Frequency of New-Onset Diabetes Mellitus and Use of Antipsychotic Drugs Among Central Texas Veterans

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Study Objectives. To determine whether the frequency of new-onset diabetes mellitus differs between patients taking atypical antipsychotic agents and those taking typical agents, whether the frequency of new-onset diabetes differs among those taking the atypical antipsychotic agents, and what clinical and demographic factors influence the occurrence of new-onset diabetes.

Design. Retrospective analysis.

Setting. Central Texas Veterans Health Care System.

Patients. Continuously enrolled adult (≥ 18 yrs) patients with no previous (6 mo) antipsychotic use and no history (previous 1 yr) of diabetes.

Measurements and Main Results. Data from the Central Texas Veterans Health Care System were extracted from September 1995–November 2002. Clinical and demographic factors used in the analysis were antipsychotic agent taken, body mass index, diabetes-related risk factors, type of mental health comorbidity, age, sex, and race. Among those who met the inclusion criteria (3469 patients), χ^2 analyses revealed no significant difference in the frequency of diabetes between the typical and atypical groups (p=0.5553) or among those taking atypical agents (p=0.6520). Multivariate logistic regression (1587 patients) revealed that increasing age (odds ratio [OR] 1.213, 95% confidence interval [CI] 1.016–1.447, p=0.0324), nonwhite race (OR 1.761, 95% CI 1.174–2.640, p=0.0062), and hyperlipidemia (OR 1.606, 95% CI 1.064–2.425, p=0.0242) were significantly related to new-onset diabetes.

Conclusions. Among veterans taking antipsychotic agents, no difference was noted in the frequency of diabetes between patients who took typical agents and those who took atypical agents. After controlling for demographic and clinical variables, still no significant difference was noted among the agents. The main factors (increasing age, nonwhite race, and hyperlipidemia) related to new-onset diabetes were those that are typically associated with the disease.

Key Words: antipsychotics, diabetes mellitus, risk factors.

(Pharmacotherapy 2004;24(11):1529–1538)

Atypical antipsychotic agents have been well received because of their increased efficacy and decreased rate of extrapyramidal symptoms compared with those of typical antipsychotics. Although the atypical agents have some distinct advantages, they also have some disadvantages. Some of the most recently noted issues involve weight gain,[1–6] elevation in triglyceride and cholesterol levels,[7–10] and new-onset diabetes mellitus and diabetes-related complications.[11–34]

The literature surrounding the issue of new-onset diabetes and its association with antipsychotic therapy is primarily populated with case reports[11–30] that date back to 1994 and a few small clinical trials.[31–34] Of the atypical antipsychotic agents, olanzapine and clozapine have

been mentioned more times regarding new-onset diabetes or diabetes-related problems compared with risperidone and quetiapine. Most of the case reports were in men and in people of African-American descent. Most of the case reports did not indicate a family or personal history of diabetes, although it is not clear if these variables were validly assessed. Some reports involved diabetic ketoacidosis, and other cases reported that discontinuation of the atypical antipsychotic resulted in normalization of blood glucose levels.

A number of researchers have conducted several large-scale studies in the last few years to substantiate the claims of treatment-emergent diabetes or exacerbation of preexistent diabetes in patients newly prescribed a particular antipsychotic.[35–46] However, the results from these large-scale studies are far from conclusive.

The mechanism for the potential link between antipsychotic agents and diabetes is not well understood. It has been proposed that the increase in weight gain through stimulation of serotonin, histamine, dopamine, prolactin, and leptin receptors could potentiate glucose dysregulation and subsequently promote new-onset diabetes mellitus.[5, 30] Another mechanism could involve the relationship among triglyceride levels, antipsychotic agents, and diabetes.[32, 33]

In one study, the authors assessed whether patients who switched to ziprasidone experienced significant changes in body mass index (BMI) and glucose, cholesterol, and triglyceride levels.[31] The study showed no significant changes in BMI or glucose level, but a significant improvement in cholesterol and triglyceride levels.

Another group conducted a retrospective study to assess differences in weight, glucose level, cholesterol level, and blood pressure in patients who received olanzapine and haloperidol.[32] Significant weight increases were found in patients receiving olanzapine compared with those receiving haloperidol. Although the olanzapine group had significantly higher glucose and cholesterol levels (when compared with those of the haloperidol group), no significant differences were noted in the frequency of increased glucose level, cholesterol level, or blood pressure.

Another group of investigators assessed the frequency of new-onset diabetes among patients treated with clozapine.[33] Diabetes mellitus was diagnosed in more than one third (36.6%) of the patients. The development of diabetes was significantly associated with increased triglyceride levels. The study also found that there was a significant increase in weight and that the weight gain was significantly associated with increased serum cholesterol and triglyceride levels.

Results of two of the above studies[32, 33] suggest that weight gain may not be the direct link to new-onset diabetes. In a Swedish study, the authors assessed the prevalence of diabetes and impaired glucose tolerance in patients taking clozapine versus those taking depot neuroleptics.[34] Although the study found that the prevalence of diabetes mellitus or impaired glucose tolerance was not statistically significant between the two groups, the percentages of patients who developed diabetes mellitus and impaired glucose tolerance were higher in the clozapine group (12% clozapine vs 6% depot neuroleptics and 10% clozapine vs 3% depot neuroleptics, respectively).

A brief review of the literature shows that the issue of new-onset diabetes among patients taking antipsychotic agents is not well understood. Interpretation of the numerous case reports is difficult because of the lack of a rigorous method to systematically combine the data from the cases. Many of the clinical trials were conducted with small sample sizes and primarily focused on one agent or comparisons of two agents. Most of the large database studies did not control for known factors related to diabetes such as weight gain, hypertension, or hyperlipidemia. In our study, we incorporated these covariates, as well as others, in a multi-variate analysis to determine the relationship between antipsychotic therapy and new-onset diabetes.

The following three objectives were the focus of this study: to determine whether the frequency of new-onset diabetes differed between those

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Supported by Eli Lilly and Company, Indianapolis, Indiana.

Presented in part at the American Psychiatric Association 55th Institute on Psychiatric Services, Boston, Massachusetts, October 31, 2003, and at the annual meetings of the American College of Clinical Pharmacy, Atlanta, Georgia, November 4, 2003, and the American Society of Health-System Pharmacists, New Orleans, Louisiana, December 11, 2003.

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taking atypical agents and those taking typical agents; to determine whether the frequency of new-onset diabetes differed among those taking the atypical antipsychotic agents; and to determine what factors (e.g., antipsychotic agent used, BMI, diabetes-related risk factors, and demographics) influenced the occurrence of new-onset diabetes.

Methods

Data Source

We used data from the Central Texas Veterans Health Care System (CTVHCS). One distinct aspect of CTVHCS is the computerized patient record system, which electronically captures most patient and clinical information from the medical chart.

Inclusion Criteria

Individual patient level claims records were extracted and analyzed for patients who were aged 18 years or older; had not received a prescription for an atypical or typical antipsychotic agent 6 months before the dispensing of an atypical or typical antipsychotic agent; had no previous use of an antidiabetic drug or diagnosis of diabetes for 1 year before a prescription for a typical or atypical antipsychotic; and were continuously enrolled for 12 months before and after the date of receiving an atypical or typical antipsychotic agent.

Study Variables

The dependent variable for all analyses was whether or not the subject developed diabetes. This was operationalized by a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision* [ICD-9] code 250.xx), blood glucose levels greater than 200 mg/dl, and/or use of an antidiabetic drug between 8 and 365 days after the index date (i.e., the date of the first prescription for an antipsychotic agent).

The primary independent variable was the type of antipsychotic agent that the patient was taking initially—typical agents or the individual atypical agents. The atypical agents were olanzapine, quetiapine, risperidone, clozapine, and ziprasidone.

The control independent variables (and possible answers) were the following: diabetes-related risk factors (yes or no), which included change to higher BMI category, previous hyperlipidemia, and change in hypertension status; persistence (total number of days without a 15-day gap); type of mental health comorbidity (yes or no), which included bipolar disorder, depression, schizophrenia, and substance abuse; age group (18–39 yrs, 40–49 yrs, 50–59 yrs, 60–69 yrs, or 70 yrs or older); sex (male or female); and race (white or nonwhite).

The BMI was calculated for the weight closest (within a 6-mo time frame) to the first use of the antipsychotic agent and for the weight closest (within a 6-mo time frame) to the last use of an antipsychotic agent. Based on their BMI, subjects were assigned to one of six BMI categories established by the National Heart, Lung, and Blood Institute.[47] A dichotomous variable was used to indicate whether or not the subject moved to a higher BMI category status from the first to the last use of the antipsychotic agent.

Previous hyperlipidemia was defined as a cholesterol level of 200 mg/dl or above, a low-density lipoprotein cholesterol level of 130 mg/dl or above, or a triglyceride level of 150 mg/dl or above within 6 months before the first antipsychotic used. Because of limited data within the study time frame, lipid level changes could not be calculated.

Blood pressure measurements were extracted closest to the first and last use of the antipsychotic within a 6-month window. Subjects were categorized into one of six blood pressure groups established by the National Heart, Lung, and Blood Institute.[48] A dichotomous variable was used to indicate whether or not the subject moved to a higher blood pressure category.

Persistence was calculated by summing the total number of continuous days the patient took an antipsychotic agent without a gap (i.e., a 15-day lapse in therapy).

The study received institutional review board approval from both the CTVHCS and the University of Texas.

Data Collection and Analysis

Data from the CTVHCS record system was extracted for the time frame of September 30, 1995–November 1, 2002. The follow-up time period was 1 year after the index date. To compare the frequency of diabetes between patients who received atypical agents and those who received typical agents, χ^2 analyses were used. To compare the frequency of new-onset diabetes among patients receiving atypical antipsychotic agents while controlling for clinical and patient-related variables, a logistic regression

analysis was used. An a priori significance level of 0.05 was used for all analyses.

Results

A total of 6735 patients were identified as taking antipsychotics in the CTVHCS database. One was excluded for being younger than 18 years, 1999 were excluded because of previous antipsychotic use, 819 were excluded because of previous diabetes, and 447 were excluded owing to a less than 12-month enrollment period after antipsychotic use. This resulted in a total of 3469 subjects meeting the inclusion criteria. Most of the sample was male (94.3%) and white (69.9%). Mean ± SD age was 59.4 ± 14.5 years, with subjects aged 50–59 years and those aged 70 years or older constituting 34% and 28% of the sample, respectively.

By using any of the three criteria mentioned in Methods for defining the dependent variable new-onset diabetes, the frequency of new-onset diabetes was 7.1%. When using single categories of elevated blood glucose levels, ICD-9 diagnosis, or antidiabetic drug as the criterion for diabetes, the frequency rates were 4.1%, 3.0%, and 2.1%, respectively. The time to diabetes onset was approximately 5 months (mean ± SD 151.9 ± 105.6 days).

More than 40% (44.3%) of the subjects were taking atypical agents, with olanzapine (23.0%) being prescribed most often, followed by risperidone (16.2%). Among the typical agents, haloperidol (20.0%) was most often prescribed. For the atypical agents, the mean number of persistent days ranged from 117–167 days (3.9–5.6 mo), and for the typical agents the range was 141–220 days (4.7–7.3 mo).

The subjects had various mental health and other comorbidities. Of the 3469 subjects, 1461 (42.1%) did not have ICD-9 data. Of the 2008 subjects with documented ICD-9 data, the diagnoses were substance abuse in 841 (41.9%) patients, depression in 715 (35.6%), and bipolar disorder in 689 (34.3%). Schizophrenia was diagnosed in 681 (33.9%) subjects. On average, the subjects had three (mean ± SD 2.5 ± 1.4) mental health comorbidities.

Subjects were categorized into one of six BMI groups established by the National Heart, Lung, and Blood Institute.[47] Changes in BMI categories from the first to the last use of an antipsychotic agent were assessed. Approximately 36% and 34% (first BMI and last BMI, respectively) of the subjects were considered to be of normal weight, and approximately 38% (both first BMI and last BMI) were categorized as overweight. Approximately 23% and 26% (first BMI and last BMI, respectively) of the patients were categorized as obese. Therefore, 61% and 64% (first BMI and last BMI, respectively) of the patients were either overweight or obese. Most subjects (88%) did not change to a higher BMI category from first to last antipsychotic use.

Thirty percent of the subjects met the criteria for previous hyperlipidemia (cholesterol level ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 130 mg/dl, or triglyceride level ≥ 150 mg/dl 6 mo before taking the first antipsychotic) when using any of the three lipid level categories.[49] Subjects were categorized into one of six hypertension groups established by the National Heart, Lung, and Blood Institute.[48] According to the guidelines, 36% and 34% (first blood pressure and last blood pressure, respectively) of the subjects had hypertension. In most subjects (72%), the hypertension status category did not change.

Table 1. Frequency of New-Onset Diabetes Mellitus in the Atypical and Typical Agent Groups

	No. (%) of Patients	
Variable	Atypical Group (n=1537)	Typical Group (n=1932)
Diabetes	105 (6.8)[a]	142 (7.3)[a]
No diabetes	1432 (93.2)	1790 (92.7)

Intent-to-treat methodology was used.
[a]χ^2=0.3479, p=0.5553.

Table 2. Frequency of New-Onset Diabetes Mellitus Among the Atypical, Typical, and Both Agents Groups

	No. (%) of Patients		
Variable	Atypical Group (n=1390)	Typical Group (n=992)	Both[a] Groups (n=1087)
Diabetes	94 (6.8)[b]	69 (7.0)[b]	84 (7.7)[b]
No diabetes	1296 (93.2)	923 (93.0)	1003 (92.3)

[a]Indicates concomitant use of both atypical and typical agents or switching between the two.
[b]χ^2=0.9160, p=0.6325.

Study Objectives

Tables 1–3 address our first objective, which was to determine whether the frequency of new-onset diabetes differed between those taking typical agents and those taking atypical agents.

Table 3. Frequency of New-Onset Diabetes Mellitus Among the Atypical+ and Typical Agent Groups

Variable	No. (%) of Patients: Atypical+[a] Group (n=2477)	No. (%) of Patients: Typical Group (n=992)
Diabetes	178 (7.2)[b]	69 (7.0)[b]
No diabetes	2299 (92.8)	923 (93.0)

[a]Includes patients taking atypical agents only, as well as those taking both atypical and typical agents.
[b]χ^2=0.0569, p=0.8115.

Table 4. Frequency of New-Onset Diabetes Mellitus Among Patients Taking Atypical Agents

Atypical Agent[a]	No. (%) of Patients: Diabetes	No. (%) of Patients: No Diabetes
Risperidone	42 (7.5)[b]	520 (92.5)
Quetiapine	9 (5.8)[b]	147 (94.2)
Olanzapine	51 (6.4)[b]	745 (93.6)

[a]Ziprasidone (2 patients) and clozapine (21 patients) were not included because of the small sample sizes.
[b]χ^2=0.8554, p=0.6520.

Table 5. Logistic Regression Analysis of Factors Related to New-Onset Diabetes Mellitus in 1587 Patients

Variable[a]	Odds Ratio	95% Confidence Interval	Wald χ^2 Value[b]	p Value
Olanzapine	0.976	0.594–1.605	0.0411	0.8394
Quetiapine	1.149	0.531–2.485	0.2330	0.6293
Risperidone	0.926	0.544–1.579	0.2283	0.6328
Increasing age	1.213	1.016–1.447	4.5773	0.0324[c]
Nonwhite	1.761	1.174–2.640	7.4881	0.0062[c]
Female	0.718	0.277–1.857	0.4679	0.4940
Persistent days	1.001	0.999–1.002	1.4273	0.2322
Comorbidity				
Depression	1.305	0.850–2.002	1.4837	0.2232
Substance abuse	0.869	0.561–1.345	0.3983	0.5280
Bipolar disorder	1.192	0.772–1.840	0.6262	0.4288
Schizophrenia	1.117	0.678–1.570	0.0215	0.8834
Body mass index	1.032	0.477–1.581	0.2137	0.6439
Hypertension	0.759	0.415–1.388	0.7994	0.3713
Previous hyperlipidemia	1.606	1.064–2.425	5.0804	0.0242[c]

[a]Reference categories for the atypical agents, nonwhite, and female variables were the typical agents, white, and male, respectively.
[b]Model χ^2=20.00, p=0.1302.
[c]Significance at p<0.05.

The results show that the frequency of new-onset diabetes was not significantly different (p=0.5553) between the atypical group (6.8%) and the typical group (7.3%).

Two additional analyses were performed to further investigate this issue. Because of the concomitant use of atypical and typical agents, the analysis was run separating the data into three groups: atypical, typical, and both. Table 2 shows that the results were similar to those of the previous analysis: no significant difference in new-onset diabetes among the three groups. The third analysis (Table 3) collapses the atypical and both categories into one group (atypical+). Once again, the results show that the frequency of new-onset diabetes was not significantly different between the typical and atypical groups.

Table 4 addresses our second objective, which was to determine whether the frequency of new-onset diabetes differed among those taking the atypical antipsychotic agents (note that clozapine and ziprasidone were dropped from the analyses due to small sample sizes). The χ^2 results show that there was no significant difference in frequency of new-onset diabetes among the atypical agents.

Tables 5 and 6 address our third objective, which was to determine what factors—antipsychotic agent used, BMI category increase, previous hyperlipidemia, increase in hypertension status category, persistence, type of mental health comorbidity, age, sex, and race—influence the occurrence of new-onset diabetes. Table 5 shows that increasing age, minority race, and previous hyperlipidemia were the only variables significantly related to new-onset diabetes. To increase power, another logistic regression analysis was run to include only

Table 6. Logistic Regression Analysis of Factors Related to New-Onset Diabetes Mellitus That Included Only Demographics and Comorbidities in 3170 Patients

Variable[a]	Odds Ratio	95% Confidence Interval	Wald χ^2 Value[b]	p Value
Olanzapine	0.941	0.639–1.384	0.0901	0.7641
Quetiapine	1.034	0.508–2.106	0.0370	0.8474
Risperidone	0.963	0.641–1.447	0.0190	0.8903
Increasing age	1.274	1.130–1.435	15.7806	<0.0001[c]
Nonwhite	1.689	1.274–2.239	13.2741	0.0003[c]
Female	0.797	0.395–1.605	0.4025	0.5258
Comorbidity				
Depression	1.302	0.895–1.893	1.9060	0.1674
Substance abuse	0.929	0.641–1.346	0.1505	0.5981
Bipolar disorder	1.321	0.907–1.925	2.1033	0.1470
Schizophrenia	0.953	0.670–1.355	0.0722	0.7881

[a]Reference categories for the atypical agents, nonwhite, and female variables were the typical agents, white, and male, respectively.
[b]Model χ^2=29.57, p=.0010.
[c]Significance at p<0.05.

demographics (age, race, and sex) and mental health comorbidities. This analysis increased the sample size from 1587 to 3170 subjects. Table 6 shows that once again, increasing age and minority race were significantly related to new-onset diabetes.

Discussion

Our study showed that among central Texas veterans who used antipsychotics, the overall frequency of diabetes was 7.1%. These results compare with those of another study that found that the frequency of diabetes was 6.3% among Ohio veterans.[38] Our study may have had a higher rate because we used a more inclusive definition of diabetes, that is to include not only ICD-9 diagnoses and antidiabetic drugs, but also elevated glucose levels. In addition, our sample population was composed of approximately 30% minorities, which may be higher than some of the other populations studied. Diabetes is more prevalent among minorities than nonminorities.

Another group found that the diabetes incidence rate for all of the patients with schizophrenia who were taking antipsychotics was 4.4/1000 person-years.[42] In another study, the incidence rates in the general population, in patients taking typical antipsychotics, and in patients taking atypical antipsychotics were 15.7, 84, and 67/1000 patient-years, respectively.[35]

Our study showed no difference in the frequency of diabetes between the atypical and typical agent groups or among those taking atypical agents in both the unadjusted and adjusted analyses. One group of authors reported that the overall diabetes rates among patients with schizophrenia who were treated with clozapine versus typical antipsychotics were 4.0% and 3.4%, respectively, which were not statistically significantly different.[43] Another group found no increased risk of diabetes when comparing clozapine with typical agents in a Medicaid population.[45] In another study, the authors found no difference in incident diabetes between the atypical and typical antipsychotic cohorts, but both groups were significantly associated with increased risk of diabetes when compared with the general population.[35] Another group found no difference in the frequency of diabetes between atypical and typical agents.[46]

In contrast to these study results, other large database studies[36, 39, 40, 42, 44] have found significant differences in the frequency of new-onset diabetes between atypical agents and typical agents and/or among atypical agents. However, one study found atypical agents to have a significant increased risk of diabetes compared with typical agents, but no difference was noted in new-onset diabetes among the atypical agents.[37] In other studies comparing the atypical agents, olanzapine was most often associated with the increased risk of diabetes,[36, 39, 40, 42, 44] whereas risperidone was associated with new-onset diabetes in two studies.[35, 46] In one of those studies, the authors compared haloperidol use to individual atypical antipsychotics and found risperidone to have a significantly increased risk of diabetes.[35] In the other study, the authors compared the occurrence of diabetes among

Table 7. Comparison of Methodologies of Retrospective Database Studies Examining Antipsychotic Use and New-Onset Diabetes Mellitus

Setting or Database	Study Time Frame	Sample Population	Study Design	Sample Size	Drugs	Clinical Covariates	Demographic Covariates
Managed care[35]	1998–2000	All AP users and general population	RC	58,751 (AP users) 5,816,473 (general population)	All APs	AP exposure duration, AP dosage	Age, sex
Quebec public health plan[36]	1997–1999	All risperidone and olanzapine users	RC	33,946	Risperidone, olanzapine	AP exposure duration, concomitant haloperidol, psychiatric diagnosis	Age, sex
VA[37]	1999–2001	Schizophrenic patients	RC, CC	12,235	All APs	Use of drugs associated with glucose intolerance	Age, sex, race, VA facility, marital status
Ohio VA (men only)[38]	1997–2000	All AP users	RC	5837	Risperidone, olanzapine, haloperidol, fluphenazine	AP exposure duration, psychiatric diagnoses, use of lithium and valproic acid, concomitant AP use	Age, race
Managed care[39]	1996–1997	Psychiatric patients	RC	7933	All APs	AP exposure duration, concurrent AP use, AP dosage, psychotropic use, psychiatric diagnoses	Age, sex, health care coverage
Managed care[40]	1997–2000	Psychiatric patients	RC	10,296	All APs	AP exposure duration, concurrent AP use, β-blocker use, prior weight gain treatment, psychotropic use, psychiatric diagnoses	Age, sex, health care coverage
United Kingdom General Practice Research[41]	1994–1998	All AP users	CC	1946 (424 cases, 1522 controls)	All APs	AP exposure duration, concurrent AP use, body mass index, smoking, use of drugs associated with glucose intolerance, alcoholism, cardiovascular history, psychiatric diagnoses	Age, sex, practice setting
United Kingdom General Practice Research[42]	1987–2000	Schizophrenic AP users	CC	3147 (451 cases, 2696 controls)	All APs	AP exposure duration, use of drugs associated with glucose intolerance	Age, sex
Iowa Medicaid[43]	1990–1994	Schizophrenic patients	RC	3013	Clozapine, typical APs	AP exposure duration	Age, sex
VA[44]	1998–1999	Schizophrenic AP users	RPC	38,632	All APs	Previous hospitalization, psychiatric diagnoses, comorbidities	Age, sex, race, income, distance to hospital, VA compensation

patients with schizophrenia and found those taking risperidone to have a higher risk compared with those taking typical agents or olanzapine.[46]

Other authors found that both olanzapine and clozapine, as well as selected typical antipsychotic agents, were associated with an increased risk of

Table 7. Comparison of Methodologies of Retrospective Database Studies Examining Antipsychotic Use and New-Onset Diabetes Mellitus (continued)

Setting or Database	Study Time Frame	Sample Population	Study Design	Sample Size	Drugs	Clinical Covariates	Demographic Covariates
New Jersey Medicaid and Medicare, Pharmaceutical Assistance to Aged and Disabled[45]	1990–1995	Psychiatric patients	CC	14,007 (7227 cases, 6780 controls)	Clozapine vs nonclozapine	Psychiatric diagnoses, psychotropic use, clozapine duration, clozapine dosage, comorbidity score, use of drugs associated with glucose intolerance	Age, sex, race, socio-economic status
Managed care[46]	1996-1998	Schizophrenic AP users	RC	815	All APs	AP exposure duration, general health comorbidities, psychiatric diagnoses	Age, sex region, enrollment status

AP = antipsychotics; RC = retrospective cohort; VA = Veterans Administration; CC = case-control; RPC = retrospective (prevalent cases).

diabetes when compared with no treatment for psychoses.[39] In a later study by the same authors, only olanzapine was associated with an increased risk of diabetes.[40] Another group compared olanzapine and risperidone and found that olanzapine was significantly associated with incident diabetes.[36] In a study that compared typical with atypical agents, the authors found that atypicals (with the exception of risperidone) were associated with increased diabetes in a large Veterans Affairs study.[44] In the younger age groups (< 40 yrs), all atypical agents were associated with increased diabetes. This discussion shows that the literature is far from conclusive regarding the relationship between antipsychotic agents and incident diabetes.

Several factors could explain differences in the results. Table 7 shows a comparison of the study methodologies. Several of the large database studies were conducted in various settings: in veterans[37, 38, 44]; in Medicaid populations[43, 45]; at managed care organizations[35, 39, 40, 46]; and outside the United States.[36, 41, 42] Comparison of results across each of the settings may have inherent biases. Also, the study designs differed in terms of inclusion criteria: all patients taking antipsychotic agents[35, 36, 38, 41] versus persons with psychiatric diagnoses.[37, 39, 40, 42–46] The studies differed in terms of comparison groups (typical vs atypicals)[35, 37, 38, 41–46]; among atypicals[36, 38, 46]; antipsychotic use versus no antipsychotic use among persons with psychoses[39, 40]; and antipsychotic use versus no antipsychotic use among the general population.[35]

Another factor that differed across the studies was the covariates used. Most studies controlled for demographics such as age[35–46] and sex,[35–37, 39–46] whereas fewer studies controlled for race.[37, 38, 44, 45] As mentioned previously, race is an important risk factor for diabetes, with minorities more likely to develop diabetes compared with nonminorities. Regarding clinical variables, several studies controlled for psychoses treatment–specific issues such as other antipsychotic use,[36, 38–41, 45] psychiatric diagnoses,[36, 38–41, 44–46] and treatment exposure duration,[35, 36, 38–43, 45, 46] and three studies controlled for dosage.[35, 39, 45] Several studies controlled for use of other drugs that may cause diabetes, such as steroids, β-blockers, anticonvulsants,[37, 38, 40–42, 45] whereas only a few captured other factors associated with diabetes such as BMI[41] and weight gain,[40] hypertension,[41, 45, 46] and dyslipidemia.[46]

One distinct aspect of our study is the use of elevated glucose levels as a proxy for incident diabetes, in addition to drug therapies and diagnoses. Another distinct aspect of our study was the inclusion of clinical covariates in the analysis. Blood pressure changes, previous hyperlipidemia, and BMI changes were incorporated into the multivariate analysis to control for known factors related to diabetes. The results showed that even after controlling for these comorbid conditions, increasing age and minority race were consistently related to new-onset diabetes. In a separate multivariate analysis, previous hyperlipidemia was also associated with new-onset diabetes. Other studies have also found age to be a significant factor in incident diabetes. One group[43] found occurrence to be more prevalent in the younger age group (20–34 yrs), whereas other studies

found increasing age to be related to incident diabetes.[35, 39, 40, 46]

In September 2003, the U.S. Food and Drug Administration issued a request for manufacturers of atypical antipsychotic agents to modify their labeling to include the risk of glucose abnormalities. They also recommended regular monitoring for hyperglycemia in patients with diabetes and those at risk for diabetes. Although our study results show no difference in new-onset diabetes between patients taking typical agents and those taking atypical agents, the overall frequency in this population was 7.1%, which is higher than the 6.3% prevalence in the general population.[50] Thus, it is important that all patients taking antipsychotic agents be monitored for symptoms of diabetes.

Limitations

Our results should be interpreted with caution. Although retrospective database studies can capture effectiveness among a large patient group, causality cannot be established. The database used in this study involved veterans in central Texas and more than 90% of the study subjects were male; thus, differences in outcomes regarding sex and other regions cannot be fully assessed. It is possible that subjects could have obtained drugs from outside the Veterans Affairs system; however, internal resources indicate that veterans tended to use the Veterans Affairs resources exclusively since they were free during the time of this study. We used an intent-to-treat analysis; this does not account for switching and concomitant use of antipsychotics, which routinely occur in practice.[38] However, in our unadjusted analyses comparing typical and atypical antipsychotic agents, we tried to overcome this limitation by performing analyses to incorporate switching and concomitant use.

We found no differences in the frequency of diabetes between the typical and atypical groups when using this method. Studies have shown that primary care, in terms of routine screening for diabetes, for the mentally ill may be suboptimal and thus, new cases of diabetes may go undetected.[51] Although we used a very inclusive definition (ICD-9, antidiabetic drugs, and elevated glucose levels) to identify new-onset diabetes, it is likely that this may have been underestimated since the American Diabetes Association reports that in nearly one third of persons with diabetes is undetected.[50] Also, we did not control for antipsychotic dosage or other nonantipsychotic drugs (e.g., lithium, steroids, thiazide diuretics) that may have been related to new-onset diabetes.

Conclusion

This study found that the frequency of new-onset diabetes mellitus among a population of veterans in central Texas was 7.1%. No significant difference was noted in the frequency of new-onset diabetes between patients taking typical agents and those taking atypical antipsychotic agents or among those taking atypical antipsychotic agents. In addition, a multivariate logistic regression analysis revealed that when controlling for demographic and clinical variables, no significant difference was noted among the antipsychotics. The analysis revealed that new-onset diabetes was significantly related to increasing age and minority race. Nevertheless, patients who are taking antipsychotic agents and have diabetes or are at risk for diabetes should be monitored for any adverse effects related to diabetes.

Acknowledgments

The authors would like to thank Eli Lilly and Company for financial support and the Central Texas Veterans Health Care System for their time and expertise in obtaining the data.

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