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The Influence of Study Design on the Results of Pharmacoepidemiologic Studies of Diabetes Risk With Antipsychotic Therapy

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Background. *Retrospective large patient database studies have reported conflicting findings regarding diabetes risks associated with antipsychotics. This study compared two study designs to assess antipsychotic-related diabetes risk.*
Methods. *Claims data were analyzed for over 60,000 patients with psychosis, both treated and untreated with antipsychotics, between January 1999 and April 2002. Diabetes odds ratios for patients treated with antipsychotics versus untreated patients were estimated. All patients and patients stratified by low, medium, and high antipsychotic dose were analyzed. Logistic regression controlled for age, sex, type of psychosis, length of observation/treatment, preexisting excess weight, and use of other drugs.*
Results. *Under a less rigorous study design, diabetes risk was statistically significant with all antipsychotics versus no treatment. Under a more rigorous design, relative odds for quetiapine and risperidone declined and became statistically nonsignificant, whereas those for olanzapine and conventional antipsychotics increased and remained significant. By dose, only quetiapine showed a lack of statistical significance at all dose levels.*
Conclusions. *In database studies estimated risks of antipsychotic-related diabetes are affected by study design. With a more rigorous design, the risk associated with quetiapine and risperidone was not significantly different from that in untreated patients. These findings may explain inconsistent findings in pharmacoepidemiologic database studies.*

Keywords Antipsychotic agents, Database study, Diabetes mellitus, Dose, Pharmacoeconomics, Study design

INTRODUCTION

A growing number of studies and case reports suggest that some antipsychotic medications may be associated with a higher risk of diabetes mellitus than others (1–22). Retrospective database studies based on claims or other patient records (10–22) offer the advantage of larger numbers but have had more varied results, which may be attributed to differences in study design. For example, some studies have been less precise in associating time of diabetes onset with time of antipsychotic treatment (10,11,13,18), whereas others have identified antipsychotic treatment episodes or used other methods to better associate diabetes onset with time of antipsychotic treatment. (14–17,19,20). Because of real-world practices of switching antipsychotics and prolonged periods of nonantipsychotic use (possibly confounded by use of other psychotropic drugs), less time-sensitive methods have a greater likelihood of spurious associations.

Other aspects of study design, including decisions to screen or not to screen patients for preexisting diabetes, to use more or

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less definite indicators of diabetes, and to restrict or not restrict comparisons to antipsychotic monotherapy, can also influence findings of diabetes risk. Screening for preexisting diabetes is particularly important if antipsychotics are subject to selection bias. Patients with preexisting diabetes may be more likely to be initiated on or switched to antipsychotics that are perceived by the practitioner to be safer. The presence of prescription claims for oral hypoglycemics or insulin is a definite indicator of diabetes, whereas medical claims showing diabetes *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes may include relatively minor glucose elevations and patients who tested negative for diabetes. False-positive reporting on medical records and claims has been documented (23–25). Lastly, where different antipsychotics are used concurrently, association of diabetes with both compounds is unavoidable and may result in an overstatement of diabetes risk for the safer product.

The objective of this study was to compare two methodologies (one more rigorous, the other less rigorous) for assessing the association of atypical and conventional antipsychotics with diabetes mellitus to demonstrate why retrospective studies reported in the literature have presented conflicting findings.

METHODS

Study Design

This was a retrospective study that used claims data from the PharMetrics patient-centric database, which at the time represented 40 US commercial health plans covering 33 million lives. The study covered the period from January 1999 through April 2002, though earlier data were used for patient history. Patients with schizophrenia, bipolar disorder, or major depression (identified using *ICD-9-CM* codes reported on medical claims) who were treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics (15 in total, dominated by haloperidol, perphenazine, thioridazine, and thiothixine) or who received no treatment (control group) were assessed for the presence of diabetes.

Diabetes risk was determined using one of two study designs (Table 1). Diabetes mellitus was identified using either medical claims or prescription claims, depending on study design. Both type 1 and 2 diabetes were included to account for inaccurate reporting. In examining the database, it was found that diabetes type was not specified or that both type 1 and type 2 were reported in a substantial percentage of patients.

Periods of continuous antipsychotic use were identified using treatment episodes. An antipsychotic treatment episode was measured from the fill date of the first prescription to the end-of-treatment date, which was determined by adding the number of days supplied by the last prescription to its fill date, or was equal to a patient's disenrollment date or the end date of the data if either of these occurred first. The beginning of a treatment episode for a given antipsychotic required that the first prescription for that antipsychotic not be preceded by an earlier prescription for that same antipsychotic by less than 120 days. Prescriptions separated by 90 days or less were judged to be part of the same treatment episode. The majority of prescriptions were for 30-day supplies. To ensure patient compliance and minimal exposure to an antipsychotic, only those patients who had at least two consecutive prescriptions for an antipsychotic were included in the study. Diabetes risk was assessed using these treatment episodes. This method ensured a more accurate association of diabetes onset or exacerbation with the time of specific antipsychotic use.

The control population consisted of patients with schizophrenia, bipolar disorder, or major depression who were not treated with antipsychotics over the period encompassed by the data. To avoid confounding the presence or absence of treatment with the duration of observation, observation periods for controls were made to vary in length, similar to antipsychotic treatment episodes. Because diabetes may be associated with schizophrenia, bipolar disorder, and major depression independently of antipsychotic use (26–32), an untreated population with these diagnoses is more suitable than the general population for measuring the incremental diabetogenic effects of antipsychotics.

Statistical Analysis

Logistic regression was used to estimate diabetes risk associated with specific antipsychotics. The effect of each antipsychotic on diabetes risk was related to the number of months

Table 1 Alternative Study Designs

Less rigorous design	Patients not screened for preexisting diabetes	Diabetes identified with medical or prescription claims*	Combined use of different antipsychotics allowed
More rigorous design	Patients screened for preexisting diabetes at 8 mo before observation/treatment†	Diabetes identified with prescription claims only*	Antipsychotic monotherapy required

*Both for prescreening and to identify emergent cases or exacerbations.
†Patients with preexisting diabetes (as identified with claims) or with insufficient data to make this determination were excluded.

that an individual was treated with that antipsychotic. A zero value for all of the antipsychotics specified in the models indicated a control patient. For each antipsychotic, the estimated odds ratio (OR) measured the proportion by which one month of treatment with that antipsychotic increased the risk of diabetes relative to an untreated patient. For longer periods of treatment, the estimated OR was raised to a power equivalent to the desired number of months, which is standard procedure for continuous variables in logistic regression (33). This form of logistic regression was used in our earlier studies (14,16,17). Other claims-based studies have also used logistic regression to estimate differences in diabetes risk among antipsychotics (11,18,21).

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: 1) men or 2) women; and 3) children (<18 years) or 4) adults. Low, medium, and high dose corresponded to the bottom, middle, and top third of the daily dose range for each patient subgroup within each antipsychotic category. Because conventional antipsychotics were grouped into 1 category and because of combined use of antipsychotics, dose was measured in risperidone-equivalent milligrams (14,16,17). Diabetes frequencies and logistically estimated ORs were generated for treated and untreated patients at all dose levels combined and for low, medium, and high doses separately.

Logistic regression adjusted for the following: length of time (months) that each patient was observed or treated with an antipsychotic; patient age and gender; patient use of other drugs with potential diabetogenic effects including valproate sodium, lithium, thiazide diuretics, beta-blockers, protease inhibitors, and SSRIs (34–38); a diagnosis of schizophrenia, bipolar disorder, or major depression whereas each may induce diabetes independent of antipsychotic use (26–32); pre-existing excess weight problem as reflected in medical or prescription claims; substance abuse or dependence as reflected in medical claims; switch from another antipsychotic within 90 days prior to start of index antipsychotic; and type of insurance coverage which may affect access to care and diagnosis of diabetes.

RESULTS

Sample and Patient Characteristics

A total of 37,250 treatment episodes with risperidone, olanzapine, quetiapine, or conventional antipsychotics were analyzed. About 10% of patients had more than one treatment episode, with the exact percentage dependent on study design. The issue of interdependence of sampling units was addressed in an earlier study and found to have minimal effect on results and to be counterbalanced by other considerations (14). The control group consisted of 33, 263 patients with psychosis who were not treated with antipsychotics over the period encompassed by the data. Number of observations equaled number of patients for the control group. The most common diagnoses for patients treated and untreated with antipsychotics were major depression (46% and 56%, respectively) and bipolar disorder (34% and 39%). The number of patients with schizophrenia was relatively small in both groups [20% (treated) and 4% (untreated)].

Characteristics of the study population are shown in Table 2. These characteristics correspond to the control variables specified in the logistic regression models. Patients treated with conventional antipsychotics were considerably older than those treated with the atypicals, particularly risperidone. The ages of untreated patients fell in between. There were more women than men among both treated and untreated patients. The risperidone- and olanzapine-treated groups had relatively more men in comparison to the other groups. The mean duration of treatment/observation periods was longest for controls and shortest for the olanzapine-treated group; median durations were similar among the study groups. Among treated patients, antipsychotic daily dose, measured in risperidone-equivalent milligrams, averaged highest for conventional antipsychotics. Patients treated with conventional antipsychotics also had the highest proportion of schizophrenia diagnoses.

Other psychotropic medications and medications with suspected diabetogenic effects were generally used more by treated than by control patients (Table 2). Selective serotonin reuptake inhibitors (SSRIs) were the most widely used of these drugs, followed by lithium and beta-blockers. Risperidone-treated patients had the highest use of SSRIs, whereas conventionally treated patients had the highest use of beta-blockers and diuretics, consistent with their older age. Substance abuse/dependence was slightly higher among olanzapine-treated patients, followed by the quetiapine group. Quetiapine-treated patients had the highest proportion with prior excess weight problems, followed by those treated with conventionals, whereas untreated patients had the smallest proportion. Patients treated with conventional antipsychotics had the smallest proportion on antipsychotic monotherapy, followed by patients treated with quetiapine. Quetiapine also had the highest proportion of patients who were switched from another antipsychotic. The mix of insurance coverage did not differ greatly between groups, with health maintenance organizations (HMOs) generally predominating.

Comparisons of Diabetes Frequencies

Diabetes frequencies of patients treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics were compared with each other and with controls using both the less

Table 2 Profile of Study Population

	Without Antipsychotic Treatment	Risperidone	Olanzapine	Quetiapine	Conventionals
Maximum N	33,263	12,409	12,572	6476	5793
Age					
Mean (SD)	35.7 (14)	33.1 (17.2)	36.1 (15)	34.7 (14.6)	41 (13.7)
Median	37.0	35.0	38.0	37.0	42.0
Sex (%)					
Women	65.9	57.1	56.5	67.4	64.8
Men	34.1	42.9	43.5	32.6	35.2
Diagnosis (%)					
Schizophrenia	4.2	16.3	18.7	14.9	33.0
Bipolar and manic disorder	39.5	33.2	38.2	36.0	27.4
Major depression	56.3	50.5	43.1	49.1	39.6
Observation period/antipsychotic treatment duration (mo)					
Mean (SD)	10.7 (7.3)	7.7 (6.4)	7.4 (6.3)	7.5 (6.2)	8.1 (6.9)
Median	5.0	5.5	5.2	5.5	5.7
Antipsychotic dose (risperidone-equivalent mg)					
Mean (SD)	NA	2.7 (4.2)	3 (3.8)	2.8 (3.2)	3.8 (7.1)
Median	NA	2.0	2.4	2.1	2.6
Use of other antipsychotic drugs and drugs with suspected diabetes risk					
Valproate sodium (%)	0.29	0.64	0.83	0.57	0.87
Lithium (%)	10.4	13.5	15.2	15.1	15.6
SSRIs (%)	32.8	40.1	36.8	35.2	32.3
Beta-blockers (%)	6.1	7.5	8.3	9.6	11.6
Thiazide diuretics (%)	2.1	2.8	2.9	3.1	4.1
Protease inhibitors (%)	0.09	0.08	0.15	0.05	0.29
Mean (SD) US dollars of above drugs per patient per mo	23.8 (48.4)	42.2 (92.6)	40.1 (152.2)	41.2 (112.9)	37.4 (75.9)
Substance abuse/dependence (%)	3.5	5.0	6.1	5.4	4.9
Prior excess weight problem (%)	1.9	2.6	2.4	3.5	3.0
Antipsychotic monotherapy (%)	NA	80.4	78.3	73.4	66.3
Switch from other antipsychotic (%)	NA	17.4	20.6	35.3	26.6
Type of insurance coverage (%)					
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	13.0	13.3	14.8	12.5
Indemnity	5.1	4.0	4.4	5.4	5.4
Other	4.9	9.9	10.1	7.1	10.1

HMO = health maintenance organization; NA = not applicable; SD = standard deviation; SSRIs = selective serotonin reuptake inhibitors.

rigorous and more rigorous study designs (Table 3). Frequencies were adjusted for differences among the patient groups in duration of observation or treatment and were stratified by antipsychotic dose. Under both the less rigorous and more rigorous study designs, diabetes relative frequencies were lower for untreated controls in comparison to all of the treated categories. Among treated patients, conventionals had the highest relative frequency under the less rigorous study design, whereas risperidone had the lowest. Under the more rigorous study design, differences in diabetes relative frequencies became more pronounced among the treated groups, with quetiapine having the lowest followed closely by risperidone. Relative frequencies for olanzapine and conventionals were much higher and exceeded those of controls by considerable margins. A tendency for diabetes frequencies to increase with dose level was seen among all three of the atypical antipsychotics. The absence of this relationship for conventional antipsychotics, particularly under the more rigorous study design, 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 patients with psychosis untreated with antipsychotics are reported in Table 4. These were estimated irrespective of dosage level and separately for patients grouped into low-, medium-, and high-dose cohorts. Ratios under the less rigorous and more rigorous study designs were estimated with logistic regression and are adjusted for patient differences. Under the less rigorous study design, ORs 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. Odds of

Table 3 Diabetes Frequencies by Antipsychotic Dose, Adjusted for Observation/Treatment Duration

	Weaker Study Design[a]		Stronger Study Design[b]	
Group	N	% Diabetic	N	% Diabetic
Without antipsychotic treatment	33,263	5.56	28,044	0.98
Risperidone				
All dose levels	12,409	8.91	7633	1.33
Low dose	4444	7.44	3117	1.17
Medium dose	4397	7.85	2914	1.16
High dose	3568	10.47	1602	2.09
Olanzapine				
All dose levels	12,572	9.43	7631	2.67
Low dose	3464	8.15	2452	1.78
Medium dose	4678	8.77	3095	2.85
High dose	4430	11.32	2084	3.61
Quetiapine				
All dose levels	6476	8.96	3823	1.05
Low dose	2327	8.28	1687	0.56
Medium dose	1987	7.86	1324	1.26
High dose	2162	10.85	812	1.72
Conventional antipsychotics				
All dose levels	5793	12.22	2726	3.38
Low dose	1877	11.78	1133	3.18
Medium dose	1359	11.63	722	3.87
High dose	2557	12.97	871	3.34

[a]No screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required.
[b]Screening for preexisting diabetes at 8 months before observation/treatment, diabetes identified with prescription claims only, and monotherapy required.

Table 4 Odds Ratios (95% CI) for 12-Month Treatment with Antipsychotics versus No Antipsychotics, Overall and Stratified by Dose

Group	Less Rigorous Study Design[a]	More Rigorous Study Design[b]
Risperidone		
All dose levels	1.388 (1.276–1.509)*	1.224 (0.962–1.562)
Low dose	1.134 (0.985–1.307)	1.132 (0.766–1.762)
Medium dose	1.502 (1.331–1.695)*	1.140 (0.784–1.657)
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 (0.987–1.970)
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 (0.742–1.612)
Low dose	1.404 (1.171–1.684)*	.667 (0.288–1.545)
Medium dose	1.276 (1.049–1.552)*	1.279 (0.760–2.151)
High dose	1.561 (1.193–1.621)*	1.677 (0.817–3.445)
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)*

*Statistically significant at $P < 0.05$.
[a]No screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required.
[b]Screening for preexisting diabetes at 8 months before observation/treatment, diabetes identified with prescription claims only, and monotherapy required.
Notes. Logistic regressions adjusted 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 diuretics, and prior excess weight problem were consistently significant and associated with higher odds of diabetes.

diabetes were significantly higher for all antipsychotics at all three dose levels, with the exception of low-dose risperidone, than among untreated patients. Odds ratios generally increased with antipsychotic dose, with this tendency being notably weaker for conventionals.

Large differences among the antipsychotics emerged when a more rigorous study design was applied. Across all dose levels, olanzapine and conventionals alone had odds of diabetes that were significantly higher than those for untreated patients (olanzapine OR = 1.858 and conventionals OR = 1.755). Overall ORs for quetiapine (1.087) and risperidone (1.224) were statistically nonsignificant and much lower than those for olanzapine and conventionals. When findings were separated by dose level, patients taking conventionals had significantly higher odds of diabetes than untreated patients at all dose levels (1.755, 1.753 and 2.013 for low, medium, and high dose, respectively). Olanzapine had significantly higher odds at medium (1.996) and high (2.283) dose levels, whereas risperidone had significantly higher odds at the high-dose level only (1.683). Quetiapine's ORs were not statistically significant at any dose level. Regardless of statistical significance, the ORs for all 3 atypical antipsychotics studied increased with dose. 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 (includes about 15 conventional antipsychotics), and the conventional antipsychotic mix may have changed considerably from one dose level to the next.

Table 5 shows the effects of the study design criteria on ORs. The removal of observations with preexisting diabetes decreased the OR for risperidone, increased those of olanzapine and conventionals, and had little effect on that of quetiapine. This finding indicates that patients treated with risperidone were more likely to have preexisting diabetes than those treated with olanzapine or conventionals. The use of prescription claims only to identify diabetes reduced quetiapine's and risperidone's ORs while increasing those of olanzapine and conventionals. This finding suggests higher proportions of definite or more serious new cases of diabetes among patients treated with olanzapine or conventionals. Also, exclusion of observations with concurrent use of multiple antipsychotics decreased the ORs of quetiapine and olanzapine, increased that of conventionals, and left risperidone's unchanged.

Among the control variables, patient age, a diagnosis of schizophrenia, a preexisting excess weight problem, and the use of beta-blockers were consistently significant and positively associated with diabetes risk. Each additional year of age increased diabetes risk by 4% to 6%, depending on study design and dose cohort. Patients with schizophrenia had a 40% to 100% greater risk of diabetes than patients with major depression and about a 30% to 70% greater risk than patients with bipolar disorder. Patients with a prior excess weight problem had about a 150% greater risk of diabetes. Use of beta-blockers increased diabetes risk by 75% to 90%. Male sex, use of thiazide diuretics and SSRIs, and switching from another antipsychotic also had significant positive but less consistent associations with diabetes risk.

DISCUSSION

The results of this study demonstrate that the risk of diabetes associated with antipsychotic treatment, as determined using a large claims database, can vary depending on the methodology used. Using a less rigorous study design resulted in similar diabetes risk among patients treated with the atypical and conventional antipsychotics tested, which was higher than that in untreated patients. However, when a more rigorous design was used, differences among the various treatments became apparent.

Evidence from retrospective database studies provides an unclear view of the risk of diabetes with antipsychotic treatment. This is in part because of the varied methodology used. Differences in study design include decisions to screen (12,16,18,19) or not screen (11) for preexisting diabetes; to use medical and prescription claims (14,18) versus prescription claims only (15,17,21,22) to identify diabetes; to restrict (15,20) or not restrict (13,14,19) comparisons to antipsychotic monotherapy; and to use more (14,15,19) or less (10,11,18) precision in relating time of diabetes onset to time of specific antipsychotic use.

Failure to screen for preexisting 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"

Table 5 Odds Ratios (CI) for 12-Month Treatment With Antipsychotics Versus No Antipsychotics: Effects of Exclusion Criteria

Group	No Screening for Preexisting Diabetes, Identification of Diabetes With Either Medical *or* Prescription Claims, Antipsychotic Monotherapy Not Required	Removal of Observations With Preexisting Diabetes	Removal of Observations Where Diabetes Identified With *ICD-9-CM* Codes Only	Removal of Observations With Concurrent Use of Another Antipsychotic
Risperidone	1.388 (1.276–1.509)*	1.268 (1.068–1.520)*	1.224 (0.985–1.512)	1.224 (0.962–1.562)
Olanzapine	1.331 (1.224–1.446)*	1.677 (1.447–1.945)*	1.945 (1.651–2.268)*	1.858 (1.549–2.238)*
Quetiapine	1.394 (1.247–1.559)*	1.409 (1.113–1.776)*	1.298 (0.991–1.719)	1.087 (0.742–1.612)
Conventionals	1.365 (1.238–1.503)*	1.494 (1.211–1.823)*	1.638 (1.319–2.018)*	1.755 (1.381–2.221)*

CI = confidence interval; *ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.*
*Statistically significant at $P < 0.05$.

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 antidiabetics do not necessarily establish the presence of this condition. Because claims are payment instruments, *ICD-9-CM* codes may not always be accurate (23–24). Growing concerns over antipsychotic-induced diabetes may have made testing more widespread, increasing the possibility of diabetes codes appearing on claims of patients whose tests were negative or showed only minor glucose elevations. Prescription claims are more definite indicators of significant diabetogenic effects. Finally, comparing situations in which different antipsychotics are used concurrently can further bias comparisons against safer products. Since diabetes emergence or exacerbation when two antipsychotics overlap must be attributed to both, the safer product may be placed at a disadvantage. Comparing only situations of antipsychotic monotherapy avoids this sort of bias.

Consistent with the above-mentioned 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 comparisons are restricted to situations of antipsychotic monotherapy. Differences among the antipsychotic categories were relatively small using the less rigorous study design. The relative risks of diabetes among treatments became more differentiated using the more rigorous design where comparisons were restricted to monotherapy, diabetes was identified with prescription claims only, and there was prescreening.

Removal of preexisting cases of diabetes reduced risperidone's OR and increased the ORs for olanzapine and conventionals (Table 5). This suggests that risperidone was more likely than olanzapine or conventionals to be prescribed to patients with pre-existing diabetes, a form of selection bias that can distort comparisons. The reason for this selection bias may be that practitioners perceived risperidone to have weaker diabetogenic effects. This interpretation is reasonable with respect to olanzapine which has been shown to be associated with a larger number of case reports of new-onset diabetes (3) and to have a larger impact on weight gain (40,41). Identification of diabetes with prescription claims decreased ORs for quetiapine and risperidone and increased those for olanzapine and conventionals, suggesting higher proportions of definite or more serious cases of diabetes among patients treated with olanzapine or conventionals. Finally, restricting comparisons to situations of antipsychotic monotherapy decreased ORs for quetiapine and olanzapine and increased that of conventionals. Monotherapy may reflect a less intensive antipsychotic therapy as well as isolation of specific diabetogenic effects.

Effects of study design on estimates of diabetes risk are revealed in other studies. Consider, for example, the study by Sernyak and colleagues (11) in which a large Veterans Affairs database was used to perform a retrospective comparison of schizophrenia patients treated with atypical and conventional antipsychotics. Diabetes was identified with medical claims (*ICD-9-CM* 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. The study found that quetiapine in conjunction with olanzapine and clozapine had significantly higher odds of diabetes than conventional antipsychotics. Similarly, a more recent and as-yet unpublished study by Cunningham et al. (39), also focusing on schizophrenia patients in a large Veterans Affairs database, found quetiapine, olanzapine, risperidone, and clozapine to have comparably higher risks for diabetes in comparison with conventionals. Although the study controlled for preexisting diabetes and antipsychotic monotherapy, medical claims were used to identify diabetes. This may have biased results in that the atypicals may have been more likely than conventionals to be associated with testing for diabetes, which may have resulted in proportionately more medical claims.

The results from the above-mentioned studies conflict with the results of the present study as well as those of one prospective trial, two studies involving chart reviews and two other retrospective studies using large databases. In a prospective trial involving more than 150 inpatients with schizophrenia or schizoaffective disorder, Lindenmayer et al. (4) found significant elevations in blood glucose among patients treated with clozapine, olanzapine and haloperidol, but not risperidone. In an examination of medical charts for several hundred patients treated with typical and conventional antipsychotics, Wirshing et al. (9) found significant glucose elevations from baseline for clozapine, olanzapine, and haloperidol but not for quetiapine or risperidone. In a chart review involving 65 schizophrenia patients who were initiated on clozapine and then switched to a clozapine-quetiapine combination, Reinstein et al. (6) found that glucose levels improved in patients who had developed diabetes under clozapine monotherapy. A study by Buse et al. (15) contains many elements argued here as constituting a "more rigorous" study design: prescription claims only were used to identify diabetes; comparisons were restricted to antipsychotic monotherapy; patients were screened for preexisting diabetes at 12 months; and antipsychotic treatment duration was measured to ensure that diabetes onset coincided with time of antipsychotic use. Among the atypicals (clozapine, risperidone, olanzapine, and quetiapine), quetiapine alone was found to have a significantly lower risk of diabetes in comparison with haloperidol. While the antipsychotic (each of the atypicals, haloperidol, and thioridazine) users had significantly higher diabetes risks than the general patient population of antipsychotic nonusers, the estimated hazard ratio was lowest for quetiapine. Another study using the same database and with similar methods and comparisons, but focusing on the elderly only, had essentially the same findings (20). Use of the general patient population as a comparator, however, prevents separation of diabetes associated with specific

antipsychotics from diabetes associated with the underlying mental disorder. The present study used as a comparison group patients with schizophrenia, bipolar disorder, or major depression who were untreated with antipsychotics and therefore may have been better able to separate these effects.

A limitation of this study is that some patients may have discontinued an antipsychotic before they were diagnosed or treated for diabetes. Because diabetes onset was measured within the confines of treatment episodes, these cases would not have been associated with the discontinued therapy. A lagged approach was not used because patients who discontinued an antipsychotic therapy may have switched to another antipsychotic or other psychotropic medications (e.g., SSRIs) with potential diasbetogenic effects. Use of a short lag, as we did in our earlier studies (14,16,17), was also judged to be problematic; case reports showed that in nearly 60 percent of cases diabetes emerged within 90 days of initiating an antipsychotic, which is consistent with the additional finding that excess weight gain was a factor in less than 50 percent of cases (3). Another limitation of this study is that the data afforded inadequate control for diabetes risk factors (undiagnosed or untreated excess weight, family history, ethnicity). Selection bias may have been present in that antipsychotics perceived to be safer may have been prescribed to patients at greater risk for diabetes. Lastly, patients on antipsychotic polypharmacy, such as represented under the "less rigorous" study design, may have been more severely ill and prescribed generally higher antipsychotic doses than patients on monotherapy. Consequently, the lower odds ratios associated with the removal of polypharmacy patients under the "more rigorous" study design may have also reflected the effects of reducing antipsychotic doses.

CONCLUSIONS

This study has demonstrated that, in retrospective analyses using claims data, findings of diabetes risk may be strongly influenced by study design. Specifically, findings may be highly sensitive to screening for preexisting diabetes, to whether diabetes is identified solely with the more definite indicator of prescription claims, and to whether comparisons are restricted to antipsychotic monotherapy. With an approach incorporating these refinements, diabetes risks in patients treated with quetiapine or risperidone were found not to differ significantly from risks in patients with psychoses who were untreated with antipsychotics. In contrast, diabetes risks in patients treated with olanzapine or conventionals were significantly higher.

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