Differential Effects of Risperidone, Olanzapine, Clozapine, and Conventional Antipsychotics on Type 2 Diabetes: Findings From a Large Health Plan Database

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Background: Case series suggest that some antipsychotics may induce or exacerbate type 2 diabetes. This study measured the association of antipsychotic treatments with diabetes at a population level.

Method: Claims data for psychosis patients (ICD-CM-9 290.xx–299.xx) within health plans encompassing 2.5 million individuals were analyzed. Patients reporting preexisting type 2 diabetes up to 8 months prior to observation were excluded. The frequency of newly reported type 2 diabetes in untreated patients and among patients treated with antipsychotics from 5 categories (risperidone, olanzapine, clozapine, and high-potency and low-potency conventionals) was compared. Logistic regression models compared the odds of diabetes based on exposure to each of the antipsychotic categories.

Results: Based on 12 months of exposure, the odds of type 2 diabetes for risperidone-treated patients (odds ratio = 0.88, 95% CI = 0.372 to 2.070) was not significantly different from that for untreated patients, whereas patients receiving other antipsychotics had a significantly greater risk of diabetes than untreated patients ($p < .05$): olanzapine, 3.10 (95% CI = 1.620 to 5.934); clozapine, 7.44 (95% CI = 0.603 to 34.751); high-potency conventionals, 2.13 (95% CI = 1.097 to 4.134); and low-potency conventionals, 3.46 (95% CI = 1.522 to 7.785). Older age and greater use of non-antipsychotic psychotropic medications also contributed to risk of type 2 diabetes. Olanzapine also showed significantly higher ($p < .01$) odds of diabetes associated with increasing dose.

Conclusion: Consistent with previously published literature, these data suggest that olanzapine, clozapine, and some conventional antipsychotics appear to increase the risk of acquiring or exacerbating type 2 diabetes and that the effect may vary by drug. In contrast to these agents, risperidone was not associated with an increased risk of type 2 diabetes.

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On the basis of several reported cases, it is suspected that some atypical antipsychotics may induce or exacerbate type 2 diabetes (also known as non–insulin-dependent and adult-onset diabetes mellitus).[1–23] Other studies have retrospectively reviewed patients for changes in insulin and glucose levels as well as new-onset diabetes associated with atypical antipsychotics.[24–28] These studies found significant elevations in glucose levels and diabetes onset after treatment with some atypical antipsychotics was initiated. A number of potential mechanisms by which the atypicals may induce type 2 diabetes have been postulated. Two recent review articles discuss the potential mechanisms of glucose dysregulation associated with antipsychotics.[29,30] Central regulation of blood glucose is controlled by the hypothalamus. Hypothalamic dopamine antagonism by conventional antipsychotics and some atypical antipsychotics may therefore lead to dysregulated blood glucose control. Several 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.[8] Actions on these receptors may result in inhibition of insulin release, insulin resistance, or impairment of glucose utilization. A significant relationship between some atypicals and excessive weight gain has been observed in clinical trials and clinical experience.[31–37] Obesity, particularly abdominal, is a risk factor for type 2 diabetes and was reported in many of the cited cases. Weight gain caused by some

atypical antipsychotics may also be related to altered glucose-insulin homeostasis. As yet, no clear mechanism of action for antipsychotic-induced diabetes has been determined. It is likely that diabetes may be attributed to multiple factors. There have also been reports associating conventional antipsychotics with type 2 diabetes.[38,39]

Despite the several case reports and logical mechanisms linking some atypical antipsychotics to type 2 diabetes, the evidence is inconclusive. Reported cases were identified as new-onset cases only because none of the afflicted individuals had a prior medical history of glucose intolerance. It is possible that glucose intolerance prior to treatment was subclinical and that treatment with atypical antipsychotics exacerbated preexisting conditions. Given the relatively high incidence of type 2 diabetes, it would be expected to observe a few cases in which the onset or worsening of this condition occurred following initiation of an antipsychotic therapy. Thus, case findings are inconclusive. A study based on sufficiently large numbers of psychosis patients is required to examine the association between antipsychotics and type 2 diabetes. A recent study by Sernyak et al.[40] compared presence of type 2 diabetes among schizophrenia patients within the Veterans Health Administration hospital system who were treated with atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine) versus those treated with conventional antipsychotics. All of the atypicals except risperidone were found to have higher odds of being associated with type 2 diabetes. While based on large numbers, the study did not control for preexisting type 2 diabetes or the level of patient exposure (e.g., treatment duration) to each of the antipsychotics.

The present study further investigated the relationship between antipsychotic therapy and type 2 diabetes using claims records of several thousand psychosis patients drawn from 2 health plans. The large numbers enabled more conclusive determination of antipsychotic contributions to the onset or exacerbation (i.e., movement from subclinical to clinical) of type 2 diabetes. The study design also controlled for preexisting (clinical) type 2 diabetes and the level of antipsychotic exposure. The study did not include type 1 (insulin-dependent) diabetes.

The onset or exacerbation of type 2 diabetes was measured among individuals treated with the various antipsychotics. As a control, the onset or exacerbation of this condition was also measured among individuals with reported psychoses but without antipsychotic treatment for the period encompassed by the data. To ensure measurement of the onset or exacerbation of type 2 diabetes rather than continuation of already existing states of health, only psychosis patients who had complete data and no documented evidence of type 2 diabetes during a specified period prior to observation were included. The period was extended to assess the sensitivity of results to preexisting type 2 diabetes.

METHOD

The analysis was based on the combined data from 2 mixed indemnity and managed care health plans encompassing 2.5 million individuals, one located in the northeast region of the United States and the other in the southeast. The data available from each of these plans extended from January 1996 through December 1997. A total of 7933 individuals within these 2 plans were identified as having some form of psychosis (ICD-CM-9 290.xx–299.xx) and either not receiving any antipsychotic medication or having antipsychotic prescriptions of at least 60 contiguous days' supply. ICD-CM-9 diagnostic criteria are related to medical claims and were used in lieu of DSM-IV criteria. Psychosis patients with antipsychotic prescriptions of fewer than 60 days' supply were excluded because it was judged that they qualified neither as treated individuals nor as controls. These almost without exception involved a single 30-day prescription, and there was no guarantee that individuals with a single antipsychotic prescription used the product (noncompliance). The presence of a second prescription provided reasonable assurance of compliance. A total of 4308 psychosis patients received at least 60 contiguous days of an antipsychotic therapy during the study period, whereas 3625 received no treatment.

Five categories of antipsychotic therapy were defined: risperidone, olanzapine, clozapine, high-potency conventionals (e.g., haloperidol, fluphenazine), and low-potency conventionals (e.g., chlorpromazine, thioridazine). For treated psychosis patients, sampling units consisted of antipsychotic treatment episodes rather than patients per se. Treatment episodes best fit the data, in that treated patients were characterized by varying degrees of antipsychotic use and by some patients being treated with the same or a different antipsychotic at different times. For each of the above antipsychotic therapies, treatment episodes were generally measured 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. Therefore, no treatment episode began before April 1, 1996. For treatment episodes truncated by disenrollment or the end of the study period, the disenrollment date or December 31, 1997, was used as the final date of treatment. Using this procedure, we determined 1591 treatment episodes with risperidone, 1178 with olanzapine, 1681 with high-potency conventionals, 556 with low-potency conventionals, and 81 with clozapine. About 16% of treated psychosis patients had more than 1 treatment episode during the April 1996 through December 1997 period with either the same antipsychotic or a different one. We considered the possibility of interdependence of sampling units and determined that it

was not a problem in this case (see Discussion). Treatment episodes with different antipsychotics overlapped in about 15% of the observations. This overlap was expected since temporary concurrent use of the prior antipsychotic is recommended when making a transition to a new antipsychotic therapy.[41]

The boundaries of a treatment episode were not strictly appropriate for associating new or resurgent cases of type 2 diabetes. Specifically, some individuals may have discontinued an antipsychotic therapy before they were diagnosed and treated for type 2 diabetes that may have been induced or exacerbated by that therapy. To adjust for this potential problem, the observation period was lagged by 30 days. For example, if a treatment episode with a particular antipsychotic extended from June 15, 1996, through March 10, 1997, the observation period for identifying type 2 diabetes was from July 15, 1996, through April 10, 1997. The 30-day lag is also consistent with the likelihood that any diabetic effects of antipsychotics will 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.[1–23]

For untreated psychosis patients, observation periods for identifying new or resurgent cases of type 2 diabetes were constructed using 3 index dates as starting points: June 1, 1996, November 1, 1996, and April 1, 1997. Untreated individuals were randomly assigned these starting dates. The purpose of the staggered observation start dates for psychosis patients untreated with antipsychotics was to create enough variation in observation period length so as not to confound it with the presence or absence of antipsychotic treatment. Observation periods ranged from 1 of the starting dates to the end of the study period (December 31, 1997) or to an individual's disenrollment date.

Individuals with type 2 diabetes were identified using ICD-CM-9 codes specifically for this condition and its manifestations or National Drug Codes for antidiabetic medications:

Type 2 diabetes ICD-CM-9 codes: 250.x0 and 250.x2.
Type 2 diabetes medications: first and second-generation sulfonylureas, metformin, rezulin, and acarbose.

Insulin, without an accompanying ICD-CM-9 code for type 2 diabetes, was not used as an indicator, because it is also the treatment for type 1 diabetes. Among the 8712 observations, a total of 647 cases of type 2 diabetes were identified using the above criteria. Many of these, however, were preexisting cases (i.e., existing prior to the observation period) and were excluded depending on the length of the screening period.

In screening for psychosis patients with preexisting type 2 diabetes, prior periods of 4 months and 8 months were applied. Patients reporting type 2 diabetes within the specified prescreening period were excluded. Patients were also excluded if their claims records did not extend back to or beyond the beginning of the specified prescreening period. The 8-month prescreening period reduced the number of observations. While this affected tests for statistical significance, it was important to assess the sensitivity of results to the preexistence of type 2 diabetes.

Because the data for this study are claims data and were not generated in a controlled trial, relative odds of type 2 diabetes could not be accurately calculated from frequency tables. Untreated psychosis patients and the 5 categories of treated patients differed in other respects that could have affected the frequency of reported type 2 diabetes within each group. For example, the likelihood of observing type 2 diabetes within a population increases with the period of observation. Also, type 2 diabetes is age related, and age differences among the groups could have caused dissimilarities in reporting. Race may also affect incidence of diabetes; however, race was not included in this analysis as it was not available from the database. Logistic regression was used to control for these and other differences among the groups. The models measured the odds of type 2 diabetes for each of the 5 antipsychotic categories versus no treatment. Two sets of logistic regressions were estimated excluding observations with preexisting type 2 diabetes at 4 and at 8 months prior to observation.

The dependent variable in a logistic model is binary taking a value of "1" if the event (type 2 diabetes) occurs for a given observation and "0" otherwise. Two sets of variables were specified in the models to capture the diabetic effects of each of the 5 antipsychotic categories:

1. Antipsychotic treatment duration. If an antipsychotic has a diabetic effect, it seems likely that this effect increases with the duration of treatment. Five variables measured treatment duration for each of the 5 antipsychotic categories as well as the absence of treatment. Each variable equaled the length of treatment in months if the observed patient used that therapy and "0" otherwise. Zeros for all 5 of the antipsychotic categories implied the sixth category—no treatment.
2. Antipsychotic dosage. The likelihood of a diabetic effect could also increase with the dosage level. Five variables measured dosage for each of the 5 antipsychotic categories as well as the absence of treatment. Each variable equaled the amount of antipsychotic used in milligrams per day of treatment. Zeros for all 5 of the antipsychotic categories implied the sixth category—no treatment. Dosages for all of the antipsychotics were expressed in risperidone-equivalent milligrams.

This was done to allow comparisons among the antipsychotic categories. High- and low-potency conventional groups each combined multiple antipsychotics, which necessitated standardization. Reported milligrams were converted to risperidone equivalents by applying weights to the doses on prescription records based on the observed range in daily dose for each antipsychotic. The range (difference between the maximum and minimum daily dose) rather than the mean daily dose was used to avoid case mix effects. Weights were calculated by dividing risperidone's daily dose range by each antipsychotic's range. For example, observed milligram ranges for risperidone and olanzapine were 6.8 mg and 17.9 mg, respectively, for a weight of 0.38 applied to olanzapine doses.

Preliminary tests indicated that antipsychotic treatment duration and dosage were highly correlated. Simultaneous inclusion of these variables would have resulted in distorted parameter estimates and unreliable tests for statistical significance. To deal with this problem, the frequently used approach of dropping 1 of the correlated variables was chosen.[42] The model was estimated twice, first with the 5 treatment duration variables only and then with the 5 dosage variables only. While this approach avoids extreme distortions in parameter estimates and allows for more reliable statistical tests, it has the limitation of omitted variable bias,[43] which in this context means that a diabetic effect attributed to the specified measure of antipsychotic exposure may in part be due to the omitted measure.

The following control variables were also specified in the models:

1. Concurrent use of antipsychotics. Concurrent use of antipsychotics, which occurred in about 21% of observations with treated patients and was normally limited to the first month or so of a new treatment, was largely taken into account by the fact that treatment episodes overlapped in such cases. A diabetic event encompassed by 2 different overlapping therapies would be assigned to both therapies. 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 confounding effects, a variable was added that measured the ratio of other antipsychotics' days' supply to treatment antipsychotic's days' supply (always "0" for untreated patients with psychosis).
2. Age. The likelihood of observing type 2 diabetes was assumed to increase with age. Age was expressed as a continuous variable.
3. Gender. The case studies cited showed a much higher proportion of males than females acquiring type 2 diabetes after initiating antipsychotic treatment. Gender was expressed as a binary variable taking a value of "1" if male and "0" if female.
4. Observation period length. The likelihood of observing type 2 diabetes increases with the period of observation, particularly in claims data, which are affected by reporting. Unlike in clinical trials, in real life antipsychotic treatment durations vary, which causes observation periods to vary. Observation period length was expressed in months.
5. Use of other psychotropic drugs. Antidepressants, anxiolytics, anticholinergics, hypnotics, and mood stabilizers are often used in conjunction with antipsychotics. A limited number of studies suggest associations between these medications and type 2 diabetes.[44,45] Individuals' use of non-antipsychotic psychotropic medications was expressed in dollars per month.
6. Type of health care coverage. Individuals in both health plans had either an indemnity or managed care form of coverage. While type of health care coverage does not affect type 2 diabetes, it may affect the likelihood that the condition is diagnosed and treated. Type of coverage was expressed as a binary variable where managed care was set equal to "1" and indemnity to "0."
7. Type of psychosis. Type 2 diabetes may be related to a specific mental health condition,[46–48] and, to the extent that the groups differed with respect to type of psychosis, this could have contributed to differences in reporting. Psychosis patients were grouped into 5 categories: schizophrenia, bipolar and manic, major depressive, dementia, and other psychoses. These were represented by binary variables for the first 4, with zeros for all 4 indicating the fifth category.

Logistic regression generates an odds ratio, expressed below, for each of the variables specified in the model:

$$[P_1/(1–P_1)]/[P_0/(1–P_0)]$$

Using treatment duration for one of the antipsychotics as an example and starting from zero treatment, this ratio is interpreted as follows:

P_1 is the probability of the event (type 2 diabetes) occurring given 1 month of treatment with the antipsychotic.
$(1–P_1)$ is the probability of the event not occurring given 1 month of treatment with the antipsychotic.
P_0 is the probability of the event occurring given no treatment with the antipsychotic.
$(1–P_0)$ is the probability of the event not occurring given no treatment with the antipsychotic.

The odds ratio for antipsychotic treatment duration measures the degree by which the base probability of type 2 diabetes is greater due to 1 additional month of treatment with that antipsychotic. The base probability depends on the base dose of the antipsychotic (assumed to be "0" in the above example) and other characteristics of the population to which the antipsychotic is applied. Odds ratios for increments of antipsychotic treatment greater than 1 month are obtained simply by raising the 1-month odds ratio to a power equal to the desired number of months of additional treatment. Using the above example, the odds ratio for 12 months of treatment with the antipsychotic versus no treatment is

$$\{[P_1/(1-P_1)]/[P_0/(1-P_0)]\}^{12}$$

This same odds ratio would also apply to 13 months of treatment with the antipsychotic versus 1 month, 14 months versus 2 months, and so forth. A similar interpretation is given to antipsychotic dosage or any other continuous variable specified in the logistic model. (For more detailed discussion of continuous variables in logistic regression, the reader is referred to Schlotzhauer[49] and Hosmer and Lemeshow.[50])

The logistic model as specified measures for each antipsychotic the odds of type 2 diabetes relative to no treatment. Odds ratios estimated as such can be manipulated to calculate the odds of type 2 diabetes of one antipsychotic relative to another. Consider, for example, antipsychotics 1 and 2:

$$\{[P_1/(1-P_1)]/[P_0/(1-P_0)]\}/\{[P_2/(1-P_2)]/[P_0/(1-P_0)]\} = [P_1/(1-P_1)]/[P_2/(1-P_2)]$$

The odds ratio for antipsychotic 1 versus untreated divided by the odds ratio for antipsychotic 2 versus untreated—the left-hand expression—yields the odds ratio for antipsychotic 1 versus antipsychotic 2—the right-hand expression.

RESULTS

Descriptive Results

Psychosis patients with type 2 diabetes were identified by the first medical claim reporting this condition or, if it appeared first, by the first prescription claim for an antidiabetic medication. (As noted, because of its use in type 1 diabetes, insulin was not used as a primary indicator.) Over 70% of diabetes cases were identified with medical claims, and 90% of these were for type 2 diabetes without complication. There were no appreciable differences between patients treated with antipsychotics and those who were untreated in how they were identified.

Table 1 reports the frequency of diabetes associated with all psychosis patients treated with antipsychotics and psychosis patients not treated with antipsychotics, as well as the frequency associated with 5 categories of antipsychotic medication. Patients were screened for preexisting diabetes at 4 and 8 months prior to observation and were eliminated when the condition was reported or there were insufficient data to make a determination. Patients were also divided according to observation period length to enable better comparisons among the groups. As would be expected, across all groups diabetes cases were relatively more frequent among patients observed over longer periods. The 4 categories of observation period length are exclusive. Also across all groups, the relative frequency of diabetes cases tended to decline as the prescreening period increased. Screening at 4 months may not exclude relatively mild, preexisting cases since for these diet and exercise alone may suffice to keep symptoms under control for long periods. Screening at 8 months is more likely to reflect new-onset type 2 diabetes or exacerbation of conditions that were previously subclinical. Regardless of the degree of prescreening, a higher percentage of treated

Table 1. Frequency of Reported Type 2 Diabetes Among Psychosis Patients by Length of Observation Period

	4-Month Prescreening			8-Month Prescreening		
		With Diabetes			With Diabetes	
Antipsychotic Treatment Group[a]	All Patients, N	N	%	All Patients, N	N	%
Untreated patients						
< 4 mo	111	0	0.0	74	0	0.0
≥ 4 to < 8 mo	166	3	1.8	94	2	2.1
≥ 8 to < 12 mo	754	12	1.6	631	8	1.3
≥ 12 mo	2030	68	3.3	939	24	2.6
All treated patients						
< 4 mo	1779	21	1.2	1447	13	0.9
≥ 4 to < 8 mo	1301	34	2.6	992	17	1.7
≥ 8 to < 12 mo	702	30	4.3	563	23	4.1
≥ 12 mo	552	38	6.9	239	14	5.9
Risperidone						
< 4 mo	556	3	0.5	440	1	0.2
≥ 4 to < 8 mo	432	6	1.4	324	4	1.2
≥ 8 to < 12 mo	188	5	2.7	140	3	2.1
≥ 12 mo	192	11	5.7	90	2	2.2
Olanzapine						
< 4 mo	462	8	1.7	440	6	1.4
≥ 4 to < 8 mo	325	11	3.4	301	7	2.3
≥ 8 to < 12 mo	200	9	4.5	189	8	4.2
≥ 12 mo	60	4	6.7	56	4	7.1
High-potency conventionals						
< 4 mo	544	6	1.1	410	4	1.0
≥ 4 to < 8 mo	395	12	3.0	271	4	1.5
≥ 8 to < 12 mo	233	13	5.6	170	9	5.3
≥ 12 mo	204	13	6.4	64	3	4.7
Low-potency conventionals						
< 4 mo	203	3	1.5	144	1	0.7
≥ 4 to < 8 mo	130	4	3.1	86	1	1.2
≥ 8 to < 12 mo	66	3	4.5	52	3	5.8
≥ 12 mo	81	8	9.9	25	4	16.0
Clozapine						
< 4 mo	15	1	6.7	13	1	7.7
≥ 4 to < 8 mo	19	1	5.3	10	1	10.0
≥ 8 to < 12 mo	15	0	0.0	12	0	0.0
≥ 12 mo	15	2	13.3	4	1	25.0

[a]Time ranges refer to length of observation period.

Table 2. Profile of Psychosis Population Without Type 2 Diabetes at 4 Months Prior to Observation[a]

Variable	All Untreated Patients	All Treated Patients	Risperidone	Olanzapine	High-Potency Conventionals	Low-Potency Conventionals	Clozapine
Age							
Mean (SD)	41.9 (14.8)	45.3 (19.3)	43.0 (20.7)	43.1 (16.9)	48.4 (18.7)	48.3 (20.5)	39.4 (14.1)
Median	43	44	43	43	47	46	40
Gender							
Male	1236	1588	550	396	465	151	26
Female	1825	2746	818	651	911	329	37
Type of health care coverage							
Managed care	1248	1295	426	308	417	115	29
Indemnity	1813	3039	942	739	959	365	34
Observation period, mo							
Mean (SD)	13.8 (4.8)	6.4 (4.6)	6.4 (4.7)	5.6 (3.5)	6.7 (4.9)	6.8 (5.0)	8.8 (5.4)
Median	14.2	4.9	4.8	4.6	5.0	4.9	7.2
Antipsychotic treatment duration, mo							
Mean (SD)	NA	6.8 (4.7)	6.8 (4.8)	6.1 (3.6)	7 (5.1)	7.1 (5.2)	9.4 (5.5)
Median	NA	5.2	5.2	5.0	5.3	5.0	7.7
Antipsychotic dosage, mg/d risperidone equivalents							
Mean (SD)	NA	2.4 (2.1)	2.3 (1.8)	3.6 (2.0)	1.7 (1.9)	1.7 (2.7)	2.5 (1.9)
Median	NA	1.8	1.7	3.3	1.1	1.0	2.2
Basis of psychosis diagnosis							
Schizophrenia (ICD-8 295.xx)	32	744	191	235	228	54	36
Bipolar and manic (ICD-9 296.0, 296.1, 296.4–296.9)	1595	932	270	260	277	113	12
Major depressive (ICD-9 296.2, 296.3)	1049	1681	579	396	508	189	9
Dementia (ICD-9 290.xx)	208	276	86	22	119	49	0
Other psychoses (ICD-9 291.xx–294.xx, 297.xx, 298.xx, 299.xx)	177	701	242	134	244	75	6
Use of other psychotropic drugs, US $/mo							
Mean (SD)	46.29 (72.91)	66.42 (90.51)	69.77 (84.09)	77.26 (107.34)	56.61 (79.97)	60.11 (76.19)	76.16 (175.52)
Median	20.21	41.38	50.40	50.72	32.85	31.23	24.35
Concurrent use of other antipsychotics, % of patients	NA	20.8	19.6	24.6	17.9	22.1	34.9

[a]Values shown as Ns unless otherwise noted.
Abbreviation: NA = not applicable.

psychosis patients reported type 2 diabetes than untreated patients. Among the 5 antipsychotic categories, risperidone consistently had the lowest percentage of patients reporting type 2 diabetes, similar to untreated patients, while clozapine had the highest. Percentages reporting type 2 diabetes for olanzapine and high- and low-potency conventionals were greater than for risperidone but less than for clozapine. Comparisons based on frequency tables, however, can be misleading if the groups being compared are dissimilar in other relevant respects.

Treated psychosis patients differed with respect to antipsychotic treatment duration and dosage, while differences in age, gender, and other patient characteristics affected all groups. These characteristics have already been identified as explanatory variables in the logistic models and are reported in Table 2. The group means and other statistics are based on the largest population used in the analysis, i.e., that screened for preexisting type 2 diabetes at 4 months prior to observation. Treated patients were older than untreated patients and had a higher proportion of females. Treated patients also had a much higher proportion of individuals with indemnity coverage versus managed care. This characteristic may affect the onset or exacerbation of type 2 diabetes because of a different emphasis on prevention as well as the likelihood of seeking professional care. Observation periods among untreated patients were more than double the length of those of treated patients, increasing the likelihood of observing type 2 diabetes in that group. Treated and untreated patients also differed considerably with respect to type of psychosis, with schizophrenia patients being virtually absent among untreated patients. The largest numbers using antipsychotics were among patients with bipolar, major depressive, and manic forms of psychosis. This is expected, as the membership of the 2 health plans comprised mostly employed individuals and their dependents, among whom schizophrenia is less likely to be found. Untreated patients had lower per capita use of other psychotropic medications than patients treated with antipsychotics.

Considerable differences also existed among the 5 antipsychotic categories. Patients treated with risperidone

Table 3. Logistic Regression Results: Type 2 Diabetes Among Psychosis Patients Excluding Preexisting Type 2 Diabetes at 4 Months Prior to Observation[a]

	Model I (treatment duration)		Model II (dose)	
Variable[b]	Odds Ratio	Probability > Chi-Square	Odds Ratio	χ^2
Treatment duration (yes = months; no = 0)				
Risperidone	1.021	0.2629	NA	NA
Olanzapine	1.082	0.0008*	NA	NA
High-potency conventionals	1.047	0.0031*	NA	NA
Low-potency conventionals	1.058	0.0090*	NA	NA
Clozapine	1.079	0.0708†	NA	NA
Dosage (yes = mg/d; no = 0)				
Risperidone	NA	NA	0.909	0.3155
Olanzapine	NA	NA	1.161	0.0012*
High-potency conventionals	NA	NA	1.090	0.1738
Low-potency conventionals	NA	NA	1.072	0.3322
Clozapine	NA	NA	1.095	0.6179
Age	1.028	0.0001*	1.030	0.0001*
Gender (male = 1)	1.079	0.6172	1.041	0.7920
Observation period (mo)	1.081	0.0001*	1.097	0.0001*
Other psychotropic drugs ($ units/mo)	1.002	0.0003*	1.002	0.0003*
Concurrent antipsychotic (ratio of days' supply)	1.060	0.8565	1.175	0.6167
Coverage (managed care = 1; indemnity = 0)	1.085	0.6144	1.071	0.6709
Schizophrenia (yes = 1; no = 0)	1.534	0.1657	1.613	0.1238
Bipolar/manic (yes = 1; no = 0)	1.157	0.5892	0.984	0.9528
Major depressive (yes = 1; no = 0)	1.192	0.5012	1.113	0.6809
Dementia (yes = 1; no = 0)	1.243	0.5080	1.166	0.6378

[a]Number reporting type 2 diabetes (1) = 206; number not reporting type 2 diabetes (0) = 7189; total observations = 7395.
[b]Patients untreated with antipsychotics are represented by zeros for each of the 5 specified antipsychotic categories.
*Significant difference at $p < .01$; †difference approaches significance at $p < .10$.
Abbreviation: NA = not applicable.

and olanzapine were similar in age, while those treated with high- and low-potency conventionals were somewhat older. Patients treated with clozapine were younger. All of the antipsychotic categories had higher proportions of females. Indemnity was the principal form of coverage across all categories. Observation periods were longest for clozapine and shortest for olanzapine, which is largely explained by the newness of olanzapine to the market at the time of the data. If not controlled for, shorter observation periods might find less diabetes in a medication group, thereby giving that medication an inappropriate advantage. Antipsychotic treatment durations, which on average were longer than observation periods, were also longest for clozapine and shortest for olanzapine. Antipsychotic dosage (risperidone-equivalent milligrams per day of treatment) differed substantially among the antipsychotics, with olanzapine having the highest dosage and low-potency conventionals the lowest. The breakdown of patients by type of psychosis shows significant differences among the antipsychotics. Clozapine had the largest proportion with schizophrenia, while low-potency conventionals had the smallest. All antipsychotic categories except clozapine had major depressive psychosis as the dominant type. Olanzapine users had the highest per capita use of other psychotropic medications, while those treated with high-potency conventionals had the lowest. Clozapine users had the highest percentage that concurrently used other antipsychotics, while users of high-potency conventionals had the lowest.

Logistic Regression Results

Logistic regression was used to estimate effects on odds of type 2 diabetes of exposure to each of the 5 antipsychotics versus no treatment. Exposure was captured by variables measuring antipsychotic treatment duration and dosage. Additional variables were specified to control for other differences among the groups that could also affect the odds of type 2 diabetes. Two versions of the logistic regression model described in the Methods section were estimated, one with treatment duration (Model I), and the other with average daily dose (Model II), as the measure of antipsychotic exposure. These 2 versions were estimated 2 times: excluding psychosis patients reporting type 2 diabetes at 4 months and at 8 months prior to observation. Model I includes the 5 variables measuring treatment duration in months with each of the antipsychotics, while Model II includes the 5 variables measuring dose in risperidone-equivalent milligrams per day. No antipsychotic treatment, the base for comparison, was represented by "zero" values for all of these variables. The odds ratio for each antipsychotic reflects the odds of type 2 diabetes associated with a 1-unit (month or milligram) increment in antipsychotic exposure.

Results based on 4 months' prescreening. Odds ratios with levels of significance are listed for the antipsychotic exposure and control variables in Table 3. The models were estimated on the basis of 7395 observations, 206 of whom reported type 2 diabetes while 7189 did not. As the odds ratios for antipsychotic treatment duration

Table 4. Logistic Regression Results: Type 2 Diabetes Among Psychosis Patients Excluding Preexisting Type 2 Diabetes at 8 Months Prior to Observation[a]

	Model I (treatment duration)		Model II (dose)	
Variable[b]	Odds Ratio	Probability > Chi-Square	Odds Ratio	χ^2
Treatment duration (yes = months; no = 0)				
Risperidone	0.989	0.7650	NA	NA
Olanzapine	1.099	0.0006*	NA	NA
High-potency conventionals	1.065	0.0252**	NA	NA
Low-potency conventionals	1.109	0.0030*	NA	NA
Clozapine	1.182	0.0104*	NA	NA
Dosage (yes = mg/d; no = 0)				
Risperidone	NA	NA	0.811	0.2367
Olanzapine	NA	NA	1.222	0.0002*
High-potency conventionals	NA	NA	1.111	0.3086
Low-potency conventionals	NA	NA	1.089	0.3062
Clozapine	NA	NA	1.304	0.1844
Age	1.025	0.0004*	1.029	0.0001*
Gender (male = 1)	0.822	0.3824	0.771	0.2432
Observation period (mo)	1.125	0.0001*	1.161	0.0001*
Other psychotropic drugs ($ units/mo)	1.002	0.0083*	1.002	0.0131**
Concurrent antipsychotic (ratio of days' supply)	1.425	0.4011	1.454	0.3950
Coverage (managed care = 1; indemnity = 0)	0.990	0.9677	0.966	0.8831
Schizophrenia (yes = 1; no = 0)	0.994	0.9897	0.939	0.8920
Bipolar/manic (yes = 1; no = 0)	1.159	0.6989	0.944	0.8786
Major depressive (yes = 1; no = 0)	1.151	0.7014	1.079	0.8350
Dementia (yes = 1; no = 0)	1.449	0.4017	1.362	0.4818

[a]Number reporting type 2 diabetes (1) = 101; number not reporting type 2 diabetes (0) = 4878; total observations = 4979. Patients untreated with antipsychotics are represented by zeros for each of the 5 specified antipsychotic categories.
*Significant difference at $p < .01$; **significant difference at $p < .05$.
Abbreviation: NA = not applicable.

indicate (Model I), risperidone had no statistically significant effect on diabetes. The diabetic effects of olanzapine, high-potency conventionals, and low-potency conventionals were all statistically significant at $p < .01$. Clozapine's diabetic effect was significant only at $p < .10$; however, this is likely due to its relatively small sample. Clozapine and olanzapine had the highest odds ratios (largest diabetic effects), which is consistent with the case literature. Each 1-month increment of treatment with olanzapine increased the odds of type 2 diabetes by 8.2%. When treatment duration was replaced with dosage (Model II), only olanzapine was statistically significant ($p < .01$). Olanzapine's odds ratio of 1.161 implies that each increment of 1 risperidone-equivalent milligram of this antipsychotic (2.6 actual milligrams of olanzapine) increased the odds of type 2 diabetes by 16.1%.

Among the control variables, age was highly significant ($p < .01$), as would be expected for type 2 diabetes. Since "age" is a continuous variable expressed in years, its odds ratio indicates the percent increment in the odds of type 2 diabetes as an individual ages by 1 year. Logically, the length of the observation period also affected the likelihood of observing type 2 diabetes ($p < .01$). The use of non-antipsychotic psychotropic medications (measured in $10 units) was highly correlated with the likelihood of type 2 diabetes ($p < .01$). Since mechanisms through which antipsychotics and other medications may affect type 2 diabetes have not been fully investigated, it is possible that antidepressants, anxiolytics, mood stabilizers, etc., also induce or exacerbate this condition. None of the other control variables were statistically significant. The variables reflecting psychosis type did not approach statistical significance, and, as Table 2 indicates, there was considerable variation among the groups in this regard.

Results based on 8 months' prescreening. Results based on 8 months' prescreening are reported in Table 4. Prescreening at 8 months further reduced observations to 4979, with 101 reporting type 2 diabetes. Results with this "cleaner" population were essentially the same as with the population prescreened at 4 months: all of the antipsychotics except risperidone showed diabetic effects. Results based on antipsychotic treatment duration (Model I) strengthened with prescreening at 8 months. Odds ratios for olanzapine, clozapine, and high- and low-potency conventionals increased and were all significant at $p < .05$ or better. In contrast, risperidone's odds ratio declined to 0.989 (still not significant). For antipsychotic dosage (Model II), olanzapine was statistically significant ($p < .01$) at 8 months' prescreening. Its odds ratio rose to 1.222, implying that a risperidone-equivalent dose of 1 mm (2.6-mg actual dose of olanzapine) increased the odds of type 2 diabetes by 22.2% over baseline. The same control variables were statistically significant with the populations prescreened at 8 months as with the population prescreened at 4 months.

Table 5 provides some useful calculations based on the odds ratios for antipsychotic treatment duration estimated

Table 5. Extrapolation of Type 2 Diabetes Odds Ratios for Antipsychotic Treatment Duration Excluding Preexisting Type 2 Diabetes at 8 Months Prior to Observation

Antipsychotic Treatment	Odds vs Untreated at 1 Month of Treatment	95% CI	Odds vs Untreated at 12 Months of Treatment	95% CI	Odds vs Risperidone at 12 Months of Treatment
Risperidone	0.989	0.921 to 1.063	0.88	0.372 to 2.070	NA
Olanzapine	1.099	1.041 to 1.160*	3.10	1.620 to 5.934*	3.53**
High-potency conventionals	1.065	1.008 to 1.126*	2.13	1.097 to 4.134*	2.42
Low-potency conventionals	1.109	1.036 to 1.187*	3.46	1.522 to 7.785*	3.93**
Clozapine	1.182	1.040 to 1.344*	7.44	1.603 to 34.751*	8.45**

*Odds ratio of 1.00, meaning effect is no different from untreated, falls outside of 95% CI.
**$p < .05$.
Abbreviation: NA = not applicable.

with the population prescreened for type 2 diabetes at 8 months prior to observation. There is a higher certainty that this population does not have preexisting diabetes; therefore, these odds ratios are more accurate indicators of antipsychotic diabetic effects. Estimated odds ratios, which reflect diabetic effects associated with 1 month of treatment, are listed in column 1. Ninety-five percent CIs are shown in column 2. These ratios were converted to reflect 12 months of treatment (column 3) with corresponding CIs (column 4). Risperidone's ratio of 0.88 implies that patients treated for 12 months with this antipsychotic face odds of type 2 diabetes that are 12% below baseline, but this is not statistically significant. In contrast, the 12-month ratios for the other antipsychotics are greater than 2.0 and are statistically significant. Olanzapine's ratio is 3.10, meaning that 12 months of treatment with this antipsychotic increases the odds of diabetes by 210% above baseline. Similar interpretations apply to clozapine and high- and low-potency conventionals. The last column shows the odds of type 2 diabetes for each of the other antipsychotics versus risperidone assuming 12 months of treatment. Olanzapine's ratio of 3.53 implies that its diabetic effect is 2.5 times greater than that of risperidone, which is statistically significant at $p < .05$ based on a chi-square test for homogeneity of odds ratios (using the Woolf method designed to compare results from separate trials[51]). Odds ratios for low-potency conventionals (3.93) and clozapine (8.45) versus risperidone are also high and statistically significant ($p < .05$). The odds ratio for high-potency conventionals versus risperidone is not statistically significant.

DISCUSSION

Recent data collected by the Schizophrenia Patient Outcomes Research Team (SPORT) suggest that people with schizophrenia may be at increased risk for type 2 diabetes because of the side effects of antipsychotic medication, poor overall physical health, less healthy lifestyles, and inadequate health care.[52] A possible relationship between the atypical antipsychotics olanzapine and clozapine and type 2 diabetes has been suggested in a number of case reports.[1–15,19–23] Three recent reports[16–18] suggested a possible association with risperidone, and earlier case reports[38,39] linked conventional antipsychotics with an increased risk of diabetes. Because of the small numbers involved and the relatively high incidence of type 2 diabetes, case findings are inconclusive.

To overcome this limitation and to provide an alternative source of evidence, this study used administrative data from 2 large health plans to investigate the medical histories of several thousand psychosis patients both treated and untreated with antipsychotics. While frequency tables were constructed to contrast treated and untreated patients and the various antipsychotic categories, in light of other important differences among the groups, logistic regression was used to more accurately estimate antipsychotic effects on the odds of type 2 diabetes.

Both frequency tables and logistic regression showed risperidone to have little or no diabetic effect. Based on logistic regression results with treatment duration as the measure of antipsychotic exposure, psychosis patients treated with risperidone were no more likely to acquire or exacerbate type 2 diabetes than untreated patients. This was true regardless of the degree of prescreening for type 2 diabetes. In contrast, the other antipsychotics, including olanzapine, clozapine, and high- and low-potency conventionals, had statistically significant effects on diabetes that were relatively large. These effects were strongest with 8 months' prescreening.

Positive and statistically significant effects of antipsychotic dosage on diabetes were observed for olanzapine only. These, too, were strongest with 8 months' prescreening. The absence of a significant dose effect for clozapine and high- and low-potency conventionals may have been due to the relative weakness of average daily dose as a measure of antipsychotic exposure. Antipsychotic dose is likely to vary over the course of treatment, and average dose, the most practical measure, may be weakly related to the dose that caused the diabetes. Also, antipsychotic dose is dependent on patient body weight, so that different doses may imply the same degree of antipsychotic exposure for patients with different body weights (patient weight is not reported in claims data).

Among the control variables, older age and greater use of non-antipsychotic psychotropic medications increased the odds of type 2 diabetes. Type of psychosis was not a statistically significant predictor of diabetes, which casts doubt on the view that diabetic effects are diagnosis related rather than antipsychotic related.

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, e.g., genes. However, the mechanism(s) through which antipsychotics may cause type 2 diabetes are still unknown, and there is little reason to assume that inherent patient characteristics play a key role. Also, we reestimated the logistic equations keeping only the first treatment episode for each patient. With the exception of clozapine, which was already compromised by a small sample, results were virtually unchanged. In any case, dropping the first or second antipsychotic episode can create bias where episodes overlap or if being first or second is not random.

A number of potential mechanisms for antipsychotic-induced diabetes have been proposed, and it is likely that no one mechanism fully describes the relationship. This study showed differential effects of antipsychotics on diabetes. This finding may indicate that different medications have different mechanisms for causing diabetes. Olanzapine and clozapine may have an increased risk of diabetes due to induction of insulin resistance, nonspecific serotonin antagonism, and/or excessive weight gain. Conventional antipsychotics are typically potent dopamine-2 receptor antagonists, which may lead to increased risk of diabetes. Risperidone has not been associated with increased insulin resistance or significant weight gain and may interact with fewer receptors implicated in changes in glucose.

Given efforts made to identify individuals with preexisting type 2 diabetes and to accurately associate new-onset cases with the antipsychotics through the use of treatment episodes, we believe that our findings are reliable. Limitations to this study include the inability to control for potential confounders to the results and the limited ability to determine previous history of and risk factors for diabetes. Both race and changes in weight can affect the incidence of diabetes. Neither of these variables was available in the database studied. The study was able only to establish that individuals did not require medical attention for type 2 diabetes for determined periods prior to initiation of specific antipsychotic therapies. Therefore, the need for diabetes medical attention after initiation of antipsychotic treatment could be interpreted as reflecting either the onset of diabetes or the exacerbation of a preexisting condition. It is suggested that future studies should include an analysis of the association of antipsychotics with diabetes controlling for changes in weight as well as ethnicity.

The present study demonstrates an increased risk of diabetes with some antipsychotics, primarily low-potency conventionals, olanzapine, and clozapine. In contrast to these, this study suggests that risperidone has no increased diabetic effect.

Drug names: acarbose (Precose), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluphenazine (Proloxin, Permitil, and others), haloperidol (Haldol and others), metformin (Glucophage and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

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