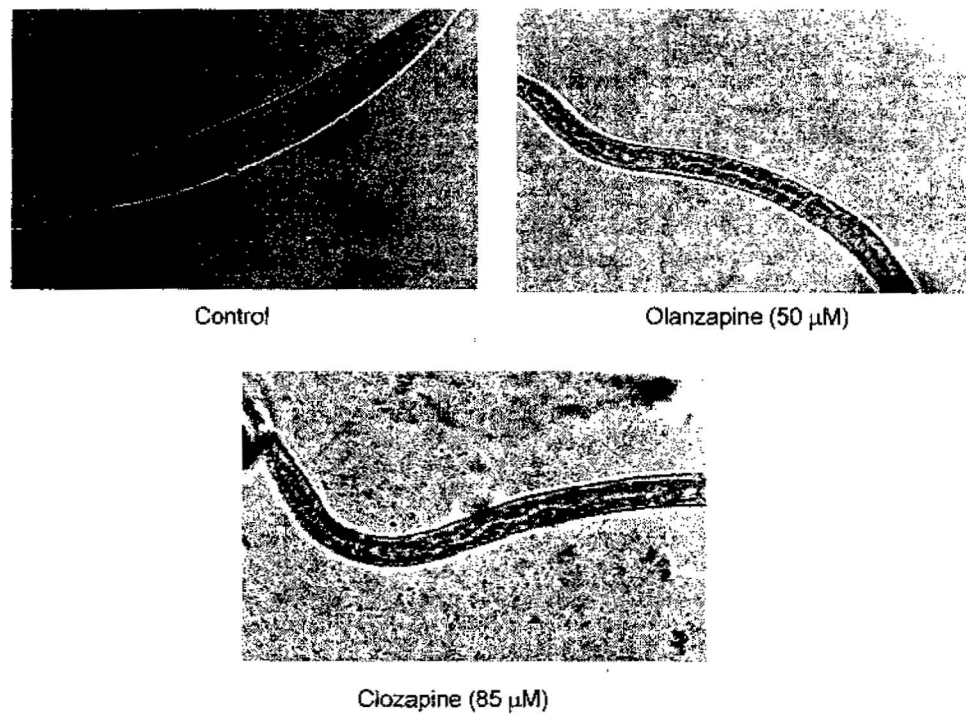

FIG. 2. Antipsychotic drugs induce lipid accumulation as measured by Sudan black staining. The photomicrographs were obtained after 48 hours of treatment with vehicle (DMSO) or drugs at the concentrations indicated and staining with Sudan black.

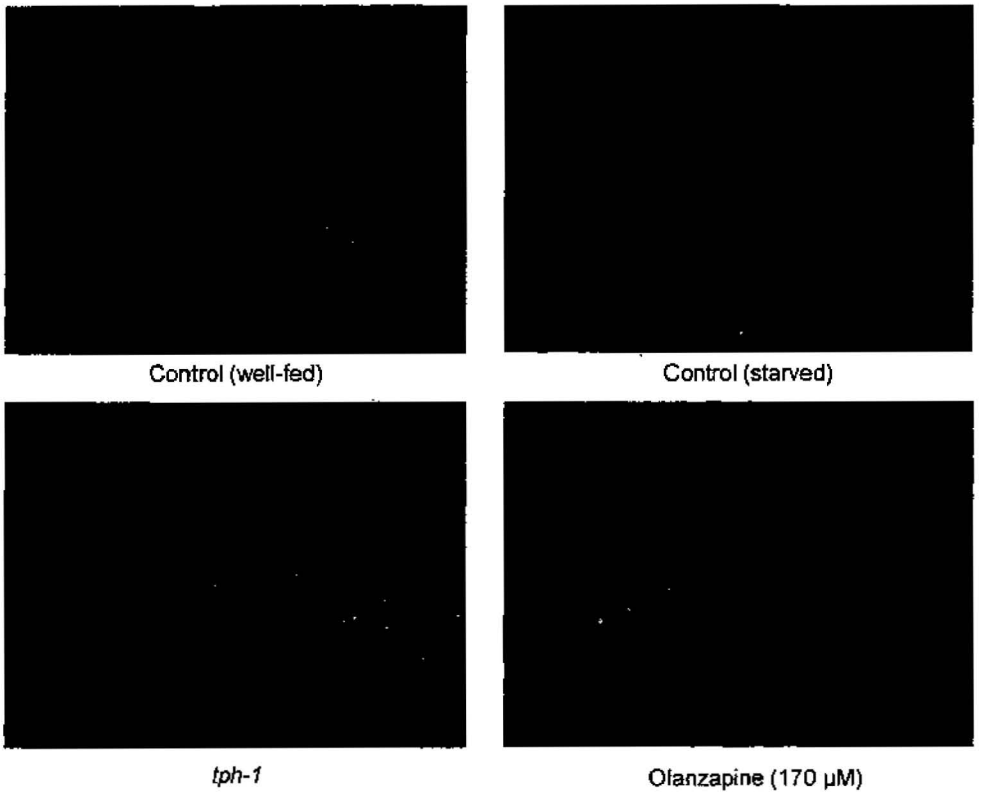

FIG. 3. Effect of olanzapine on the accumulation of Nile red in lipid stores of *C. elegans*.

presence of olanzapine (170 μM). As a positive control, we used *tph-1* animals that, due to a deficiency in serotonin, accumulate significant amounts of lipid (Sze *et al.*, 2000). At the L4 stage, the animals were paralyzed with 50 mM sodium azide and were examined for dye accumulation with a fluorescence microscope. As expected, the *tph-1* animals showed an increase in Nile red staining (reflecting the size of lipid stores) compared with well-fed and starved control animals (Fig. 3). Animals treated with olanzapine also stained more brightly with Nile red than the controls (Fig. 3).

These initial studies of drug-induced accumulation of lipophilic dyes encouraged more in-depth analysis of the response. Olanzapine was tested over a range of concentrations for its ability to stimulate accumulation of Nile red. Accumulation was quantified by digital analysis of fluorescence images and the results are summarized in Fig. 4A. Animals (20–30) from two separate plates were analyzed for mean fluorescence intensity compiled over equivalent anatomical areas. As a positive control, the *tph-1* mutant was analyzed and showed a significant elevation (1.5- to 2-fold) of staining compared to control animals. Olanzapine produced a dose-dependent increase in the accumulation of Nile

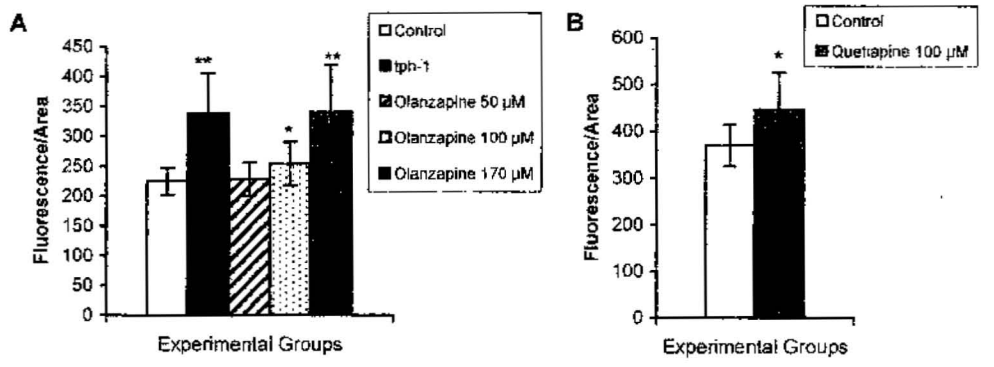

FIG. 4. Quantification of Nile red staining in *C. elegans* in response to antipsychotic drugs. Animals were exposed to Nile red in the absence (control and *tph-1*) or presence of drugs at the concentrations indicated. After 48 hours, animals (N = 40–60) from each group were analyzed for mean fluorescence over equivalent anatomical areas. The data were averaged and significant differences from the control group are indicated by asterisks ($*p < 0.05$; $**p < 0.01$).

red fluorescence, which reached significance at 100 μM and above. In addition, quetiapine induced significant accumulation of Nile red in *C. elegans* (Fig. 4B). The response to quetiapine was somewhat less than to olanzapine. Preliminary studies showed that fluphenazine, which is not associated with weight gain in patients, did not stimulate the accumulation of Nile red in the animals. Thus, several different antipsychotic drugs that are associated with weight gain and lipid disturbances in patients promote the accumulation of lipid-sensitive dyes in *C. elegans*. There are no obvious changes in feeding behavior, although there is a tendency for animals exposed to clozapine to spend less time on the bacterial lawn, which argues against an increase in food consumption as a contributing factor in lipid deposition in cells. *C. elegans* appears to represent a valuable model system for characterization of the mechanisms involved in the metabolic disturbances induced by antipsychotic drugs.

IV. Possible Targets of Antipsychotic Drugs

A. Established Pharmacology

The second-generation or atypical antipsychotic drugs tend to bind with high affinity to a wider variety of neurotransmitter receptors than the older conventional drugs and generally display greater antagonism at serotonergic receptors as judged by the ratio of antagonism of serotonergic versus dopaminergic receptors (Deutch *et al.*, 1991; Meltzer, 1999). This profile may contribute to the metabolic

liability of these drugs; however, it must be remembered that conventional dugs, including chlorpromazine and thioridazine, produce similar adverse effects. Thus far, there is little evidence that connects the actions of the antipsychotic drugs at a particular neurotransmitter receptor to the drug-induced hyperglycemia and diabetes in patients. This may be due in part to the fact that glucose abnormalities induced by the drugs are much less common than weight gain and are therefore more difficult to study at the population level. The existence of the glucose–fatty acid cycle means that at some level there is a connection between weight gain/lipid abnormalities and impaired glucose regulation. This connection is likely to include a common biochemical origin.

In terms of weight gain liability, analysis from various studies, including correlational data, genetic risk analysis, and gene deletion studies in mice, points to a possible role for several major established drug targets, including H_1, 5-HT_{2C}, β_3-, and α_1-adrenergic receptors. Each candidate has particular merits, but also striking exceptions that cast serious doubt that drug actions at a single receptor account for the weight gain and lipid and glucose disturbances. The importance of the histamine H_1 receptor in drug-induced weight gain has been touted by some groups (Kroeze *et al.*, 2003; Wirshing *et al.*, 1999) and questioned by others (Goudie *et al.*, 2003). Two separate studies found no association between genetic polymorphisms in the H_1 receptor gene and drug-induced weight gain (Basile *et al.*, 2001; Hong *et al.*, 2002). In addition, most H_1 receptor antagonist drugs that are used clinically to treat allergies are not associated with significant weight gain, and in fact the H_1 antagonist with greatest reported weight gain liability (astemizole) does not enter the CNS (Kaliner, 1992). H_1 Receptor knockout mice show no significant metabolic differences from control mice until about 30 weeks of age, after which time they gradually begin to gain weight and show evidence of impaired responsiveness to leptin (Masaki *et al.*, 2003, 2004). The weight gain appears to arise mainly from hyperphagia and altered feeding behavior (Masaki *et al.*, 2004). There is no significant change in the levels of serum triglycerides, free fatty acids, or glucose in the H_1-receptor −/− strain. As discussed earlier, mice with a deletion of the gene encoding histidine decarboxylase ultimately display a metabolic syndrome characterized by increased visceral adiposity, hyperinsulinemia, hyperleptinemia, and impaired glucose tolerance (Fulop *et al.*, 2003). However, these mice develop normally for the first 3–4 months and triglyceride and cholesterol levels remain normal even when other metabolic disturbances are clearly manifested. The weight gain in these mice appears to be related more to changes in feeding behavior, the sleep–wake cycle, and thermoregulation. Finally, the increased intake of lipid-rich emulsions that is induced in rats by antipsychotic drugs is not mimicked by administration of H_1-receptor antagonists (Hartfield *et al.*, 2003b).

The 5-HT_{2C} receptor has been a leading candidate to explain the drug-induced weight gain because clozapine and olanzapine are potent antagonists at this receptor and because animals lacking functional 5-HT_{2C} receptors are overweight and store more fat in adipose tissue (Tecott *et al.*, 1995). However, the substantial weight gain in these mutant mice is mainly due to hyperphagia and plasma levels of glucose, free fatty acids, and insulin remain normal at 12–14 weeks of age. Older mutant mice with significant weight gain eventually developed impaired glucose tolerance and reduced responsiveness to insulin and leptin; however, triglycerides and fatty acids remained normal (Nonogaki *et al.*, 1998). Another limitation to the 5-HT_{2C} receptor as the main mechanism for drug-induced weight gain concerns the relative affinity of antipsychotics for this receptor. Ziprasidone has a greater affinity for the 5-HT_{2C} receptor than clozapine, chlorpromazine, and risperidone, yet it produces much less weight gain in patients. On the other hand quetiapine, which has a low affinity for 5-HT_{2C} receptors, induces moderate weight gain. Although Reynolds *et al.* (2002, 2003) reported a significant association between antipsychotic-induced weight gain and the presence of an SNP in the 5-HT_{2C} receptor gene, two other groups failed to replicate this finding (Basile *et al.*, 2002; Tsai *et al.*, 2002).

The α_1- and β_3-adrenergic receptors have been proposed as possible drug targets involved in weight gain in patients. Basile *et al.* (2001) found a trend toward an association between weight gain with clozapine and an Arg347Cys polymorphism in the α_{1A}-adrenergic receptor. Kroeze *et al.* (2003) reported a correlation between α_{1A}-receptor antagonism and weight gain liability for an extensive panel of antipsychotic drugs. However, α_{1A}-receptor knockout mice show no weight gain or metabolic abnormalities (Tanoue *et al.*, 2003). Moreover, olanzapine, which has one of the highest weight gain liabilities, is a weaker antagonist of α_{1A}–receptors compared to ziprasidone and aripiprazole, which are weight neutral (Kroeze *et al.*, 2003). The β_3-adrenergic receptor is involved in regulation of adipocyte metabolism (Emorine *et al.*, 1994), and a Trp64Arg mutation in this receptor is implicated in insulin resistance and weight gain (Clement *et al.*, 1995; Widen *et al.*, 1995). A trend toward association of this genotype with clozapine-induced weight gain has been reported (Basile *et al.*, 2001). However, most of the antipsychotic drugs are exceedingly weak ligands at β-adrenergic receptors. Moreover, disruption of the β_3-adrenergic receptor gene is accompanied by modest metabolic changes in mice that consist mainly of increased adiposity. Weight gain and disturbance of serum lipid and glucose levels are not observed. It remains to be seen whether other receptors that are targeted by antipsychotic drugs, especially muscarinic receptors, are the major site of action for drug-induced weight gain.

Thus, it does not appear that the actions of antipsychotic drugs at a single receptor adequately account for the weight gain observed in patients. It has been suggested that combined effects of the drugs at two or more neurotransmitter

receptors may be required to explain the adverse metabolic effects (Casey and Zorn, 2001; Meltzer *et al.*, 2003; Mueller *et al.*, 2004). This is a distinct possibility; however, it is worth noting that many other drugs are also associated with weight gain and adverse metabolic effects in patients. This includes older tricyclic antidepressants, glucocorticoids, Ca^{++} channel blockers, and protease inhibitors (Kalucy, 1980; Montastruc and Senard, 1992; Pijl and Meinders, 1996; Wirshing *et al.*, 2002). Two possibilities can be entertained: (1) each class of drug has a unique mechanism of action with respect to induction of weight gain, or (2) there may be a common mode of action for many of the offending drugs. We favor the latter possibility. It seems unlikely that one of the neurotransmitter receptors mentioned here will constitute that common thread. Rather, we feel that it may be more fruitful to consider alternative mechanisms that might help to explain the weight gain and metabolic effects produced by a wide array of drugs.

B. Novel Pharmacological Actions

Previously, we showed that antipsychotic drugs inhibit glucose transport in neuronal and other cell types by interacting directly with the GLUT protein (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999a,b). We suggested that interference with glucose transport may contribute to the emergence of metabolic disturbances in patients taking antipsychotic drugs (Ardizzone *et al.*, 2001; Dwyer *et al.*, 1999b, 2001). Recent studies of knockout mice with a deletion of the insulin-regulated glucose transporter, GLUT4, provide evidence that supports this suggestion. Although homozygous GLUT4 null mice fail to thrive and die very early, heterozygous knockout mice develop diabetes and other metabolic abnormalities (Stenbit *et al.*, 1997). Moreover, when GLUT4 is specifically ablated in adipose tissue, the mutant mice exhibit insulin resistance, elevated blood glucose levels, hyperinsulinemia, and even severe diabetes in some cases (Abel *et al.*, 2001). Acute injection of mice with antipsychotic drugs that inhibit glucose transport produces significant hyperglycemia within 30 minutes to 1 hour (Dwyer and Donohoe, 2003). Furthermore, administration of cytochalasin B, a selective antagonist of GLUTs, induces acute hyperglycemia in mice of a similar magnitude as the antipsychotic drugs despite an absence of effect of this compound on the neurotransmitter receptors targeted by antipsychotic drugs (Dwyer and Donohoe, 2003; Dwyer *et al.*, 2002). Thus, a reduction in glucose transport by either drugs or genetic approaches is sufficient to cause hyperglycemia, insulin resistance, and even diabetes in mice. The GLUT4 heterozygous knockout mice showed normal lipid profiles for the most part, whereas elimination of a GLUT analog in *C. elegans* via RNAi promoted fat storage in these animals and produced a fat phenotype (Ashrafi *et al.*, 2003). The possibility that GLUTs and glucose metabolism represent a common mechanism for weight gain and metabolic

disturbances is strengthened by the observation that a wide variety of drugs that produce these same effects in patients (including tricyclic antidepressants, corticosteroids, Ca^{++} channel blockers, and protease inhibitors) affect glucose transport/metabolism (Dwyer *et al.*, 2002).

It is noteworthy that mice with a tissue-specific deletion of the insulin receptor in muscle display elevated triglycerides and fatty acids and increased fat mass (Minokoshi *et al.*, 2003). Therefore, the combination of decreased glucose transport (via drugs or reduction in GLUTs) in fat or other tissues and insulin resistance in muscle produces the same spectrum of metabolic abnormalities observed in patients treated with antipsychotic drugs.

This last point suggests that modulation of insulin-signaling pathways by antipsychotic drugs may contribute to the metabolic disturbances in patients. Elsewhere, we have reported that second-generation antipsychotics (including olanzapine and quetiapine) associated with weight gain and hyperglycemia activate the serine/threonine kinase Akt (Lu *et al.*, 2004). Akt is a major downstream target in the insulin-signaling pathway and is involved in recruitment of GLUTs to the cell surface and adipocyte differentiation and function. Pretreatment of 3T3-L1 preadipocytes with olanzapine reduces the subsequent activation of Akt in response to insulin (this article; Lu and Dwyer, 2005). Perhaps initial activation of Akt by drug leads to temporary desensitization of this signaling pathway at the level of the insulin receptor and reduced responsiveness to endogenous molecules including insulin. This might explain some of the metabolic effects of the antipsychotic drugs. Alternatively, the drugs may act, in part, through activation of the mitogen-activated protein kinase (MAPK) ERK1/2 (Lu *et al.*, 2004). ERK is involved in the differentiation of preadipocytes and the regulation of adipocyte function (Prusty *et al.*, 2002). Chronic activation of ERK by antipsychotic drugs might increase the number of adipocytes and their fat storage capacity while stimulating the production of triglycerides and fatty acids.

The antipsychotic drugs appear to activate Akt and ERK via G proteins, specifically G_i (Lu *et al.*, 2004). This may provide an additional clue because genetic downregulation of the $G_{i\alpha 2}$ subunit leads to impaired insulin sensitivity and glucose tolerance in transgenic mice (Moxham and Malbon, 1996). Further downstream of $G_\alpha i$/Akt signaling are the forkhead transcription factors such as AFX and FOXC2. Importantly, AFX is jointly regulated by Akt and AMPK (Yang *et al.*, 2002). Finally, FOXC2 is intimately involved in the regulation of weight gain, triglyceride production, and insulin sensitivity (Cederberg *et al.*, 2001). Perhaps the signal transduction pathways activated by the target(s) of the antipsychotic drugs converge on transcription factors that play a critical role in adipocyte biology, including FOXC2 and C/EBP.

Recent research by Ashrafi *et al.* (2003) provided additional candidate genes to explain drug-induced weight gain in patients. This group disrupted the expression of more than 16,500 genes in *C. elegans* with specific RNAi and

identified genes whose elimination produced either a thin or fat phenotype. Several particular genes were noteworthy because they have been shown to be affected either directly or indirectly by antipsychotic drugs. The list includes the aryl hydrocarbon receptor, potassium channels, a glutamate receptor, and PI3K. As discussed earlier, the *tph-1* tryptophan hydroxylase mutants also exhibit a fat phenotype, which is interesting in view of the established role of serotonin in satiety and feeding.

We suggest the following scheme to attempt to explain the metabolic disturbances caused by antipsychotic drugs. At the level of the CNS, the drugs may block H_1 and 5-HT_{2C} receptors to affect satiety and feeding, and inhibit glucose transport in specialized neurons to affect glucose sensing. Impaired glucose sensing by the brain may underlie the carbohydrate craving reported by many patients (Bernstein, 1987; Zimmermann *et al.*, 2003). Even more insidiously, the drugs produce significant adverse effects on peripheral tissues. Direct actions of the drugs on adipocytes, hepatocytes, and β-islet cells may lead to increased fat synthesis and storage, enhanced gluconeogenesis, and altered insulin secretion, respectively. The effects on these tissues may be mediated through direct drug interactions with adrenergic receptors (β_3 and α_1), GLUTs, or Akt, ERK, and AMPK signaling pathways. The net effect will be the sensation of glucose deprivation with an increase in gluconeogenesis and glucose output from the liver. In addition, impairment in Akt signaling would tilt the balance toward reduced insulin responsiveness and intermittent hyperglycemia, which would then drive the synthesis of fatty acids and triglycerides. As this vicious cycle progresses, patients begin to gain weight and some develop insulin resistance, hypertriglyceridemia, and even diabetes.

Why don't all patients taking antipsychotics gain significant weight or develop glucose intolerance? As many as 70–80% gain weight while taking antipsychotic drugs, up to 36% may develop diabetes during treatment, and glucose intolerance is widespread in patients taking these drugs. Thus, the number of patients who show no evidence of metabolic abnormalities may be fewer than imagined. In the population that fails to gain weight or develop glucose intolerance while taking antipsychotic drugs, relative resistance may be explained by several factors. First, these patients may express genetic polymorphisms in drug target gene(s) that protect against adverse metabolic effects of the drugs. Second, the full-blown emergence of weight gain and diabetes may require additional susceptibility genes besides the actual drug targets. Moreover, genetic differences related to drug metabolism and clearance may determine relative susceptibility to metabolic disturbances. Rather than attempting to attribute the drug-induced metabolic effects to receptors that are uniquely targeted by antipsychotic drugs, we wish to emphasize common mechanisms that might explain similar effects of the many different drugs (including tricyclic antidepressants, glucocorticoids,

protease inhibitors, and so on) that cause weight gain and glucose impairment in patients. A search for common ground may ultimately prove more fruitful in the identification of drug targets involved in the metabolic disturbances than the biased approach that has been applied to the problem thus far.

V. Clinical Implications

The weight gain and glucose intolerance induced by antipsychotic drugs seriously threatens patient compliance with treatment and elevates the risk of cardiovascular disease, diabetes, and stroke. Clearly, the emergence of these metabolic disturbances demands a timely response by the clinician responsible for care. Recently the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity issued a set of guidelines and recommendations regarding the monitoring of metabolic side effects of antipsychotic drugs (American Diabetes Association, Consensus Statement, 2004). The guidelines call for periodic evaluation of weight (body mass index, BMI), waist circumference, serum lipid and glucose levels, and blood pressure. If a patient gains more than 5% of his or her initial body weight or shows elevated glucose or triglyceride levels, the clinician should consider switching medications from one with a high risk for these problems to ziprasidone or aripiprazole, which appear to produce less weight gain and fewer metabolic abnormalities. However, it is not always possible to switch antipsychotic medications. Many patients who are taking clozapine have not benefited from therapy with other drugs. If they show significant clinical improvement with this drug of last resort, they may have to continue taking this medication despite the weight gain liability. Naturally, it is always good clinical practice to encourage patients to exercise and maintain a healthy diet. Some groups have reported success in limiting weight gain in patients taking antipsychotics with a comprehensive behavioral approach that includes exercise and close dietary monitoring (Menza *et al.*, 2004). In the case where a patient's psychotic symptoms are well controlled by a particular drug that is causing weight gain, treatment with adjunctive therapies may minimize the increase in weight and other metabolic effects. Nizatidine was reported to reduce weight gain in patients taking clozapine (McIntyre *et al.*, 2001). The antidiabetic drug, metformin, was reported to prevent weight gain in adolescents in response to antipsychotic drugs (Morrison *et al.*, 2002); however, this drug proved less successful in a pilot study in adult patients (Baptista *et al.*, 2001). Of course, any strategy to prevent antipsychotic-induced weight gain with the use of adjunctive medications

and Malhotra, 2004; Mueller *et al.*, 2004). We briefly summarize the major findings with special focus on those genes that showed significant associations with weight gain or a strong trend in this direction. For the most part, the genetic studies investigated polymorphisms in neurotransmitter receptors that are targeted by antipsychotic drugs and known to participate in the regulation of feeding and satiety. Several additional candidate genes have been investigated, including tumor necrosis factor-α (TNF-$\alpha\alpha$), leptin, and the cytochrome P450 metabolic enzymes CYP2D6 and CYP1A2.

The serotonin $(5\text{-HT})_{2C}$ receptor is an attractive candidate for some of the effects of the antipsychotic drugs because mice with a functional deletion of this gene are obese and because serotonergic agonists are used as weight loss agents (Curzon *et al.*, 1997; Tecott *et al.*, 1995). Two major polymorphisms in the 5-HT_{2C} receptor gene have been identified: a Cys23Ser mutation in the coding region and a single nucleotide polymorphism (SNP) −759C/T in the promoter region. Reynolds *et al.* (2002), in a study of weight gain induced mainly by chlorpromazine and risperidone, reported that patients with the −759T variant allele gained significantly less weight than patients with the −759C genotype. However, two other groups were unable to replicate this finding for clozapine-induced weight gain (Basile *et al.*, 2002; Tsai *et al.*, 2002), and one of the groups actually reported the opposite trend (Basile *et al.*, 2002). In a follow-up study, Reynolds *et al.* (2003) showed findings similar to their original work in patients treated with clozapine. Notwithstanding the inconsistencies, the −759C/T polymorphism accounts for at best about 25% of the weight gain observed in the studies by Reynolds and colleagues. The Cys23Ser polymorphism in the 5-HT_{2C} receptor showed no association with antipsychotic-induced weight gain (Basile *et al.*, 2001; Rietschel *et al.*, 1997) nor did polymorphisms in other 5-HT receptors (Hong *et al.*, 2001).

Genes related to drug metabolism could conceivably affect weight gain liability; this possibility has been evaluated in two studies. Ellingrod *et al.* (2002) reported a significant association between weight gain with olanzapine and the *1/*3 or *1/*4 genotypes for the CYP2D6 P450 enzyme. Patients who expressed the *1/*1 genotype were relatively protected against severe weight gain. The authors suggested that patients with the susceptible genotypes may have higher serum concentrations of olanzapine, although this was not verified in the study. Basile *et al.* (2001) investigated a possible relationship between CYP1A2 and weight gain in patients treated with clozapine. Although their findings were not significant, there was a trend for patients with the C/C genotype in intron 1 to gain more weight than patients homozygous for A/A at this position. Additional studies will be necessary to strengthen the case for involvement of P450 genes in susceptibility to drug-induced weight gain.

To our knowledge, the only other report of significant genetic association to drug-induced weight gain is by Zhang *et al.* (2003), who showed a relationship between a functional polymorphism in the promoter region of the leptin gene

will face the general limitation of frequent noncompliance in schizophrenic patients.

VI. Conclusions

Weight gain and metabolic disturbances are serious side effects; however, they are also indicative of a true biological response to the antipsychotic drugs. This is important because placebo effects are common in the treatment of psychiatric illness. Furthermore, some antipsychotic drugs may barely reach effective blood concentrations in patients and thus cause little weight gain because they are used at relatively low doses to avoid side effects such as extrapyramidal movement disorders or cardiac arrhythmias. Aripiprazole and ziprasidone may offer safer alternatives with fewer adverse metabolic effects; however, it remains to be seen whether they match the clinical effectiveness of clozapine and olanzapine against psychotic symptoms and cognitive deficits. Moreover, there are always patients who respond well to one drug, but not to a second one, regardless of the close pharmacological properties of the two drugs. In the future, it may be possible to develop drugs that lack the potential to produce adverse metabolic effects, but it will first be necessary to better understand how the current generation of drugs produces these problems. Of course, if the weight gain is inherent to inhibition of particular receptors (5-HT_{2C} and D_2) and inhibition of these receptors is necessary to treat psychosis, then the metabolic consequences of drug treatment may be an unavoidable risk. Genetic studies aimed at the identification of polymorphisms associated with drug-induced metabolic disturbances will continue to provide useful clues. Knockout mice and model organisms, including *C. elegans*, are also likely to be valuable resources in the quest to understand drug-induced weight gain. We believe that the most fruitful approach to identification of mechanisms involved in the metabolic effects of antipsychotic drugs will be to search in an unbiased manner for common threads shared by other drug classes that produce weight gain. This may include gene array studies, broad-based RNAi disruption of gene expression, and genetic screens in tractable organisms. Drug discovery programs focused on development of next-generation antipsychotic drugs would benefit from the inclusion of a screening program in an appropriate animal model to identify candidate compounds with liability for weight gain and/or glucose disturbances and to exclude these candidates from further consideration. Finally, as we begin to develop new antipsychotic drugs that address the neurodevelopmental insults that give rise to schizophrenia, we may find that the adverse metabolic effects have faded from view because the pharmacology of the new drugs is likely to be quite different from those in our current armamentarium.

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Table 63 Glucose regulation laboratory data, change from randomization to end of treatment (Randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 336	PLA+ LI/VAL N = 367	QTP+ LI N = 143	PLA+ LI N = 153	QTP+ VAL N = 193	PLA+ VAL N = 214
Glucose (mg/dL)							
N [a]		310	329	134	138	176	191
Randomization	Mean(SD)	93.97(21.261)	96.16(18.807)	95.71(18.117)	95.01(13.637)	92.64(23.337)	96.99(21.791)
End of treatment	Mean(SD)	97.97(20.142)	95.81(18.189)	100.35(21.577)	96.81(17.749)	96.16(18.838)	95.09(18.513)
Change	Mean(SD)	4.00(18.896)	-0.35(16.215)	4.64(16.951)	1.80(14.160)	3.52(20.286)	-1.90(17.422)
	Median	3.00	0.00	2.00	1.50	3.00	-1.00
	Min to Max	-132.00 to 84.00	-85.00 to 67.00	-68.00 to 72.00	-27.00 to 50.00	-132.00 to 84.00	-85.00 to 67.00
HbAlC (%)							
N [a]		307	338	130	137	177	201
Randomization	Mean(SD)	5.40(0.617)	5.39(0.530)	5.28(0.561)	5.23(0.480)	5.49(0.641)	5.51(0.535)
End of treatment	Mean(SD)	5.56(0.622)	5.44(0.557)	5.44(0.572)	5.28(0.477)	5.66(0.641)	5.54(0.583)
Change	Mean(SD)	0.17(0.403)	0.04(0.294)	0.16(0.285)	0.05(0.245)	0.17(0.472)	0.04(0.323)
	Median	0.10	0.00	0.20	0.00	0.10	0.00
	Min to Max	-1.60 to 3.80	-1.10 to 1.40	-0.90 to 1.10	-0.70 to 0.90	-1.60 to 3.80	-1.10 to 1.40
Insulin (pmol/L)							
N [a]		254	276	106	111	148	165
Randomization	Mean(SD)	110.04(125.974)	119.75(136.348)	93.89(84.008)	99.56(90.356)	121.61(148.151)	133.34(158.858)
End of treatment	Mean(SD)	130.67(149.765)	122.54(159.380)	125.21(140.838)	124.73(135.721)	134.58(156.199)	121.07(173.880)

Table 63 Glucose regulation laboratory data, change from randomization to end of treatment (Randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 336	PLA+ LI/VAL N = 367	QTP+ LI N = 143	PLA+ LI N = 153	QTP+ VAL N = 193	PLA+ VAL N = 214
Change	Mean(SD)	20.63(143.118)	2.79(166.281)	31.32(103.506)	25.17(134.958)	12.97(165.706)	-12.27(183.247)
	Median	7.00	0.00	20.00	7.00	0.00	-6.00
	Min to Max	-882.00 to 799.00	-895.00 to 1660.00	-243.00 to 611.00	-319.00 to 646.00	-882.00 to 799.00	-895.00 to 1660.00
HOMA-R							
N [a]		259	275	110	113	149	162
Randomization	Mean(SD)	4.16(7.615)	4.35(5.628)	3.38(3.803)	3.39(3.219)	4.73(9.469)	5.02(6.753)
End of treatment	Mean(SD)	4.54(5.683)	4.45(6.374)	4.18(4.221)	4.57(5.703)	4.81(6.558)	4.37(6.820)
Change	Mean(SD)	0.39(6.702)	0.10(6.630)	0.79(3.661)	1.18(5.642)	0.08(8.259)	-0.65(7.160)
	Median	0.22	0.01	0.44	0.22	0.16	-0.14
	Min to Max	-50.60 to 33.46	-29.01 to 62.54	-10.47 to 15.52	-12.27 to 29.09	-50.60 to 33.46	-29.01 to 62.54
QUICKI							
N [a]		259	275	110	113	149	162
Randomization	Mean(SD)	0.3387(0.0431)	0.3342(0.0430)	0.3416(0.0429)	0.3414(0.0426)	0.3366(0.0432)	0.3293(0.0427)
End of treatment	Mean(SD)	0.3316(0.0425)	0.3338(0.0425)	0.3321(0.0433)	0.3335(0.0431)	0.3312(0.0421)	0.3341(0.0423)
Change	Mean(SD)	-.0071(0.0385)	-.0004(0.0394)	-.0095(0.0376)	-.0079(0.0399)	-.0054(0.0392)	0.0048(0.0383)
	Median	-.006	-.001	-.008	-.007	-.005	.0027
	Min to Max	-0.1476 to 0.0959	-0.1279 to 0.1208	-0.1133 to 0.0897	-0.1152 to 0.0889	-0.1476 to 0.0959	-0.1279 to 0.1208

[a] Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HbAlC Hemoglobin Alc.
HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin n(uU/ml) + log10(glucose e(mg/dl))].
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Table corresponds to Table 11.3.8.4- 16.

There were increases in mean glucose and insulin levels for the quetiapine treatment group compared to the placebo group during randomized treatment. Glucose levels increased by a mean of 4.00 mg/dL (median 3.0) in the quetiapine group, compared with a –0.35 mg/dL decrease (median 0.0) in the placebo group. Insulin levels increased by a mean of 20.63 pmol/L (median 7.0)in the quetiapine treatment group, compared with an increase of 2.79 pmol/L (median 0.0) in the placebo group. The glucose and insulin data were highly variable in the treatment groups. There was also an increase in HbA_{1c} (mean 0.17%, median 0.10%) in quetiapine-treated patients compared to placebo-treated patients (mean 0.04%, median 0.00%).

Insulin resistance (HOMA-R) increased in the quetiapine-treated patients (mean 0.39, median 0.22) and remained stable in the placebo-treated patients (mean 0.10, median 0.01). The insulin sensitivity (QUICKI) decreased in the quetiapine group (mean -0.0071, median –0.006) and remained stable in the placebo group (mean 0.0004, median –0.001).

The mean change from baseline in glucose regulation laboratory data for patients with diabetes (defined as having baseline glucose ≥126 mg/dL or HbA1c above ULN or a history of diabetes), patients at risk for diabetes (defined as having a history of gestational diabetes or a BMI of ≥35 or impaired presumably fasting glucose ≥100 to <126 mg/dL), and patients with no known diabetic risk is summarized by treatment group in Table 64, and by mood stabilizer in Table 11.3.8.4- 18.

Table 64 Glucose regulation data, change from randomization, diabetic subgroups, by treatment group (Randomized safety population)

		QTP+LI/VAL N=336				PLA+LI/VAL N=367			
Parameter		**N[a]**	**Mean**	**SD**	**Median**	**N[a]**	**Mean**	**SD**	**Median**
Glucose, fasting (mg/dL)	Diabetic	23	-20.43	34.755	-18.00	33	-5.70	33.416	-6.00
	Diabetic risk	87	3.67	15.537	3.00	88	-4.14	13.122	-3.00
	Non diabetic	200	6.96	15.450	4.00	208	2.11	12.447	2.00
HbA1C (%)	Diabetic	23	-0.14	0.552	-0.10	33	-0.04	0.518	-0.10
	Diabetic risk	86	0.23	0.412	0.15	89	0.05	0.294	0.00
	Non diabetic	198	0.17	0.363	0.10	217	0.05	0.244	0.00
Insulin (pmol/L)	Diabetic	21	-46.57	140.639	-14.00	27	-33.63	81.113	-14.00
	Diabetic risk	69	15.61	196.189	0.00	77	-1.31	129.698	7.00
	Non diabetic	163	29.33	104.159	14.00	172	10.34	188.982	0.00
HOMA-R	Diabetic	21	-6.18	13.166	-1.58	27	-1.57	3.837	-0.61
	Diabetic risk	71	0.23	6.945	0.00	77	-0.23	5.392	0.20
	Non diabetic	167	1.28	4.725	0.47	171	0.52	7.411	0.01
QUICKI	Diabetic	21	0.0134	0.0281	0.0125	27	0.0043	0.0270	0.0073
	Diabetic risk	71	-0.0011	0.0350	-0.0000	77	0.0022	0.0331	-0.0028
	Non diabetic	167	-0.0122	0.0400	-0.0110	171	-0.0023	0.0434	-0.0009

[a] Number of patients with assessment at baseline and at least one after baseline.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
Note: Diabetics defined as having documented fasting glucose >=126 mg/dL or non-documented fasting glucose >=200 mg/dL
at baseline or a history of diabetes, or HbAlc above ULN at baseline,
Diabetic risk defined as having a history of gestational diabetes or a BMI of >= 35
or impaired documented fasting glucose >=100 to <126 mg/dL;
Non-diabetic defined as not meeting criteria for diabetes or diabetic risk.
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Table corresponds to Table 11.3.8.4- 17.

Decreases in glucose regulation data were observed in diabetics during the randomized treatment phase in both treatment groups. Small decreases were also observed in patients at risk for diabetes in the placebo group. Non-diabetic patients remained relatively stable on most glycemic measures during randomized treatment. There was little change in measures of insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) during randomized treatment.

There were relatively few diabetic patients (23 total in the quetiapine group and 33 total in the placebo group), thus comparisons of this subgroup are made with caution. Nonetheless, in diabetic patients glucose values decreased during randomized treatment in both treatment groups: a mean change of –20.43 mg/dL (median –18) in the quetiapine treatment group and –5.70 mg/dL (median –6.00) in the placebo group. $HbA1_C$ (measured in %) in diabetic patients decreased during randomized treatment by a mean change of –0.14 (median -0.10) in the quetiapine treatment group, and by –0.04 (median –0.10) in the placebo group. Insulin values decreased during randomized treatment in diabetic patients in both treatment groups: mean change of –46.57 pmol/L (median -14.00) in the quetiapine treatment group compared to –33.63 pmol/L (median –14.00) in the placebo group. Changes in measures of insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflect the changes described above.

In patients at risk for diabetes there was a small increase in glucose values during randomized treatment in the quetiapine treatment group (mean increase of 3.67 mg/dL, median 3.00) and a small decrease (mean change of –4.14 mg/dL, median –3.00) in the placebo group. $HbA1_C$ (measured in %) in patients at risk for diabetes increased during randomized treatment by a mean change of 0.23 (median 0.15) in the quetiapine treatment group, and by a mean change of 0.05 (median 0.00) in the placebo group. Insulin values increased during randomized treatment in patients at risk for diabetes in the quetiapine treatment group (mean change 15.61 pmol/L; median 0.00), and decreased in the placebo group (mean change of –1.31 pmol/L, median 7.00). The results in insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflects the results above.

There was a small increase in glucose values during randomized treatment in non-diabetic patients in the quetiapine treatment group (mean increase of 6.96 mg/dL, median 4.00) and in the placebo group (mean change of 2.11 mg/dL, median 2.00). $HbA1_C$ (measured in %) in increased during randomized treatment by a mean change of 0.17 (median 0.10) in the quetiapine treatment group, and by a mean change of 0.05 (median 0.00) in the placebo group. Insulin values increased in non-diabetics in the quetiapine treatment group (mean change 29.33 pmol/L; median 14.00) and in the placebo group (mean change of 10.34 pmol/L, median 0.00). The results in insulin resistance (HOMA-R) and insulin sensitivity (QUICKI) reflects these results.

A more detailed examination of the mean change from baseline in glucose regulation laboratory data for patients with diabetes, at risk for diabetes, and patients with no known diabetic risk is summarized by treatment group and mood stabilizer in Table 11.3.8.4- 19, Table 11.3.8.4- 20, and Table 11.3.8.4- 21, respectively. Change from randomization to Week 12, 28, 40, 52, 68, 84 and 104 in glucose regulation laboratory data (observed cases) is shown in Table 11.3.8.4- 22.

TABLE 27 Frequencies of clinically significant values of selected vital signs and weight (number and percentage of patients)

Assessment	SEROQUEL 450 mg (bid) (n = 192)			SEROQUEL 450 mg (tid) (n = 204)			SEROQUEL 50 mg (bid) (n = 196)		
	Number with significant value (%)		Mean % days with significant valuo	Number with significant value (%)		Mean % days with significant value	Number with significant value (%)		Mean %days with significant value
Postural changes in systolic BP	20	(10)	29	18	(9)	28	12	(6)	22
Postural changes in pulse rate	54	(28)	34	71	(35)	34	56	(29)	35
Postural changes in systolic BP and pulse rate	7	(4)	33	2	(1)	14	5	(3)	29
Supine pulse rate	10	(5)	27	16	(8)	21	3	(2)	23
Weight	26	(14)	n/a	27	(13)	n/a	13	(7)	n/a

n/a = not available

Postural changes in blood pressure and/or pulse rate occurred with similar incidence in each of the three treatment groups. Only 2% of all patients met the criteria for combined postural changes in systolic blood pressure and pulse and the incidence of these changes did not appear to be related to the dose of SEROQUEL.

The incidence of postural changes in systolic blood pressure was slightly higher in the two SEROQUEL 450 mg groups than in SEROQUEL 50 mg (bid) group. The mean time of onset was slightly later in the SEROQUEL 450 mg (bid) group (20 days) and in the SEROQUEL 450 mg (tid) group (19 days) compared with the SEROQUEL 50 mg (bid) group (16 days). The percentage of days on which a clinically significant postural change in blood pressure was present was also higher in the SEROQUEL 450 mg groups than in the SEROQUEL 50 mg (bid) group.

The majority of patients who had changes in vital signs that met the pre-defined criteria for clinical significance did not have adverse events (postural hypotension, tachycardia) associated with these alterations (Section 5.3.1).

These results support the conclusion that SEROQUEL is associated with mild or moderate postural changes in systolic blood pressure and supine pulse rate in a minority of patients, which are not generally associated with clinical symptomatology.

The incidence of clinically significant weight gain (an increase of 7% or more from baseline), was approximately 14% in the SEROQUEL 450 mg (bid) group and 13% in the SEROQUEL 450 mg (tid) group, compared with 7% in the SEROQUEL 50 mg (bid) group. These results suggest that SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher incidence of clinically significant weight gain than SEROQUEL 50 mg (bid).

In summary, these results suggest that SEROQUEL was associated with mild or moderate postural changes in blood pressure or pulse which were not generally associated with adverse events. The incidence of these changes was not related to the dose of SEROQUEL and the incidence of combined postural changes in blood pressure and pulse rate was low. SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher

incidence of clinically significant weight gain than SEROQUEL 50 mg (bid). There was little difference between the two SEROQUEL 450 mg groups in the incidence of weight gain.

5.7 Plasma concentrations of ICI 204,636

Summary tables: *plasma levels of ICI 204,636; T20.1 to T20.2*

Individual patients listings: *median trough plasma levels of ICI 204,636; G15*

Plasma samples were to be collected at selected centres for measurement of plasma concentrations of ICI 204,636 (Section 2.8.2). However, only five centres agreed to do this. A total of 17 patients from Centres 002, 045, 046, 050 and 083 had at least one plasma sample collected. (The other patients at these centres did not give consent to the extra blood samples required.) Due to small sample sizes, only descriptive statistics are presented for the median weekly trough plasma concentrations and for the median pre- and post-dose plasma concentrations (Table T20). No assessment of the relationship between plasma concentrations and response to treatment was made due to the extremely small sample sizes.

5.8 Overall evaluation of safety

Approximately half the patients in each of the SEROQUEL 450 mg treatment groups experienced at least one adverse event during the study; the proportion of patients was slightly lower in the SEROQUEL 50 mg (bid) group (44%). The most frequent adverse events in each of the three treatment groups were somnolence and insomnia.

Somnolence occurred with similar incidence in the two SEROQUEL 450 mg groups and with lower incidence in the SEROQUEL 50 mg (bid) group. It was generally mild or moderate in severity, although some patients only in the SEROQUEL 450 mg groups experienced severe somnolence. The onset of somnolence tended to occur on first exposure to treatment or during the dose-titration phase. These results suggest that SEROQUEL 450 mg (bid) and SEROQUEL 450 mg (tid) were associated with a higher incidence and more severe somnolence than SEROQUEL 50 mg (bid). SEROQUEL 450 mg (bid) was not associated with more somnolence than SEROQUEL 450 mg (tid).

Adverse events of dry mouth occurred with higher incidence in the two SEROQUEL 450 mg groups than in the SEROQUEL 50 mg (bid) group, suggesting that the higher dose of SEROQUEL may cause more anticholinergic effects.

Dizziness was reported with similar frequency in the two SEROQUEL 450 mg groups and less frequently in the SEROQUEL 50 mg (bid) group, suggesting it was related to the higher dose of SEROQUEL. Adverse events of postural hypotension occurred with similar incidence in each treatment group. These events tended to occur on first exposure or during the dose-escalation phase. SEROQUEL was also associated with mild or moderate postural changes in blood pressure or pulse in some patients, although these findings were generally not recorded as adverse events.

Symptoms of schizophrenia, such as anxiety, agitation and insomnia were commonly reported as adverse events and in some cases were severe. In the SEROQUEL 50 mg (bid) group, new cases of agitation were reported throughout the study, which may represent lack of efficacy of this dose.

Table 62 Glucose regulation data, change from randomization to end of treatment (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 310	PLA+ LI/VAL N = 313	QTP+ LI N = 131	PLA+ LI N = 134	QTP+ VAL N = 179	PLA+ VAL N = 179
Glucose (mg/dL)							
N [a]		278	282	118	118	160	164
Randomization	Mean(SD)	93.57(18.459)	92.79(21.370)	93.83(19.225)	92.90(15.385)	93.38(17.932)	92.71(24.846)
End of treatment	Mean(SD)	99.68(57.054)	93.08(19.577)	99.82(35.500)	93.52(19.106)	99.57(68.874)	92.76(19.962)
Change	Mean(SD)	6.11(54.526)	0.29(22.597)	5.99(34.190)	0.62(17.385)	6.19(65.721)	0.05(25.752)
	Median	1.00	0.00	3.50	0.00	0.50	1.00
	Min to Max	-84.00 to 776.00	-121.00 to 87.00	-84.00 to 287.00	-52.00 to 75.00	-81.00 to 776.00	-121.00 to 87.00
HbAlC (%)							
N [a]		278	280	121	116	157	164
Randomization	Mean(SD)	5.42(0.672)	5.38(0.659)	5.24(0.509)	5.19(0.482)	5.56(0.747)	5.52(0.733)
End of treatment	Mean(SD)	5.62(0.820)	5.41(0.580)	5.43(0.706)	5.24(0.405)	5.76(0.874)	5.53(0.652)
Change	Mean(SD)	0.20(0.515)	0.03(0.401)	0.19(0.375)	0.04(0.363)	0.20(0.603)	0.01(0.426)
	Median	0.20	0.00	0.20	0.00	0.10	0.00
	Min to Max	-2.60 to 3.20	-2.80 to 2.30	-0.70 to 2.00	-2.10 to 1.40	-2.60 to 3.20	-2.80 to 2.30
Insulin (pmol/L)							
N [a]		248	255	106	103	142	152
Randomization	Mean(SD)	156.16(171.317)	151.77(171.654)	147.68(146.945)	145.73(166.399)	162.49(187.722)	155.87(175.552)
End of treatment	Mean(SD)	188.63(201.983)	171.20(238.199)	187.87(165.924)	163.62(176.921)	189.20(225.754)	176.33(272.456)

Table 62 Glucose regulation data, change from randomization to end of treatment (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP+ LI/VAL N = 310	**PLA+ LI/VAL N = 313**	**QTP+ LI N = 131**	**PLA+ LI N = 134**	**QTP+ VAL N = 179**	**PLA+ VAL N = 179**
Change	Mean(SD)	32.48(181.691)	19.42(256.848)	40.19(192.725)	17.89(204.534)	26.72(173.468)	20.46(287.592)
	Median	7.00	0.00	7.00	0.00	7.00	0.00
	Min to Max	-771.00 to 729.00	-945.00 to 2125.00	-771.00 to 660.00	-945.00 to 1049.00	-569.00 to 729.00	-944.00 to 2125.00
HOMA-R							
N [a]		246	248	105	101	141	147
Randomization	Mean(SD)	5.63(7.504)	5.57(9.124)	5.50(6.963)	5.31(8.026)	5.73(7.906)	5.76(9.830)
End of treatment	Mean(SD)	7.53(11.133)	6.79(12.378)	7.85(12.733)	6.11(8.504)	7.30(9.816)	7.25(14.461)
Change	Mean(SD)	1.91(10.749)	1.21(14.039)	2.35(13.567)	0.80(10.179)	1.57(8.074)	1.49(16.195)
	Median	0.25	0.05	0.51	0.03	0.22	0.09
	Min to Max	-41.47 to 103.32	-85.08 to 86.29	-41.47 to 103.32	-57.69 to 52.79	-30.68 to 33.99	-85.08 to 86.29
QUICKI							
N [a]		246	248	105	101	141	147
Randomization	Mean(SD)	0.3218(0.0403)	0.3251(0.0419)	0.3236(0.0421)	0.3250(0.0408)	0.3204(0.0390)	0.3252(0.0427)
End of treatment	Mean(SD)	0.3147(0.0436)	0.3209(0.0419)	0.3126(0.0443)	0.3204(0.0414)	0.3163(0.0432)	0.3213(0.0424)
Change	Mean(SD)	-0.0071(0.0413)	-0.0042(0.0407)	-0.0111(0.0436)	-0.0046(0.0381)	-0.0042(0.0394)	-0.0039(0.0424)
	Median	-0.0045	-0.0013	-0.0062	-0.0010	-0.0020	-0.0017
	Min to Max	-0.1477 to 0.1206	-0.1582 to 0.1246	-0.1477 to 0.0912	-0.1582 to 0.0724	-0.1421 to 0.1206	-0.1091 to 0.1246

[a] Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HbAlC Hemoglobin Alc.
HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5. QUICKI 1/[log10(insulin n(uU/ml) + log10(glucose e(mg/dl))].
/csre/dev/seroquel/d1447c00127/sp/output/tlf/t1103080416.rtf chem207.sas 10APR2007:14:26 luchen
Table corresponds to Table 11.3.8.4- 16.