

## ORIGINAL REPORT

# Antipsychotic exposure and type 2 diabetes among patients with schizophrenia: a matched case-control study of California Medicaid claims<sup>†</sup>

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## SUMMARY

**Purpose** To examine the risk of developing type 2 diabetes mellitus among people with schizophrenia exposed to atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone) compared to those exposed to conventional antipsychotics.

**Methods** A matched case-control design was used to examine California Medicaid beneficiaries. Cases developed diabetes subsequent to being diagnosed with schizophrenia (ICD-9295), were 18 years or older, and were exposed to at least one antipsychotic medication at some point during the 12 weeks preceding diabetes diagnosis. Diabetes was defined by diagnostic claim (ICD-9250) or prescription for antidiabetic agents. A total of 3663 cases were matched to 14 523 non-diabetic controls (people with schizophrenia matched on gender and age  $\pm 5$  years). All had to be continuously eligible for benefits during the 12-week period preceding diabetes onset in the case. Conditional logistic regression modeled the risk of exposure, controlling for age, ethnicity, and exposure to selected concomitant medications. Analyses were repeated with 24- and 52-week exposure windows.

**Results** Using a 12-week exposure window, olanzapine (OR = 1.36, 95%CI 1.20–1.53), clozapine (OR = 1.34, 95%CI 1.16–1.55), and combination atypical therapy (OR = 1.58, 95%CI 1.33–1.88), but not risperidone or quetiapine, were associated with increased odds of developing diabetes compared to conventional antipsychotics. Changing to a 24-week exposure window, the risks were: olanzapine (OR = 1.38, 95%CI 1.22–1.56), clozapine (OR = 1.32, 95%CI 1.14–1.53), or combinations (OR = 1.54, 95%CI 1.29–1.84). With a 52-week exposure window, the risks were: olanzapine (OR = 1.41, 95%CI 1.24–1.60), clozapine (OR = 1.41, 95%CI 1.21–1.65), combinations (OR = 1.58, 95%CI 1.31–1.90). Risk for olanzapine increased with dose. Hispanic, African American, and unknown ethnicity were significant risks for development of type 2 diabetes as was exposure to selected concomitant medications.

**Conclusions** Exposure to olanzapine or clozapine is associated with a 34–41% increase in the developing of type 2 diabetes among California Medicaid recipients with schizophrenia. Prospective, randomized trials are needed to confirm these retrospective, observational findings. Copyright © 2005 John Wiley & Sons, Ltd.

**KEY WORDS** — antipsychotic; neuroleptic; adverse effects; type 2 diabetes mellitus; schizophrenia; Medicaid; matched case-control study

## INTRODUCTION

Atypical antipsychotic medications have proven to be at least as effective as older medications (e.g., haloperidol) in the treatment of schizophrenia.<sup>1–8</sup> At the same time, they are less likely to cause extrapyramidal symptoms and tardive dyskinesia, serious

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side effects caused by typical antipsychotics.<sup>9</sup> Certain atypical antipsychotic medications cause substantially more weight gain than their predecessors.<sup>10–14</sup> In several recent studies, these medications have been linked to development of impaired glucose tolerance and type 2 diabetes,<sup>15–19</sup> hyperlipidemia,<sup>15,20,21</sup> and increased mortality.<sup>22</sup> The present study assesses the extent to which an increased risk of new-onset type 2 diabetes among patients with schizophrenia may be associated with exposure to new generation antipsychotic medications when compared to the older antipsychotic medications.

Evidence of a possible link between diabetes and atypical antipsychotic medications first appeared in the form of case reports.<sup>17</sup> New-onset type 2 diabetes, glucose dysregulation, or diabetic ketoacidosis have been reported in patients taking clozapine,<sup>23–31</sup> olanzapine,<sup>24–27,30–38</sup> quetiapine,<sup>30,39,40</sup> and risperidone.<sup>30,41–44</sup> In addition to the case reports, several retrospective studies have reported an association between new generation antipsychotic medications and type 2 diabetes mellitus.<sup>18,45–49</sup>

Lund *et al.* used Iowa Medicaid claims data to compare the incidence of new-onset diabetes among patients receiving either clozapine or any conventional antipsychotic medication. They found a null overall effect of exposure to clozapine. However, there was a significantly increased risk of diabetes for clozapine among the youngest age group only (20–34 years of age).<sup>46</sup> This study, which was limited to clozapine, did not control for the concomitant use of other medications that might cause diabetes (e.g., beta-blockers, thiazide diuretics, corticosteroids).

A more recent study of national data from the Veterans Health Administration of the Department of Veterans Affairs examined the risk of diabetes associated with exposure to clozapine, olanzapine, quetiapine, and risperidone.<sup>45</sup> A 9% increased risk of diabetes was reported for patients taking any atypical antipsychotic medication compared to those taking any conventional antipsychotic. In the overall analysis, the risk was significantly greater than conventional medications for clozapine, olanzapine, and quetiapine but not for risperidone. As in the study of clozapine, the risk appeared to be greatest among the youngest cohort of patients with schizophrenia. Important limitations of the VA study included failure to differentiate between new and existing cases of diabetes and failure to control for the concomitant use of other potentially diabetogenic medications.

Fuller *et al.*<sup>18</sup> compared olanzapine and risperidone to haloperidol and fluphenazine using 4 years of electronic data on veterans receiving treatment in Ohio.

After controlling for a number of other covariates, they found that olanzapine increased the risk of new-onset diabetes by 37%. This study included all users of antipsychotics, regardless of diagnosis. In yet another recent database study, Buse *et al.*<sup>49</sup> used data from a pharmacy benefit manager (AdvancePCS) to compare old and new generation antipsychotics to one another and to patients with no antipsychotic exposure. They found no differences in head-to-head comparisons between older and newer drugs. This study was limited by the absence of information on diagnostic data and by its failure to control for exposure to other medications that may cause diabetes.

The current study seeks to extend this line of research. Our objective was to quantify the risk of type 2 diabetes mellitus associated with exposure to selected atypical antipsychotic medications, as compared to the risk for patients taking conventional antipsychotics.

## METHOD

### *Design*

The present study used a matched case-control design, with cases and controls matched on gender and age  $\pm 5$  years.<sup>50,51</sup> The case-control study was nested within a cohort of people with schizophrenia and within a larger cohort of California Medicaid beneficiaries.

### *Data source, case-control selection, and matching*

Data came from California Medicaid (i.e., Medi-Cal) medical and prescription claims filed between 1 January 1995 and 30 September 2000.<sup>52</sup> Figure 1 illustrates the process of case and control selection as well as eligibility determination. Cases were adult patients who developed type 2 diabetes mellitus after being diagnosed with schizophrenia. Controls were adult patients who were diagnosed with schizophrenia but did not have type 2 diabetes mellitus at the time diabetes was diagnosed in the matched case. Patients who subsequently developed diabetes were eligible to serve as controls until the date of their diabetes diagnosis. As such, one individual could serve as both a case and a control.<sup>53</sup> The same individual could not serve as a control for more than one case.

To identify cases, first all patients with schizophrenia were identified by the presence of a diagnostic claim for ICD-9 code 295.00–295.99 on two separate days. Next, all patients with diabetes were identified by the presence a diagnostic claim for ICD-9 code 250 on two

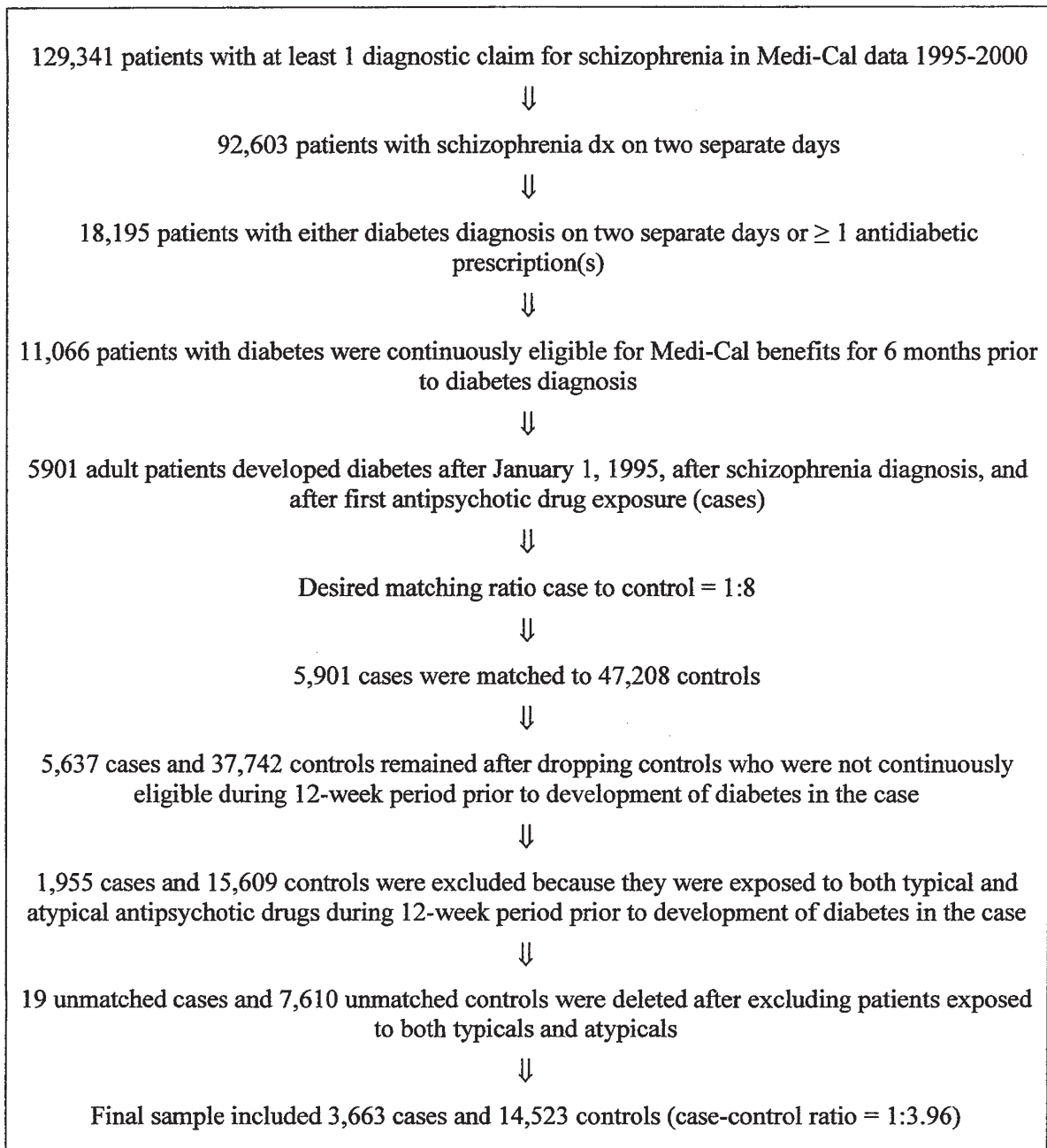


Figure 1. Flow chart for case selection and matching (12-week retrospective exposure window)

separate days (excluding juvenile types indicated by ICD-9 code 250.x1 or 250.x3) or by receipt of an antidiabetic agent (glimepiride, chlorpropamide, glyburide, glipizide, metformin hydrochloride, insulin, acarbose, or troglitazone).

#### *Definition of antipsychotic exposure*

In the main analysis, medication exposure was defined with reference to prescription claims filed during the 12 weeks prior to diabetes diagnosis. Subsequent

analyses extended the exposure window to 24 and 52 weeks. Drug exposure did not need to be continuous. Both cases and controls had to have been exposed to at least one antipsychotic medication at some point during the exposure window. We defined four categories of exposure: (a) exposure to any typical or combination of typical; (b) exposure to a single atypical; (c) exposure to any combination of atypicals; and (d) exposure to any combination of typical and atypicals. Patients exposed to both typical and atypical antipsychotics (category (d)) during exposure window were excluded. All other exposure patterns were included.

The atypical antipsychotic medications studied were clozapine, olanzapine, quetiapine, and risperidone. The typical antipsychotic medications studied were chlorpromazine, fluphenazine, loxapine, pimozide, promazine, trifluoperazine, haloperidol, perphenazine, prochlorperazine, thioridazine, chlorprothixine, molindone, thiothixene, and mesoridazine. Within the Medi-Cal database, all medications were identified by their National Drug Codes (NDC).<sup>54,55</sup> To get strength data for the dose-response analyses, NDC codes were used to index into FDA's NDC database.<sup>55</sup>

#### *Additional exclusion criteria*

The diagnosis of diabetes or receipt of an antidiabetic medication had to occur after the date of the first diagnostic claim for schizophrenia. For cases, a minimum 6-month continuous eligibility period prior to the index date was used to screen for prevalent diabetes. Prevalent cases were excluded. Both cases and controls had to be continuously eligible for Medicaid benefits during the 12 (24- or 52-) week exposure window prior to diabetes onset in the case. Our goal was to achieve a final 1:4 ratio of cases to controls.<sup>56</sup> Anticipating losses due to our exclusion criteria, we initially searched for eight controls for every case.<sup>50,51</sup> After eliminating patients who were exposed to both typical and atypicals or who were not continuously eligible for Medicaid benefits during the 12 weeks prior to the onset of diabetes in the case, the final ratio of cases to controls was 1:3.96 (see Figure 1).

#### *Analysis plan*

The first step in our analysis was to compute simple descriptive statistics for the cases and controls. Next, we built conditional logistic regression models to predict new-onset type 2 diabetes. Conditional logistic regression is more appropriate than standard logistic regression when highly stratified data (as in matched

case-control designs) result in small sample sizes within each stratum.<sup>57</sup> We used SAS's PROC PHREG to form our conditional logistic models.<sup>58</sup> Hypothesis tests involving planned comparisons between different atypicals were done using the TEST option to PROC PHREG. The independent variables were five dummy-coded dichotomous variables corresponding to exposure to a single atypical antipsychotic medications (clozapine, olanzapine, quetiapine, or risperidone) or any combination of atypicals, the reference group being any typical antipsychotic (or combination thereof). The control variables were: (a) four dummy-coded dichotomous variables representing Hispanic, African American, other and unknown ethnicity, the reference group being whites and (b) nine dichotomous variables representing exposure to (classes of) medications associated with new-onset diabetes (corticosteroids, phenytoin, oral contraceptives containing norgestrel, beta-blockers, alpha-blockers, thiazide diuretics, tricyclic antidepressants, SSRIs, and ACE inhibitors). The list of generic names for these medications can be obtained from the first author.

For each atypical antipsychotic, we conducted dose-response analyses. We defined high, medium, and low doses, based on the empirical distribution of actual doses and on expert clinical judgment (see Table 1). For each atypical drug, we built a separate conditional logistic regression model with dose represented by three dichotomous variables corresponding to low, medium, and high doses. Any dose of a typical was the reference. Differences between doses were tested using the TEST option to SAS PROC PHREG. Only when the omnibus test of equality between all doses (i.e., low = medium = high) was significant did we report differences between dose levels. Note that for a given drug's (e.g., clozapine's) dose-response model, cases and controls not on either clozapine or typicals were excluded. When this process resulted in a case or control being unmatched, those patients were excluded also. As a result, the *n*'s for each dose level do not sum to the overall *N* for given drug in main analysis.

Finally, because the exact time course of the development of antipsychotic-associated diabetes is unknown, we repeated all analyses after lengthening the exposure window to 24 and 52 weeks, respectively. We report results from the extended exposure windows briefly in the text.

## RESULTS

Table 1 shows the results of analyses based on the 12-week exposure window. Controlling for ethnicity and exposure to other diabetes-causing medications,

Table 1. Association between antipsychotic exposure and development of type 2 diabetes among patients with schizophrenia (12-week exposure window)

Characteristic	Cases ( <i>N</i> = 3663)		Controls ( <i>N</i> = 14 523)		Crude OR	Adjusted OR
	Mean	SD	Mean	SD		
Age					1.04 (1.03–1.05)	1.04 (1.03–1.06)
Mean (SD)	45.3	13.7	45.3	13.3		
Min		18		18		
Max		94		99		
	<i>n</i>	%	<i>n</i>	%		
Gender (1, male)						
Male	1709	46.7	6634	45.7		
Female	1954	53.3	7889	54.3		
Ethnicity						
White	1745	47.6	8237	56.7		
Hispanic	61	1.7	200	1.4	1.2 (0.9–1.6)	1.4 (1.0–1.9)
African American	769	21.0	2342	16.1	1.4 (1.3–1.5)	1.6 (1.4–1.8)
Others	41	1.1	133	0.9	1.2 (0.8–1.7)	1.4 (1.0–2.0)
Unknown	1046	28.6	3608	24.8	1.2 (1.1–1.3)	1.4 (1.3–1.5)
Concomitant medications						
ACE inhibitors	491	13.4	1056	7.3	2.0 (1.8–2.2)	1.8 (1.6–2.0)
Alpha-blockers	59	1.6	187	1.3	1.3 (0.9–1.7)	0.9 (0.7–1.3)
Beta-blockers	337	9.2	970	6.7	1.4 (1.2–1.6)	1.3 (1.1–1.5)
Corticosteroids	470	12.8	1130	7.8	1.7 (1.6–2.0)	1.7 (1.5–1.9)
Oral contraceptives	15	0.4	52	0.4	1.1 (0.6–2.0)	1.1 (0.6–2.0)
containing norgestrel						
Phenytoin	176	4.8	688	4.7	1.0 (0.9–1.2)	1.0 (0.8–1.2)
SSRIs	534	14.6	1696	11.7	1.3 (1.2–1.4)	1.2 (1.1–1.3)
Thiazide diuretics	165	4.5	353	2.4	1.9 (1.6–2.3)	1.4 (1.2–1.7)
Tricyclic antidepressants	759	20.7	2616	18.0	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Antipsychotic exposure (mean daily dose)						
Typicals	1993	54.4	8657	59.6		
Olanzapine	576	15.7	1857	12.8	1.3 (1.2–1.5)	1.4 (1.2–1.5)
Low (<7.5 mg)	81	4.0	214	3.3	1.2 (1.0–1.6)	1.1 (0.9–1.5)
Medium (7.5 ≤ <i>x</i> ≤ 12.5 mg)	182	7.3	356	4.7	1.6 (1.3–1.9)	1.6 (1.3–1.9)
High (>12.5 mg)	285	11.4	598	7.9	1.5 (1.3–1.7)	1.5 (1.2–1.8)
Risperidone	521	14.2	2169	14.9	1.0 (0.9–1.2)	1.0 (0.9–1.2)
Low (<3 mg)	108	4.4	284	3.6	1.2 (1.0–1.6)	1.0 (0.8–1.3)
Medium (3 ≤ <i>x</i> ≤ 6 mg)	241	9.9	735	9.3	1.1 (0.9–1.2)	0.9 (0.8–1.1)
High (>6 mg)	143	5.9	444	5.6	1.0 (0.9–1.3)	1.0 (0.8–1.3)
Clozapine	303	8.3	1061	7.3	1.2 (1.1–1.4)	1.3 (1.2–1.5)
Low (<300 mg)	73	3.3	154	2.3	1.5 (1.1–2.0)	1.5 (1.1–2.0)
Medium (300 ≤ <i>x</i> ≤ 600 mg)	157	7.1	345	5.0	1.4 (1.2–1.8)	1.5 (1.2–1.8)
High (>600 mg)	59	2.7	188	2.8	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Quetiapine	47	1.3	169	1.2	1.2 (0.9–1.7)	1.2 (0.8–1.7)
Low (<250 mg)	15	0.8	17	0.3	2.6 (1.3–5.2)	1.9 (0.9–4.1)
Medium (250 ≤ <i>x</i> ≤ 500 mg)	12	0.6	22	0.4	1.6 (0.8–3.2)	1.2 (0.6–2.4)
High (>500 mg)	11	0.6	16	0.3	2.0 (0.9–4.3)	1.6 (0.7–3.6)
Combination	223	6.1	610	4.2	1.6 (1.4–1.9)	1.6 (1.3–1.9)

Note: Crude and adjusted odds ratios are not given for gender because it was used as a matching variable, and they are not given for white ethnicity or typical antipsychotics because those categories served as the reference groups.

patients with schizophrenia who developed type 2 diabetes were more likely than controls to have been exposed to clozapine (OR = 1.34, 95%CI 1.16–1.55), olanzapine (OR = 1.36, 95%CI 1.20–1.53), or combination atypical therapy (OR = 1.58, 95%CI 1.33–1.88). The reference group for exposure was any typical antipsychotic. Tests comparing the model

coefficients for each drug to each other drug revealed that the coefficient for olanzapine was significantly greater than risperidone ( $\chi^2 = 12.54$ ,  $p = 0.0004$ ); clozapine was greater than risperidone ( $\chi^2 = 8.23$ ,  $p = 0.004$ ); and combination therapy was greater than risperidone ( $\chi^2 = 17.82$ ,  $p < 0.0001$ ). A statistically significant additive risk of new-onset type 2 diabetes

was also associated with African American and unknown ethnicity, as well as with exposure to several concomitant medications. For the 12-week exposure window, dose did not affect the odds of developing diabetes for clozapine, olanzapine, quetiapine, or risperidone. For olanzapine, there was a trend towards increasing risk with higher doses, but it did not reach conventional levels of statistical significance.

Using a 24-week exposure window, the odds ratios for olanzapine (OR = 1.38, 95%CI 1.22–1.56) and clozapine (OR = 1.32, 95%CI 1.14–1.53) changed only slightly. The odds ratio for combinations of atypicals decreased slightly (OR = 1.54, 95%CI 1.29–1.84). Odds ratios for clozapine, olanzapine, and combination therapy were all significantly greater than for risperidone. Neither quetiapine nor risperidone were associated with increased odds of developing diabetes. None of the drugs showed significant dose-response relationships.

With a 52-week exposure window, the odds ratios increased for olanzapine (OR = 1.41, 95%CI 1.24–1.60), clozapine (OR = 1.41, 95%CI 1.21–1.65), and combinations of atypicals (OR = 1.58, 95%CI 1.31–1.90). Odds ratios for clozapine, olanzapine, and combination therapy were all significantly greater than for risperidone. Neither quetiapine nor risperidone was associated with increased odds of developing diabetes. There was a significant dose response only for olanzapine when using the 52-week exposure window. The odds ratio for low doses (OR = 1.25, 95%CI 1.00–1.57) was significantly smaller than for medium (OR = 1.84, 95%CI 1.53–2.22) or high doses (OR = 1.87, 95%CI 1.58–2.21).

## DISCUSSION

Exposure to clozapine or olanzapine, but not quetiapine or risperidone, was associated with a 34–41% increase in the odds of developing new-onset type 2 diabetes when compared to typical antipsychotics. The odds increased 58% for patients exposed to combinations of atypical drugs. These associations were present when the effects of age, gender, ethnicity, and exposure to other medications were controlled and when the retrospective exposure window was 12, 24, or 52 weeks. These findings are largely consistent with recently published studies.<sup>18,45–48</sup> The small number of patients on quetiapine in our sample and the consequent imprecision and low power may explain why we did not detect a significant association between quetiapine exposure and diabetes as others have.<sup>45</sup> Other discrepancies between previous findings and our own are

likely due to differences in populations studied, definitions of diabetes and antipsychotic exposure, covariates, and statistical analysis plans.<sup>19</sup> The present study adds to the body of observational evidence indicating that certain atypical antipsychotics may be associated with a significantly increased risk of developing new-onset type 2 diabetes.<sup>18,45–48</sup> To our knowledge, we are the first to report that the magnitude of the association between olanzapine exposure and diabetes risk may be dose-dependent.

For many clinicians, the broader implications of this study and of the emerging consensus about the risk of diabetes associated with exposure to certain antipsychotics boil down to a simple set of questions: How can I quantify the risks (and benefits) in terms my patients and I can understand and relate to? When is it safe to use these medications? In which patient populations? What sort of monitoring is necessary when these medications are used? There are no simple answers to these questions, although some recommendations have begun to appear.<sup>19,48,59,60</sup>

One way of illustrating the risk is to move from odds ratios to more easily interpretable numbers. For example, we estimated that the odds of developing type 2 diabetes among patients of all ages exposed to olanzapine was 36% greater than the risk for those on typical antipsychotic medications (34% greater for clozapine). To move the discussion from relative to absolute risk, we need to know the incidence of type 2 diabetes among patients with schizophrenia generally. That number is not, to our knowledge, available in the literature.<sup>61</sup> The incidence of type II diabetes is approximately 0.35% per year in the general population.<sup>61,62</sup> Under the conservative assumption that the risks of diabetes among adults with schizophrenia is no greater than that of the general population, exposure to olanzapine would increase the incidence of diabetes from approximately 1 in 286 to 1 in 210 or from 3.5 per thousand to 4.8 per thousand. Assuming the risk of diabetes among adults with schizophrenia is at least twice that of the general population, arguably a more realistic assumption,<sup>61–64</sup> exposure to olanzapine, for example, would increase diabetes incidence from 1 in 143 to 1 in 105 or from 7 per thousand to 9.6 per thousand.

The clinical implications of the increased diabetes risk are different for clozapine and olanzapine. Clozapine is indicated for patients with treatment-refractory psychosis, but because of its known risk of agranulocytosis, its use is restricted and must be carefully monitored. Any additional risk of diabetes for patients using clozapine might need to be tolerated, since patients on clozapine have few alternatives. On

the other hand, olanzapine is one among several equally effective options. If it were definitively shown to have a substantially different risk-benefit profile than other atypical antipsychotics, then clinicians could choose another drug.

Finally, when considering whether or not to use one of the potentially diabetogenic atypical drugs, prescribers must also consider other risk factors for diabetes as well as the clinical, psychosocial, and economic context of treatment. Most salient in the current study were ethnicity and several classes of concomitant medications (e.g., beta-blockers, thiazide diuretics, corticosteroids, and ACE inhibitors). The greater risk of diabetes faced by Hispanics and African Americans is well known and was reinforced by our data.<sup>61,65</sup>

The results of this investigation should be interpreted in light of several limitations. Diagnostic (ICD-9) codes were not independently validated. Thus it is possible that some patients identified in the database as having schizophrenia or diabetes may have been misdiagnosed. Due to limitations in the Medi-Cal claims database, we were unable to control for body mass index, a known risk factor for type 2 diabetes and a factor thought to mediate the relationship between atypical exposure and the development of diabetes. For similar reasons, we are unable to control for family history of diabetes.

Because of left censoring, we cannot be certain that all of the first-listed claims for diabetes represented new onsets of illness. However, the requirement of a 6-month diabetes-free eligibility window prior to the index date mitigates this concern. Also, diabetes has a prolonged, asymptomatic clinical course, and its detection is dependent on contact with a clinician. This may have resulted in biased selection of control patients.<sup>66</sup> We did not examine the effects of exposure to ziprasidone or aripiprazole because neither was on the California Medicaid formulary during the period covered by the claims data we studied.

Children (under the age 21), women, people with low incomes, and people of African American and Hispanic ethnicity are overrepresented in the Medicaid population compared to the general population.<sup>67–70</sup> Our results may or may not generalize to the increasing number of patients who take atypical antipsychotic medications for conditions other than schizophrenia. Also, we studied ongoing users, without any antipsychotic-free washout period. Studies of ongoing users may be vulnerable to certain biases that are not present when observations are restricted to new users.<sup>71</sup> The results reported here give evidence of association between exposure and disease, but they do

not establish causation. Prospective, randomized trials are needed to confirm and more precisely quantify findings from this and similar observational studies.

## CONCLUSION

Among people with schizophrenia in the California Medicaid system, exposure to clozapine or olanzapine but not quetiapine or risperidone, was associated with an increased risk of developing type 2 diabetes when compared to typical antipsychotic medications. These effects persisted after adjustment for age, gender, ethnicity, and concomitant exposure to other potentially diabetogenic medications. Age, Hispanic and African American ethnicity as well as exposure to other medications were significant, independent risk factors. More research needs to be done to quantify the personal and societal risk/benefit ratio associated with use of these medications. In the meantime, clinicians should carefully weigh the risk of type 2 diabetes when deciding whether or not to prescribe clozapine or olanzapine, especially among patients who may be predisposed to develop diabetes (e.g., due to ethnicity, positive family history, age, or body mass). Patients who do receive these medications should be monitored in accordance with recently published guidelines.<sup>19</sup>

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