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ORIGINAL REPORT

Atypical antipsychotic drugs and diabetes mellitus in a large outpatient population: a retrospective cohort study†

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SUMMARY

Purpose Previous research has suggested an association between use of atypical antipsychotics and onset of diabetes mellitus. We sought to compare the incidence of new onset diabetes among patients receiving atypical antipsychotics, traditional antipsychotics or antidepressants.

Methods Retrospective cohort study of outpatients with claims for atypical antipsychotics ($n = 10\,265$) compared to controls with claims for traditional antipsychotics ($n = 4607$), antidepressants ($n = 60\,856$) or antibiotics ($n = 59\,878$) in the administrative claims database of a large pharmaceutical benefit manager between June 2000 and May 2002. Main outcome measures were adjusted and unadjusted incidence rates of diabetes (new cases per 1000 per year) in a 12-month period, as measured using new prescriptions for antidiabetic drugs after a 6-month lead-in period.

Results Annual unadjusted incidence rates of diabetes (new cases per 1000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics. In multivariable analyses, age, male sex and Chronic Disease Score were associated with greater odds of diabetes onset. There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups. Multivariable comparisons among specific agents showed increased odds of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone), but these comparisons did not reach statistical significance.

Conclusions In a large prescription claims database, outpatients taking atypical antipsychotics did not have higher rates of diabetes onset, compared to subjects taking traditional antipsychotics or antidepressants. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotic agents; cohort studies; diabetes mellitus; pharmaceutical services, insurance; pharmacoepidemiology; prescriptions, drug

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Use of atypical antipsychotic drugs has increased dramatically in the short time since the drugs were introduced. Although approved for the management of manifestations of psychotic illness, these drugs are prescribed for a variety of conditions.[1] Annual sales of atypical antipsychotics in the United States have reached approximately $3 billion.[2]

The primary advantage of atypical antipsychotics over traditional antipsychotics is their lower risk of extrapyramidal side effects.[3] However, atypical antipsychotics have been shown to stimulate appetite and induce weight gain.[4,5] A recent review of the Food and Drug Administration's MedWatch database found 384 reports of hyperglycemia among patients who were treated with clozapine.[6] Numerous case reports and some clinical and claims-based studies[7–26] suggest that atypical antipsychotics may increase the occurrence of diabetes mellitus and diabetic ketoacidosis, possibly through their tendency to induce weight gain. The proposed association has been reported in adolescents as well.[27] The exact mechanism for the association is unclear, and the putative latent period has varied from weeks to months.

Given the extensive and increasing use of atypical antipsychotics—and the seriousness of diabetes as a potential complication—further investigation of the presence and extent of an association is of considerable public health interest. We sought to compare the incidence of diabetes among patients receiving atypical antipsychotics, traditional antipsychotics, antidepressants (as a comparison group of patients receiving another type of psychotropic drug) or antibiotics (as a population comparison group).

METHODS

We accessed the outpatient prescription claims database of AdvancePCS (Irving, TX, and Scottsdale, AR), the largest pharmaceutical benefit manager in the United States. Health insurance carriers contract with AdvancePCS to manage their formularies and adjudicate their prescription drug claims. Advance PCS maintains a computerized pharmacy system that records data on each prescription drug dispensed to its beneficiaries, whether through a retail or mail-order pharmacy. More than 98% of the claims in the database are submitted and processed electronically at the time the prescriptions are filled (AW [awright@apclinical.com], e-mail, August 27, 2001).

We limited our analysis to subjects whose health plans or insurance carriers required AdvancePCS to track claims at the individual subject level. Subjects whose plans used the same identifier for multiple family members were excluded. The analysis dataset included all prescription drug claims adjudicated for 170 030 subjects who were continuously enrolled from June 2000 through May 2002 and who filed at least one prescription drug claim during that period. All claims relating to the same individual were linked using a unique beneficiary identifier that was encrypted to ensure confidentiality for this study. A total of 1171 health insurance carriers were represented in the data, covering all 50 states, as well as US territories. The institutional review board of Duke University Medical Center approved this study.

Study design

The study employed a retrospective cohort design. We used claims for prescriptions filled as a proxy for actual use of the exposure medications and of hypoglycemic agents. We considered the first 6 months of the study period to be the lead-in period and the ensuing 18 months to be the follow-up period. We excluded subjects with claims for insulin or oral hypoglycemic drugs during the lead-in period, as well as subjects for whom the claim for an antidiabetic drug predated the claim for an exposure drug. The main analysis included subjects for whom the first prescription for an exposure drug occurred after the lead-in period. Subjects whose first claim for an exposure drug occurred during the lead-in period were considered separately, but were excluded from the main analysis.

Exposure categories and covariates

The primary exposure group consisted of subjects who filled prescriptions for any of the five atypical antipsychotic agents (i.e. clozapine, olanzapine, quetiapine, risperidone, ziprasidone or a combination of two or more of these drugs) at any time during the follow-up period. These drugs were also considered individually. Inclusion in the primary exposure group required that claims for other psychotropic drugs were not filed during the study period.

The primary control group consisted of subjects who filled prescriptions for conventional antipsychotic agents (i.e. acetophenazine, chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, triflupromazine) during the follow-up period. Haloperidol and thioridazine were also considered individually. Inclusion in the control group required

that no prescriptions for other psychotropic drugs were filled during the study period.

A secondary comparison group consisted of a 10% simple random sample of subjects who filled prescriptions for antidepressants (i.e. amitriptyline, amoxapine, bupropion, chlordiazepoxide and amitriptyline combination, citalopram, clomipramine, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, perphenazine and amitriptyline combination, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine) at any time during the follow-up period. This group included only individuals who had not received any antipsychotic agents during the study period.

Finally, a 'general population' comparison group of a simple random sample of subjects who filled a prescription for an antibiotic but not for any psychotropic drug during the study period was followed for the same time period. A prescription for an antibiotic was not considered an 'exposure' *per se*, but was used as a criterion for inclusion in the control group.

We extracted several additional variables from the database, including age, sex, time of first and subsequent prescription claims, dosage and duration of the drugs in question.

We calculated a Chronic Disease Score according to the method outlined by von Korff[28] and later refined by Clark.[29] This pharmacy-based risk-adjustment score increases with the number of chronic diseases and the complexity of the treatment regimen.[30] The medications included in the scoring algorithm target diseases, not symptoms. Consequently, medications frequently used in the management of symptomatic conditions (e.g. analgesics, anti-inflammatory drugs, sedatives) are not included. None of the medications used to define exposure groups for this study are included in the Chronic Disease Score algorithm. For this analysis, the score was calculated on the basis of prescription claims filed during the lead-in period.

Outcome measures

The primary outcome was the prescription filled for any antidiabetic drug. We extracted the date of first and subsequent prescriptions for insulin or oral hypoglycemic drugs (i.e. tolbutamide, acarbose, tolazamide, repaglinide, glyburide, chlorpropamide, glipizide, metformin, acetohexamide, glimepiride, rosiglitazone). The time of first filled prescription for any of these medications served as a proxy for the time of onset of diabetes.

Data analysis

We compared the occurrence of diabetes (i.e. first prescription filled for insulin or an oral hypoglycemic drug) in the main exposure group to that in each of the three control groups. The primary comparison was between the atypical antipsychotic group and the traditional antipsychotic group. In separate analyses, individual atypical antipsychotics were compared to each other and to the traditional antipsychotic group.

The proportion of subjects in each exposure group who developed diabetes within 3 months, 6 months, 9 months and 1 year were compared to each other, and the annual incidence rate of diabetes was calculated for each exposure group and for individual atypical antipsychotics.

Multivariable analyses were performed using a logistic regression model of diabetes onset. We examined the effect of type, dosage and duration of antipsychotic drugs, adjusting for age, sex and Chronic Disease Score.

The primary ('pure') multivariable models included only subjects who belonged exclusively to one of the four exposure groups. Secondary multivariable models also included subjects with concurrent or sequential exposure to agents from different psychotropic drug classes. In these secondary models, the variable for exposure drug indicates exposure to a specific drug, but not to the exclusion of other exposure drugs.

RESULTS

Nearly 7 million subjects were enrolled for at least 12 months during the study period. Our analytical subset included 10 265 subjects who filled a new prescription for an atypical antipsychotic, 4607 subjects who filled a new prescription for a traditional antipsychotic and 60 586 subjects who filled a new prescription for an antidepressant. In addition, our analysis included 59 878 'population controls' who received antibiotics but no psychotropic drugs during the study period. In all, 170 030 subjects who filled new prescriptions for drugs in one or more of the four exposure categories during the study period were included in the analysis (Table 1).

Male subjects were more prevalent in the atypical antipsychotic and traditional antipsychotic groups, whereas female subjects were more prevalent in the antidepressant and antibiotic groups. Claims for atypical antipsychotics were filled by subjects in all age groups, with a relatively large number of prescriptions in the youngest age groups. Risperidone claims were most common in the youngest and oldest age groups. Traditional antipsychotics, especially

Table 1. Subject characteristics*

Characteristic	Cohort				
	Overall study population ($n = 170\,030$)	Atypical antipsychotics ($n = 10\,265$)†	Traditional antipsychotics ($n = 4607$)†	Antidepressants ($n = 60\,586$)†	Antibiotics ($n = 59\,878$)†
Male	64 796 (38.1)	5689 (55.4)	2396 (52.0)	18 217 (30.1)	24 507 (40.9)
Age, mean (SD), year	41.9 (21.5)	42.3 (27.5)	57.0 (21.2)	43.6 (16.5)	37.8 (23.5)
Age group					
0–19 year(s)	31 819 (18.7)	3148 (30.7)	279 (6.1)	4561 (7.5)	18 059 (30.1)
20–29 years	15 172 (8.9)	891 (8.7)	197 (4.3)	7091 (11.7)	3799 (6.3)
30–39 years	27 465 (16.2)	1162 (11.3)	456 (9.9)	12 949 (21.3)	7001 (11.7)
40–49 years	34 812 (20.5)	1229 (12.0)	750 (16.2)	15 750 (26.0)	10 092 (16.9)
50–59 years	26 596 (15.6)	780 (7.6)	803 (17.4)	10 895 (18.0)	9319 (15.6)
60–69 years	14 653 (8.6)	602 (5.9)	651 (14.1)	4820 (8.0)	5975 (10.0)
70–79 years	11 223 (6.6)	974 (9.5)	677 (14.7)	2896 (4.8)	3990 (6.7)
≥80 years	8290 (4.9)	1479 (14.4)	794 (17.2)	1624 (2.7)	1643 (2.7)
Chronic Disease Score					
Mean (SD)	3.1 (3.3)	3.0 (3.1)	3.5 (3.3)	2.7 (3.0)	2.8 (3.1)
0	57 778 (34.0)	3598 (35.1)	1240 (27.0)	22 898 (37.8)	22 065 (36.9)
1	12 284 (7.2)	511 (5.0)	320 (7.0)	5556 (9.2)	3955 (6.6)
2	11 244 (6.6)	590 (5.8)	218 (4.7)	4038 (6.7)	4644 (7.8)
3	29 641 (17.4)	2233 (21.8)	950 (2.6)	9703 (16.0)	10 027 (16.8)
4	12 364 (7.3)	720 (7.0)	391 (8.5)	4455 (7.4)	3970 (6.6)
≥5	46 719 (27.5)	2613 (25.5)	1488 (32.3)	13 936 (23.0)	15 217 (25.4)
Drug exposure groups‡					
Atypical antipsychotics	35 717 (21.0)				
Traditional antipsychotics	10 607 (6.2)				
Antidepressants	92 659 (54.5)				
Antibiotics	76 908 (47.8)				

*Values are expressed as number (percentage) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class.
‡Subjects may be included in more than one drug exposure group.

haloperidol, were more commonly used in older age groups. The mean ages of the subjects in each group were 42.3 years for atypical antipsychotics, 57.0 years for traditional antipsychotics, 43.6 years for antidepressants and 37.8 years for antibiotics.

Subjects who received quetiapine or multiple atypical antipsychotics had higher Chronic Disease Scores (i.e. poorer health) than those receiving other atypical antipsychotics, as did subjects who received traditional antipsychotics. Subjects who received antidepressants had slightly lower Chronic Disease Scores than those in the main exposure groups, while subjects in the antibiotic comparison group had the lowest scores.

Table 2 shows the occurrence of incident diabetes mellitus as measured by a first prescription for insulin or an oral hypoglycemic drug after a prescription for one of the exposure drugs. The overall numbers of new cases were low in all groups. The unadjusted rate among subjects in the traditional antipsychotic group (11.3 per 1000 per year) was somewhat higher than the rate in the atypical antipsychotic group (7.5 per 1000 per year), while the overall unadjusted rate was about the same in the antidepressant group (7.8 per 1000 per year) and lower in the antibiotic group (5.1 per 1000 per year).

With regard to individual atypical antipsychotics, the overall annual incidence rates of diabetes among subjects who received clozapine, olanzapine or ziprasidone were higher than among subjects who received quetiapine or risperidone. For traditional antipsychotics, incidence rates for subjects who received haloperidol and thioridazine were similar and somewhat higher than those of most atypical antipsychotics. No clear pattern emerged when we examined the duration from prescription for any exposure drug to the occurrence of diabetes.

Table 3 presents univariate and multivariable relationships between the onset of diabetes and the exposure groups. These models included only subjects who received prescriptions in a single drug class of interest during the study period. The univariate odds ratios were consistent with the rates presented in Table 2, with traditional antipsychotics, antidepressants, age and male sex significantly associated with onset of diabetes, and antibiotics inversely so. In the

Table 2. Occurrence of new prescriptions for insulin or oral hypoglycemic drugs by drug exposure group

Drug	Total exposed	Diabetes onset*				Unadjusted annual incidence†
		1–3 months	4–6 months	7–9 months	10–12 months	
Atypical antipsychotics	10 265	17 (0.2)	24 (0.2)	22 (0.2)	14 (0.2)	7.5
Clozapine	127	0	1 (0.8)	0	0	7.9
Olanzapine	3190	10 (0.3)	5 (0.2)	9 (0.3)	6 (0.2)	9.4
Quetiapine	1111	1 (0.1)	4 (0.4)	0	1 (0.1)	5.4
Risperidone	4859	4 (0.1)	10 (0.2)	12 (0.3)	3 (0.1)	6.0
Ziprasidone	69	1 (1.5)	0	0	0	14.5
Multiple drugs	909	1 (0.1)	4 (0.4)	1 (0.1)	4 (0.4)	11.0
Traditional antipsychotics	4607	10 (0.2)	16 (0.3)	15 (0.3)	11 (0.2)	11.3
Haloperidol	1766	3 (0.2)	6 (0.3)	5 (0.3)	4 (0.2)	10.2
Thioridazine	567	2 (0.4)	4 (0.7)	0	0	10.6
Other	2274	5 (0.2)	6 (0.3)	10 (0.4)	7 (0.3)	12.5
Antidepressants	60 586	114 (0.2)	121 (0.2)	147 (0.2)	91 (0.2)	7.8
Antibiotics	59 878					5.1

*Values represent the actual number of subjects who received a first diabetes-related prescription in the 3-month period. Values in parentheses represent percentages based on all subjects followed throughout the 3-month period.
†New cases per 1000 per year.

first multivariable model, in which users of any traditional antipsychotic constituted the reference group, atypical antipsychotics were associated with a lower risk of diabetes than were traditional antipsychotics. However, the effect was not statistically significant. Subjects in the antibiotic comparison group had the lowest risk estimate for diabetes, and the difference between the antibiotic and traditional antipsychotic groups was statistically significant. Age, male sex and Chronic Disease Score remained statistically significant predictors of diabetes.

The second multivariable model included only users of antipsychotic agents. The most frequently prescribed atypical antipsychotic, risperidone, was used as the reference category. Subjects who received clozapine, olanzapine or ziprasidone had an increased but not statistically significant risk of diabetes. Age and Chronic Disease Score had the same significant effects

Table 3. Characteristics associated with diabetes in the 'pure' exposure cohort*

	Model 1 ($n = 135\,336$)†		Model 2 ($n = 14\,872$)‡	
	Univariate	Multivariable	Univariate	Multivariable
Atypical antipsychotics				
Clozapine			0.91 (0.13–6.53)	1.13 (0.15–8.37)
Olanzapine			1.11 (0.74–1.67)	1.34 (0.83–2.15)
Quetiapine			0.60 (0.27–1.37)	0.66 (0.28–1.57)
Risperidone			0.60 (0.39–0.90)	1.00
Ziprasidone			1.69 (0.23–12.24)	2.64 (0.35–19.90)
Any	1.13 (0.89–1.43)	0.86 (0.60–1.23)		
Traditional antipsychotics				
Haloperidol			1.35 (0.85–2.15)	1.00 (0.57–1.74)
Thioridazine			1.46 (0.65–3.25)	1.27 (0.54–2.98)
Other			1.55 (1.06–2.25)	1.43 (0.89–2.31)
Any	1.73 (1.30–2.29)	1.00		
Antidepressants	1.34 (1.17–1.53)	1.08 (0.81–1.45)		
Antibiotics	0.69 (0.61–0.79)	0.68 (0.50–0.92)		
Age (per 10 years)	1.40 (1.36–1.46)	1.21 (1.17–1.26)	1.25 (1.16–1.34)	1.16 (1.06–1.26)
Male	1.13 (0.99–1.29)	1.26 (1.10–1.45)	0.68 (0.48–0.97)	0.89 (0.62–1.28)
Chronic Disease Score	1.27 (1.25–1.29)	1.23 (1.21–1.25)	1.23 (1.18–1.28)	1.19 (1.14–1.25)
Likelihood ratio		993.35		98.31
c-statistic		0.78		0.75

*Values are expressed as odds ratio (95% confidence interval) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class during the study period.
‡Subjects filled prescriptions for only one psychotropic drug during the study period.

Table 4. Characteristics associated with diabetes in the overall study population*

	Univariate ($n = 170\,030$)	Multivariable ($n = 170\,030$)
Drug†		
Atypical antipsychotic	2.49 (2.32–2.67)	1.70 (1.58–1.83)
Traditional antipsychotic	3.14 (2.86–3.45)	2.08 (1.88–2.30)
Antidepressant	2.28 (2.11–2.46)	2.12 (1.96–2.30)
Age	1.46 (1.44–1.49)	1.31 (1.22–1.41)
Male	1.15 (1.07–1.23)	1.24 (1.21–1.26)
Chronic Disease Score	1.34 (1.32–1.35)	1.28 (1.26–1.29)
Likelihood ratio		6033.92
c-statistic		0.85

*Values are expressed as odds ratio (95% confidence interval) unless otherwise indicated.
†Indicator variable indicating prescription of drug in this class (relative to no prescription of drug in this class).

as in the first model. An exploratory analysis (suggested by earlier studies[24,31]) that grouped clozapine and olanzapine together but maintained the same exposure and confounding variables used in the second model, suggested an increased but not statistically significant risk of diabetes for the combined group (odds ratio, 1.32; 95% confidence interval, 0.83–2.12).

We also performed analyses including subjects with a prevalent psychiatric disorder (i.e. subjects who received psychotropic drugs during the lead-in period), and the results were fully congruent with the models in Table 3 (data not shown). We constructed more complex models that included dosage and duration of exposure drugs, but these models showed no significant difference between the two antipsychotic groups or among individual atypical antipsychotics (data not shown).

Table 4 presents the multivariable models pertaining to the larger 'mixed' groups, wherein individuals could have been exposed to agents from one or more exposure groups. Where the 'reference category' consisted of subjects without exposure to psychotropic drugs, exposure to any of the three classes of psychotropic drugs was significantly associated with development of diabetes, as were age, male sex and Chronic Disease Score.

DISCUSSION

Using prescription claims data from a large national database, we found that the rate of incident diabetes was not significantly higher for subjects taking atypical antipsychotics as compared to subjects taking traditional antipsychotics. There was a trend toward higher incidence of diabetes in the combined olanzapine/clozapine group, when compared to rates for the other antipsychotics. Comparisons among specific drugs must be performed with caution, however, given the relatively limited number of outcome events in each group. Among users of atypical antipsychotics, rates of diabetes were not significantly higher than among users of antidepressants, but they were significantly higher than in our population reference group.

The analyses of the overall population, allowing exposure to more than one psychotropic drug, show that exposure to a drug from any one of the three classes considered is significantly related to the development of diabetes mellitus. In fact, the antidepressant group has the highest risk. It is difficult to disentangle effects among the subjects who received more than one drug, partly because this may be a special population of patients, and partly because there may be variable interactions among the drugs. We, therefore, consider the findings based on the 'pure' groups (Table 3) as stronger than those based on the overall group (Table 4).

Our findings complement results from several case reports and an increasing number of clinical and claims-based studies.[7–26,31,32] The mechanism for the proposed association between use of antipsychotics and diabetes remains unclear, but it is possible that antipsychotics may increase weight through their effect on insulin secretion and resistance.[23] In a clinical study of antipsychotics,[15] 14% of patients—mostly those receiving atypical antipsychotics—developed abnormally high glucose levels. Newcomer *et al.*[34] also found increased elevation of plasma glucose after glucose load in patients receiving olanzapine, but not among patients receiving risperidone or traditional antipsychotics. Weight gain and obesity may, therefore, link the use of these drugs to the development of diabetes. Our findings of little or no difference between the traditional and the atypical antipsychotics may point toward a causal pathway from schizophrenia *per se* to diabetes rather than a pathway involving the antipsychotic drugs. A possible association between schizophrenia and increased risk of diabetes has been documented previously.[31]

In previous claims-based studies, the presence and strength of the association between antipsychotics and diabetes have varied. A study in Quebec found that olanzapine was associated with an increased risk of diabetes compared to risperidone, especially during the first 3 months of treatment.[32] Gianfrancesco *et al.*[24] found that olanzapine, clozapine and traditional antipsychotics were associated with increased rates of diabetes, but that risperidone was not. Koro *et al.*[25] found that both olanzapine and risperidone were associated with increased rates of diabetes, but only the association with olanzapine was statistically

significant. In contrast, Wang *et al.*[33] found that exposure to clozapine was not related to development of diabetes, while other antipsychotics were. Differences in results among these studies may be due to differences in study populations, differences in outcome ascertainments and different lengths of follow-up.

A previous study based on prescription data from the same database as our study, but from an earlier time period,[26] concluded that users of both atypical and traditional antipsychotics had higher rates of prescription of oral hypoglycemic drugs and insulin than a control group, but the authors did not find a difference between the two groups taking antipsychotic agents. That study, based on a comparison with a reference group of subjects using a variety of medications, did not consider subjects on antidepressants as a separate comparison group, and the analyses were not adjusted for the presence of other chronic diseases. In spite of these differences, our results are consistent. Since the Chronic Disease Score is related to diabetes, the consistency between the studies is possibly due to the fact that the Chronic Disease Score is poorly related to the use of antipsychotics.

There are several strengths to our analyses. The primary analyses included only new users (i.e. an inception cohort). Thus, we eliminated the potential for bias caused by depletion of susceptibles, which can affect studies that include both new and continuing users. Other strengths include the large size and national representativeness of our dataset, the inclusion of only incident prescriptions for the exposure groups, the 6-month lead-in period to minimize confounding with prevalent diabetes, the ability to control for demographic factors and Chronic Disease Score, and comparison groups that included not only traditional antipsychotics, but also antidepressants and antibiotics as population controls.

Our study also has some limitations. Although prescription claims databases are considered to be reliable and valid for studying drug use,[35,36] they record only claims filed, not whether the drugs were actually taken. In addition, subjects may have had alternative sources of prescription drug coverage; such out-of-plan drug use would not be included in the analysis. Furthermore, the database likely underrepresents the elderly and persons with lower socioeconomic status, groups that are less likely to have private prescription drug insurance.

As with other claims-based studies, information regarding weight and other clinical variables were not directly available in our dataset. Thus, we were unable to explore potential interrelationships among underlying disease states, use of antipsychotics, weight gain, obesity and diabetes. However, we did control for age, sex and Chronic Disease Score. In the same way that clinical data would have been better for accurately identifying diabetes mellitus, clinical data would also have been better than the Chronic Disease Score for determining comorbidity.[37]

We also used claims filed for antidiabetic agents as an indicator of diabetes. Prescription claims data are well suited for studies in which diabetes is the outcome of interest, because prescriptions for insulin and oral hypoglycemic drugs are highly specific to diabetes. However, some subjects using antipsychotics may have developed impaired glucose tolerance and milder or transient forms of diabetes. These symptoms may have been reversed with discontinuation of the drug or successfully treated by dietary means. Therefore, our estimates of the occurrence of diabetes are likely underestimates, including only more severe forms of diabetes. Moreover, although earlier studies have indicated that the latent period from the start of atypical antipsychotic use until the development of diabetes may be only weeks or months, it is possible that cumulative exposures over a longer period than the follow-up period in our study could lead to higher rates of diabetes. In general, however, our annual diabetes incidence rates are comparable with national rates based on diagnosed diabetes. Estimates from the Centers for Disease Control and Prevention's diabetes surveillance system indicate an annual age-standardized incidence rate ranging from 2.5 to 3.5 per 1000 per year for the period 1990 through 1996.[38]

Our study demonstrates the potential for using pharmaceutical benefit manager data for postmarketing surveillance of approved and marketed drugs and for examining the 'near real-time' use of prescription drugs. In general, the availability of a large number of nationally representative, detailed, prescription-level data presents opportunities to examine how frequently individual drugs and drug combinations of interest are dispensed. Large pharmaceutical benefit manager datasets may also be useful for exploring the extent of associations observed in case reports.

In summary, we did not find a higher rate of antidiabetic drug prescriptions among subjects using atypical antipsychotics compared to subjects using traditional antipsychotics, although both groups had higher rates than the general population. Concern about a potential association remains, and continued vigilance combined with further clinical and epidemiological studies is required to further elucidate whether this effect is due to underlying illness, weight gain or the drugs themselves.

KEY POINTS

- We did not observe a higher rate of antidiabetic drug prescriptions among subjects using atypical antipsychotics, as compared to subjects using traditional antipsychotics.
- Subjects using antipsychotic drugs—either traditional or atypical—had higher rates of antidiabetic drug use than did subjects in the general population.
- Concern about a potential association between atypical antipsychotics and diabetes remains; therefore, continued vigilance and further research are required.
- Our study demonstrates the potential for using pharmaceutical benefit manager data for post-marketing surveillance of approved and marketed drugs and for examining the real-time use of prescription drugs.
- Large pharmaceutical benefit manager datasets may also be useful for exploring the extent of associations observed in case reports.

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