Original Article

Rate of New-Onset Diabetes Among Patients Treated With Atypical or Conventional Antipsychotic Medications for Schizophrenia

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Abstract and Introduction

Abstract

Context: Understanding the association between use of antipsychotics and onset of diabetes.

Objective: To compare the rates of new-onset diabetes mellitus (DM) between patients treated for schizophrenia with atypical or conventional antipsychotics.

Design: Retrospective analysis of medical and pharmacy claims data.

Setting: 61 US health plans.

Patients: Patients with schizophrenia who were treated with atypical or conventional antipsychotics between September 1996 and June 2001 and were enrolled for 12 or more months before and 3 or more months after therapy initiation.

Main Outcome Measures: New-onset DM was defined based on 2 or more claims with a diabetes diagnosis or initiation of antidiabetic therapy during follow-up. Rates of DM were compared between patients receiving atypical and conventional antipsychotics, and among 4 subgroups of patients receiving atypical antipsychotics (olanzapine, clozapine, risperidone, quetiapine). Statistical analyses employed logistic regression and Cox proportional hazards models.

Results: Patients treated with atypical antipsychotics (N = 1826) were younger, had a lower rate of diagnosed hypertension, and longer duration of therapy than those receiving conventional antipsychotics (N = 617). The crude incidence of DM did not differ (2.46% vs 2.76% for atypical antipsychotics and conventional antipsychotics, *P* = .525). In Cox proportional hazards models, patients treated with atypical antipsychotics had a statistically significant, moderately increased risk of DM relative to conventional antipsychotics (hazard ratio [HR] = 1.17, 95% confidence interval [CI] = 1.06, 1.30); no significant differences in risk were observed when atypical antipsychotic cohorts were compared. In logistic regression models, no significant differences in DM risk were observed.

Conclusions: Patients with schizophrenia treated with atypical antipsychotics had a moderately increased risk of DM relative to those treated with conventional antipsychotics, as measured by Cox proportional hazards models; such risk was not significantly different among patients treated with individual atypical medications.

Introduction

Schizophrenia is a disabling condition characterized by profound disruption in cognition and emotion, affecting language, thought, perception, affect, and sense of self. The array of symptoms, while substantially varied among patients, frequently includes psychotic manifestations such as hallucinations and delusions.[1] Prior research has documented that in addition to psychiatric difficulties, patients with schizophrenia are also at greater risk than the general population of concurrent medical conditions such as vision and dental problems, high blood pressure, diabetes, and sexually transmitted diseases.[2,3]

Beginning in 1990, a new generation of antipsychotic medication was introduced. These "atypical" antipsychotic medications, in comparison with first-generation (or "conventional") antipsychotics, have been associated with improved efficacy in treating both positive and negative symptoms of schizophrenia, and have exhibited a superior safety profile in regard to adverse events such as extrapyramidal symptoms.[4,5] In the past decade, atypical antipsychotics such as risperidone, olanzapine, and quetiapine have become first-line treatment options for patients with schizophrenia.

Although atypical antipsychotics have greatly improved the treatment of schizophrenia, weight gain, increased serum prolactin levels, and QTc prolongation have been reported during treatment with some atypical antipsychotics.[6-9] More recently, the results of several case reviews and database studies have examined a potential association between atypical antipsychotic use and increased insulin resistance or risk of developing overt DM.[9-23] These studies have varied greatly, however, in their study populations, methods, results, magnitude of identified risk, and implication of specific atypical medications over others. For example, using logistic regression techniques, Gianfrancesco and colleagues[20] found DM risk for risperidone users to be similar to that among untreated subjects, while excess risk was observed among olanzapine, clozapine, and selected conventional drugs. In contrast, findings from survival-based research on 2 databases by Sowell and colleagues[19] indicated that risperidone and olanzapine had similar effects on DM risk; in fact, a significantly greater risk was attributed to risperidone in one of these analyses.

While all of these methodologic factors may contribute to discrepant findings, choice of methodology is an actionable variable that may have a significant effect on study conclusions. Although fixed follow-up techniques are widely accepted, the introduction of accrued person-time (ie, allowing all candidate populations to contribute observation times of varying duration) provides an alternative that may better reflect the nature of usual psychiatric practice for patients with schizophrenia in the United States. Specifically, antipsychotic therapy is often sporadic, and patients may be lost to follow-up for a variety of reasons (eg, changes in healthcare coverage, death, confinement, or imprisonment).

The present study examined the rate of new-onset DM in a large, geographically diverse, commercially insured population treated with atypical or conventional antipsychotics. We present findings using both fixed follow-up and accrued person-time techniques to examine the effects of choice of methodology on these results.

Methods

Data Source

Data were obtained from the PharMetrics Patient-Centric Database, which is composed of medical and pharmaceutical claims for approximately 36 million unique patients from 61 health plans across the United States. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats), as well as both standard and mail order prescription records; available data on prescription records include the NDC code as well as days supplied and quantity dispensed. All medical and pharmaceutical claims include dates of service. Additional data elements include demographic variables (age, gender, geographic region), health plan type (eg, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

Because all pertinent patient information in the database is encrypted and privacy-protected, no informed consent or approval by institutional review boards was required.[24]

Sample Selection

The sample included patients with 1 or more medical claims with a listed diagnosis of schizophrenia (ICD-9-CM code 295.XX) as well as 1 or more paid pharmacy claims for an antipsychotic medication (generic product index

class code 2816080000) between September 30, 1996 and June 30, 2001. All medical and pharmacy claims were then compiled for these patients for the period September 30, 1995-September 30, 2001. The first observed antipsychotic pharmacy claim was deemed the "index date"; a pretreatment period of 12 months' duration was compiled in relation to this date. Patients with prescriptions for more than 1 antipsychotic on the same date were excluded from the sample (this constituted less than 1% of the candidates for inclusion in the study). All patients also were required to have a minimum of 3 months of follow-up; follow-up was allowed to vary, as techniques to account for right-censored data were employed in primary data analyses.

Patients were grouped by type of antipsychotic received on the index date -- atypical (ie, clozapine, risperidone, quetiapine, or olanzapine) or conventional (eg, haloperidol or fluphenazine) antipsychotics. A list of antipsychotics included can be found in Table 1. Ziprasidone, sertindole, and aripiprazole were not included in the atypical antipsychotic group, as they are newer atypical medications, and the timeframe used for this study did not allow for creation of sufficiently sized samples of patients receiving these medications. In addition, prochlorperazine was excluded from consideration as a conventional antipsychotic, as its use is primarily nonpsychiatric (eg, antiemesis). All patients who had evidence of use of an atypical or conventional antipsychotic in the 6 months prior to the index date were excluded from the study sample, as were those who had evidence of DM (based on medical claims or prescriptions for DM medications) throughout the entire 12-month pretreatment period. In addition, all members of health plan contributors to the PharMetrics database that "carve out" mental health services (6 of the 61 plans) were excluded from the sample because complete utilization data were not available for these patients. Finally, patients who were not continuously eligible for health and drug benefits throughout the pretreatment and follow-up periods were excluded.

A total of 1826 patients receiving atypical antipsychotics (n = 937, 690, 164, and 35 for olanzapine, risperidone, quetiapine, and clozapine, respectively) and 617 patients receiving conventional medications were selected for analysis.

Measures

The primary measure of interest in this analysis was the incidence of new-onset DM at any time during the year after initiation of antipsychotic therapy. Patients were deemed to have been diagnosed with DM if they had 1 or more paid pharmacy claims for an oral DM medication, insulin, or insulin syringes, or if they had 2 or more claims with a listed DM-related diagnosis (ICD-9-CM 250.XX, 362.01, 362.02), on or after the index date.

A variety of demographic and clinical characteristics also were examined for the study sample, including age, gender, health plan type (eg, HMO, PPO), geographic region (Northeast, Midwest, South, and West), calendar year of drug initiation, number of DM screening tests (CPT-4 codes 80048-80050, 80054, 80069, 81000-81005, 82947-82954), number of laboratory tests overall, and other psychiatric diagnoses (ie, other than schizophrenia) recorded in the pretreatment or follow-up periods (ie, bipolar disorder [ICD-9-CM 296.0-296.1, 296.4-296.9], and/or depression [296.2-296.3; 300.4]) as well as other medical diagnoses known to be risk factors or concomitant conditions with DM -- specifically, hypertension (ICD-9-CM 401.XX-405.XX), cardiovascular disease (ICD-9-CM 410.XX-414.XX, 420.XX-429.XX, 433.XX-436.XX, 437.0, 437.1, 440.XX-442.XX), obesity (278.0X), and impaired glucose tolerance (790.2). The total duration of therapy (calculated based on the period of time between the last fill and first fill dates for the index medication) also was calculated, as was the number of prescriptions for the index medication.

Measures were examined comparing the atypical and conventional antipsychotic cohorts on an overall basis as well as among the individual atypical antipsychotic cohorts (ie, risperidone, olanzapine, clozapine, and quetiapine).

Analyses

Primary analyses were conducted on an intent-to-treat basis; all patients with at least 1 prescription for an index medication of interest were therefore included in these analyses. Findings were presented as group means and percentages, along with appropriate measures of precision (ie, standard deviations, 95% confidence intervals).

Demographic and clinical characteristics of the study sample as well as the incidence of new-onset DM were reported for patients receiving atypical and conventional antipsychotics. Analyses were replicated for patients receiving atypical antipsychotics, and compared between the 4 cohorts available for analysis (olanzapine, risperidone, quetiapine, and clozapine). In all such analyses, comparisons of categorical variables were performed using an overall chi-square test or Fisher's Exact Test (ie, for cell sizes less than 5); comparisons of mean age were

performed using a t-test.

In addition to unadjusted comparisons, 2 modeling techniques were employed to compare the rate of new-onset DM between cohorts. In the overall cohorts, Cox proportional hazards models were employed to estimate DM rates in the setting of variable follow-up. In the subgroup of patients with 12 months of continuous enrollment subsequent to the index date, logistic regression techniques were used to examine DM rates. Explanatory variables in both base models included the demographic and clinical variables described above. Model specifications and HRs or odds ratios (ORs) (along with corresponding 95% CIs) were set forth for the overall population as well as the comparisons performed among atypical medications. For these risk estimates, a *P* value < .05 was considered statistically significant.

All analyses were conducted using Statistical Analysis Software (SAS®), version 8.2.

Results

A total of 18,134 patients were initially identified for analysis. After application of study enrollment criteria, a total of 12,368 remained. Finally, exclusion of patients without a schizophrenia diagnosis in their claims history yielded a total of 2443 patients remaining (n = 1826 and 617 for atypical and conventional users, respectively) (Table 2). The mean duration of follow-up was 435 days and was significantly longer among patients in the conventional group (485.0 vs 418.8 days for atypicals, *P* < .0001). Patients receiving atypical medications were significantly younger (mean [± SD] age: 38.0 [± 12.4] vs 42.4 [± 11.7] years for conventional antipsychotics, *P* < .0001). The mean duration of therapy was approximately 9 months in both groups while the mean number of prescriptions was significantly higher in the atypical group (8.5 vs 6.6; *P* < .0001). Distribution of calendar year of therapy initiation was significantly different between patients receiving atypicals and conventionals (*P* = .0003). Patients receiving atypical medications were also significantly more likely to have additional psychiatric diagnoses, but significantly less likely to have a pretreatment diagnosis of hypertension (12.5% vs 17.2% for conventional medications, *P* = .0033). Slightly more than half of selected patients had sufficient follow-up for logistic regression analyses (n = 953 and 363 for atypical and conventional antipsychotics, respectively). For these analyses, demographic and clinical characteristics, as well as differences between atypical and conventional antipsychotic cohorts, were essentially identical to those with variable follow-up.

A total of 45 patients in the atypical medication group and 17 patients in the conventional group were identified as having developed DM during follow-up; given the shorter duration of follow-up in the atypical group, its crude DM incidence rate was nonsignificantly lower than that of the typical group (2.46% vs 2.76% for atypical and conventional medications, respectively, *P* = .5252). The mean time to event across both groups was 62.2 (± 35.8) days.

Among atypical antipsychotic users, nearly all patients had an index medication of olanzapine (n = 937) or risperidone (n = 690); the totals were 164 and 35 for quetiapine and clozapine, respectively (Table 3). Patients in the 4 groups were similar with respect to age, duration of follow-up, and duration of use of index medication. Significant differences were observed, however, with respect to distribution by health plan type, geographic region, number of prescriptions for index therapy, and calendar year of initiation. Risperidone users were more frequently observed in more stringently managed (ie, HMO) settings and Southern health plans, while olanzapine was seen more frequently in Western plans. Clozapine users had a higher number of prescriptions on average as compared with the other atypical groups. A larger proportion of patients receiving olanzapine began therapy in 2001 and fewer began therapy in the previous years as compared with patients receiving risperidone, clozapine, and quetiapine. Olanzapine, risperidone, and quetiapine users were significantly more likely to have psychiatric comorbidities than clozapine users, although these results should be interpreted with caution due to small sample sizes in the latter group.

Of the 45 cases of new-onset DM during follow-up for patients receiving atypical antipsychotics, 23 (2.45%), 16 (2.32%), 2 (5.71%), and 4 (2.44%) were among olanzapine, risperidone, clozapine, and quetiapine users, respectively. These differences were not statistically significant (*P* = .9363).

The results of Cox proportional hazards analyses are presented in Table 4. When the overall atypical and conventional antipsychotic cohorts were compared, atypical antipsychotic use was temporally associated with a moderately increased risk of DM at 1 year after therapy initiation relative to conventional antipsychotics (HR = 1.172, 95% CI = 1.061, 1.300; *P* = .0063). Among other variables in the model, age, number of DM and other laboratory tests, and the presence of a bipolar disorder diagnosis all conferred moderately protective effects with respect to DM

risk. Each increase in calendar year of therapy initiation, however, was associated with a more than threefold increase in DM risk independent of therapeutic choice (HR = 3.581, 95% CI = 3.492, 3.659; *P* < .0001).

When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset DM (HR = 1.049, 95% CI = 0.930, 1.168, *P* = .4308; HR = 1.170, 95% CI = 0.967, 1.372, *P* = .1291; and HR = 1.467, 95% CI = 0.967, 1.968, *P* =.1332 for olanzapine vs risperidone, quetiapine, and clozapine, respectively). Findings with respect to covariates were similar to those observed in overall comparisons of patients treated with atypical vs conventional medications.

In logistic regression comparisons among those enrolled for at least 12 months after index date, follow-up constraints necessitated collapse of the quetiapine and clozapine cohorts into a single "other" category. In these models, a similar magnitude of difference in risk between the atypical and conventional antipsychotic cohorts was observed, although this was not statistically significant (OR = 1.193 for atypical antipsychotics vs conventional medications, 95% CI = 0.505, 2.820; *P* = .6871) (Table 5). Among other explanatory variables included in this model, no statistically significant differences were observed. DM risk also did not significantly differ among the 3 atypical medication cohorts available in this analysis.

Discussion

To assess, under conditions of general practice, the rate of new-onset DM in schizophrenic patients treated with atypical vs conventional antipsychotics, we retrospectively examined patient data from a US-based, patient-level database of integrated medical and pharmacy claims. The rate of new-onset DM was studied during the first year after therapy initiation, and was examined on a crude and adjusted basis. We found that, in a managed-care population, patients receiving atypical antipsychotic medications for schizophrenia had a statistically significant, moderately increased risk of new-onset DM relative to patients treated with conventional medications. Results were similar in a subset of these patients followed for 12 months or more after therapy initiation. However, in contrast to findings from other studies that have implicated selected atypical medications,[10,20] our results do not suggest any material differences among the patients treated with major atypical medications in use during the study period, regardless of the analytic paradigm employed (ie, fixed follow-up or accrued person-time). It is worth noting that we were able to follow patients for 15 months after therapy initiation on average, a duration of follow-up that exceeds that available in other database studies on this topic.[18,20] While it is premature to conclude that differences among patients treated with various atypical medications in terms of DM risk do not exist, further study is needed to evaluate whether risk differences highlighted after relatively short drug exposure converge over time.

Of note, the variable most predictive, by far, of new-onset DM was calendar year of therapy initiation, which imparted nearly a fourfold increased risk of DM with *each* successive year between 1996 and 2001. This finding may be correlated to the amount of research focused on this topic, suggesting that increased awareness of DM risk may be leading to a heightened amount of scrutiny for DM symptoms in antipsychotic-treated patients. If screening intensity is found to differ by class of antipsychotic or type of atypical medication, however, significant biases may be inherent in any retrospective study of this phenomenon; the true answer may only be determined through the conduct of prospective studies in which DM screening is controlled and unbiased.

The findings of this study also indicate that patients treated for schizophrenia are at higher risk of developing DM than those in the general population. Rates of DM in this study ranged from 1% to 2.5% over 1 year of follow-up, which is 2-10 times the age-adjusted annual rate for US residents as a whole.[25-27] Other published database studies have also found that patients treated with atypical or conventional antipsychotics have an increased risk of developing DM as compared with the general population.[18,19]

Our results are similar to those of other retrospective studies that have relied on automated administrative data. In an analysis of medical and pharmacy claims among patients with schizophrenia enrolled in the Iowa Medicaid program, Lund and colleagues[11] found that the incidence of DM did not materially differ between patients receiving clozapine and those receiving conventional medications over approximately 2 years of follow-up. While a significantly greater risk was noted among clozapine patients aged 20-34 years, this study design did not feature a "washout" period (ie, a period during which prior mental health or DM claims could not have been observed). Findings may have therefore been confounded by experience prior to Medicaid enrollment.

Similarly, in a large study (n = 38,632) of workload data at Veteran's Administration outpatient facilities, the prevalence of DM was essentially identical (approximately 19%) in patients receiving atypical and conventional antipsychotics.[12] The same age-related phenomenon noted in the Lund study was observed here; in addition,

patients treated with clozapine, olanzapine, and quetiapine, but not risperidone, had a significantly increased prevalence of DM in logistic regression analyses. However, systematic differences were noted in the 2 populations, including a higher propensity for hospitalization among atypical users (which may have resulted in opportunistic case finding).

In contrast, Koro and colleagues[10] conducted a nested case-control study using a database of physician records in the United Kingdom, in which use of olanzapine was associated with a fourfold increased risk of diabetes relative to conventional antipsychotics, whereas no such association was observed among patients receiving risperidone. Findings from this study may be limited, however, by the following: (a) data are only included in this database when certain research standards are met (reducing the availability of historical data) and only three quarters of specialist interactions are captured electronically; and (b) the confidence interval around DM risk was quite large among users of atypical medications (which was likely due in part to a very small number of incident events in this group). This phenomenon was not observed in the much larger group with conventional medication exposure, suggesting that a different analytic paradigm with a larger representation of medications in the atypical class (as we feel our study represents) may yield different results.

While our sample included patients diagnosed with schizophrenia who were newly started on antipsychotic medications, it is likely that many of these patients were not newly diagnosed. Patients may have ceased antipsychotic therapy more than 6 months before our defined index date and were therefore retained in our sample, or may have been hospitalized during much of the preindex period. Indeed, the fact that the average age of our sample was older than typical for a cohort of newly diagnosed schizophrenics supports the notion that patients in our sample were a mix of the newly diagnosed and "restarted." While it could be argued that ICD-9-CM coding of mental health disorders is neither highly sensitive nor specific, we allowed medication use to be the final arbiter of sample inclusion, as most of the other studies on this topic have done.

We note some important limitations of our analysis. First, the data sources for the PharMetrics database consist of processed healthcare claims from managed care organizations; as such, we could not control for certain clinical or other differences between treatment groups (eg, baseline body mass index, lipid levels, family history) that may have confounded our findings. Also, privacy regulations prohibit the capture of race or ethnicity in the database, a well-documented confounding variable when assessing DM incidence.

In addition, as with all quasi-experimental research using retrospective data, we cannot rule out the possibility that selection bias may have influenced our findings; nevertheless, our results were unchanged when we controlled for differences in those demographic and clinical variables that were available to us in this database.

We also note that antipsychotic exposure was estimated based on prescription filling behavior as a proxy for actual consumption. If patients receiving atypical medications are in fact more or less likely to comply with prescribed treatment regimens than those receiving conventional agents, a bias may be introduced to our study. In this sample, however, *persistence* (as measured by duration of therapy) was quite similar across these cohorts while number of prescriptions was significantly higher in the atypical group, suggesting that they were behaviorally similar in persistence while atypical patients may have been more compliant with therapy.

Given the above discussion, this sample is likely to be fundamentally different from the US schizophrenic population, many of whom are insured by public sources or uninsured. Still, the large number of data sources that feed into this database speaks to the study's internal validity. In addition, the biologic effects of antipsychotic medication on DM incidence should not be subject to great variability across cohorts, even given the potential differences in risk factor profiles across groups.

Despite these limitations, the results of our study suggest that attribution of an increased risk of diabetes to a particular brand of antipsychotic may represent a premature conclusion. Patients treated with atypical antipsychotics appear to have a moderately increased risk of diabetes relative to patients treated with older medications. However, further rigorously controlled, long-term, prospective studies are needed.

Tables

Table 1. Conventional and Atypical Antipsychotic Medications Included in Analyses

Conventional	Atypical
Acetophenazine	Clozapine
Chlorpromazine	Olanzapine
Chlorpromazine HCL	Quetiapine
Chlorprothixene	Risperidone
Fluphenazine	
Fluphenazine decanoate	
Fluphenazine enanthate	
Fluphenazine HCL	
Haloperidol	
Haloperidol decanoate	
Haloperidol lactate	
Loxapine	
Loxapine HCL	
Loxapine succinate	
Mesoridazine besylate	
Molindone HCL	
Perphenazine	
Pimozide	
Promazine	
Promazine HCL	
Thioridazine	
Thioridazine HCL	
Thiothixene	
Thiothixene HCL	
Trifluoperazine	
Triflupromazine	

Table 2. Demographic and Clinical Characteristics as Well as Diabetes Incidence Among Schizophrenia Patients, by Antipsychotic Treatment Group

Characteristic	Atypical (N = 1826)		Conventional (N = 617)		P Value
"Age in years (mean, SD)"	38.0	12.4	42.4	11.7	< .0001
Gender (% male)	877	48.0%	300	48.6%	0.8272
"Duration of follow-up (mean, SD)"	418.8	247.2	485.0	285.7	< .0001
"Index medication use (mean, SD):"					

Total duration of therapy	260.8	247.6	252.4	273.5	0.4889
Number of prescriptions	8.5	9.6	6.6	7.6	< .0001
Year of therapy initiation:					0.0003
1996	9	0.5%	7	1.1%	
1997	16	0.9%	13	2.1%	
1998	274	15.0%	130	21.1%	
1999	693	38.0%	220	35.7%	
2000	645	35.3%	188	30.5%	
2001	189	10.4%	59	9.6%	
Plan type:					0.535
HMO	879	48.1%	309	50.1%	
PPO	259	14.2%	96	15.6%	
POS	201	11.0%	57	9.2%	
Indemnity	117	6.4%	41	6.6%	
Other	370	20.3%	114	18.5%	
Geographic region:					0.276
Northeast	297	16.3%	98	15.9%	
South	554	30.3%	212	34.4%	
Midwest	591	32.4%	179	29.0%	
West	384	21.0%	128	20.7%	
Psychiatric diagnosis:					
Bipolar disorder	796	43.6%	193	31.3%	< .0001
Depression	972	53.2%	232	37.6%	< .0001
Medical diagnosis:					
Hypertension	228	12.5%	106	17.2%	0.0033
Cardiovascular disease	188	10.3%	50	8.1%	0.1068
Obesity	69	3.8%	24	3.9%	0.8952
Impaired glucose tolerance	2	0.1%	1	0.2%	0.7463
"Laboratory tests (mean, SD):"					
Diabetes screening	1.0	1.9	1.1	2.1	0.1098
All other	5.8	11.5	5.9	13.2	0.8428
Incidence of diabetes at one year (%)	45	2.46%	17	2.76%	0.5252

Table 3. Demographic and Clinical Characteristics and Diabetes Incidence Among Schizophrenia Patients, by Atypical Antipsychotic Group

	Olanzapine	**Risperidone**	**Clozapine**	**Quetiapine**	***P***

Characteristics	(N = 937)		(N = 690)		(N = 35)		(N = 164)		Value
Age (mean SD)	38.4	12.4	37.2	12.3	36.8	9.5	39.7	11.1	0.0695
Gender (% male)	469	50.1%	334	48.4%	16	45.7%	58	35.4%	0.0039
Duration of follow-up (mean SD):	415.4	236.8	429.4	257.3	388.9	263.0	399.8	234.3	0.1295
Index medication use (mean SD):									
Total duration of therapy	261.4	236.6	260.5	256.6	329.5	260.5	244.1	238.0	0.237
Number of prescriptions	8.3	8.4	7.5	7.0	32.0	26.8	9.0	11.1	< .0001
Year of therapy initiation:									< .0001
1996	0	0.0%	9	1.3%	0	0.0%	0	0.0%	
1997	9	1.0%	6	0.9%	1	2.9%	0	0.0%	
1998	160	17.1%	101	14.6%	3	8.6%	10	6.1%	
1999	379	40.4%	243	35.2%	14	40.0%	57	34.8%	
2000	297	31.7%	266	38.6%	11	31.4%	71	43.3%	
2001	92	9.8%	65	9.4%	6	17.1%	26	15.9%	
Plan type:									0.0001
HMO	449	47.9%	345	50.0%	13	37.1%	72	43.9%	
PPO	117	12.5%	99	14.3%	4	11.4%	39	23.8%	
POS	104	11.1%	74	10.7%	7	20.0%	16	9.8%	
Indemnity	55	5.9%	38	5.5%	7	20.0%	17	10.4%	
Other	212	22.6%	134	19.4%	4	11.4%	20	12.2%	
Geographic region:									< .0001
Northeast	153	16.3%	114	16.5%	4	11.4%	26	15.9%	
South	244	26.0%	240	34.8%	5	14.3%	65	39.6%	
Midwest	309	33.0%	212	30.7%	20	57.1%	50	30.5%	
West	231	24.7%	124	18.0%	6	17.1%	23	14.0%	
Psychiatric diagnosis:									
Bipolar disorder	407	43.4%	293	42.5%	7	20.0%	89	54.3%	0.003
Depression	481	51.3%	375	54.3%	12	34.3%	104	63.4%	0.0071
Medical diagnosis:									
Hypertension	118	12.6%	81	11.7%	2	5.7%	27	16.5%	0.3264
Cardiovascular disease	97	10.4%	70	10.1%	2	5.7%	19	11.6%	0.5879
Obesity	31	3.3%	25	3.6%	2	5.7%	11	6.7%	0.2903
Impaired glucose tolerance	1	0.1%	0	0	1	2.9%	0	0	< .0001
Lab tests (mean SD):									
Diabetes screening tests	1.0	2.1	0.9	1.8	0.7	1.7	1.1	1.7	0.705
All other general lab tests	5.4	10.0	5.8	11.6	15.7	27.5	6.2	11.4	< .0001
Incidence of diabetes (%)	23	2.45%	16	2.32%	2	5.71%	4	2.44%	0.9363

Table 4. Results of Cox Proportional Hazards Model of Risk of Diabetes at 1 Year Post-Index Among Schizophrenia Patients, by Comparison Cohort

Variable	Coefficient	Standard Error	Chi-Square	P Value	Hazard Rate	95% CI Lower	95% CI Upper
Atypical vs Conventional	0.1608	0.059	7.4044	0.0063	1.172	1.061	1.30
Olanzapine vs:							
Risperidone	0.0477	0.0606	0.6206	0.4308	1.049	0.930	1.168
Quetiapine	0.1566	0.1032	2.3035	0.1291	1.170	0.967	1.372
Clozapine	0.3834	0.2553	2.2549	0.1332	1.467	0.967	1.968

Table 5. Results of Logistic Regression Model of Risk of Diabetes Among Schizophrenia Patients Followed for 12 Months Post-Index, by Comparison Cohort

Variable	Coefficient	Standard Error	Chi-Square	*P* Value	Odds Ratio	95% CI Lower	95% CI Upper
Atypical vs Conventional	0.0884	0.2194	0.1623	0.6871	1.193	0.505	2.82
Olanzapine vs:							
Risperidone	-0.1481	0.4521	0.1073	0.7433	0.521	0.182	1.490
Other	-0.1481	0.4521	0.1073	0.7433	1.232	0.138	11.001

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