Antipsychotic-Induced Type 2 Diabetes: Evidence From a Large Health Plan Database

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Abstract: Case evidence suggests that some of the atypical antipsychotics may induce type 2 diabetes. The objective of this study was to evaluate the association of antipsychotic treatment with type 2 diabetes in a large health plan database. Claims data for patients with psychosis within a health plan of nearly 2 million members were analyzed using logistic regression. Frequencies of newly treated type 2 diabetes in patients untreated with antipsychotics and among patients treated with quetiapine, risperidone, olanzapine, and conventional antipsychotics were compared. Based on exposure measured in months of antipsychotic treatment, quetiapine and risperidone patients had estimated odds of receiving treatment for type 2 diabetes that were lower than those of patients untreated with antipsychotics (not statistically significant); patients treated with conventional antipsychotics had estimated odds that were virtually equivalent to those of patients untreated with antipsychotics; olanzapine alone had odds that were significantly greater than those of patients untreated with antipsychotics (P = 0.0247). Odds ratios based on 8 months of screening for pre-existing type 2 diabetes and assuming 12 months of antipsycho-With No Type 2 Diabetestic treatment were: risperidone = 0.660 (95% CI 0.311–1.408); olanzapine = 1.426 (95% CI 1.046–1.955); quetiapine = 0.976 (95% CI 0.422–2.271); and conventional antipsychotics = 1.049 (95% CI 0.688–1.613). Case reports, prospective trials, and other retrospective studies have increasingly implicated olanzapine and clozapine as causing or exacerbating type 2 diabetes. Few have implicated risperidone while evidence on quetiapine has been limited. This study supports earlier findings on risperidone versus olanzapine and builds evidence on quetiapine. Additional studies are needed to evaluate the association of antipsychotic treatment with type 2 diabetes.

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Atypical antipsychotics approved by the Food and Drug Administration for sale in the United States include clozapine, risperidone, olanzapine, quetiapine, and recently, ziprasidone. These agents have a major advantage over conventional antipsychotics such as haloperidol and perphenazine in that they are less likely to produce extrapyramidal side effects or elevate prolactin levels while being at least as effective in treating the symptoms of schizophrenia and related psychoses.[1–12] However, atypical and conventional antipsychotics have other side effects that need to be considered when assessing overall safety and efficacy. For example, risk of agranulocytosis, a very serious and potentially fatal blood disorder, has limited the use of clozapine.[13] This study further investigates the association between antipsychotics and type 2 diabetes.

In a number of reported cases, patients became glucose intolerant after initiating antipsychotic treatment. Most of these cases involved the atypical antipsychotics clozapine[14–27] and olanzapine,[19,27–35] with quetiapine suspected in 2 cases[36,37] and risperidone in 3 cases.[38–40] The earlier case literature has also associated some conventional antipsychotics with type 2 diabetes.[41–43] Prospective trials involving relatively small numbers of schizophrenia patients have also examined the association between antipsychotics and diabetes. Lindenmayer et al[44] found clozapine, olanzapine, and haloperidol, but not risperidone, to be associated with an increase of plasma glucose level. Newcomer et al[45] found olanzapine-treated and clozapine-treated patients to have significant glucose elevations in comparison to both patients treated with conventional antipsychotics and to healthy controls, while risperidone-treated patients had significantly higher elevations with respect to healthy controls only.

The propensity of antipsychotics to cause weight gain has been postulated as a frequent but not sole mechanism by which they may induce type 2 diabetes,[19] and many antipsychotics have been associated with excessive weight gain in clinical trials and clinical experience.[46,47] Potential mechanisms of glucose dysregulation associated with antipsychotics have also been discussed in the literature.[48,49] Central regulation of blood glucose is controlled by the hypothalamus, and hypothalamic dopamine antagonism by

some antipsychotics may lead to dysregulated blood glucose control. Other receptors have also been postulated to be associated with antipsychotic-induced diabetes, including serotonin 5-HT_{1A} and 5-HT_{2c} and histamine-1.[19]

Retrospective studies based on large populations have also examined the association between antipsychotics and type 2 diabetes. Hedenmalm et al[50], using a WHO database, found treatment with clozapine, olanzapine, and risperidone, but not with haloperidol and chlorpromazine, to be significantly associated with glucose intolerance. Sernyak et al[51] compared schizophrenia patients within the U.S. Veterans Administration system who were treated with the atypicals, such as clozapine, risperidone, olanzapine, and quetiapine, versus those treated with conventional antipsychotics and found all of the atypicals except risperidone to have higher risk of diabetes. A study by Koro et al[52] using data from the United Kingdom compared schizophrenia patients treated with risperidone or olanzapine and found olanzapine, but not risperidone, to be associated with higher risk of diabetes. Caro et al,[53] using a Quebec database of patients treated with olanzapine or risperidone and with no prior diabetes, found olanzapine-treated patients to be associated with a higher risk of developing diabetes. Gianfrancesco et al,[54] using data for psychosis patients within two U.S. health plans, found olanzapine, clozapine, and conventional antipsychotics, but not risperidone, to be associated with a significantly higher risk of diabetes. The study controlled for pre-existing diabetes and the level of patient exposure to each of the antipsychotics.

The present study applied methods similar to Gianfrancesco et al[54] to more recent data, but used more restrictive criteria to identify type 2 diabetes. Actual treatment for the disease was required as evidenced by prescription claims for antidiabetes medications or insulin. The appearance of a type 2 diabetes diagnosis (ie, ICD-CM-9 code) on a medical claim may simply mean that the patient was examined for this condition and does not necessarily mean that the patient tested positively. The examination itself may have been prompted by the patient's history, including excessive weight gain caused by a prior medication. It may also have been prompted by a perceived risk of diabetes associated with the newly prescribed antipsychotic.

MATERIALS AND METHODS

Design

This was a retrospective analysis of a Blue Cross/Blue Shield claims database with nearly 2 million members who had both medical and drug coverage. The available data extended from April 1997 through October 2000. Antipsychotic effects on type 2 diabetes were estimated by comparing patients with psychosis who received antipsychotic treatment to patients with psychosis who were not treated with antipsychotics (controls). This control group was used because psychoses may be linked to diabetes independently of the use of antipsychotics.[55–58]

Patients were identified as having a psychotic disorder (ICD-CM-9 290.xx-299.xx) and who were either not using any antipsychotics or on antipsychotic therapy for 60 consecutive days or more. Continuous use of antipsychotics and at least 1 medical claim for psychosis were deemed sufficient to establish that a patient had psychosis. For individuals not treated with antipsychotics during the study period, at least 4 medical claims for psychosis were required to establish that they were psychotic. Patients with psychosis on antipsychotic therapy for less than 60 days were excluded. Because of the possibility of noncompliance, one 30-day prescription (the typical size) was judged insufficient to indicate that the antipsychotic was actually used.

Four categories of antipsychotic therapy were defined: risperidone, olanzapine, quetiapine, and conventional antipsychotics (perphenazine, fluphenazine, trifluoperazine, thiothixene, haloperidol, molindone, loxapine, prochlorperazine, acetophenazine, chlorpromazine, promazine, trifluprom azine, thioridazine, mesoridazine, chlorprothixene). Patients treated with clozapine were ultimately excluded from the treated group because the number was too small. Ziprasidone, which was approved in early 2001, was also not included.

Treatment episodes were used to identify periods of antipsychotic use. Treatment episodes were defined as the time from the date of the first prescription for an antipsychotic to the final date of treatment calculated from the date of the last prescription plus its days' supply. Identification of a prescription as the first prescription in a treatment episode required that it not be preceded by another prescription for that antipsychotic for at least 90 days. Patients could have more than 1 treatment episode. In addition, treatment overlaps were possible due to temporary concurrent use of a prior antipsychotic when transitioning to a new antipsychotic therapy.[59]

Diabetes observation periods for treated patients were constructed to lag antipsychotic treatment episodes by 30 days to account for individuals diagnosed and treated for type 2 diabetes after discontinuation of therapy. A 30-day lag period is also consistent with the likelihood that any diabetogenic effects of antipsychotics would take some time to emerge after initiating therapy. Nearly all of the case literature reported diabetic effects occurring in excess of 30 days beyond the start of an antipsychotic therapy.

The main goal of the research design was to avoid arbitrary assignment of diabetes to the antipsychotics being compared. The use of antipsychotic treatment episodes rather than index dates to assign diabetes cases insured that the onset of diabetes was linked to the actual time that an antipsychotic was used. If treatment episodes with different antipsychotics overlapped and diabetes occurred within the overlap (ie, beyond the 30-day lag), the diabetes case was

assigned to both antipsychotics. While multiple and potentially overlapping antipsychotic treatment episodes for the same patient raised the possibility of interdependence among observations, this was judged to be a lesser problem than that of arbitrary assignment of diabetes. Dropping the 1st or 2nd antipsychotic treatment episode to avoid interdependence can result in arbitrary assignment and create other bias if being 1st or 2nd is not random (eg, quetiapine was far more likely than risperidone and olanzapine to have been a 2nd-line therapy).

For untreated patients, observation periods for type 2 diabetes were constructed using 18 index dates separated by 2-month intervals and starting on December 1, 1997. Untreated individuals were randomly assigned with these starting dates. This procedure was necessary to create sufficient variation in length of observation period for the untreated group to avoid confounding period length with the presence or the absence of antipsychotic treatment. Observation periods lasted from the selected index date to the end of the study period (October 31, 2000); only untreated individuals enrolled for the entire study period were included.

Type 2 diabetes was assumed only if a patient received treatment for this condition. Those treated for type 2 diabetes were identified with prescription claims containing National Drug Codes for antidiabetic medications (1st-generation and 2nd-generation sulfonylureas, biguanides, glucosidase inhibitors, meglitinides, and thiazolidinediones) and National Drug Codes for insulin if individuals also had medical claims with ICD-CM-9 codes for this condition. Insulin is used primarily for type 1 diabetes and acute onset diabetic acidosis secondary to some antipsychotics, whereas antidiabetic medications are used exclusively for type 2 diabetes. The ICD-CM-9 codes for type 2 diabetes are 250.x0 and 250.x2.

An interval of 8 months before each diabetes observation period was used to screen for subjects with prior evidence of type 2 diabetes. Subjects with medical or prescription claims for type 2 diabetes during this period were excluded. The 8-month interval was selected because a shorter interval would have been less sensitive (greater likelihood of including patients with pre-existing type 2 diabetes) and a longer interval would have substantially reduced the sample size.

Analysis

Logistic regression was used to estimate the effects on odds of acquiring type 2 diabetes treatment for patients within each of the 4 antipsychotic categories versus controls. Each of the categories was represented by a continuous variable, which measured months of antipsychotic treatment, with zero values for all 4 categories indicating no antipsychotic treatment. Because antipsychotic treatment duration varied among treated psychosis patients, categorical (1, 0) variables were judged inappropriate for measuring patient exposure to each antipsychotic. Several other variables were specified in the model to control for other patient characteristics potentially affecting risk of type 2 diabetes or the likelihood of treatment These included: patient age, sex, length of observation period (which corresponded to length of antipsychotic treatment episode for treated psychosis patients), use of other psychotropic drugs measured in dollars per month (eg, lithium and SSRIs have been associated with glucose intolerance),[60,61] use of β-blockers measured as a categorical variable (these antihypertensives have been associated with higher risk of type 2 diabetes),[62] type of healthcare coverage, type of psychosis, and prior treatment for weight gain measured as a categorical variable . A diabetic event, encompassed by 2 overlapping antipsychotic therapies, was assigned to both. However, an antipsychotic treatment episode in which another antipsychotic is also used is not the same as one involving monotherapy. To account for this difference and its potential effects, a variable was added that measured the ratio of other antipsychotic days' supply to treatment antipsychotic days' supply.

Logistic regression generated an odds ratio for each of the variables specified in the model. The odds ratio for each of the 4 variables measuring antipsychotic exposure measured the degree (%) by which some base probability of type 2 diabetes was greater due to 1 month of treatment with that antipsychotic. The base probability depended on other characteristics of the population to which the antipsychotic was applied. Odds ratios for months of antipsychotic treatment >1 were obtained by increasing the 1-month odds ratio to a power equal to the desired months of treatment. The same interpretation applies to other continuous variables specified in the logistic model. This is standard procedure for continuous variables in logistic regression.[63]

RESULTS

A total of 6582 patients with psychosis received at least 60 consecutive days of antipsychotic therapy during the study period, whereas 10,296 received no antipsychotic treatment. For the treated patients, there were 2860 treatment episodes identified for risperidone, 2703 for olanzapine, 922 for quetiapine, and 2756 for conventional antipsychotics. About 30% of the treated patients had more than 1 treatment episode with either the same or a different antipsychotic. Also, treatment episodes with different antipsychotics overlapped in 27% of the observations.

Patients treated with antipsychotics were somewhat younger than untreated patients and had a larger proportion of males (Table 1). Observation periods among untreated patients were almost twice as long as those of treated patients, increasing the likelihood of observing type 2 diabetes in that group. Although treated and untreated patients differed considerably with respect to type of psychosis, major depression was the most common diagnosis in

both groups (38% and 76%, respectively) and schizophrenia occurred at low rates (14% and 1%, respectively). Untreated patients had a lower per-capita use of other psychotropic medications and of β-blockers, and a lower percentage indicating a prior problem with weight gain.

Differences in patient characteristics also existed among the 4 antipsychotic categories. Observation period and duration of treatment were longest for conventional antipsychotics and shortest for quetiapine, which may be explained by its relative newness to the market at the time of the data collection [April 1997-October 2000]. Patients treated with quetiapine had the highest per-capita use of other psychotropic medications and the highest percentage of patients indicating a prior problem with weight gain; both of these conditions may be partly explained by the fact that patients treated with quetiapine were 2 to 3 times more likely to have been switched from another antipsychotic. Patients treated with conventionals had the highest percent using β-blockers while those treated with risperidone had the lowest, consistent with the average ages of these 2 groups. The breakdown of patients by type of psychosis was roughly similar among the antipsychotic categories.

Table 2 shows frequencies of treated type 2 diabetes among the antipsychotic categories. Across all groups, type 2 diabetes treatment tended to be relatively more frequent among patients with longer observation periods. Overall, patients treated with antipsychotics had higher rates of type 2 diabetes treatment than patients untreated with antipsychotics. While this suggests that antipsychotics as a class have diabetic effects, the differences were not large. Among the 4 antipsychotic categories, risperidone and quetiapine had the lowest percentages of patients treated for type 2

TABLE 1. Profile of Psychosis Patients

	Without Antipsychotic Treatment	With Antipsychotic Treatment	Risperidone	Olanzapine	Quetiapine	Conventionals
Age						
Mean (SD)	39.5 (14.3)	37.5 (15.1)	33.4 (16.3)	37.1 (14.5)	35.6 (14.5)	43 (12.6)
Median	42	40	36	39	38	44
Sex						
Female	0.64	0.59	0.55	0.57	0.65	0.64
Male	0.36	0.41	0.45	0.43	0.35	0.36
Type of health care coverage						
Managed care	0.66	0.62	0.65	0.62	0.59	0.61
Indemnity	0.34	0.38	0.35	0.38	0.41	0.39
Observation period						
Mean (SD) length in months	18.2 (10.6)	9.7 (9.7)	9.1 (8.9)	8.7 (8.7)	7.1 (6.2)	12.1 (11.8)
Median length in months	17.3	5.9	5.7	5.5	5	7.3
Antipsychotic treatment duration						
Mean (SD) length in months	NA	9.9 (9.8)	9.4 (9.1)	9 (8.9)	7.5 (6.3)	12.3 (12)
Median length in months	NA	6.1	6	5.6	5.3	7.4
Diagnosis						
Schizophrenia	0.01	0.14	0.1	0.11	0.1	0.18
Bipolar and manic	0.16	0.35	0.36	0.37	0.37	0.32
Major depressive	0.76	0.38	0.39	0.39	0.43	0.36
Other psychoses	0.07	0.13	0.15	0.13	0.1	0.14
Use of other psychotropic drugs						
Mean (SD) dollars per month	57 (77)	96 (120)	98 (120)	99 (108)	112 (151)	86 (118)
Median dollars per month	30	67	68	71	81	54
β-Blocker use (percent of patients)	8.03	10.04	7.34	11.17	10.41	12.01
Concurrent use of other antipsychotics						
Percent of patients	NA	27	22	27	33	31
Prior weight gain problem						
Percent of patients	1.4	2.3	2.2	2.3	4	2

NA, not applicable.

TABLE 2. Frequency of Type 2 Diabetes Treatment Among Antipsychotic Categories

	Total	Treated for Diabetes	Percent
Without antipsychotic treatment			
<4 months observation	1090	0	0.0
4–8 months observation	1083	0	0.0
8–12 months observation	1077	3	0.3
>12 months observation	6439	84	1.3
With antipsychotic treatment			
<4 months observation	1995	3	0.2
4–8 months observation	1479	3	0.2
8–12 months observation	721	7	1.0
>12 months observation	1055	17	1.6
Risperidone			
<4 months observation	619	2	0.3
4–8 months observation	483	1	0.2
8–12 months observation	244	0	0.0
>12 months observation	329	2	0.6
Olanzapine			
<4 months observation	687	1	0.1
4–8 months observation	467	1	0.2
8–12 months observation	234	3	1.3
>12 months observation	331	10	3.0
Quetiapine			
<4 months observation	266	0	0.0
4–8 months observation	219	1	0.5
8–12 months observation	83	1	1.2
>12 months observation	114	1	0.9
Conventionals			
<4 months observation	423	0	0.0
4–8 months observation	310	0	0.0
8–12 months observation	160	3	1.9
>12 months observation	281	4	1.4

diabetes, while olanzapine and conventional antipsychotics had the highest.

Table 3 presents odds ratios for type 2 diabetes treatment for the 4 antipsychotic categories versus no antipsychotic treatment, as estimated using logistic regression. Antipsychotic exposure was captured by variables measuring duration of treatment. Additional variables were specified to control for other differences among the groups that could also affect the odds of type 2 diabetes treatment. The number of observations was 14,914, with 117 treated for type 2 diabetes. Olanzapine alone had odds of type 2 diabetes treatment that were significantly greater ($P = 0.0247$) than those of patients untreated with antipsychotics (OR = 1.03 for 1 month of olanzapine treatment). This suggests that 1 month of treatment with olanzapine increased the likelihood of type 2 diabetes treatment by 3% above that of untreated psychosis patients. Risperidone and quetiapine had estimated odds that were lower than for untreated patients (not significant), whereas conventional antipsychotics had odds that were virtually equivalent to untreated patients.

Among the control variables, age was highly significant ($P < 0.0001$), as would be expected for type 2 diabetes. Because age was a continuous variable expressed in years, its odds ratio indicates the percent increment in the odds of type 2 diabetes treatment as an individual aged by 1 year. Logically, the length of the observation period also affected the likelihood of observing type 2 diabetes ($P < 0.0001$). Use of β-blockers was associated with higher odds of diabetes treatment ($P = 0.0002$). Significantly lower odds were associated with bipolar disorder ($P = 0.01$) and major depression ($P = 0.0015$) in comparison to other psychoses, which included alcohol-related and drug-related disorders. While schizophrenia also had lower estimated odds, this was not statistically significant. Other factors, such as patient use of other psychotropic drugs and prior weight gain problems, were not statistically significant.

In Table 4, the odds ratios estimated for 1 month of antipsychotic treatment were converted to 12 months of treatment by increasing the 1-month odds ratios to a power of 12.[63] Ninety-five percent confidence intervals for these are also shown. The 12-month odds ratio of olanzapine was highest (1.426), implying a 42.6% greater likelihood of type 2 diabetes than among untreated patients.

DISCUSSION

A possible relationship between antipsychotics, particularly the atypical antipsychotics olanzapine and clozapine, and type 2 diabetes has been suggested in a number of case reports[14–35] and at least 2 prospective trials.[44,45]. A recent study by Glick et al[64] comparing olanzapine and ziprasidone showed that after only 6 weeks of treatment with olanzapine, weight, fasting insulin, total cholesterol, and triglycerides rose significantly compared with ziprasidone. Evidence that antipsychotics have differential effects on weight gain also suggests that they may have differential effects in causing or exacerbating type 2 diabetes, with excess body weight as a major risk factor for this disease. According to 2 comprehensive studies,[46,47] olanzapine and clozapine are more likely to cause excessive weight gain than other antipsychotics.

Because of the small numbers involved, case findings and prospective trials may be limited in their ability to demonstrate statistical associations between specific antipsychotics and type 2 diabetes, particularly over the diverse patient populations using these medications. To overcome this limitation and to provide an alternative source of evidence, this study and earlier studies[50–54] used health plan data to investigate the medical histories of thousands of patients with psychosis. The current study, which used

TABLE 3. Logistic Regression Results: Treated Type 2 Diabetes Among Psychosis Patients

	Model 1 (Treatment Duration)	
Variable	**Odds Ratio**	**Pr > χ^2**
Antipsychotic treatment duration (yes = months; no = 0)		
Risperidone	0.966	0.2848
Olanzapine	1.030	0.0247
Quetiapine	0.998	0.9593
Conventionals	1.004	0.8099
Age	1.055	0.0001
Sex (male = 1)	1.200	0.2947
Observation period (months)	1.067	0.0001
Other psychotropic drugs (dollars per month)	0.999	0.4068
β-Blocker use (yes = 1; no = 0)	2.107	0.0002
Concurrent antipsychotics (ratio of days supply)	0.971	0.9589
Coverage (managed care = 1; indemnity = 0)	0.819	0.2461
Schizophrenia (yes = 1; no = 0)	0.445	0.1076
Bipolar/manic (yes = 1; no = 0)	0.444	0.0100
Major depressive (yes = 1; no = 0)	0.449	0.0015
Prior weight gain problem (yes = 1; no = 0)	0.960	0.9364

Number treated for type 2 diabetes (1) = 117; number not reporting type 2 diabetes (0) = 14,797; total observations = 14,914. Patients with diabetes medical claims during observation but without prescription claims for antidiabetics or insulin are excluded. This group cannot be definitely classified as having or not having type 2 diabetes. Patients untreated with antipsychotics are represented by zeros for each of the four specified antipsychotic categories.

methods similar to Gianfrancesco et al,[54] is more restrictive than earlier studies in that treatment of type 2 diabetes with oral hypoglycemic medications or insulin was required as evidence of this disease.

The frequency of type 2 diabetes treatment was compared among patients with psychosis who were untreated with antipsychotics and those treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics. Because of important differences among the groups, logistic regression was used to more accurately estimate antipsychotic effects on the odds of type 2 diabetes treatment. Antipsychotic exposure was measured in treatment duration (months). Olanzapine alone had odds of type 2 diabetes treatment that were significantly greater than those of patients with psychosis who were untreated with antipsychotics ($P = 0.0247$). The odds ratio of olanzapine based on 12 months of treatment was 1.426, suggesting a 42.6% greater likelihood of type 2 diabetes than in untreated patients with psychosis.

While not reported, this study did address another measure of antipsychotic exposure, dosage level. As with Gianfrancesco et al,[54] antipsychotic dose (measured in risperidon-equivalent milligrams) was specified as an alternative measure, but did not achieve statistical significance. Antipsychotic dose is less efficient than duration of treatment. It is dependent on patient body weight, so that different doses may imply the same degree of antipsychotic exposure for patients with different body weights. While patient weight is not reported in claims data, the relationship between antipsychotic dose and body weight was reflected in the fact that male daily doses averaged 28% higher than female doses. Also, the average dose (the only practical way of capturing this effect) does not reflect the varying dosage levels and their timing during the course of treatment. Consequently, the average dose may be weakly related to diabetes.

The sampling units in this study were antipsychotic treatment episodes rather than patients. Because some patients had more than 1 treatment episode, interdependence of sampling units was considered as a potential statistical problem. Multiple antipsychotic treatment episodes for the same patient may violate the independence of sampling units if the type 2 diabetes is linked to inherent patient characteristics (eg, genes). However, the mechanism(s) through which

TABLE 4. Odd Ratios Converted to 12-Month Treatment Duration

	Odds Ratio	Confidence Interval
Risperidone	0.660	0.311–1.408
Olanzapine	1.426	1.046–1.955
Quetiapine	0.976	0.422–2.271
Conventionals	1.049	0.688–1.613

antipsychotics may cause type 2 diabetes is still unknown, and there is little reason to assume that inherent patient characteristics play a key role. Also, interdependence of sampling units can be caused by other factors (eg, 2 different patients being treated by the same physician). The boundaries set by antipsychotic treatment episodes are crucial for accurate assignment of diabetes cases. When patients use multiple antipsychotics for varying durations, the use of the patient as the sampling unit may result in arbitrary associations. Assignment of diabetes to an antipsychotic should depend not only on whether the patient was treated with that antipsychotic, but on when the diabetes occurred in relation to the treatment.

The approach taken in this study was conservative in that diabetes cases were counted as such only if there was treatment with oral hypoglycemic medications or insulin. This excluded a considerable number of cases in which type 2 diabetes appeared as a diagnosis on medical claims but for which there was no subsequent treatment. While these may have reflected mild cases of glucose intolerance, they may have also reflected patients who tested negative for this condition. A diagnosis of type 2 diabetes may appear on a medical claim if a patient is examined for this condition, but does not necessarily mean that the patient tested positively. Because examination for type 2 diabetes may not be random, but may depend on perceptions of diabetes risk associated with the newly prescribed antipsychotic, dependence on medical claims may create bias.

Under this more conservative approach, patients treated with olanzapine alone were shown to face higher odds of type 2 diabetes than patients with psychosis untreated with antipsychotics. In contrast, risperidone and quetiapine had estimated odds that were less than those of untreated patients, although this difference was not statistically significant. With regard to the risk of type 2 diabetes, these atypical antipsychotics appear to be safer than olanzapine.

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REFERENCES

1. Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull.* 1995;21: 579–591.
2. Claghorn J, Honigfeld G, Abuzzahab FS Sr, et al. The risks and benefits of clozapine versus chlorpromazine. *J Clin Psychopharmacol.* 1987;7: 377–384.
3. Wirshing DA, Marshall BD Jr, Green MF, et al. Risperidone in treatment-refractory schizophrenia. *Am J Psychiatry.* 1999;156:1374–1379.
4. Davies A, Adena MA, Keks NA, et al. Risperidone versus haloperidol: I. Meta-analysis of efficacy and safety. *Clin Ther.* 1998;20:58–71.
5. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol.* 1993;13:25–40.
6. Breier A, Hamilton SH. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Biol Psychiatry.* 1999;45:403–411.
7. Tran PV, Tollefson GD, Sanger TM, et al. Olanzapine versus haloperidol in the treatment of schizoaffective disorder. Acute and long-term therapy. *Br J Psychiatry.* 1999;174:15–22.
8. Dev V, Raniwalla J. Quetiapine: a review of its safety in the management of schizophrenia. *Drug Saf.* 2000;23:295–307.
9. Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. *Int Clin Psychopharmacol.* 2000;15:121–131.
10. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand.* 1997; 96:265–273.
11. Daniel DG, Copeland LF. Ziprasidone: comprehensive overview and clinical use of a novel antipsychotic. *Expert Opin Investig Drugs.* 2000;9:819–828.
12. Keck PE Jr, Reeves KR, Harrigan EP. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol.* 2001;21:27–35.
13. Alvir JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med.* 1993;329:162–167.
14. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry.* 2000;157:975–981.
15. Wehring H, Alexander B, Perry PJ. Diabetes mellitus associated with clozapine therapy. *Pharmacotherapy.* 2000;20:844–847.
16. Wu G, Dias P, Chun W, et al. Hyperglycemia, hyperlipemia, and periodic paralysis: a case report of new side effects of clozapine. *Prog Neuropsychopharmacol Biol Psychiatry.* 2000;24:1395–1400.
17. Smith H, Kenney-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis. *Aust N Z J Psychiatry.* 1999;33:120–121.
18. Colli A, Cocciolo M, Francobandiera F, et al. Diabetic ketoacidosis associated with clozapine treatment. *Diabetes Care.* 1999;22:176–177.
19. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry.* 1998;44:778–783.
20. Ai D, Roper TA, Riley JA. Diabetic ketoacidosis and clozapine. *Postgrad Med J.* 1998;74(874):493–494.
21. Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J Clin Psychiatry.* 1998;59:294–299.
22. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. *J Clin Psychiatry.* 1997;58:108–111.
23. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry.* 1996;153:737–738.
24. Kostakoglu AE, Yazici KM, Erbas T, et al. Ketoacidosis as a side-effect of clozapine: a case report. *Acta Psychiatr Scand.* 1996;93:217–218.
25. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. *Am J Psychiatry* 1994;151(10):1520–1521.
26. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine. *Am J Psychiatry.* 1994;151:1395.
27. Muench J, Carey M. Diabetes mellitus associated with atypical antipsychotic medications: new case report and review of the literature. *J Am Board Fam Pract.* 2001;14:278–282.
28. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 2000;61(10):742–749.
29. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. *Ann Pharmacother.* 2000;34(7–8):865–867.
30. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical anti-psychotic drugs—a report of three cases. *Diabet Med.* 2000;17: 484–486.
31. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics.* 1999;40:438–443.

32. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis with olanzapine treatment. *Diabetes Care*. 1999;22:1002–1003.
33. Lindenmayer JP, Patel R. Olanzapine-induced ketoacidosis with diabetes mellitus. *Am J Psychiatry*. 1999;156:1471.
34. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine. *Am J Psychiatry*. 1999;156:970.
35. Fertig MK, Brooks VG, Shelton PS, et al. Hyperglycemia associated with olanzapine. *J Clin Psychiatry*. 1998;59(12):687–689.
36. Procyshyn RM, Pande S, Tse G. New-onset diabetes mellitus associated with quetiapine [letter]. *Can J Psychiatry*. 2000;45:668–669.
37. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment [letter]. *J Clin Psychiatry*. 1999;60:556–557.
38. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics*. 2000;41:369–370.
39. Melamed Y, Mazeh D, Elizur A. Risperidone treatment for a patient suffering from schizophrenia and IDDM [letter]. *Can J Psychiatry*. 1998;43:956.
40. Mohan D, Gordon H, Hindley N, et al. Schizophrenia and diabetes mellitus [letter]. *Br J Psychiatry*. 1999;174:180–181.
41. Aruna, Paulose AP. Chlorpromazine induced diabetes mellitus. *J Assoc Physicians India*. 1995;43:146.
42. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry*. 1983;44:347–348.
43. Proakis AG, Mennear JH, Miya TS, et al. Phenothiazine-induced hyperglycemia: relation to CNS and adrenal effects. *Proc Soc Exp Biol Med*. 1971;137:1385–1388.
44. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003;160:290–296.
45. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002;59:337–345.
46. Taylor DM, McAskill R. Atypical antipsychotics and weight gain—a systematic review. *Acta Psychiatr Scand*. 2000;101:416–432.
47. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999; 156(11):1686–1696.
48. Mir S, Taylor D. Atypical antipsychotics and hyperglycaemia. *Int Clin Psychopharmacol*. 2001;16:63–73.
49. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. *Eur Neuropsychopharmacol*. 2001;11:25–32.
50. Hedenmalm K, Hagg S, Stahl M, et al. Glucose intolerance with atypical antipsychotics. *Drug Saf*. 2002;25:1107–1116.
51. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 2002;159:561–566.
52. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ*. 2002;325(7358):243.
53. Caro JJ, Ward A, Levinton C, et al. The risk of diabetes during olanzapine use: a retrospective database analysis. *J Clin Psychiatry*. 2002; 63:1135–1139.
54. Gianfrancesco F, Grogg A, Mahmoud R, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry*. 2002;63:920–930.
55. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000;26: 903–912.
56. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68–73.
57. Lilliker SL. Prevalence of diabetes in a manic-depressive population. *Compr Psychiatry*. 1980;21:270–275.
58. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry*. 1999;156:1417–1420.
59. Borison RL. Changing antipsychotic medication: guidelines on the transition to treatment with risperidone. The Consensus Study Group on Risperidone Dosing. *Clin Ther*. 1996;18:592–607; discussion 591.
60. Martinez-Maldonado M, Terrel J. Lithium carbonate-induced nephrogenic diabetes insipidus and glucose intolerance. *Arch Intern Med*. 1973;132:881–884.
61. Breum L, Bjerre U, Bak JF. Long-term effects of fluoxetine on glycemic control in obese patients with non-insulin-dependent diabetes mellitus or glucose intolerance: influence on muscle glucogen synthase and insulin receptor kinase activity. *Metabolism*. 1995;44: 1570–1576.
62. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med*. 2000;342:905–912.
63. Hosmer DW. *Applied Logistical Regression*. New York, NY: Wiley; 1989.
64. Glick ID, Fryburg D, O'Sullivan RL, et al. Ziprasidone's benefits versus olanzapine on weight and insulin resistance. Presented at: Annual Meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, LA.