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Do Certain Atypical Antipsychotics Increase the Risk of Diabetes? A Critical Review of 17 Pharmacoepidemiologic Studies

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Background. *Some atypical antipsychotics have been linked to hyperglycemia, diabetes mellitus, and diabetic ketoacidosis. We reviewed evidence comparing excess risk and relative risk of type-2 diabetes associated with atypical antipsychotics.*
Methods. *Studies were identified on MEDLINE (January 1966–June 2003) using "antipsychotics and diabetes," "atypical antipsychotics and diabetes," and "schizophrenia and diabetes" as search terms. Studies presented at psychiatric scientific meetings between January 2000–June 2003 were identified via meeting attendance, conference proceedings, and published abstracts. The authors examined all retrospective epidemiologic studies including secondary data analyses addressing relative risk of developing diabetes in patients receiving atypical antipsychotics. Case reports, prospective trials, review articles, and MedWatch data were excluded. Extracted data were reviewed by all investigators according to predetermined criteria related to study design, treatment and comparison groups, definition of outcome measure, inclusion of covariates, and statistical analysis.*
Results. *Four studies meeting criteria for acceptable methods demonstrated that olanzapine, but not risperidone, is associated with a significantly increased risk of new-onset diabetes versus untreated major psychiatric disorder. Studies of relative risk did not demonstrate greater risk of diabetes with risperidone versus conventional antipsychotics. Of nine studies comparing relative risk of diabetes with olanzapine and risperidone, six demonstrated significantly greater risk with olanzapine. Risk was higher in women in two studies. Definitive conclusions could not be reached for clozapine and quetiapine due to limited data.*
Conclusions. *The preponderance of current epidemiologic evidence indicates that olanzapine therapy poses a higher risk of diabetes than untreated major psychiatric illness, and that olanzapine confers greater risk of diabetes than risperidone.*

Keywords Atypical antipsychotics, Diabetes, Epidemiology, Schizophrenia, Relative risk, Critical review

INTRODUCTION

Compared with conventional antipsychotics, the atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are associated with a lower risk of

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movement disorders, and some have superior efficacy for negative symptoms (1), relapse prevention (2), and cognitive deficits (3) of schizophrenia. However, some atypical antipsychotics have been linked to potentially serious metabolic adverse effects, including weight gain, type 2 diabetes mellitus, hyperglycemia, and diabetic ketoacidosis (4–9). Most case reports of diabetes and diabetic ketoacidosis involve clozapine and olanzapine (10–29), whereas a smaller number involve risperidone and quetiapine (17,30–35). To

date, no reports have involved ziprasidone or aripiprazole, but patient exposure to these drugs is limited (36).

Because much of the information concerning the possible link between diabetes and atypical antipsychotics is based on case reports, retrospective chart reviews, a few naturalistic studies, and cross-sectional studies, considerable controversy exists over the precise nature of the risk, as well as whether this risk is a class effect common to all atypical agents. Although some argue that definitive conclusions cannot be drawn in the absence of head-to-head clinical trials, growing evidence from epidemiologic data suggests that treatment with certain atypical antipsychotics can increase the risk of diabetes. Because no large controlled trials are under way, it may be ill advised for physicians to ignore the available evidence when making treatment decisions.

Interpretation of the epidemiologic data, however, has not been clear cut. Reports of relative risk of diabetes between treated and untreated groups and between treatment groups are inconsistent (37–53). To add to the complexity of the issue, factors such as age, ethnicity, sex, weight, antipsychotic dose, and concomitant medications can affect the risk of diabetes and are not controlled for in some studies. This is further complicated by the fact that abnormal glucose regulation and diabetes occur more commonly in patients with schizophrenia or other major psychiatric illnesses than in the general population. (53–55)

Nevertheless, the onus is on clinicians to balance the considerable benefits of atypical antipsychotics against the risks of metabolic disturbances when choosing among antipsychotics (56). To help guide clinical decision making, it is useful to frame the controversy in the form of 3 questions: (1) What is the increased risk of diabetes associated with the use of antipsychotics beyond that posed by the presence of a major psychiatric illness? (2) What is the relative risk of diabetes associated with the use of individual antipsychotic agents with respect to each other? (3) What treatment choices can optimally balance the risks and benefits of a particular antipsychotic drug?

To address these questions, the authors reviewed the literature for epidemiologic studies of the association between diabetes and atypical antipsychotics. The purpose was to examine the data and to venture an objective summary of the preponderance of evidence. Because poor study design or model specification can interfere with drawing substantive conclusions, the authors tried to determine whether seeming contradictions in the findings of various epidemiologic studies arise from true differences in evidence or whether inconclusive or divergent results were reached due to limitations in study design. A framework of rules based on generally accepted epidemiologic methods was created for assessing these studies.

METHODS

Data Sources

Studies were identified by searching MEDLINE from January 1966 through June 2003 using the terms "antipsychotics and diabetes," "atypical antipsychotics and diabetes," and "schizophrenia and diabetes." Additional articles were identified from the reference lists of articles identified during the database search. Because using only published sources of information can bias the results of systematic reviews (57,58), the authors also examined posters and abstracts. Relevant data presented at major U.S. and European annual scientific psychiatry meetings from January 2000 to June 2003 were identified via abstract books, meeting scientific programs, and attendance by the authors and colleagues.

Study Selection Criteria

All systematic retrospective studies assessing risk of diabetes associated with exposure to an atypical antipsychotic with diabetes as an outcome measure were included. Case reports, data from prospective clinical studies, small retrospective chart review studies, and reviews were excluded. Analyses of spontaneous reports such as World Health Organization and MedWatch data were excluded, as these tend to be self-selected reports that may not provide reliable estimates of risk. For purposes of comparability, only studies that expressed risk in terms of hazard ratios, risk ratios, or odds ratios for individual antipsychotic agents were included.

Data Extraction

Data were extracted by one of the authors (KR) and evaluated independently by all authors. Sample, design, and execution of each study were evaluated to assess the merits of the findings. Factors reviewed included selection of treatment and comparison groups, overall study design, definition of outcome measure, selection and inclusion of covariates, and statistical tests used.

The following methodologic issues were considered:

Reference Group

Given the greater risk of type 2 diabetes in patients with schizophrenia or mood disorders compared with the general population (53–55), only data from studies that used populations of untreated patients with major psychiatric illness as a reference group in assessing relative risk were considered in order to avoid confounding. In studies reporting relative risk of diabetes for a specific atypical antipsychotic compared with other antipsychotics, the allowable reference groups were patients receiving therapy with another atypical agent, another conventional agent, or combined groups of all atypical or all conventional antipsychotics.

Longitudinal versus Cross-sectional Study Design

Longitudinal studies allow for estimation of incidence-based rate ratios, which provide a truer approximation of risk than do prevalence rate ratios. Prevalence studies ignore temporality of

association between risk factor and outcome and therefore cannot establish causality; however, they are useful as preliminary measures of risk. Thus both types of studies were included in this review.

Cohort versus Case-control Design

The case-control design identifies cases with the outcome of interest and typically addresses covariates such as age, sex, and other risk factors by matching patients to this group with respect to these factors. This is a sound design for assessing relative risk between 2 risk factors, especially when incidence rates of the outcome are small. The retrospective cohort design identifies patients with the putative risk factor as of an index date and follows them for a fixed time period, permitting calculation of incidence rates, excess risk, and relative risks for multiple risk factors. Both types of studies were included.

Temporal Relationships

Studies that accounted for the temporal association between outcome and purported risk factor, including duration of exposure to antipsychotics and uniformity of observation period across groups, were considered of sounder design than those that did not.

Definition of Outcome Measure

Because use of a diagnosis code to identify cases of diabetes may underestimate numbers of patients with undiagnosed diabetes or those in whom a diagnosis is made but not assigned a formal code, and because prescription claims may underestimate those diagnosed but not receiving or filling prescriptions for antidiabetic medication, use of both sources of information for the incidence of diabetes was considered to be more sensitive than use of either one alone.

Identification of Risk Factors

Numerous factors, including duration of drug exposure, switching between drugs, doses administered, and number of antipsychotics coprescribed, could substantially affect risk of diabetes. Studies that accounted for these factors were considered to be of sounder design.

Selection and Inclusion of Covariates

Studies were reviewed to determine whether they considered potential confounders such as patient age, severity of disease, sex, race, and concomitant medications. In addition, because known diabetogenic drugs, such as adrenergic blockers, thiazide diuretics, corticosteroids, phenytoin, norgestrel-containing oral contraceptives, and valproate, are commonly prescribed in patients with schizophrenia, studies that included this factor in covariate analysis were considered better designed.

RESULTS

Of the more than 350 citations found, 17 epidemiologic studies satisfied criteria for inclusion in our review (Table 1), of which 9 were published in peer-reviewed journals, and 1 in a non-peer-reviewed journal. The remaining 7 were presented as posters at scientific meetings. All were secondary analyses of private insurance, managed care, or governmental claims databases. No naturalistic prospective trials were identified.

All studies examined were based on large claims databases, and many had large numbers of patients exposed to antipsychotics (Tables 2–4). Three studies examined the relative risk of diabetes in patients treated with antipsychotics versus untreated patients (44,48,52), 5 reported data for both relative risk of diabetes between treated and untreated patient groups and relative risk of diabetes between treated patient groups (41–43, 47, 49), and 9 compared relative risk of diabetes only between treated patient groups (37–40, 45, 46, 50, 51, 53).

Three studies (47–49) compared antipsychotic users with a general patient population. Because the increased risk of diabetes inherently conferred by the presence of schizophrenia or mood disorders is a confounder not accounted for in these studies, the relative risk data between treated and untreated groups from these studies were not considered of sufficient quality and were excluded from this analysis. Only the relative risk data between treatment groups from the Buse et al. and Feldman et al. studies were included; the Cavazzoni et al. study is included only for the purpose of discussion of methodology.

Five additional epidemiologic studies did not meet inclusion criteria. One case-control study (59) did not report data for individual atypical antipsychotics, and 4 retrospective studies (17,18,59,60) were based on spontaneous report data.

Relative Risk Compared with Untreated Patients

Five studies (41–44, 52) addressed the risk of new-onset diabetes associated with treatment with atypical antipsychotics by making comparisons between patients treated with atypical antipsychotics and patients with untreated psychiatric illness (Table 2). Four of these 5 (41–44) presented data for both olanzapine and risperidone, and each demonstrated a statistically significant increased risk of diabetes associated with the use of olanzapine and no significant increased risk associated with the use of risperidone. Gianfrancesco et al. (42) and Wang et al. (52) also presented data for clozapine. Gianfrancesco et al. (42) reported a statistically significant increased risk of diabetes associated with the use of clozapine, while Wang et al. (52) reported no increased risk. Only one study presented data for quetiapine (44), reporting no increased risk of diabetes associated with the use of this atypical antipsychotic.

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Table 1 Characteristics of Studies Assessing the Risk of Diabetes Mellitus among Patients Taking Antipsychotics

Study author; industry support	Publication type	Study design	Sample population source	Psychiatric diagnosis (results)	Duration of antipsychotic exposure	Criteria for diabetes	AP switching addressed	Dosage considered	Major covariates addressed
Studies that compared atypical antipsychotic treatment to nontreatment only[a]									
Cavazzoni et al., 2001 Lilly Research Laboratories	scientific meeting poster presentation	cohort	UK General Practice Research (Rx claim) database, Jan 1996 to Dec 1997	various	variable; mean 156 days, all APs combined	dx or Rx	no	no	age, sex, obesity
Wang et al., 2002 None	peer-reviewed journal article	case-control	New Jersey Medicare, Medicaid and pharmaceutical assistance programs, Jan. 1990–June 1995	various	variable	Rx	yes	yes	age, sex, race, comorbid illness, number of medications, healthcare use, corticosteroids, psychiatric dx, other diabetogenic drugs
Gianfrancesco et al., 2003b AstraZeneca Pharmaceuticals, L.P.	peer-reviewed journal article	cohort	2 mixed indemnity and managed care plans, April 1997–Oct. 2000	various; schizophrenia, bipolar and manic, major depressive, other psychosis	mean 9.9 months; 1-month exposure projected for 12 months	Rx	yes, 30-day washout specified	yes	age, sex, observation period length, diagnosis, type of insurance, prior weight gain, psychotropic drugs, APs, β-blocker
Studies that compared atypical antipsychotic treatment to both nontreatment and conventional antipsychotics[b]									
Buse et al., 2003 Eli Lilly and Company	peer-reviewed journal article	cohort	Advance PCS prescription claim database; with, MCOs, Medicaid, Medicare; enrollment Dec. 1998–Feb. 29, 2000	various; unspecified	mean 90 days, atypical AP; 67 days, conventional AP	Rx	no; monotherapy only; switchers excluded	ratios calculated by dosage quartiles	age, sex, amount of antipsychotic
Feldman et al., 2002 Eli Lilly and Company	scientific meeting poster presentation	cohort	Advance PCS Rx claims database, subset of patients age ≥ 60, first AP Rx Dec. 1999–Feb. 2000	any	mean 70.2 days conventional, 90.6 days atypical AP	Rx	yes; switchers excluded	no	age, sex, treatment duration
Gianfrancesco et al., 2002 Janssen Pharmaceutica Products, L.P.	peer-reviewed journal article	cohort	2 mixed indemnity and managed care plans; Jan. 1996–Dec. 1997	any psychosis	mean, 6.8 months; 1-month risk projected for 12 months	dx or Rx	yes, 30-day washout required	yes	age, sex, observation period, diagnosis, insurance, diabetogenic drugs
Gianfrancesco et al., 2003a Janssen Pharmaceutica Inc.	peer-reviewed journal article	cohort	2 mixed indemnity and managed care plans; Jan. 1996–Dec. 1997	mood disorders	mean, 6.5 months; 1-month risk projected for 12 months	dx or Rx	yes, 30-day washout specified	yes	age, sex, observation period, type of mood disorder, type of insurance, psychotropic drugs

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Study	Publication	Design	Database / Setting	Diagnosis	Exposure duration	Case definition			Covariates adjusted for
Koro et al., 2002 Bristol-Myers Squibb (provided database)	peer-reviewed journal article	case control	UK General Practice Research Data-base, June 1987–Sept. 2000	schizophrenia	variable	dx or Rx	yes	no	age, sex, duration of follow-up, index year, diabetogenic drugs
Studies that compared atypical antipsychotic treatment to conventional antipsychotics and to other atypical antipsychotics[b]									
Caro et al., 2002 Janssen Ortho, Inc.	peer-reviewed journal article	cohort	seniors, welfare, uninsured; government claims database, Quebec; Jan. 1997- Dec. 1999	schizophrenia and unspecified	variable; included exposure duration in risk estimation	dx or Rx	no	no	age, sex, concomitant antipsychotics, diagnosis of schizophrenia, treatment duration
Fuller et al., 2003 Janssen Pharmaceutica Products, L.P.	peer-reviewed journal article	cohort	VISN-10 VA database, Jan. 1997–Dec. 2000; males only	Various; psychotic, mood, other disorders	NR; treatment duration included in statistical model	dx or Rx	yes, treatment group as a time-dependent variable	no	age, race, psychiatric dx, concomitant medication, psychiatric dx, substance abuse
Grogg et al., 2003 Janssen Pharmaceutica Products, L.P.	scientific meeting poster presentation	cohort	California Medicaid patients < age 65	various; bipolar and/ or schizophrenia	NR; however, exposure days included in logistic regression	dx and/ or Rx	no	yes	age, race, dosage, sex, hypertension, medical/psychiatric comorbidities, antidepressants mood stabilizers, anxiolytics
Lage et al., 2001 Eli Lilly and Company	scientific meeting poster presentation	cohort	Rx, outpatient, hospitalization claims database; indemnity and PPO	schizophrenia, bipolar disorder, depression, other	NR, not accounted for in regression	dx or Rx	no	no	age, gender, mental health co-morbidities, regional differences
Lambert et al., 2002 Bristol-Myers Squibb; Otsuka America Pharmaceutical, Inc.	scientific meeting poster presentation	Case control	California Medicaid 1997–2000	schizophrenia	≥12 weeks	dx	no	no	race, age, sex, diabetogenic drugs
Lee et al., 2002 Eli Lilly and Company	journal article not peer reviewed	cohort	US MCO: Sept. 1997–Dec. 1999; age < 65 years	schizophrenia, bipolar disorder, depression, other	mean 126.10 days atypical 108.3 days conventional AP; relative risk projected for 1 year of exposure	dx or Rx	no, switchers retained in index group (ITT)	no	age, sex, geographic region, mental health disorder, hypertension, heart disease, duration of AP
L'Italien et al., 2002 Bristol-Myers Squibb	scientific meeting poster presentation	case control	Regenstrief Record System–Indianapolis healthcare provider database	schizophrenia	approximately 2.2 yrs atypical AP, 5.6 yrs conventional	Dx	NR	no	age, sex, comorbidities, healthcare use, benztropine, obesity
Moisan et al., 2001 Janssen-Ortho, Inc.	scientific meeting poster presentation	cohort	seniors, welfare, uninsured; government Rx claims database, Quebec; Jan. 1997–Aug. 2000	unspecified	varied	Rx	yes, data censored upon switch-ing	no	age, sex
Sernyak et al., 2002 none	peer-reviewed journal article	prevalence	VA workload database; Oct, 1998–Sept, 1999	schizophrenia	varied, point prevalence estimate only	dx	no	no	age, sex, race, comorbid psychiatric dx, days psychiatric hospitalization, degree of disability, travel

AP = antipsychotic; Dx = diagnosis; MCO = managed care organization; Rx = prescription; VA = Veterans Administration.
[a]Patients with major psychiatric illness not taking an antipsychotic.
[b]Individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

Table 2 Relative Risk of Diabetes in Patients with Major Psychiatric Illness Associated with Atypical Antipsychotic Treatment Compared with No Antipsychotic Treatment

Study	Untreated patients (n)	Antipsychotic	Treated patients (n)	Odds ratio	95% Confidence interval
Gianfrancesco et al., 2002	1738	Clozapine	39	7.44	1.60–34.75*
		olanzapine	986	3.10	1.62–5.93*
		risperidone	994	0.88	0.37–2.07
Gianfrancesco et al., 2003a	2644	olanzapine	656	4.289	2.102–8.827*
		risperidone	849	1.024	0.351–3.015
Gianfrancesco et al., 2003b	10,296	olanzapine	2703[†]	1.426	1.046–1.955*
		risperidone	2860[†]	0.660	0.311–1.408
		quetiapine	922[†]	0.976	0.422–2.271
Koro et al., 2002	NR	olanzapine	970	5.8[‡]	2.0–16.7*
		risperidone	1683	2.2[‡]	0.9–5.2
Wang et al., 2002	NR	clozapine	NR	0.98	0.74–1.31

NR = not reported.
*Statistically significant at $P < .05$ level.
[†]Reported as treatment episodes only; total treated patients = 6582.
[‡]Derived from case-control data; case-control n's are smaller than cohort n's.

Relative Risk: Atypical Antipsychotics versus Conventional Antipsychotics

Results of the studies assessing relative risk of diabetes associated with atypical antipsychotics compared with conventional antipsychotics varied and depended on whether comparisons were made with conventional antipsychotics as a group or with haloperidol alone (Table 3). Most comparisons did not reach statistical significance. In the study by Buse et al., (47), compared with haloperidol, there was a marginally significant increased risk of diabetes associated with risperidone, a significantly lower relative risk with quetiapine, and no significant difference in relative risk for olanzapine and clozapine. The Feldman et al. (49) study demonstrated significant increased risk of diabetes in older patients treated with risperidone compared with those treated with haloperidol, (OR = 1.295) but no significant difference in relative risk for olanzapine, clozapine, and quetiapine compared with haloperidol. The study also reported no significant difference in relative risk for atypical antipsychotics as a group compared with haloperidol. In contrast, Fuller et al. (40) reported no statistically significant difference in risk between haloperidol and risperidone.

Nine studies (Table 3) compared grouped conventional antipsychotics with risperidone, olanzapine, clozapine, or grouped atypical antipsychotics (39, 41, 42, 45–47, 49–51). Lee et al. (51) and Lage et al. (50) found no significantly greater relative risk of diabetes associated with risperidone or olanzapine or with atypical antipsychotics as a group relative to conventional antipsychotics. L'Italien et al. (46) and Koro et al. (41) found an increased risk of diabetes in patients taking olanzapine compared with patients taking conventional antipsychotics as a group, but no increased risk for patients taking risperidone compared with the same conventional antipsychotic group.

Both Lambert et al. (45) and Sernyak et al. (39) found significantly greater risk for developing diabetes in patients taking olanzapine, clozapine, and quetiapine, but no greater risk for patients taking risperidone, compared with patients on conventional antipsychotics. Sernyak et al. (39) did report significantly greater risk for all atypical antipsychotics as a group. Gianfrancesco et al. (42) separately compared low- and high-potency conventional antipsychotics with risperidone and found a significantly increased risk of diabetes associated with both low- and high-potency conventional antipsychotic use relative to risperidone.

Nine studies assessed the relative risk of diabetes associated with olanzapine compared with that for risperidone (Table 4). Of these, 6 studies (37,38,40,42,43,53) found a significantly increased risk of diabetes associated with olanzapine compared with risperidone, whereas 3 studies (48,51,52) found no statistically significant difference in risk of diabetes associated with olanzapine compared with risperidone.

DISCUSSION

What conclusions may be reasonably drawn from these studies? There appears to be some congruence of results, as well as some unresolved differences among the studies.

Increased Risk Compared with Nontreatment

On the issue of increased risk of diabetes from antipsychotic treatment compared to untreated major psychiatric illness alone, the results appear congruent. Findings from all 4 studies (41–44) where the risk of developing diabetes from treatment with olanzapine and risperidone was compared with nontreatment suggest that treatment of patients with schizophrenia or other

Table 3 Risk of Diabetes Associated with Atypical Antipsychotics and Conventional Antipsychotics

Studies comparing atypical AP to conventional AP

Study	Atypical antipsychotic	n	Conventional antipsychotic	n	Risk ratio: atypical vs conventional AP	95% Confidence interval
Buse et al., 2003	risperidone	20,633	haloperidol	8476	1.23[†]	1.01–1.50*
	olanzapine	13,863	haloperidol	8476	1.09[†]	0.86–1.37
	clozapine	277	haloperidol	8476	1.3[†]	0.60–2.86
	quetiapine	4196	haloperidol	8476	0.67[†]	0.46–0.97*
	any (grouped)	38,969	any (grouped)	8476	0.97[†]	0.84–1.11
Feldman et al., 2002	risperidone	12,244	haloperidol	6481	1.295	1.05–1.60[‡]
	olanzapine	117	haloperidol	6481	1.403	0.57–3.47
	clozapine	5382	haloperidol	6481	1.172	0.92–1.50
	quetiapine	1664	haloperidol	6481	0.732	0.49–1.10
	any (grouped)	19,407	any (grouped)	11,546	1.071	0.92–1.25
Koro et al., 2002	risperidone	970	any (grouped)	18,443	1.6[a]	0.7–3.8
	olanzapine	1638	any (grouped)	18,443	4.2	1.5–12.2*
Lage et al., 2001	risperidone	1598	any (grouped)	3208	1.453	0.972–2.173
	olanzapine	1530	any (grouped)	3208	1.136	0.727–1.775
	any (grouped)	3,232	any (grouped)	3208	1.228	0.869–1.736
Lee et al., 2002	risperidone	750	any (grouped)	981	1.074	0.612–1.885
	olanzapine	513	any (grouped)	981	0.864	0.431–1.732
	any (grouped)	1334	any (grouped)	981	1.010	0.612–1.668
L'Italien et al., 2002	risperidone	150	any (grouped)	482	2.22[a]	0.5–10.6
	olanzapine	112	any (grouped)	482	3.92	1.0–15.6
Lambert et al., 2002	risperidone	2483	any (grouped)	NR	1.06[a]	0.94–1.19
	clozapine	861	any (grouped)	NR	1.35	1.14–1.60*
	olanzapine	3177	any (grouped)	NR	1.30	1.16–1.44*
	quetiapine	348	any (grouped)	NR	1.22	0.95–1.58
Sernyak et al., 2002[b]	risperidone	9903	any (grouped)	15,984	1.05	0.98–1.12
	clozapine	1207	any (grouped)	15,984	1.25	1.07–1.46*
	olanzapine	10,970	any (grouped)	15,984	1.11	1.04–1.18*
	quetiapine	955	any (grouped)	15,984	1.31	1.11–1.55*
	any (grouped)	22,648[c]	any (grouped)	15,984	1.09	1.03–1.15*

Studies comparing conventional AP to atypical AP

Study	Conventional antipsychotic	n	Atypical antipsychotic	n	Risk ratio: conventional vs atypical AP	95% Confidence interval
Gianfrancesco et al., 2002	low potency	307	risperidone	994	3.93	NR; P < .05*
	high potency	915	risperidone	994	2.42	NR; NS
Fuller et al., 2003	fluphenazine	428[d]	risperidone	2493[d]	1.11[†]	0.68–1.79
	haloperidol	1790[†]	risperidone	2493[†]	0.89[†]	0.67–1.17

AP = antipsychotic; NR = not reported; NS = not significant.

*Statistically significant at P < .05 level.

[†]Reported as hazard ratio; all others reported as odds ratio or unspecified (risk ratio).

[‡]Significant at P < .05 level for all patients and for subgroup of patients aged ≥ 75; not significant for subgroup aged 60–74.

[a]Derived from case-control data; case-control n's are smaller than cohort n's.

[b]Prevalence study; patients with preexisting diabetes not excluded.

[c]Some patients received prescriptions for more than one atypical antipsychotic.

[d]The total number of patients who received the drug during the study, either at the index date or subsequently.

major psychiatric illness with olanzapine significantly increases the risk of diabetes mellitus compared with untreated patients with these disorders. Results are consistent with the conclusion that treating a patient with olanzapine increases the risk of developing diabetes approximately 40% to 500% over and above the already elevated risk associated with the disease itself. These studies also demonstrated that there is no consistently significant difference in risk of diabetes associated with risperidone compared with nontreatment.

Confounders and covariates including age, sex, diagnosis, exposure to at least some other diabetogenic drugs, and switching between antipsychotics were consistently controlled for in all 4 studies. The demonstration in the Gianfrancesco et al. and studies (42,43) that risk was dose-dependent and exposure-dependent adds further weight to the findings. It must be noted that different patient populations by diagnosis (mood disorders, mixed psychiatric diagnoses) or different sampling intervals were extracted from the same database in the 3 Gianfrancesco

Table 4 Risk of Diabetes Associated with Olanzapine Compared with Risperidone

Study	Olanzapine (n)	Risperidone (n)	Risk ratio	95% Confidence interval
Caro et al., 2002 (all patients)	17,142	12,259	RR = 1.20	1.00–1.43
Females only			RR = 1.30	1.05–1.65*
Gianfrancesco et al., 2002	986	994	OR = 3.53	NR; P < .05*
Gianfrancesco et al., 2003a	656	849	OR = 4.189	NR; P = .0296*
Grogg et al., 2003[a]	8550	7895	OR = 1.30	1.05–1.62*
Moisan et al., 2000	12,945	15,197	IRR = 1.209	1.001–1.460
Fuller et al., 2000	3056[b]	2493[b]	RR = 1.37	1.06–1.76*
Buse et al., 2003	13,863	20,633	HR = 0.90	0.76–1.07
Lage et al., 2001	1530	1598	OR = 0.752	0.471–1.201
Lee et al., 2002	513	750	OR = 0.786	0.384–1.610

HR = hazard ratio; IRR = incidence rate ratio; RR = relative risk; OR = odds ratio; NR = not reported.
*Statistically significant at P < .05 level.
[a]This study also reported no statistically significant difference in risk between quetiapine (n = 1578) and risperidone (OR = 0.72; 95% CI = 0.46–1.12).
[b]The total number of patients who received the drug during the study, either at the index date or subsequently.

studies (42–44) with consistent results, which supports the conclusion that the results reached are valid, but may limit generalizability. Results of the Gianfrancesco studies are supported by the similar results of the UK-based study by Koro et al. (41). Although the number of diabetes cases in the Koro et al. study is small, the case-control design, 6:1 matching of controls to cases, and rigorous accounting for covariates in the regression model strengthens the study. In contrast, the Cavazzoni et al. (48) study of the same database, which reported greater risk of diabetes for all antipsychotic users, risperidone, and thioridazine, used a cohort design, and the risk data cannot be meaningfully interpreted due to use of a general population rather than untreated psychiatric patients as a reference group. This study was further limited by extremely small and unbalanced cell sizes, unequal exposure periods, and inadequate control of covariates, such as switching from conventional antipsychotics.

Findings regarding risk associated with clozapine are inconclusive, in large part due to limitations of the studies involving this drug. The number of clozapine users in the Gianfrancesco et al. (42) study was small, and Wang et al. (52) matched each case of diabetes to less than one control, a serious limitation in a case-control study. Although there are many case reports in the literature of diabetes and diabetic ketoacidosis in patients taking clozapine, such reports may have been influenced by observer bias and by the increased frequency of screening required for patients taking clozapine because of its association with blood dyscrasias. Only one study (44) examined quetiapine use in relation to untreated psychiatric illness and found no increased risk of diabetes.

Relative Risk

Four studies compared grouped atypical antipsychotics with conventional antipsychotics. Three (49–51) of the 4 studies did not demonstrate a significantly greater risk of diabetes for atypical antipsychotics as a group compared with conventional antipsychotics. The only study that did demonstrate a significantly greater risk for atypical antipsychotics as a group was the prevalence study by Sernyak et al. (39). The results suggest that while some atypical antipsychotics may have a lower risk than conventional antipsychotics, others have a higher risk, and grouping them together tends to bias analysis toward the null.

Some lines of evidence appear to converge across the studies. For instance, comparisons with conventional antipsychotics as a group consistently indicated that risperidone did not pose a greater relative risk of diabetes (Table 3). There also appeared to be no greater risk for risperidone compared with haloperidol (40) or grouped high-potency conventional antipsychotics (42) in 2 of 4 studies that made these comparisons. The two (47,49) that reported a greater relative risk for risperidone compared with haloperidol studied low doses of antipsychotics, but dosage was not accounted for in the hazards models, making interpretation difficult. In the Buse et al. (47) study, the finding of greater risk was marginally significant (Table 3). In the Feldman et al. (49) study, the finding appeared to be largely driven by a subset of patients older than age 75, and no comorbidities or concomitant medications were examined in this susceptible population.

Comparisons of olanzapine with conventional antipsychotics yielded varying results. The most rigorously designed study that makes this comparison is that by Koro et al. (41), which concluded that there is a significantly higher risk of diabetes with olanzapine; however, this study had few cases of diabetes. Three studies (39,45,46) concluded that there was a small but significantly increased risk compared with conventional antipsychotics. However, the Sernyak et al. (39) study was a prevalence study that did not account for pre-existing diabetes or temporality issues, thus precluding any inference of causality. The case-control study by Lambert (45) had a larger number of diabetics and controlled for covariates such as known diabetogenic agents and ethnicity. Both Buse et al. (47) and Feldman

et al. (49) concluded that there was no differential risk for olanzapine at low dosage levels versus haloperidol. These data appear internally consistent, as they were based on slightly different populations as defined by age extracted from the same claims database. In addition, the studies by Lage et al. (50) and Lee et al. (51) found no added risk with either olanzapine or risperidone compared to grouped conventional antipsychotics.

In order to understand these contradictory findings with respect to olanzapine, it is useful to examine the direct comparison between risperidone and olanzapine, as well as the differences in design among the contradictory studies. Six of the 9 studies that compared relative risk of diabetes for olanzapine versus risperidone demonstrated that treatment with olanzapine conferred a greater risk than risperidone (Table 4). Although 3 of the 9 studies did not demonstrate a statistically significant difference in risk between the 2 drugs, differences in methods may account for these disparate results. Among the studies that demonstrated a significant difference in relative risk for olanzapine and risperidone, the 3 studies by Gianfrancesco (42–44), Fuller et al. (40) and to a lesser extent the Grogg et al. (53) study accounted for most identifiable covariates in their model, including dose, duration of exposure, and switching between antipsychotics (Table 1). Two of the studies by Gianfrancesco (42–44) used an exponential extrapolation of risk for 1 month of exposure to 12 months, which, although a standard method in logistic regression (61), may imprecisely estimate the magnitude of risk if the risk of developing diabetes is not cumulative over time. However, similar results of smaller magnitude were also found by Grogg et al. (53) and Fuller et al. (40). The congruence of the all-patient, adjusted results of the Caro et al. (38) and Moisan et al. (37) studies of a Canadian population involving relatively long periods of exposure (approximately 1 year) and observation (2 and 4 years, respectively) lend weight to the strength of these findings.

In contrast, the studies by Buse et al. (47), Lee et al. (51), and Lage et al. (50) found no difference in risk of diabetes between risperidone and olanzapine. All 3 failed to control for concomitant use of other drugs, including known diabetogenic agents, whereas 5 of the 6 studies that demonstrated differential risk controlled for some or many of these agents. The studies by Lee et al. (51) and Lage et al. (50) did, however, control for comorbid conditions, such as heart disease and hypertension, which may be a proxy for known diabetogenic drugs used for these conditions. This was not done in the studies by Gianfrancesco et al. (42–44).

Additional methodologic differences in these studies are related to duration of antipsychotic exposure. Duration of exposure to antipsychotics was 3 to 4 months in the Buse et al. (47) and Lee et al. (51) studies and not accounted for in the Lage et al. (50) study, whereas exposure times in the majority of studies that demonstrated differential risk for olanzapine and risperidone were approximately 6 to 12 months or longer (37,42,43,46). A short exposure time may fail to detect cases of diabetes that manifest with increasing duration of exposure, including diabetes secondary to progressive weight gain, the liability for which is greater for olanzapine than for other atypical antipsychotics (8).

Considerations related to patient age, antipsychotic dosage, and switching between antipsychotics might have obscured differences in relative risk. Although Lage et al. (50) found increasing age to be a significant predictor of diabetes, both Lee et al. (51) and Lage et al. (50) restricted their analysis to patients younger than age 65. In addition, the Buse et al. (47) study (as well as the Caro et al. (38) study that demonstrated differential relative risk) converted age into a categorical variable that consigned all persons over age 65 into one category. Treating age as a continuous variable, as in the 3 Gianfrancesco et al. (42–44) studies, using finer categories, or case-control matching (as in the Koro (41) study) are better methods for accounting for age in a regression analysis. This may be particularly important when there are significant differences in age in the 2 groups compared, as in the Buse et al. (47) study, in which the risperidone group had a disproportionately greater proportion of older patients.

Four of the studies reporting a higher risk for olanzapine (40,42,43,53) used various methods to account for switching between antipsychotics, whereas none of the studies finding no elevated risk for olanzapine did so, an important distinction in a population in which switching between antipsychotics is common. Use of an intent-to-treat analysis, as in the Lee et al. (51) study, may confound the results towards the null, and excluding all patients who switch between antipsychotics, as in the Buse et al. (47) and Feldman et al. (49) studies, may create an artificial sample of patients, making it difficult to generalize results to a wider population.

Lastly, in all 3 studies that demonstrated no difference in relative risk of olanzapine and risperidone, the mean dosages of antipsychotics were low (47,49), or unknown (51), and dosage was not accounted for in the statistical models, whereas the Gianfrancesco et al. (42,43) and Grogg et al. (53) studies that demonstrated differential risk accounted for dosage in their models and found it to be a significant predictor of risk. In contrast, Buse et al. (47) found that in the general population all dose quartiles of antipsychotics including olanzapine were associated with an increased risk, but this was only in the unadjusted comparison with the general population, which makes interpretation difficult.

In the study by Caro et al. (38), the difference in relative risk between olanzapine and risperidone was marginally significant for the overall population, but significant for women alone. Greater excess risk in women than men was also demonstrated in the Koro et al. study (41) for which sex was examined as a covariate, and has been reported in the literature (32); women are also known to be at greater risk of diabetes than men in the general population (54,62). However, the greater risk for olanzapine than risperidone in the Fuller et al. (40) study, which included only male patients, suggests that this difference in relative risk is not confined to women alone.

The two studies (39,45) of relative risk associated with clozapine with respect to grouped conventional antipsychotics

suggested that clozapine has a greater relative risk of diabetes compared with grouped conventional antipsychotics. However, one of these studies (39) was a prevalence study. The only study that compared clozapine with haloperidol (49) did not demonstrate a significant difference; this was a low-dose study in the elderly. Two studies of quetiapine (47,49) appeared congruent, reporting a lower or no increased relative risk compared with haloperidol; while both used lower doses, the examination of dose quartiles in Buse et al. (47) adds greater consistency to the results. In addition, the well-designed case-control study by Lambert et al. (45) reported that compared with conventional antipsychotics as a group, quetiapine did not appear to pose a greater risk. However the number of patients on quetiapine in all these studies was small compared to the numbers examined for olanzapine and risperidone. Further studies may be necessary to clarify the risk of diabetes associated with clozapine and quetiapine.

Conclusions that can be reached from these studies are limited by the general lack of information regarding race and weight gain and inconsistent handling of covariates, including age, antipsychotic dosage, concomitant medications, and comorbid illnesses. Further, most of these studies were based on North American populations, in which incidence of diabetes is relatively high; risks may not be generalizable to other populations (63). In addition, the proportions of patients with specific psychiatric diagnoses varied between studies with mixed-diagnosis populations, and some studies considered only patients with schizophrenia or with mood disorders.

When the relative strength of existing data is considered, it appears that treatment with risperidone does not pose a risk of development of new-onset diabetes greater than that associated with untreated major psychiatric illness or treatment with conventional antipsychotics. The preponderance of evidence also suggests that treatment with olanzapine is associated with a higher risk of developing diabetes than untreated major psychiatric illness. Whether clozapine is associated with a greater risk of diabetes than untreated major psychiatric disorder is unclear, although findings suggest it may be associated with a greater relative risk than conventional antipsychotics. Data regarding risk of diabetes associated with quetiapine are based on small numbers of patients. Finally, the preponderance of data on the relative risk of diabetes associated with olanzapine compared with risperidone suggests that olanzapine is associated with greater risk than risperidone, although the magnitude of this risk varies greatly from study to study. Comparative clinical studies are needed to clarify these results.

Clinical Significance

Psychotic and major mood disorders, in particular schizophrenia and bipolar disorder, generally require lifelong treatment (64,65). Given the onset of these illnesses in early adulthood in most patients, treatment can extend over many years. Antipsychotic-related adverse events may further add to the lifelong burden of illness and decreased quality of life associated with a major psychiatric disorder. The link between risk of diabetes and some atypical antipsychotics suggests that micro- and macrovascular complications of diabetes may further contribute to the morbidity and mortality associated with psychosis (55,66,67) or mood disorders (68–70). The risks and benefits of long-term antipsychotic treatment must therefore be weighed for each individual when prescribing antipsychotics and in choosing among individual antipsychotic agents.

In light of the epidemiologic evidence of differential risk associated with individual antipsychotics, one of the factors clinicians should consider when choosing among individual agents is the presence or absence of specific factors that place the patient at risk for diabetes. Many patients with schizophrenia or bipolar disorder have several risk factors for diabetes, including obesity, sedentary lifestyle, smoking, dyslipidemia, hyperglycemia, and poor diet (54,71). Clinicians must exercise particular caution when choosing antipsychotics associated with diabetes for Hispanic, Asian, Native-American, or African-American patients and those with a family history of diabetes.

In patients already stabilized on an antipsychotic with high excess and relative risk of diabetes, studies suggest that switching from one atypical antipsychotic to another is safe and does not result in deterioration of psychotic symptoms (72,73) Because clozapine is often given when other atypical antipsychotics fail, the risk-benefit ratio associated with clozapine may differ from that of olanzapine.

In the absence of general guidelines for monitoring of metabolic adverse events in patients taking antipsychotics, many experts recommend monitoring weight, body mass index, fasting blood glucose, serum insulin, hemoglobin A1C, and lipid levels annually. In the opinion of the authors, patients with additional risk factors, particularly those taking olanzapine and possibly clozapine, should be monitored quarterly. Elevated fasting blood glucose or serum insulin should warrant discontinuation of the current antipsychotic and consideration of a switch to another antipsychotic with a lower risk for inducing diabetes; antipsychotic-related glucose and lipid abnormalities improve or are reversed in 50% to 60% of patients when therapy is switched to another agent (17,18). Ongoing prospective long-term trials may further clarify the risk of diabetes associated with individual atypical antipsychotics, including the newer agents ziprasidone and aripiprazole, for which published data are currently limited. As more data become available, clinicians may be better able to tailor the choice of antipsychotic to prevent this potentially serious adverse effect.

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