Diabetes Risk Associated with Use of Olanzapine, Quetiapine and Risperidone in VA Patients with Schizophrenia

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ABSTRACT

To evaluate risk of new onset type 2 diabetes associated with use of selected antipsychotics, we conducted a new-user cohorts study in a national sample of U.S. Veterans Health Administration patients with schizophrenia and no pre-existing diabetes. We studied 15,767 patients who initiated olanzapine, risperidone, quetiapine, or haloperidol in 1999-2001 after at least three months with no antipsychotic prescriptions. Patients were followed for just over one year, and new onset diabetes was identified by diabetes medication prescriptions and diagnostic codes. Using Cox proportional hazards regression to adjust for potential confounders and with haloperidol initiators as the reference group, diabetes risk was increased equally with new use of olanzapine (Hazard ratio=1.64, 95% confidence intervals=1.22, 2.19), risperidone (1.60, 1.19, 1.14,) or quetiapine (1.67, 1.01, 2.76). Diabetes risks were higher in patients under 50 years of age. When the data were re-analyzed with prevalent-user cohorts and matched case-control designs, the results were similar except for slightly less elevated risk estimates. Assuming the observed associations are causal, about one third of new diabetes may be attributed to the use of olanzapine, risperidone, and quetiapine in patients using these medications. Prescribers should be mindful of diabetes risks when treating patients with schizophrenia.

Keywords: Schizophrenia, diabetes mellitus, antipsychotic agents, cohort studies, case-control studies, pharmacoepidemiology

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 antipsychotics (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). Some of the newer drugs have been associated with metabolic disturbances, however, 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 antipsychotics 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 likely related to differences in the patient populations studied, reference groups, definitions of diabetes, exposure definitions, and controls for potential confounding. Furthermore, most of the studies failed to restrict the exposure to new users or to those on single agents, so that 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 diabetes in relation to newly initiated, single-agent antipsychotic use in Veterans Health Administration (VA) 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 of a prevalent-users cohort and a matched case-control analysis.

METHODS

Data Sources

This study uses electronic data available for all VA patients nationally (51). This includes information for all VA medical encounters (outpatient, inpatient, and long term care) obtained from the Austin Automation Center, VA outpatient and inpatient prescription data from the Pharmacy Benefits Management Strategic Healthcare Group, and death records from the Beneficiary Identification and Record Locator file, a registry of all veterans who applied for VA death benefits 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 and Bedford VAs.

Sample Selection

We identified VA patients with schizophrenia and constructed a series of new-user cohorts of patients who began receiving antipsychotic medication after twelve or more weeks without an antipsychotic prescription. Schizophrenia patients were identified based on the presence of ICD-9-CM codes for schizophrenia (295.xx) in records for inpatients 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 with prescriptions for antipsychotic medications during the first 12 weeks of national prescription data, from October 1, 1998 through December 31, 1998. In order to study new onset diabetes only, we also excluded patients who had any sign of diabetes prior to their first antipsychotic exposure (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 VA system (based on the presence of any prescription, procedure, or diagnostic records in inpatient or outpatient data) was fewer than 12 weeks prior to their first antipsychotic exposure. In this way we could be reasonably sure that patients were using the VA on an on-going basis and unlikely to be receiving antipsychotics from other sources.

Definition of Diabetes

Patients were considered to have new onset diabetes if they had 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, meglitinides). This definition has been shown to be reliable and valid in the VA system (52). The date of diabetes was defined as the earliest sign of diabetes (either first diagnosis or prescription) for a subsequently confirmed case.

Analysis

Analyses were conducted using SAS version 8.0 (53). Four new-user cohorts were constructed consisting of schizophrenic patients newly initiating one of three selected second generation antipsychotic medications (olanzapine, quetiapine, or risperidone) or haloperidol, the most commonly used conventional antipsychotic. There were insufficient numbers of new users of clozapine, ziprasidone, and aripiprazole to be included in the new-user cohort analysis.

Cohort samples were characterized and compared in terms of demographics and other study variables. Cox proportional hazards regression was used to estimate hazards ratios with 95% confidence intervals for new onset diabetes developing over the period of follow-up (54). Observation began on the day they received their first antipsychotic prescription (after January 1, 1999) and continued until the first occurrence of diabetes, death, initiation of a second

antipsychotic, or last contact with the VA 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, 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 each second generation antipsychotic medication with those initiating haloperidol as the reference category. To facilitate comparison to other studies, we also present some results of parallel analyses that used patients initiating any conventional antipsychotic (e.g., chlorpromazine, etc.) as the reference group.

This is a study of patients on single-agent antipsychotic 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, our initial analysis would miss these cases when perhaps they should have been attributed to the pre-switch drug. To examine this possibility, we re-ran our models including any cases of diabetes that occurred 30, 60 or 90 days after switching.

Hazard ratios for the various second generation antipsychotics were compared and differences were evaluated using the Wald Test (TEST statement in PROC PHREG in SAS). Effect modification by age and other factors was evaluated using interaction terms in the overall models and running separate models in each stratum of age. Linear trends in hazards ratios by

age were evaluated using an ordinal term. Estimates of attributable risk percent were calculated using hazards ratios obtained from proportional hazards modeling (57).

Additional Analyses: Prevalent-Users Cohorts and Case Control Designs

We conducted two additional analyses. In the first, we implemented a prevalent-users cohort design, identical to the new-user cohorts except that we did not exclude patients with antipsychotic exposure in 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 used in the analysis.

In the second additional analysis, we conducted a matched case-control analysis nested in the prevalent-users cohort. Among those initiating antipsychotics, new onset cases of diabetes were matched on sex, age (± 5 years), and location of VA care with up to six controls who showed no evidence of diabetes over the course of the study. Medication exposures prior to diabetes in the case and in the same time period for matched controls were examined, without restriction to newly initiated use. Patients in the case control study had to be on one and only one antipsychotic during the retrospective exposure period. Because there is little consensus on the timing of the putative effects of antipsychotics 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% 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 used 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. Findings from parallel prevalent-users cohorts 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 age, sex, race or 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 one year) except for quetiapine, which was only approved for use during the study. Annual incidence (unadjusted) of new onset diabetes over the course of follow-up ranged from 2.0 per hundred person years of exposure in users of haloperidol to 3.6 per hundred person years in quetiapine users.

Table 2 gives the hazard ratios and 95% confidence intervals for olanzapine, risperidone and quetiapine with patients initiating haloperidol as the reference group. For all three second generation antipsychotics, the hazard ratio was 1.6 to 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 antipsychotics. When 30, 60 or 90 days were added to follow-up in patients switching to another antipsychotic, the results were similar but with slightly narrower confidence intervals. There appeared to be effect modification by age with generally higher odds ratios in younger patients, at least for olanzapine and risperidone ($p=0.05$ and 0.03,

respectively, in tests of homogeneity of hazards between those older and younger than 50 years). Estimates of attributable risk percent were 33.3%, 32.0% and 35.0% for olanzapine, risperidone; and quetiapine, respectively.

Table 3 summarizes results from the new-user cohort in comparison with those from the two additional analyses implementing prevalent-user cohorts and case control designs. The more expanded sample of patients studied in these analyses was compared to patients in the new-user cohort design (Table 4); except for a slightly smaller percentage of racial minority patients, there were no substantial differences of more than a few percentage points in the distributions of demographics, other medications, or laboratory tests. Except for quetiapine in the prevalent-users cohort, the relative risk of diabetes was increased with use of all three second generation antipsychotics, regardless of design. Estimates ranged from 1.2 to 1.8. In the prevalent-users cohorts, risk was elevated for both olanzapine and risperidone, but risk with olanzapine was significantly greater than 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, the pattern of results was essentially unchanged but with somewhat lower estimates of effect. The hazard ratios were between 1.4 and 1.5 in the new-user cohort 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 racial minorities. The hazard ratio for clozapine from the prevalent-users cohort analysis was 2.15 (1.74, 2.66) and was significantly higher than those for olanzapine, risperidone, and quetiapine ($p<0.001$). From

the case control analyses, the odds ratio was 1.34 (0.98, 1.82) for the 12 week exposure period and increased to 1.41 and 1.60 for the 24 and 52 week periods respectively.

DISCUSSION

Second generation antipsychotics are widely used as first line therapy for psychotic illnesses, accounting for 80% of all antipsychotic prescriptions in the U.S 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 at a lower rate, while offering efficacy equal to or better than 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 antipsychotics. This complicates the comparison between newer and older antipsychotics (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 antipsychotics and diabetes risk first came to light in case reports. Most reported diabetic ketoacidosis, new-onset diabetes, or hyperglycemia in patients initiating either clozapine (26-33, 65), or olanzapine, the two second generation antipsychotics that have been on the market for the longest time, and have been associated most often with weight gain (66). Subsequently, there appeared reports of diabetes occurring in

patients taking one of the other second generation antipsychotics, 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 antipsychotics. However, the increase in risk is relatively small and there are inconsistencies in the findings, particularly with respect to variation in risk among the individual agents (23, 25, 47-49, 68). Compared with conventional antipsychotics, clozapine has been associated with more than a two-fold increased risk of diabetes in younger patients (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 VA patients with schizophrenia (48). In most studies, more modest risk increases of 20% to 80% have been reported for the other, newer second generation antipsychotics.

Two previous studies of VA patients provide much of the published evidence on this issue. In a prevalent-user cohorts analysis of VA patients with schizophrenia, those taking second generation antipsychotics were just 9% more likely to have diabetes compared to those 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 (less than 50 years of age). This study was limited by its mixing of new and on-going users of one or more of these agents, its failure to differentiate between new and existing cases of diabetes, and a more limited adjustment of potential confounders .

In a second study of VA patients from Ohio, a prevalent-user cohorts analysis was performed with all patients prescribed antipsychotics, not just those with schizophrenia. Compared to haloperidol, olanzapine but not risperidone was associated with about a 50% increased risk of diabetes (23). While they 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 olanzapine (4.2) and risperidone (1.6, $p>0.05$), relative to conventional antipsychotic medication (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 compared to the general (non-psychiatric) population. Compared with haloperidol, diabetes risk was greater with risperidone (HR=1.23) but not with olanzapine or quetiapine use. This study also restricted their sample to new users and evaluated risks for patients on 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 confounder adjustment.

In the present study, there were negligible differences in diabetes risk associated with olanzapine, risperidone, and quetiapine. Each appeared to increase risk by 60% to 70% compared to haloperidol. Elevations in risk were higher among younger patients with schizophrenia. However, since incidence of diabetes climbs steeply with age, a greater number of cases of

diabetes may be attributable to second generation antipsychotic use in older users as compared to younger users, and switching to lower risk agents may actually prevent more cases of diabetes among older patients.

We believe that the risk of diabetes can be attributed confidently to each agent 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). All previous studies except one (25) have either 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, about one case per hundred patients per year or one third of new onset diabetes is attributable to use of these agents compared to patients on haloperidol.

Differences in study design may explain why our results are partially at variance with other studies. The analysis of our data using prevalent-user cohorts and nested case control study designs was performed to evaluate this question. Results from the prevalent-user cohorts analysis are comparable to those which 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 to risperidone (23, 48). The other finding from this analysis is a higher risk of diabetes associated with clozapine use, about a doubling of the risk, and this is also consistent with previous reports (48, 49). Risk estimates from the case control analysis are not as high as those from the published report of a study using this design (47) but are similar to the results from our new-user cohorts analysis. Indeed, while there are some differences in risk estimates coming

from the analyses using different designs, they are similar and consistent statistically with one another in suggesting modestly increased diabetes risk 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 cohorts analysis, more modest associations with diabetes risk were found in the prevalent-user cohorts 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 under-representation in the sample may have resulted in the somewhat weaker associations observed with the prevalent-user cohorts design. It is important to recognize that potential confounding or problems of differences between switchers and long-term users cannot be resolved entirely through cohort design. Nevertheless, we believe the new-user cohorts design is preferable as a method to reduce these potential problems (50).

Other considerations warrant caution in interpreting these findings. While systems are present to improve the quality of the study data, pharmacy or diagnostic data may have been inaccurate or incomplete. Although conservative definitions of schizophrenia and diabetes were used (52), we did not validate these diagnoses, and there may have been misclassification. Confounding by contraindication remains as a possible explanation for our results, particularly since we lacked critical information to adjust for baseline diabetes risk such as initial weight, change in weight, caloric intake, existing hypertension or hypercholesterolemia, and family history of diabetes. It is conceivable that prescribers who knew some drugs caused more weight

gain than others may have steered patients with high diabetes risk away from drugs believed to cause the most weight gain (e.g., clozapine or olanzapine). If this did occur, the risk for drugs known at the time to cause weight gain 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 only minute differences in the intensity of diagnostic screening between users of the different drugs. Nevertheless, confounding by contraindication remains as a possible source of bias in this and previously reported observational studies of antipsychotic use and diabetes, none of which controlled for baseline diabetes risk.

There are other limitations to our research. Medications taken prior to the three month period used to identify patients for the new-user cohorts analysis may have influenced subsequent risk. We had no information on those prescriptions. Restricting our study to patients exposed to only one antipsychotic 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 to cause diabetes.

Some caution in generalizing the results of our study to other antipsychotic users is also warranted. We studied patients with schizophrenia. Effects may be different in the broader population of patients taking antipsychotic drugs for other indications. Patients in our new-user cohorts who did not receive antipsychotic medication in the VA for at least three months may be different from the larger population of VA patients with schizophrenia. Although some of these patients may have used non-VA services during the time when they were not receiving

antipsychotic drugs from the VA, they were unlikely to obtain outpatient medications from non-VA sources where costs are higher and access 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 VA population should be done with caution, especially since there were so few women in the sample.

Evidence of an association between selected second generation antipsychotic medications and metabolic problems should be placed in a broad context. Decisions concerning selection of antipsychotic medications should be based on safety, efficacy, tolerability, and cost (61, 63). The relative weights assigned to these factors will differ with the clinical and financial context of the treatment. In the long run, scientific studies of drug safety, efficacy, and cost inform and support rational prescribing practices (76, 77).

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Table 1. Characteristics of the four new-user cohorts of U.S. veterans with schizophrenia, 1999-2001

Variable	Olanzapine (n=5981)	Risperidone (n=5901)	Quetiapine (n=877)	Haloperidol (n=3008)
Age (standard deviation)	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
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
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
Metabolic panels per patient	0.18 (0.74)	0.18 (0.73)	0.15 (0.64)	0.19 (0.83)
Days of follow-up - mean	367.4	371.6	244.3	364.5
Days to event - mean (SD)	240.8 (196.1)	267.3 (228.9)	214.1 (175.3)	304.1 (260.8)
New diabetes #	200	193	21	60
Incidence per 100 person years of exposure	3.3	3.2	3.6	2.0

Table 2. Cox proportional hazards regression for risk of diabetes by second generation antipsychotic medication, new-user cohorts of U.S. veterans with schizophrenia, 1999-2001, all ages and stratified by age.

Analysis	Second Generation Antipsychotics					
	Olanzapine (n=5981)		Risperidone (n=5901)		Quetiapine (n=877)	
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)
Adjusted 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)
Adjusted by age group						
< 45 (n=4928)	3.06	(1.41, 6.63)	3.40	(1.56, 7.42)	2.98	(0.95, 9.31)
45-54 (n=6312)	1.54	(0.99, 2.39)	1.38	(0.88, 2.16)	1.04	(0.44, 2.41)
55-64 (n=2177)	0.84	(0.44, 1.60)	1.15	(0.63, 2.10)	1.11	(0.36, 3.44)
65-74 (n=1329)	1.22	(0.55, 2.72)	1.14	(0.49, 2.65)	2.59	(0.74, 8.97)
>=75 (n=1021)	3.15	(0.66, 15.21)	2.46	(0.52, 11.51)	3.21	(0.26, 39.23)

* Hazard ratios and 95% confidence intervals with haloperidol as the reference category

** Models include terms for sex, age, race, marital status, other potential 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 new antipsychotic.

Table 3. Comparison of results from new-user cohorts, prevalent-users cohorts, and case-control designs, U.S. veterans with schizophrenia, 1999-2001

Second Generation Antipsychotic	New-user Cohorts Hazard Ratio (95% confidence interval)	Prevalent User Cohorts HR (95% CI)	Case-Control by Exposure Period*		
			12-Week	24-Week	52-Week
			Odds Ratio (95% CI) Num. Cases / Num. Controls	OR (95% CI) Num. Cases / Num. Controls	OR (95% CI) Num. Cases / Num. Controls
Olanzapine	1.64 (1.22, 2.19) N=5981	1.39 (1.26, 1.54) N=19,780	1.37 (1.19, 1.58) N=1302 / 3270	1.39 (1.20, 1.62) N=1138 / 2886	1.32 (1.11, 1.58) N=801 / 2147
Risperidone	1.60 (1.19, 2.14) N=5901	1.26 (1.14, 1.40) N=19,639	1.20 (1.03, 1.38) N=1001 / 2808	1.21 (1.04, 1.42) N=869 / 2484	1.35 (1.12, 1.62) N=668 / 1763
Quetiapine	1.67 (1.01, 2.76) N=877	1.19 (0.89, 1.59) N=1578	1.46 (1.14, 1.87) N=147 / 348	1.47 (1.13, 1.92) N=124 / 293	1.82 (1.32, 2.49) N=89 / 186

HR=hazard ratio. OR=odds ratio. In all cases, patients exposed to haloperidol are the reference group.*The 12-week case-control study had 414 haloperidol cases and 1378 controls. The 24-week case-control study had 351 haloperidol cases and 1180 controls. The 52-week case-control study had 244 haloperidol cases and 821 controls. In the prevalent user cohorts analysis, the hazards 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.

Table 4. Characteristics of prevalent-users cohort patients by drug (n=55,808), U.S. veterans with schizophrenia, 1999-2001

Variable	Olanzapine (n=19780)	Risperidone (n=19639)	Quetiapine (n=1578)	Clozapine (n=1293)	Haloperidol (n=13518)
Age (standard deviation)	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
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
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
Metabolic panels/patient	0.24 (0.92)	0.22 (0.86)	0.18 (0.81)	0.22 (0.91)	0.24 (0.92)
Days of follow-up-mean	495.5	522.5	270.9	609.5	505.5
Time to event-mean (SD)	290.3 (280.8)	301.1 (288.5)	137.5 (151.6)	350.6 (349.0)	295.8 (285.2)
New diabetes #	1098	1026	50	106	571
Incidence per 100 person years of exposure	4.1	3.9	4.3	4.9	3.0

Table 5. Hazard ratios and 95% confidence intervals for covariates in new-users cohort and prevalent users cohort, U.S. veterans with schizophrenia, 1999-2001

Variable	New-user Cohorts HR (95% confidence interval)		Prevalent User Cohorts HR (95% CI)	
Age (standard deviation)	1.00	(0.99, 1.01)	1.01	(1.01, 1.02)
Female	0.90	(0.61, 1.33)	1.09	(0.93, 1.27)
Ethnicity				
African-American	1.14	(0.92, 1.42)	1.32	(1.20, 1.44)
Hispanic White	1.65	(1.17, 2.34)	1.68	(1.46, 1.93)
Hispanic Black	0.55	(0.08, 3.92)	1.95	(1.29, 2.94)
Indian	4.28	(1.36, 13.46)	1.83	(1.04, 3.23)
Asian	0.48	(0.07, 3.41)	1.22	(0.79, 1.90)
Unknown ethnicity	1.21	(0.92, 1.61)	1.11	(0.99, 1.26)
Marital Status				
Divorced	0.69	(0.54, 0.89)	0.82	(0.74, 0.91)
Never married	0.84	(0.67, 1.06)	0.77	(0.70, 0.84)
Separated	0.94	(0.23, 3.83)	0.77	(0.32, 1.86)
Widowed	1.01	(0.64, 1.59)	0.90	(0.74, 1.10)
Unknown marital	0.69	(0.30, 1.57)	0.84	(0.63, 1.12)
Medications potentially inducing diabetes				
Beta-blockers /thiazide diuretics	2.16	(1.77, 2.64)	2.66	(2.44, 2.89)
Lithium	1.80	(1.33, 2.44)	1.88	(1.66, 2.12)
Corticosteroids	2.07	(1.35, 3.20)	1.46	(1.19, 1.79)
Phenytoin	1.15	(0.64, 2.05)	1.06	(0.82, 1.38)
Basic Metabolic Panels	1.19	(1.14, 1.25)	1.10	(1.08, 1.12)
Comp. Metabolic Panels	1.16	(1.03, 1.31)	1.09	(0.93, 1.27)