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

Jeff J. Guo, Ph.D., Paul E. Keck, Jr., M.D., Patricia K. Corey-Lisle, Ph.D., Hong Li, Ph.D., Dongming Jiang, Ph.D., Raymond Jang, Ph.D., and Gilbert J. L'Italien, Sc.D.

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

Design. Retrospective nested case-control study.

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

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

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

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

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

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

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

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

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

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

Methods

Data Source

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

From the College of Pharmacy, University of Cincinnati Medical Center, Cincinnati, Ohio (Drs. Guo and Jang); the Institute for Health Policy and Health Services Research, University of Cincinnati, Cincinnati, Ohio (Dr. Guo); the Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr. Keck); the Mental Health Care Line and General Clinical Research Center, Cincinnati Veterans Affairs Medical Center, Cincinnati, Ohio (Dr. Keck); Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut (Drs. Corey-Lisle, Li, and L'Italien); and the Biostatistics Division, GlaxoSmithKline Pharmaceutical, Philadelphia, Pennsylvania (Dr. Jiang).

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Address reprint requests to Jeff J. Guo, Ph.D., University of Cincinnati Medical Center, 3225 Eden Avenue, Cincinnati, OH 45267-0004; e-mail: jeff.guo@uc.edu.

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

Study Design

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

Study Cohort Identification

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

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

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

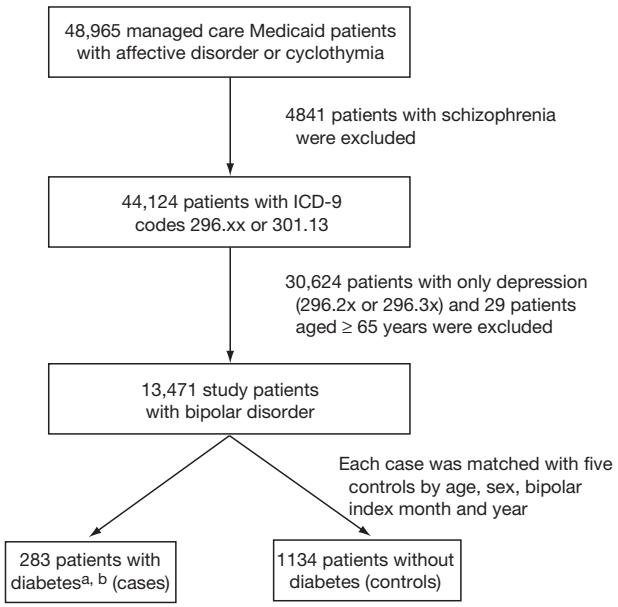

Figure 1. Patient flow diagram of incident cases of diabetes mellitus and controls from patients with bipolar disorder in the United States managed care Medicaid population, 1998–2002. [a]Incident cases of diabetes were identified by either earliest diagnosis of *International Classification of Diseases,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

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

Drug Use and Covariates

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

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

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

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

Statistical Analysis

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

Results

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

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

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

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

Table 1. Characteristics of the Study Patients

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

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

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

Discussion

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

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

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

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

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

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

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

Table 2. Hazard Ratios for Diabetes Risk

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

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

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

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

Conclusion

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

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

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