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Original Contribution

Diabetes Risk Associated with Use of Olanzapine, Quetiapine, and Risperidone in Veterans Health Administration Patients with Schizophrenia

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To evaluate risk of new-onset type 2 diabetes associated with use of selected antipsychotic agents, the authors conducted a new-user cohort study in a national sample of US Veterans Health Administration patients with schizophrenia (and no preexisting diabetes). The authors studied 15,767 patients who initiated use of olanzapine, risperidone, quetiapine, or haloperidol in 1999–2001 after at least 3 months with no antipsychotic prescriptions. Patients were followed for just over 1 year. New-onset diabetes was identified through diagnostic codes and prescriptions for diabetes medication. In Cox proportional hazards regression adjusting for potential confounders, with patients initiating haloperidol use designated the reference group, diabetes risk was increased equally with new use of olanzapine (hazard ratio (HR) = 1.64, 95% confidence interval (CI): 1.22, 2.19), risperidone (HR = 1.60, 95% CI: 1.19, 2.14), or quetiapine (HR = 1.67, 95% CI: 1.01, 2.76). Diabetes risks were higher in patients under age 50 years. When data were reanalyzed with prevalent-user cohorts and matched case-control designs, results were similar, with slightly less elevated risk estimates. Assuming that the observed associations are causal, approximately one third of new cases of diabetes may be attributed to use of olanzapine, risperidone, and quetiapine in patients taking these medications. Prescribers should be mindful of diabetes risks when treating patients with schizophrenia.

antipsychotic agents; case-control studies; cohort studies; diabetes mellitus; pharmacoepidemiology; schizophrenia; veterans

Abbreviation: VHA, Veterans Health Administration.

The introduction of a new generation of antipsychotic drugs has been heralded as an important advance in the treatment of schizophrenia. The ''atypical'' or second-generation antipsychotic agents (e.g., olanzapine) are at least as effective as older drugs (e.g., haloperidol) in treating schizophrenia but are less likely to cause extrapyramidal side effects and tardive dyskinesia (1–11). However, some of the newer drugs have been associated with metabolic disturbances,

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including weight gain (12–17), hyperlipidemia (18–20), hyperglycemia, and new-onset diabetes mellitus (18, 21–25).

Evidence for a possible link between use of second-generation antipsychotic agents and diabetes has come from case reports (26–46), case-control studies (47), and cohort studies of ongoing users (23, 25, 48, 49). While most studies have reported an association, the magnitude of the risk and the differences in risk among agents in this class have varied between studies. This inconsistency is probably related to differences in the patient populations studied, reference groups, definitions of diabetes, exposure definitions, and control for potential confounding. Furthermore, most of the studies failed to restrict the exposure to new users or to persons using single agents, so confounding related to discontinuation or switching of medication may have biased the results (50).

We conducted a study to determine the risk of new-onset type 2 diabetes in relation to newly initiated use of single-agent antipsychotic medications among Veterans Health Administration (VHA) patients with schizophrenia. We attempted to improve exposure definition, reduce selection bias, adjust for multiple confounders, and minimize the influence of previous antipsychotic agents on the observed outcome. To facilitate comparisons with previous studies and to illustrate the impact of design choices on results of observational studies, we also describe the results obtained in a prevalent-user cohort analysis and a matched case-control analysis.

MATERIALS AND METHODS

Data sources

In this study, we used electronic data available for all VHA patients nationally (51). This includes information on all VHA medical encounters (outpatient, inpatient, and long-term-care) obtained from the Austin Automation Center, VHA outpatient and inpatient prescription data from the Pharmacy Benefits Management Strategic Healthcare Group, and death records from the Beneficiary Identification Records Locator Subsystem, a registry of all veterans who applied for VHA death benefits that is supplemented by data from Social Security records. This study was approved by the institutional review boards of the University of Illinois at Chicago and the Hines Veterans Health Administration (Hines, Illinois).

Sample selection

We identified VHA patients with schizophrenia and constructed a series of new-user cohorts of patients who began receiving antipsychotic medication after 12 or more weeks without an antipsychotic prescription. Schizophrenia patients were identified on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes for schizophrenia (295.xx) in records of inpatient stays or outpatient visits on at least two separate days from October 1, 1996, through September 30, 2001. Study subjects were restricted to those who had filled at least one prescription for an antipsychotic drug from January 1, 1999, through September 30, 2001. To study new users only, we further excluded those patients who had been prescribed antipsychotic medication during the first 12 weeks of collection of national prescription data, from October 1, 1998, through December 31, 1998. To study new-onset diabetes only, we also excluded patients who had any sign of diabetes prior to their first exposure to antipsychotic agents (a diabetes diagnostic code (250.xx) going back to October 1, 1996, or a prescription for a diabetes medication going back to October 1, 1998). We also excluded all patients whose first contact with the VHA system (based on the presence of any prescription, procedure, or diagnostic record in inpatient or outpatient data) was fewer than 12 weeks prior to their first antipsychotic drug exposure. In this way, we could be reasonably sure that patients were using the VHA on an ongoing basis and were unlikely to be receiving antipsychotic agents from other sources.

Definition of diabetes

Patients were considered to have new-onset diabetes if they were given diabetes diagnostic codes (250.xx) on at least two separate days or if they filled a prescription for an antidiabetic drug (insulin, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, or meglitinides). This definition has been shown to be reliable and valid in the VHA system (52). The date of diabetes was defined as the earliest sign of diabetes (the first diagnosis or prescription) for a subsequently confirmed case.

Analysis

Analyses were conducted using SAS, version 8.2 (53). Four new-user cohorts were constructed consisting of schizophrenic patients newly initiating use of one of three selected second-generation antipsychotic medications (olanzapine, quetiapine, or risperidone) or haloperidol, the most commonly used conventional antipsychotic agent. There were insufficient numbers of new users of clozapine, ziprasidone, and aripiprazole for these persons to be included in the new-user cohort analysis.

Cohort samples were characterized and compared in terms of demographic factors and other study variables. Cox proportional hazards regression was used to estimate hazard ratios with 95 percent confidence intervals for new-onset diabetes developing over the course of follow-up (54). Observation began on the day a patient received his or her first prescription for an antipsychotic agent (after January 1, 1999) and continued until the first occurrence of diabetes, death, initiation of use of a second antipsychotic agent, or last contact with the VHA system prior to September 30, 2001. The proportional hazards assumption was confirmed using ''log-log'' plots (55).

Multivariate regression models were constructed to adjust for potential confounders, including sex, age, race/ethnicity, marital status, exposure to other medications that may cause diabetes (beta-blockers, thiazide diuretics, lithium, phenytoin, corticosteroids) (56), and number of basic or comprehensive metabolic panels that included glucose testing performed during follow-up. The last factor was included to adjust for potential bias related to intensity of screening

for diabetes that may have varied among patients using different antipsychotic medications.

In this analysis, we present hazards for initiating use of each second-generation antipsychotic medication, with persons initiating haloperidol as the reference category. To facilitate comparison with other studies, we also present some results of parallel analyses that used patients initiating any conventional antipsychotic agent (chlorpromazine, etc.) as the reference group.

This is a study of patients on single-agent antipsychotic drug therapy, since we censored patients when they switched to another antipsychotic drug. It is possible that some patients may have been switched from one drug to another after showing signs of glucose dysregulation. If such patients developed diabetes after switching medications, our initial analysis would have missed these cases when perhaps they should have been attributed to the preswitch drug. To examine this possibility, we reran our analyses including in the models any cases of diabetes that were diagnosed 30, 60, or 90 days after switching medications.

Hazard ratios for the various second-generation antipsychotic agents were compared and differences were evaluated using the Wald test (the TEST statement in PROC PHREG in SAS). Effect modification by age and other factors was evaluated using interaction terms in the overall models and conducting separate analyses in each stratum of age. Linear trends in hazard ratios by age were evaluated using an ordinal term. Estimates of attributable risk percentage were calculated using hazard ratios obtained from proportional hazards modeling (57).

Additional analyses: prevalent-user cohorts and case-control designs

We conducted two additional analyses. In the first, we implemented a prevalent-user cohort design, which was identical to that for the new-user cohorts except that we did not exclude patients who had been exposed to antipsychotic agents during the prior 12-week period. These cohorts were larger and consisted mostly of schizophrenia patients on continuing antipsychotic drug therapy. Observation began with the first antipsychotic prescription, regardless of prior prescriptions, and continued as in the new-user cohort design, with proportional hazards regression being employed in the analysis.

In the second additional analysis, we conducted a matched case-control analysis nested in the prevalent-user cohorts. Among persons initiating use of antipsychotic agents, new-onset cases of diabetes were matched on sex, age (±5 years), and location of VHA care with up to six controls who showed no evidence of diabetes over the course of the study. Medication exposures prior to diabetes diagnosis in the case and during the same time period for matched controls were examined, without restriction to newly initiated use. Patients in the case-control study had to have been taking one and only one antipsychotic medication during the retrospective exposure period. Because there is little consensus on the timing of the putative effects of antipsychotic agents on diabetes risk, we used three different retrospective exposure periods: 12, 24, and 52 weeks prior to the development of diabetes in the case. Conditional logistic regression was used in the analysis to compute odds ratios and 95 percent confidence intervals for each of the second-generation antipsychotic medications, with haloperidol as the reference category (58). These models included terms for covariates identical to those entered in the proportional hazards regression models utilized in the new-user cohort design as described above, except for sex, since it was used in matching.

In conducting these additional analyses, we found sufficient numbers of patients prescribed clozapine to evaluate diabetes risk associated with this second-generation antipsychotic agent. Findings from parallel prevalent-user cohort and case-control analyses of this medication using similar methods are presented separately.

RESULTS

We observed 15,767 patients in the four cohorts of antipsychotic initiators studied (table 1). Patients in these cohorts were broadly similar in terms of age, sex, race/ethnicity, marital status, use of other potentially diabetogenic medications, and number of diabetes screening tests. There were slightly more women and fewer racial minority patients among the quetiapine users, and more never-married and African-American patients among those prescribed haloperidol. Otherwise, frequency distributions varied by no more than a few percentage points across the four cohorts. Average length of follow-up was also similar (just over 1 year), except for quetiapine, which was only approved for use during the study. The annual incidence (unadjusted) of new-onset diabetes over the course of follow-up ranged from 2.0 per 100 person-years of exposure in users of haloperidol to 3.6 per 100 person-years in quetiapine users.

Table 2 gives the hazard ratios and 95 percent confidence intervals for initiation of olanzapine, risperidone, and quetiapine, with patients initiating haloperidol used as the reference group. For all three second-generation antipsychotic agents, the hazard ratio was 1.6–1.7, and adjustment for potential confounders had little effect on the estimates. There were no significant differences in effects among the three second-generation antipsychotic agents. When 30, 60, or 90 days were added to follow-up in patients switching to another antipsychotic agent, the results were similar but with slightly narrower confidence intervals. There appeared to be effect modification by age, with generally higher odds ratios being seen in younger patients, at least for olanzapine and risperidone ($p = 0.05$ and $p = 0.03$, respectively, in tests of homogeneity of hazards between persons aged $\geq$50 years and $<$50 years). Estimates of attributable risk percentage were 33.3 percent, 32.0 percent, and 35.0 percent for olanzapine, risperidone, and quetiapine, respectively.

Table 3 summarizes results from the new-user cohort design in comparison with those from the two additional analyses implementing prevalent-user cohort and case-control designs. The more expanded sample of patients studied in these analyses (see table 4) was compared with patients in the new-user cohort design; except for a slightly smaller percentage of racial minority patients, there were no differences

TABLE 1. Characteristics of four cohorts of new users of antipsychotic medication ($n = 15,767$) among US veterans with schizophrenia, 1999–2001

Variable	Antipsychotic agent			
	Olanzapine ($n = 5,981$)	Risperidone ($n = 5,901$)	Quetiapine ($n = 877$)	Haloperidol ($n = 3,008$)
Mean age (years)	50.3 (11.2)*	51.1 (12.2)	50.6 (11.7)	52.0 (12.1)
Sex (%)				
Male	94.1	93.2	91.7	95.1
Female	5.9	6.8	8.3	4.9
Race/ethnicity (%)				
White	48.4	47.7	58.3	44.0
African-American	28. 8	30.8	21.2	39.4
Hispanic	6.8	4.8	4.1	5.4
Other	0.8	0.6	0.6	0.6
Unknown	15.2	16.2	15.8	10.6
Marital status (%)				
Married	22.3	22.4	21.3	16.9
Never married	40.5	40.0	39.2	46.5
Divorced, separated	32.6	32.1	33.7	30.0
Widowed	2.8	4.0	3.8	3.4
Unknown	1.8	1.4	1.9	2.1
Use of medications potentially inducing diabetes (%)				
Beta-blockers/thiazide diuretics	16.0	16.5	17.8	14.8
Lithium	5.9	5.2	5.9	5.1
Corticosteroids	1.6	1.5	0.8	1.8
Phenytoin	1.9	2.0	1.4	2.2
No. of metabolic panels per patient	0.18 (0.74)	0.18 (0.73)	0.15 (0.64)	0.19 (0.83)
Mean duration of follow-up (days)	367.4 (299.6)	371.6 (300.5)	244.3 (246.8)	364.5 (325.7)
Mean time to event (days)	240.8 (196.1)	267.3 (228.9)	214.1 (175.3)	304.1 (260.8)
No. of new cases of diabetes diagnosed during study period	200	193	21	60
Diabetes incidence per 100 person-years of exposure	3.3	3.2	3.6	2.0

* Numbers in parentheses, standard deviation.

of more than a few percentage points in the distributions of demographic factors, other medications, or laboratory tests. Except for quetiapine in the prevalent-user cohorts, the relative risk of diabetes was increased with use of all three second-generation antipsychotic agents, regardless of design. Estimates ranged from 1.2 to 1.8. In the prevalent-user cohorts, risk was elevated for both olanzapine and risperidone, but risk associated with olanzapine was significantly greater than that associated with risperidone ($p = 0.02$). Otherwise, there were no significant differences in diabetes-related risks for the three medications in any of the analyses.

When the reference group was changed from patients exposed to haloperidol to patients exposed to any conventional antipsychotic agent, the pattern of results was essentially unchanged, with somewhat lower estimates of effect. The hazard ratios were between 1.4 and 1.5 in the new-user cohorts and between 1.1 and 1.3 in the prevalent-user cohorts.

In parallel analyses, there were 1,293 patients in the clozapine cohort (110 without a prescription in the first 12-week period), and 106 developed new-onset diabetes during follow-up. Clozapine patients tended to be younger, and fewer of them were married or members of racial/ethnic

TABLE 2. Risk of developing diabetes according to initiation of use of second-generation antipsychotic medication among US veterans with schizophrenia, 1999–2001*

Analysis	Second-generation antipsychotic agent					
	Olanzapine ($n = 5,981$)		Risperidone ($n = 5,901$)		Quetiapine ($n = 877$)	
	HR†	95% CI†	HR	95% CI	HR	95% CI
Unadjusted (all ages)	1.63	1.22, 2.18	1.58	1.18, 2.11	1.66	1.01, 2.73
Adjusted						
All ages‡	1.64	1.22, 2.19	1.60	1.19, 2.14	1.67	1.01, 2.76
All ages + 30 days to follow-up§	1.57	1.19, 2.08	1.55	1.17, 2.05	1.67	1.04, 2.70
By age group (years)						
<45 ($n = 4,928$)	3.06	1.41, 6.63	3.40	1.56, 7.42	2.98	0.95, 9.31
45–54 ($n = 6,312$)	1.54	0.99, 2.39	1.38	0.88, 2.16	1.04	0.44, 2.41
55–64 ($n = 2,177$)	0.84	0.44, 1.60	1.15	0.63, 2.10	1.11	0.36, 3.44
65–74 ($n = 1,329$)	1.22	0.55, 2.72	1.14	0.49, 2.65	2.59	0.74, 8.97
≥75 ($n = 1,021$)	3.15	0.66, 15.21	2.46	0.52, 11.51	3.21	0.26, 39.23

* Cox proportional hazards regression analysis of new-user cohorts. Users of haloperidol were the reference category.

† HR, hazard ratio; CI, confidence interval.

‡ Models included terms for sex, age, race/ethnicity, marital status, use of other potentially diabetes-inducing medications (beta-blockers, thiazide diuretics, lithium, phenytoin, and corticosteroids), and number of basic or comprehensive metabolic panels performed during follow-up.

§ Follow-up extended to 30 days after discontinuing medication and switching to a new antipsychotic agent.

minority groups. The hazard ratio for clozapine from the prevalent-user cohort analysis was 2.15 (95 percent confidence interval: 1.74, 2.66) and was significantly higher than the hazard ratios for olanzapine, risperidone, and quetiapine ($p < 0.001$). From the case-control analyses, the odds ratio was 1.34 (95 percent confidence interval: 0.98, 1.82) for the 12-week exposure period, and it increased to 1.41 and 1.60 for the 24- and 52-week periods, respectively.

DISCUSSION

Second-generation antipsychotic agents are widely used as first-line therapy for psychotic illnesses, accounting for 80 percent of all antipsychotic medications prescribed in the United States in 2002 (59). Conventional antipsychotic drugs such as haloperidol may cause movement disorders and tardive dyskinesia—stigmatizing and sometimes debilitating side effects that harm patients' functioning and well-being (60). Some second-generation antipsychotic drugs may cause these side effects, but at a lower rate, while offering efficacy equal to or better than that of the older drugs (11, 61).

There is growing evidence of metabolic side effects, such as hyperglycemia and weight gain, following the use of certain second-generation antipsychotic agents. This complicates the comparison between newer and older antipsychotic drugs (59, 61, 62). Prescribing choices must now be based on an assessment of each drug's efficacy as well as its potential to cause movement disorders or metabolic side effects. Apart from clozapine, the evidence is equivocal as to whether or not second-generation antipsychotic drugs differ from one another in effectiveness, and it is not certain that they are more effective than their older counterparts (11, 59, 61–64). If and when additional benefits of second-generation agents are confirmed, they must be weighed against the risk of metabolic problems and their higher acquisition costs.

The association between second-generation antipsychotic agents and diabetes risk first came to light in case reports. In most of these, observers reported diabetic ketoacidosis, new-onset diabetes, or hyperglycemia among patients initiating either clozapine (26–33, 65) or olanzapine, the two second-generation antipsychotic agents that have been on the market for the longest time and have most often been associated with weight gain (66). Subsequently, there appeared reports of diabetes occurring in patients taking one of the other second-generation antipsychotic agents, risperidone (32, 43–46) or quetiapine (32, 41, 42), leading to uncertainty about which agents in this class carry the highest risk of diabetes. While the weight gain associated with use of these agents may contribute to the increased risk of diabetes, the mechanism appears to be complex, possibly involving direct effects of the agents on insulin sensitivity and serotonin receptor activity (22, 32, 67).

Epidemiologic studies have largely confirmed the association of new-onset diabetes with use of second-generation antipsychotic agents. However, the increase in risk is relatively small, and there are inconsistencies in the findings, particularly with respect to variation in risk among individual agents (23, 25, 47–49, 68). Compared with conventional antipsychotic agents, clozapine has been associated with more than a twofold increased risk of diabetes in younger

TABLE 3. Results from cohort and case-control analyses of diabetes risk according to use of second-generation antipsychotic medication among US veterans with schizophrenia, 1999–2001*

Second-generation antipsychotic agent	Cohort study design							Case-control study design							
	New-user cohorts			Prevalent-user cohorts†				12-week exposure period‡				24-week exposure period§			
	No. of cases	HR#	95% CI#	No. of cases	HR	95% CI		No. of cases	No. of controls	OR#	95% CI	No. of cases	No. of controls	OR	95% CI
Olanzapine	5,981	1.64	1.22, 2.19	19,780	1.39	1.26, 1.54		1,302	3,270	1.37	1.19, 1.58	1,138	2,886	1.39	1.20, 1.62
Risperidone	5,901	1.60	1.19, 2.14	19,369	1.26	1.14, 1.40		1,001	2,808	1.20	1.03, 1.38	869	2,484	1.21	1.04, 1.42
Quetiapine	877	1.67	1.01, 2.76	1,578	1.19	0.89, 1.59		147	348	1.46	1.14, 1.87	124	293	1.47	1.13, 1.92

Second-generation antipsychotic agent	52-week exposure period¶		
	No. of cases	No. of controls	OR	95% CI
Olanzapine	801	2,147	1.32	1.11, 1.58
Risperidone	668	1,763	1.35	1.12, 1.62
Quetiapine	89	186	1.82	1.32, 2.49

* In all analyses, patients exposed to haloperidol were the reference group.
† In the prevalent-user cohort analysis, the hazard ratios for olanzapine and risperidone were significantly different from each other at $p < 0.05$. There were no other significant differences between antipsychotic drugs within each design.
‡ The 12-week case-control study included 414 haloperidol cases and 1,378 controls.
§ The 24-week case-control study included 351 haloperidol cases and 1,180 controls.
¶ The 52-week case-control study included 244 haloperidol cases and 821 controls.
# HR, hazard ratio; CI, confidence interval; OR, odds ratio.

patients (ages 20–34 years) with schizophrenia. This was reported from a cohort analysis of Iowa Medicaid claims data (49) and subsequently confirmed in a larger study of VHA patients with schizophrenia (48). In most studies, more modest risk increases of 20–80 percent have been reported for the other, newer second-generation antipsychotic agents.

Two previous studies of VHA patients have provided much of the published evidence on this issue (23, 48). In a prevalent-user cohort analysis of VHA patients with schizophrenia, persons taking second-generation antipsychotic agents were just 9 percent more likely to have diabetes than persons taking conventional antipsychotic medications (48), with relative risks ranging from 1.1 to 1.3 for clozapine, olanzapine, quetiapine, and risperidone. Risk increases were greater in younger patients (age <50 years). This study was limited by its mixing of new and ongoing users of one or more of these agents, its failure to differentiate between new and existing cases of diabetes, and limited adjustment for potential confounders. In a second study of VHA patients from Ohio, a prevalent-user cohort analysis was performed that included all patients prescribed antipsychotic agents, not just those with schizophrenia. Compared with haloperidol, olanzapine (but not risperidone) was associated with an approximately 50 percent increased risk of diabetes (23). While the investigators attempted to address the effect of medication-switching in the analysis, they did not examine the potential influence of the pattern of switching (i.e., whether different drugs were taken simultaneously or sequentially and, if so, in what sequence), nor did they consider potential bias related to the functional form of their time-dependent covariates (69).

Findings bearing on this question have been reported from two other studies. In a nested case-control analysis of the United Kingdom General Practice Research Database, high odds ratios for diabetes were found for use of olanzapine (odds ratio = 4.2) and risperidone (odds ratio = 1.6) relative to conventional antipsychotic medication ($p > 0.05$) (47). In a second study (25), a follow-up analysis of a large prescription claims database, risk of diabetes was increased with use of any antipsychotic medication as compared with the general (nonpsychiatric) population. Compared with haloperidol, diabetes risk was greater with use of risperidone (hazard ratio = 1.23) but not with olanzapine or quetiapine use. These investigators also restricted their sample to new users and evaluated risks for patients using single antipsychotic agents. However, the sample was not limited to patients with schizophrenia, diagnosis of diabetes was based solely on prescription data, and there was more limited adjustment for confounders.

In the present study, there were negligible differences in diabetes risk associated with use of olanzapine, risperidone, and quetiapine. Each appeared to increase risk by 60–70 percent in comparison with haloperidol. Elevations in risk were higher among younger patients with schizophrenia. However, since the incidence of diabetes climbs steeply with age, a greater number of diabetes cases may be attributable to second-generation antipsychotic agents in older users as compared with younger users, and switching to lower-risk agents may actually prevent more cases of diabetes among older patients.

TABLE 4. Characteristics of five cohorts of prevalent users of antipsychotic medication ($n = 55,808$) among US veterans with schizophrenia, 1999–2001

Variable	Antipsychotic agent				
	Olanzapine ($n = 19,780$)	Risperidone ($n = 19,639$)	Quetiapine ($n = 1,578$)	Clozapine ($n = 1,293$)	Haloperidol ($n = 13,518$)
Mean age (years)	50.0 (11.5)*	51.1 (12.4)	49.8 (11.6)	47.6 (8.7)	53.0 (12.3)
Sex (%)					
Male	93.7	93.2	90.4	95.1	95.6
Female	6.3	6.8	9.6	4.9	4.4
Race/ethnicity (%)					
White	53.2	52.2	56.5	75.8	49.0
African-American	24.4	26.4	20.3	14.1	33.2
Hispanic	6.8	5.0	3.3	2.9	5.8
Other	1.0	0.9	1.0	1.2	1.0
Unknown	14.6	15.5	18.9	5.9	11.2
Marital status (%)					
Married	23.0	23.1	22.0	9.5	19.2
Never married	43.2	42.6	40.2	66.4	48.0
Divorced, separated	29.1	29.1	33.0	21.0	26.7
Widowed	2.7	3.6	2.9	1.2	3.3
Unknown	2.0	1.6	2.0	2.0	2.6
Use of medications potentially inducing diabetes (%)					
Beta-blockers/thiazide diuretics	14.0	13.7	15.5	15.5	14.9
Lithium	6.6	5.8	7.2	4.4	6.6
Corticosteroids	1.6	1.6	1.1	0.6	1.6
Phenytoin	1.6	1.7	1.2	0.5	2.0
No. of metabolic panels per patient	0.24 (0.92)	0.22 (0.86)	0.18 (0.81)	0.22 (0.91)	0.24 (0.92)
Mean duration of follow-up (days)	495.5 (391.8)	522.5 (389.5)	270.9 (288.1)	609.5 (441.7)	505.5 (399.1)
Mean time to event (days)	290.3 (280.8)	301.1 (288.5)	137.5 (151.6)	350.6 (349.0)	295.8 (285.2)
No. of new cases of diabetes diagnosed during study period	1,098	1,026	50	106	571
Diabetes incidence per 100 person-years of exposure	4.1	3.9	4.3	4.9	3.0

* Numbers in parentheses, standard deviation.

We believe that the risk of diabetes can be attributed confidently to each agent evaluated in this study because of the new-user cohort design and because each study patient was exposed to one and only one drug during the follow-up period. Without this design, there may be important confounding related to discontinuation or switching of medications, and the effects of the agent under study may be biased by other prior or concurrent medications used (50). To our knowledge, all previous studies but one (25) either have not addressed these potential problems or have accounted for them using other methods (23, 48, 49, 68, 70). The estimates from our study suggest that, in patients with schizophrenia using olanzapine, quetiapine, or risperidone, approximately one case per 100 patients per year or one third of new-onset diabetes is attributable to use of these agents as compared with use of haloperidol.

Differences in study design may explain why our results are partially at variance with those of other studies. We evaluated this by analyzing our data using alternative study designs. Results from the prevalent-user cohort analysis are comparable to those that have been reported for studies of this kind, in that the relative risk estimates are somewhat closer to 1.0 and diabetes risk is higher with use of olanzapine compared with risperidone (23, 48). The other

finding from this analysis is a higher risk of diabetes associated with clozapine use—about a doubling of risk—and this is also consistent with previous reports (48, 49). Risk estimates from the case-control analysis are similar to those from our new-user cohort analysis. Indeed, while there are some differences in risk estimates coming from the analyses using different designs, they are similar and are statistically consistent with one another in suggesting a modestly increased risk of diabetes with use of clozapine, olanzapine, quetiapine, and risperidone. In making these comparisons, caution is warranted in using large study samples to evaluate such small differences in risk estimates—differences that may be the result of unexplained bias.

In comparison with the new-user cohort analysis, more modest associations with diabetes risk were found in the prevalent-user cohort design. This sampling strategy is more likely to include patients who were long-term users and tolerated their drugs well, since patients who gained more weight or had other metabolic problems may have had their medications discontinued or changed prior to the time of our study. Their underrepresentation in the sample may have resulted in the somewhat weaker associations observed with the prevalent-user cohort design. It is important to recognize that potential confounding or problems of differences between switchers and long-term users cannot be resolved entirely through the use of a cohort design. Nevertheless, we believe that the new-user cohort design is preferable as a method of reducing these potential problems (50).

Other considerations warrant caution in interpreting these findings. The pharmacy or diagnostic data may have been inaccurate or incomplete, and there may have been misclassification in the identification of schizophrenia and diabetes, although conservative definitions were used (52). Confounding by contraindication remains a possible explanation for our results, particularly since we lacked critical information with which to adjust for baseline diabetes risk, such as data on initial weight, change in weight, caloric intake, existing hypertension or hypercholesterolemia, and family history of diabetes. Prescribers who believed that some drugs (e.g., clozapine or olanzapine) caused more weight gain than others may have steered patients with high diabetes risk away from these agents. If this did occur, the risk for these drugs may have been underestimated, while risk for more weight-neutral drugs (e.g., risperidone or quetiapine) may have been overestimated. Concern about this potential source of confounding is mitigated by our finding of only minute differences in the intensity of diagnostic screening between users of the different drugs. Nevertheless, confounding by contraindication remains a possible source of bias in this study and in previously conducted observational studies of antipsychotic agents and diabetes, none of which controlled for baseline diabetes risk.

There are other limitations to our research. Medications taken prior to the 3-month period used to identify patients for the new-user cohort analysis may have influenced subsequent risk, and we had no information on those prescriptions. Restricting our study to patients exposed to only one antipsychotic agent limited our ability to assess the potential diabetogenic effects of simultaneous or sequential exposures to more than one antipsychotic drug—patterns that may be common in clinical practice. Since we did not study ziprasidone or aripiprazole, the newest second-generation antipsychotic agents, no conclusions should be drawn from our study about their potential for causing diabetes.

Some caution in generalizing the results of our study to users of other antipsychotic agents is also warranted. We studied patients with schizophrenia, and effects may be different in patients taking antipsychotic drugs for other indications. Patients in our new-user cohorts who did not receive antipsychotic medication at the VHA for at least 3 months may have been different from the larger population of VHA patients with schizophrenia. Although some of these patients may have used non-VHA services during that time, they were unlikely to obtain outpatient medications from non-VHA sources, where costs are higher and access is more limited (71, 72). Poor adherence to treatment is a significant issue in schizophrenia (73–75), and substantial time periods without treatment are not unusual. The lack of differences in patient characteristics between the new-user cohorts and the prevalent-user cohorts partially mitigates these concerns. Generalizing these results beyond the VHA population should be done with caution, especially since there were so few women in the sample.

The evidence presented here for an association between selected second-generation antipsychotic medications and metabolic problems should be placed in a broad context. Decisions concerning selection of specific antipsychotic medications should be based on safety, efficacy, tolerability, and cost (61, 63). The relative weights assigned to these factors will depend on the clinical and financial context of treatment (76, 77).

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