Association between Antipsychotic Treatment and Hyperlipidemia among California

Medicaid Patients with Schizophrenia

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Abstract

Objective: To examine the risk of hyperlipidemia among people with schizophrenia exposed to new antipsychotics (clozapine, olanzapine, quetiapine, risperidone) compared to those exposed to older generation antipsychotics. **Method**: A case-control study of Medi-Cal claims. Cases developed hyperlipidemia after being diagnosed with schizophrenia (ICD-9: 295) and were exposed to only one antipsychotic drug at some point within 12 weeks prior to the hyperlipidemia diagnosis. Hyperlipidemia was defined by diagnostic claim (ICD-9: 272.1–272.4) or prescription claim for antilipemic agents. Cases were matched on gender and age $\pm$ 3 years to patients with schizophrenia who did not develop hyperlipidemia. Conditional logistic regression assessed the risk of antipsychotic exposure, controlling for age, ethnicity, prior type 2 diabetes or hypothyroidism, and exposure to other medications that may cause hyperlipidemia. Analyses were repeated using a 24- and 52-week retrospective exposure windows. **Results:** For the 12-week exposure window, olanzapine (OR=1.20, 95% CI 1.08–1.33) was associated with increased risk of developing hyperlipidemia compared to older antipsychotic medications. Exposure to clozapine (OR=1.16, 95% CI 0.99–1.37), risperidone (OR=1.00, 95% CI 0.90–1.12) and quetiapine (OR=1.01, 95% CI 0.78–1.32) were not. Hypothesis tests comparing the four atypicals to one another revealed that the odds ratio for olanzapine was greater than that for risperidone (p=0.002). Other than clozapine's odds ratio being significant at 24-weeks (OR=1.22, 95% CI 1.03–1.45), increasing the exposure window to 24 or 52 weeks did not substantially alter the results. **Conclusions:** Compared to older generation antipsychotics, exposure to olanzapine and, somewhat less consistently, to clozapine is associated with an increased risk of hyperlipidemia among people with schizophrenia.

Introduction

Recent evidence suggests that a variety of metabolic disturbances, including weight gain, hyperglycemia, diabetes, and hyperlipidemia, may be associated with exposure to certain new generation antipsychotics.[1-8] The link between atypical antipsychotic exposure and hyperlipidemia has been observed in case reports, chart reviews, claims-based studies, and a single randomized controlled trial.

Case reports described temporal associations between hyperlipidemia and the administration of new generation antipsychotics. Wu and colleagues reported the case of a 25 year old Chinese man who developed hyperlipidemia (and other metabolic disorders) after high-dose clozapine treatment. The patient's triglyceride levels were correlated with reduction in psychotic symptoms and returned to near normal levels when low dose clozapine therapy was initiated.[9] Similarly, a fifteen year old African American boy taking 20 mg of olanzapine per day developed hyperlipidemia that resolved when olanzapine was discontinued.[10] Numerous additional cases involving clozapine, quetiapine, and olanzapine have been reported.[11-15]

In the wake of these case reports, several chart review studies have examined the association. Gaulin et al. reviewed the charts of 222 psychiatric inpatients treated with either clozapine or haloperidol, and found a significant increase in serum triglycerides among men treated with clozapine.[16] In a 5-year observational study of a group of predominantly young, Caucasian men, treatment with clozapine was associated with significant increases in serum triglycerides but not total cholesterol.[17] A prospective observational study of 14 patients on olanzapine monotherapy showed that the majority developed hypercholesterolemia and hypertriglyceridemia during a median follow up period of five months.[18] A retrospective chart review comparing 37 olanzapine treated patients to 39 risperidone treated patients found

significantly greater increases in triglycerides and in cholesterol for the patients on olanzapine.[19]

Another larger scale chart review study comparing newer antipsychotics (clozapine, olanzapine, quetiapine, risperidone) to older drugs (haloperidol and fluphenazine) again found significantly greater increases in triglycerides for patients on olanzapine and clozapine compared to other groups.[20]

Following these chart review and observational studies, two retrospective claims-based studies were conducted. The first, by Lund and others, looked at 3013 patients exposed to clozapine or older antipsychotic drugs.[21] They found no difference in hyperlipidemia incidence in the overall sample, but among the youngest cohort (aged 20-34), clozapine exposure was associated with a significantly greater risk of hyperlipidemia compared to older drugs. The second study used a nested case-control design to examine hyperlipidemia risk among 8866 patients from the British General Practice Research Database who were exposed to various antipsychotics during the twelve weeks prior to development of hyperlipidemia in the case. Olanzapine and clozapine, but not risperidone or combination therapy, were associated with a significantly increased risk of hyperlipidemia.[22] Most recently, a randomized, double-blind, controlled trial on 101 hospitalized patients with psychosis showed that olanzapine and clozapine, but not risperidone or haloperidol, caused significant increases in total cholesterol.[23]

Limitations in the previous two claims-based studies motivated the current investigation. For example, Lund et al. only studied clozapine and did not assess the risk associated with exposure to other new generation antipsychotics.[21] In fact, they explicitly called for confirmatory studies in other populations and settings. Lund and colleagues also did not adjust for ethnicity, concomitant medications, or comorbid conditions that might have modified the relationship between antipsychotic exposure and hyperlipidemia. Koro et al. did not give risk estimates for

clozapine or quetiapine, nor did they control for ethnicity.[22] In addition, theirs was a European

sample based on patients of general practitioners.

We sought to address some of these limitations and extend this line of research using a

different population of patients. The present study examined the association between

antipsychotic exposure and the development of hyperlipidemia in a large population of low-

income, publicly financed patients with schizophrenia.

Method

Design

The present study used a matched case-control design, with cases and controls matched

on gender and age $\pm$ 3 years.[24, 25] The design was similar to that used in recently published papers

on related topics.[22, 26] Cases were patients 18 years or older who developed hyperlipidemia after

being diagnosed and treated for schizophrenia. Controls were patients 18 years or older who

were diagnosed and treated for schizophrenia but not hyperlipidemia.

Data Source, Case-Control Selection and Matching

Data came from California Medicaid (i.e., Medi-Cal) diagnostic and prescription claims

filed between July 1, 1997 and December 31, 2000.[27] Figure 1 illustrates the process of case and

control selection. To be a case, patients had to show evidence of diagnosis or treatment for

hyperlipidemia subsequent to schizophrenia diagnosis, be 18 years or older, and be exposed to

one and only one antipsychotic medication during the 12 weeks prior to their hyperlipidemia

diagnosis. To identify cases, first all patients with schizophrenia were identified. Schizophrenia

was operationally defined by the presence of at least one diagnostic claim with ICD-9 code

295.00-295.99. Next, all patients with hyperlipidemia were identified. Hyperlipidemia was

operationally defined by the presence of at least one diagnostic claim for ICD-9 code 272.0-

272.4 or by receipt of at least one antilipemic agent. The antilipemics included atorvastatin, cholestyramine, clofibrate, colesevelam, colestipol, fenofibrate, fluvastatin, gemfibrozil, lovastatin, pravastatin, and simvastatin. Antipsychotic medication exposure was defined with reference to prescription claims filled during the 12 weeks prior to hyperlipidemia diagnosis in the case. Antipsychotic exposure was assessed during exactly same time period for both cases and matched controls. Prescriptions filled more than 12 weeks prior to the index date were counted if the supply of medication overlapped the 12 week retrospective observation period. Only patients exposed to one and only one antipsychotic were included. The new generation antipsychotic medications included were clozapine, olanzapine, quetiapine and risperidone. The older antipsychotic medications included were chlorpromazine, fluphenazine, loxapine, pimozide, promazine, trifluoperazine, haloperidol, perphenazine, prochlorperazine, and thioridazine. Within the Medi-Cal database, all medications were identified by their National Drug Codes (NDC).[28, 29]

The diagnosis of hyperlipidemia or receipt of an antilipemic medication had to occur after the date of the first diagnostic claim for schizophrenia and after the initiation of antipsychotic drug therapy. Patients diagnosed or treated for hyperlipidemia prior to being diagnosed and treated for schizophrenia were excluded. Cases and controls had to be continuously eligible for Medicaid benefits during the 12-week period prior to hyperlipidemia onset in the case. Our goal was to achieve a final 1:3 ratio of cases to controls.[30] Anticipating losses due to single drug exposure and continuous eligibility criteria, we initially searched for 5 controls for every case.[24, 25] After eliminating patients who were either exposed to more than one antipsychotic or were not continuously eligible for Medicaid benefits during the 12 weeks prior

to the onset of hyperlipidemia in the case, the final ratio of cases to controls was 1:1.87 (see

Figure 1).

(Insert Figure 1 about here)

Although previously published studies have used 12 weeks of retrospective observation

to define drug exposure, the time period is somewhat arbitrary.[22, 26] To examine the sensitivity of

the results to changes in the time period used to define drug exposure, we repeated the steps

outlined above, but this time we used a 24- and a 52-week retrospective observation period to

define drug exposure. In other words, from the index date (when hyperlipidemia is first

diagnosed or treated), we looked back 24 or 52 weeks instead of 12 weeks. During this time,

patients had to be exposed to one and only one antipsychotic and be continuously eligible for

Medi-Cal benefits.

We also controlled for exposure to concomitant medications that may cause

hyperlipidemia. These included beta-blockers and thiazide diuretics, loop diuretics,

anticonvulsants, protease inhibitors, and corticosteroids.[31] Exposure to these agents was defined

with reference to the 12-, 24-, or 52-week period prior to onset of hyperlipidemia in the case.

Finally, we controlled for pre-existing type 2 diabetes mellitus and hypothyroidism, two

conditions known to cause hyperlipidemia.[22] Hypothyroidism was defined by the presence of a

diagnostic code (ICD9: 243 or 244.0-3, 244.8-9). Type 2 diabetes mellitus was defined by the

presence of a diagnostic code (ICD9: 250, excluding juvenile types) or by the receipt of an

antidiabetic prescription.

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

hyperlipidemia. 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.[32] We used SAS's PROC PHREG to form conditional logistic models.[33] Planned comparisons were done using the TEST option to PROC PHREG. The independent variables were four dummy-coded dichotomous variables corresponding to exposure to selected new generation antipsychotic medications (clozapine, olanzapine, quetiapine, or risperidone), the reference group being any older antipsychotic. The control variables were (a) four dummy-coded dichotomous variables representing Hispanic, African American, other or unknown ethnicity, the reference group being whites; and (b) five dichotomous variables representing exposure to (classes of) medications that may cause hyperlipidemia (beta-blockers and thiazide diuretics, loop diuretics, anticonvulsants, protease inhibitors, and corticosteroids[31, 34]), and (c) two dichotomous variables representing the presence or absence of pre-existing type 2 diabetes and hypothyroidism respectively. The list of generic names for the concomitant medications is quite lengthy and can be obtained from the first author. Analyses were completed for both 12-, 24-, and 52-week drug exposure windows.

Results

Table 1 gives the odds ratios and confidence intervals for the overall conditional logistic regression model for the 12-, 24- and 52-week exposure windows. The reference group for exposure was any older antipsychotic. Patients who developed hyperlipidemia were more likely to have been exposed to olanzapine (OR=1.20, 95% CI 1.08–1.33) than to a typical antipsychotic. Although it did not quite reach the conventional level of statistical significance, the 95% confidence interval for clozapine (OR=1.16, 95% CI 0.99–1.37) suggests it may also be associated with a significantly increased risk of hyperlipidemia. Exposure to risperidone

(OR=1.00, 95% CI 0.90–1.12) and quetiapine (OR=1.01, 95% CI 0.78–1.32) were not associated

with significantly increased risk of hyperlipidemia when compared to older antipsychotics.

Planned comparisons of model coefficients for each drug with each other drug revealed that odds

ratio for olanzapine was significantly greater than risperidone (p = 0.002). African-American and

unknown ethnicity significantly were associated with increased the risk of hyperlipidemia

compared to whites, as was exposure to corticosteroids. Pre-existing type 2 diabetes and

hypothyroidism were also associated with significantly increased risk. Increasing age was

associated with significantly decreased risk of hyperlipidemia (OR=0.71, 95% CI 0.69–0.73), as

was exposure to anticonvulsants.

(Insert Table 1 about here)

When the analyses were repeated using 24- and 52-weeks prior to the index date to define

drug exposure, the results were comparable. At 24-weeks, clozapine (OR=1.22 95% CI 1.03–

1.45) and olanzapine (OR=1.24, 95% CI 1.12–1.38) were associated with increased risk of

hyperlipidemia, compared to older antipsychotics. Quetiapine (OR=0.83, 95% CI 0.61–1.13) and

risperidone (OR=1.01, 95% CI 0.90–1.13) were not. Planned comparisons indicated that the odds

ratio for olanzapine was significantly greater than quetiapine (p = 0.01) and risperidone (p =

0.001). The odds ratio for clozapine was significantly greater than quetiapine (p = 0.03) and

risperidone (p = 0.04). African-American, other, and unknown ethnicity were associated with

increased risk of hyperlipidemia compared to whites, as was exposure to beta-blockers and

thiazide diuretics and corticosteroids (see Table 3). Pre-existing type 2 diabetes and

hypothyroidism were also associated with significantly increased the risk of hyperlipidemia. The

results for the 52-week exposure duration were comparable to the 24-week results, except that

clozapine did not reach the conventional level of statistical significance (OR=1.20 95% CI 0.99–

1.46) at 52-weeks (see Table 4). When interpreting these results, readers should focus on the

odds ratios and confidence intervals as well as the p-values. At both 24- and 52-weeks,

increasing age was associated with reduced risk of hyperlipidemia, as was exposure to

anticonvulsants.

Discussion

The results of this investigation should be interpreted in light of certain limitations.

Patients exposed to more than one antipsychotic during the period prior to development of

hyperlipidemia in the case were excluded from our analysis. Therefore, the results reported here

may not generalize to patients who switch between different antipsychotics or to patients who are

treated with more than one antipsychotic at the same time. Because of left censoring, we could

not be certain that all of the first-listed claims for hyperlipidemia represented new onsets of

illness. We did not control for family history, body mass or behavioral factors such as smoking,

alcohol use or dietary fat intake because information on such factors was not available in the

database. We did not examine the effects of exposure to ziprasidone or aripirazole because

neither was on the Medi-Cal formulary during the period covered by the claims data we studied.

Medicaid recipients with schizophrenia are not representative of the general population with

schizophrenia (e.g., they may be younger and of lower socioeconomic status). Also, our results

may or may not generalize to patients who take atypical antipsychotic medications for conditions

other than schizophrenia.

Medi-Cal data did not include information about diagnostic testing, so we could not

control for possible surveillance bias. We can not definitively rule out the possibility that the

increased risk observed for clozapine and olanzapine was due to more frequent diagnostic testing

of these patients, perhaps prompted by increased weight gain or heightened awareness of risk

due to published reports of adverse metabolic effects associated with these drugs.

Several previously published reports argue against this possibility, however. Perhaps the

most compelling is Lindenmayer's double-blind, prospective study, which examined the effect of

olanzapine, clozapine, risperidone and haloperidol on glucose and cholesterol levels. In that

study, with identical monitoring for each drug, olanzapine and clozapine increased cholesterol

levels but risperidone and haloperidol did not.[23] Koro et al. found that the association between of

olanzapine and hyperlipidemia persisted even when intensity of diagnostic screening was

controlled, but that study used a database from the United Kingdom and reported odds ratios

much larger than those seen here, suggesting that it may not be strictly comparable with ours.[22]

When examining clozapine exposure in relation to diabetes, hyperlipidemia and hypertension,

Lund and colleagues also considered the possibility of surveillance bias.[21] They discounted the

possibility because they did not observe a parallel increase in the incidence of hypertension.

Such an increase would have been expected if observed effects had been due to increased

monitoring of patients taking clozapine. Nor did they observe an increased incidence of diabetes

over time, which also would have been expected as awareness of the antipsychotic-diabetes link,

and related monitoring, became more widespread over time. In addition, Gaulin's chart-review

study of 306 inpatients on either clozapine or haloperidol showed an increase in serum lipid

levels for clozapine patients compared to haloperidol patients when each group was monitored in

precisely the same manner.[16] Meyer reported a greater increase in lipid levels among olanzapine

treated patients compared to risperidone-treated patients, as did Garyfallos, with no differences

in monitoring.[19, 35] The repeated finding that clozapine and olanzapine are associated with

increases in lipid levels, even when monitoring regimens are the same, suggests that the

association between these drugs and lipid levels is not exclusively due to surveillance bias. Even so, the lack of information on the timing and frequency of blood lipid levels for patients in the present study makes it impossible to exclude confounding due to surveillance bias as an explanation for the differences we observed.

One must also keep in mind that the results reported here give evidence of association between exposure and disease, but they do not establish causation. Finally, there are limitations inherent in any study that uses claims data, including potentially incomplete and inaccurate codes for diagnoses and prescriptions.

In spite of these limitations, we observed a pattern of results that is consistent with previously published studies reporting that exposure to clozapine and olanzapine, but not risperidone or quetiapine, is associated with increasing lipid levels.[21-23] Given the consistency of this pattern across several studies using different designs, analysis plans, and study populations, clinicians can be reasonably confident that the increased risk of hyperlipidemia associated with exposure to olanzapine and clozapine is real. One area in need of further clarification concerns the magnitude of the effects. For example, in a large epidemiologic study similar in design to ours, the odds ratio for olanzapine was 4.65, nearly 4 times greater than what we observed.[22] One potential explanation for this inconsistency is that in Koro et al.'s study, the number of olanzapine exposures was small (n=43), and odds ratios can be inflated in such circumstances.[36] A more precise estimate of the effect size must await additional prospective studies or meta-analyses.

Our finding that increasing age was associated with a decreased risk of developing hyperlipidemia deserves further clarification. This finding, reported by others as well[19, 21], is somewhat surprising since the risk of hyperlipidemia ordinarily increases with age.[37] This

finding may simply reflect the failure of our age-matching process to completely control for age differences. Although we matched on age +/- 3 years when matching controls to cases, controls were still, on average, one year older than cases (43.6 vs. 42.5 years in the 12-week analysis). Another explanation is that this not a real effect but is rather an artifact of our design. A phenomenon known as "depletion of susceptibles" may have been at work. Generally, depletion of susceptibles means that, with increasing age, patients who are most susceptible to the outcome of interest (hyperlipidemia) are withdrawn from exposure and moved to the untreated category or to treatments associated with smaller risks. This leaves fewer high-risk individuals remaining in the population at older ages and creates an apparent, but spurious, negative association between age and risk.

In our study, depletion of susceptibles was a consequence of the sample selection process. To make sure we were only studying incident (and not prevalent) cases, we excluded all patients with previous history of lipid abnormalities. Consequently, older patients who met our inclusion criteria were only those who, all other things being equal, were least susceptible to developing hyperlipidemia. (In a random sample of 65-year olds, one would expect a large proportion of persons with hyperlipidemia, but in our carefully selected sample, there were none.) Thus, the observed association between increased age and decreased hyperlipidemia risk may be an artifact of a selection bias that was most pronounced among older patients. In fairness we should acknowledge that the stronger association between antipsychotic use and hyperlipidemia in younger as opposed to older patients is also consistent with the surveillance bias explanation of the observed effects, since older subjects would be more likely to have blood lipid levels measured for reasons other than being treated with a particular antipsychotic drug,

and the differential effect of drug treatment on lipid monitoring would be less prominent in older than in younger patients.

Even if one acknowledges the increased risk associated with olanzapine and clozapine, the implications are complex. It seems uncontroversial that elevated lipid levels are related to cardiovascular morbidity and mortality. Given that people with schizophrenia are already at higher risk for cardiovascular disease due to lifestyle and the prevalence of other comorbid conditions such as obesity and type 2 diabetes mellitus, the added risk of hyperlipidemia cannot simply be disregarded.[38] As a result, some have suggested that patients prescribed olanzapine and clozapine should have their lipid levels checked at baseline and at six month intervals thereafter.[23]

Emerging evidence of an association between new generation antipsychotic medications and metabolic problems should be placed in a broad context. Decisions concerning selection of antipsychotic medications should reflect known efficacy, other safety issues, tolerability, and cost. In practice, the relative weights assigned to these factors will likely differ with the clinical and financial context of the treatment. In the long run, sound scientific studies of drug safety, efficacy, and cost inform and support rational prescribing practices.[39, 40] The present study contributes to the literature on the comparative safety of selected new and older generation antipsychotics.

Compared to older antipsychotics, exposure to olanzapine and, somewhat less consistently, to clozapine, is associated with roughly a 20% increase in the odds of developing new-onset hyperlipidemia. Exposure to quetiapine or risperidone is not. Given the increased baseline risk of cardiovascular disease among people with schizophrenia, the benefits of

prescribing olanzapine or clozapine for a given individual should be weighed against the

possibility of increased cardiovascular risk, and patients should be monitored accordingly.

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129,341 schizophrenia patients in Medi-Cal data July 1, 1997- December 31, 2000

⇓

34,337 patients with either hyperlipidemia diagnosis or hyperlipidemia prescription(s)

⇓

11,868 adults developed hyperlipidemia both after 10/1/97 and after schizophrenia diagnosis (cases); 89,251 adults had schizophrenia but not hyperlipidemia (controls)

⇓

Desired matching ratio, case to control = 1:3

⇓

Eliminate patients exposed to more than one antipsychotic or those not continuously eligible during 12 weeks prior to development of hyperlipidemia in the case

⇓

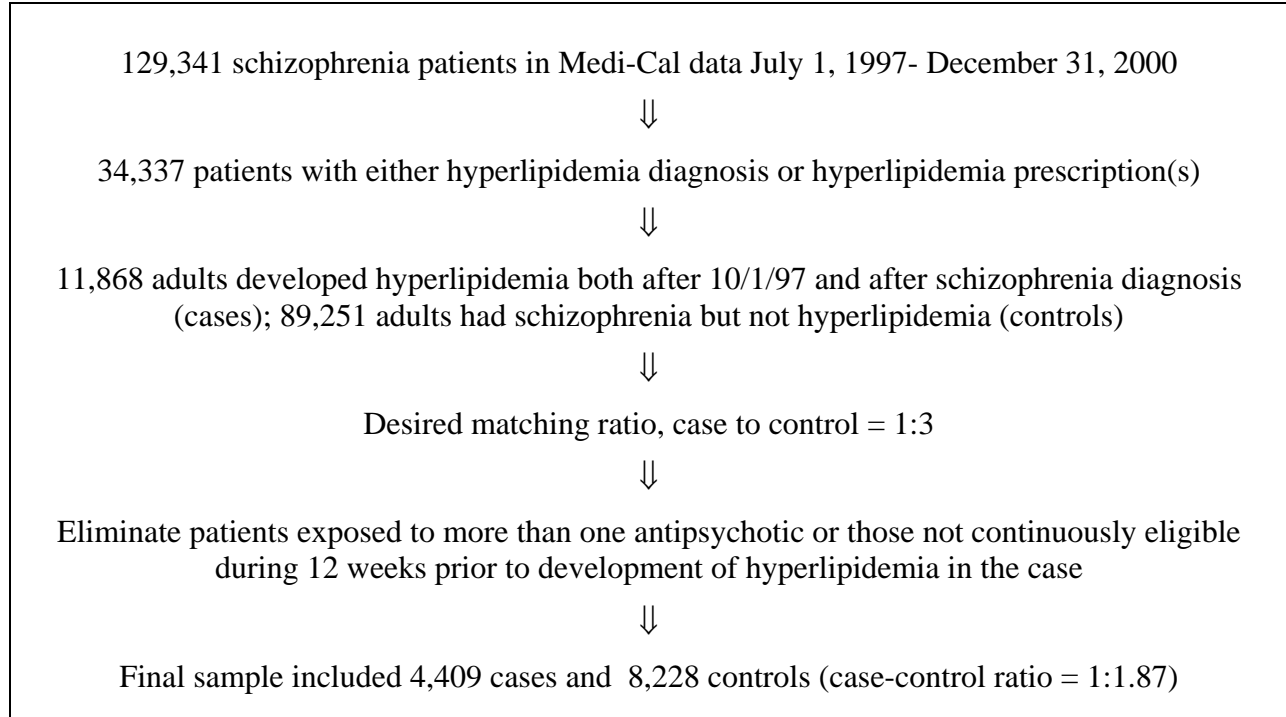Final sample included 4,409 cases and 8,228 controls (case-control ratio = 1:1.87)

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

Table 1. Odds ratios for conditional logistic regression model predicting development of hyperlipidemia in patients with schizophrenia exposed to different antipsychotic medications (12-, 24- and 52-week exposure windows).

Variable	12 Week Exposure Window[a]			24 Week Exposure Window[b]			52 Week Exposure Window[c]		
	N	Odds Ratio	P (95% CI)	N	Odds Ratio	P (95% CI)	N	Odds Ratio	P (95% CI)
Atypical Antipsychotics									
Clozapine	879	1.16	0.07 (0.99–1.37)	766	1.22	0.03 (1.03–1.45)	603	1.20	0.06 (0.99–1.46)
Olanzapine	3322	1.20	0.00 (1.08–1.33)	2935	1.24	<.0001 (1.12–1.38)	2036	1.17	0.01 (1.04–1.32)
Quetiapine	322	1.01	0.92 (0.78–1.32)	243	0.83	0.25 (0.61–1.13)	140	0.80	0.27 (0.53–1.20)
Risperidone	2612	1.00	0.98 (0.90–1.12)	2365	1.01	0.91 (0.90–1.13)	1819	0.94	0.34 (0.83–1.27)
Age	12637	0.71	<.0001 (0.69–0.73)	11954	0.70	<.0001 (0.68–0.72)	10099	0.70	<.0001 (0.68–0.72)
Ethnicity									
Hispanic	208	1.05	0.76 (0.77–1.43)	205	1.06	0.73 (0.77–1.45)	159	0.81	0.27 (0.56–1.17)
African-American	2174	1.13	0.03 (1.01–1.26)	2065	1.19	0.00 (1.06–1.33)	1810	1.18	0.01 (1.05–1.34)
Other Ethnicity	129	1.21	0.33 (0.82–1.80)	112	1.55	0.04 (1.02–2.35)	104	1.91	0.00 (1.23–2.97)
Unknown Ethnicity	3333	1.19	0.00 (1.08–1.30)	3158	1.18	0.00 (1.07–1.30)	2693	1.12	0.03 (1.01–1.25)
Co-Morbid Conditions									
Diabetes	896	1.42	<.0001 (1.22–1.66)	862	1.45	<.0001 (1.24–1.69)	734	1.37	0.00 (1.16–1.63)
Hypothyroidism	1743	1.41	<.0001 (1.25–1.58)	1681	1.47	<.0001 (1.65–1.31)	1402	1.53	<.0001 (1.35–1.74)
Concomitant Medications									

Variable	12 Week Exposure Window[a]			24 Week Exposure Window[b]			52 Week Exposure Window[c]		
	N	Odds Ratio	P (95% CI)	N	Odds Ratio	P (95% CI)	N	Odds Ratio	P (95% CI)
Beta-blockers and thiazide diuretics	1200	1.16	0.11 (0.97–1.39)	1288	1.18	0.05 (1.00–1.40)	1271	1.23	0.01 (1.05–1.45)
Loop diuretics	451	1.26	0.06 (0.99–1.60)	510	1.13	0.29 (0.90–1.40)	480	1.14	0.26 (0.91–1.42)
Anticonvulsants	1466	0.82	0.03 (0.68–0.98)	1502	0.79	0.01 (0.67–0.93)	1450	0.90	0.19 (0.76–1.06)
Protease Inhibitors	71	1.24	0.43 (0.73–2.11)	73	1.33	0.29 (0.79–2.23)	63	1.40	0.24 (0.81–2.42)
Corticosteroids	3462	1.24	0.01 (1.06–1.46)	3728	1.35	<.0001 (1.17–1.57)	3680	1.32	0.00 (1.15–1.53)

[a]Reference group for clozapine, quetiapine, olanzapine, and risperidone was all other typical antipsychotics (n = 5,502). Reference for ethnic groups was whites (n = 6,793). Total N = 12,637, with 8,228 cases and 4,409 controls.

[b]Reference group for clozapine, quetiapine, olanzapine, and risperidone was all other typical antipsychotics (n = 5,645). Reference for ethnic groups was whites (n = 6,414). Total N = 11,954 with n = 4,205 cases and n = 7,749 controls.

[c]Reference group for clozapine, quetiapine, olanzapine, and risperidone was all other typical antipsychotics (n = 5,501). Reference for ethnic groups was whites (n = 5,333). Total N = 10,099, with n = 3,640 cases and n = 6,459 controls.