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]

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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.

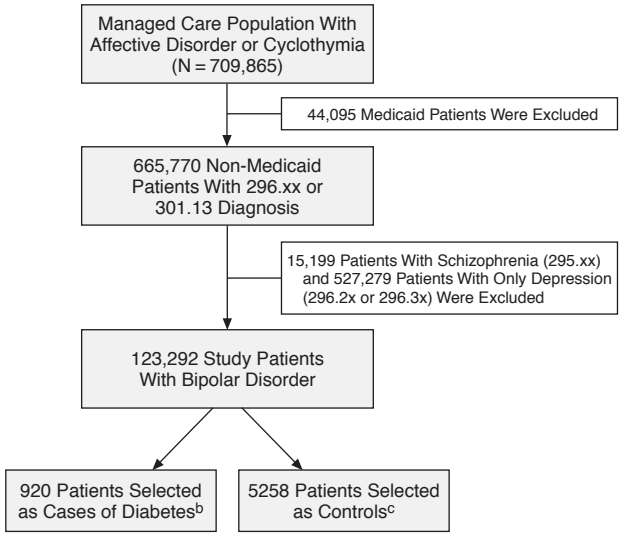
Diabetes is a known and infrequent adverse effect of olanzapine and risperidone. Drug-induced diabetes onset has not been adequately quantified in patients with bipolar disorder, although atypical antipsychotics are being increasingly used in the treatment of bipolar disorder. Published reports indicated 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 month's 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 month's 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.

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.

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.

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),[24,35–37] 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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