Article

Hyperlipidemia Following Treatment With Antipsychotic Medications

Mark Olfson, M.D., M.P.H.

Steven C. Marcus, Ph.D.

Patricia Corey-Lisle, Ph.D., R.N.

A.V. Tuomari, M.S.

Patricia Hines, A.S.

Gilbert J. L'Italien, Ph.D.

Objective: This study attempted to estimate the relative risk of developing hyperlipidemia after treatment with antipsychotics in relation to no antipsychotic treatment.

Method: A matched case-control analysis was performed with pharmacy and claims data from California Medicaid (Medi-Cal). Patients were excluded if they were treated for medical disorders or prescribed medications known to increase their risk of hyperlipidemia. Cases were ages 18 to 64 years with schizophrenia, major depression, bipolar disorder, or other affective psychoses and incident hyperlipidemia. Cases were matched to up to six control subjects by age, sex, race, and psychiatric diagnosis. Both groups were prescribed either no antipsychotic medication or had two or more prescriptions for one and only one antipsychotic medication during the 60 days prior to the first indication of hyperlipidemia (cases) or matched index date (controls) in the billing record. Conditional logistic regressions were used to derive odds ratios and 95% confidence intervals (95% CIs) of each antipsychotic medication in relation to no antipsychotic medication.

Results: A total of 13,133 incident cases of hyperlipidemia were matched to 72,140 control subjects. As compared with no antipsychotic medication, treatment with clozapine (odds ratio: 1.82, 95% CI: 1.61–2.05), risperidone (odds ratio: 1.53, 95% CI: 1.43–1.64), quetiapine (odds ratio: 1.52, 95% CI: 1.40–1.65), olanzapine (odds ratio: 1.56, 95% CI: 1.47–1.67), ziprasidone (odds ratio: 1.40, 95% CI: 1.19–1.65), and first-generation antipsychotics (odds ratio: 1.26, 95% CI: 1.14–1.39), but not aripiprazole (odds ratio: 1.19, 95% CI: 0.94–1.52) was associated with a significant increase in risk of incident hyperlipidemia.

Conclusions: These findings suggest that most commonly prescribed antipsychotic medications increase the risk of developing hyperlipidemia in patients with schizophrenia or mood disorders.

(Am J Psychiatry 2006; 163:1821–1825)

There is accumulating empirical evidence and growing clinical concern that some of the newer antipsychotic medications may increase the risk of hyperlipidemia. Case reports have linked treatment with clozapine and olanzapine to hyperlipidemia that disappears when antipsychotic medications are discontinued (1–5). Medical record reviews further support a connection between clozapine and olanzapine and the increased risk of hypertriglyceridemia (6–9). A small prospective observational study demonstrated that most patients developed hyperlipidemia during the first few months of olanzapine treatment (10).

Clinical epidemiological studies provide a second line of evidence linking treatment with antipsychotic medications to an increased risk of hyperlipidemia (11, 12). In one case-control study, olanzapine and clozapine, but not risperidone or combination therapy, were associated with a significantly increased risk of hyperlipidemia (11). A second study reported no overall differences in the risk of hyperlipidemia between patients treated with clozapine or first-generation antipsychotic medications, although clozapine was associated with an increased risk of hyperlipidemia in the young adult cohort (12).

Prospective research further suggests that antipsychotic medications may adversely affect serum lipids. In one randomized double-blind controlled trial, olanzapine and clozapine resulted in significant increases in total serum cholesterol (13). A second 3-week prospective randomized trial reported that treatment with olanzapine or quetiapine was associated with a significant increase from baseline in fasting triglyceride levels (14). In a 4-week trial, olanzapine (+13.8%) and risperidone (+5.1%) in combination with divalproex were associated with statistically nonsignificant increases in total serum cholesterol (15).

In relation to the accumulation of evidence linking clozapine and olanzapine to a worsening of the lipid profile, considerably less is known about the metabolic effects of the other second-generation antipsychotic medications. In the current study, we estimated the relative risk of hyperlipidemia after initial treatment with first-generation

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TABLE 1. Characteristics of Subjects With Psychotic Disorders with New-Onset Hyperlipidemia and Matched Comparison Subjects[a]

Characteristic	Subjects With New-Onset Hyperlipidemia (%) (N=13,133)	Comparison Subjects (%) (N=72,140)[b]
Sex		
Women	59.8	59.8
Men	40.2	40.2
Race		
Black	10.4	10.4
White	50.8	50.8
Other	38.8	38.8
Primary diagnosis		
Schizophrenia	35.4	35.4
Major depression without psychotic features	37.0	37.0
Major depression with psychotic features	3.2	3.2
Bipolar disorder	22.1	22.1
Other affective psychosis	2.3	2.3

[a] Data from 2001–2004 California Medicaid program. Comparison subjects were matched to subjects with new-onset hyperlipidemia by age, sex, race, and primary diagnosis.

[b] For comparisons with fewer than six control subjects per case, each control subject was weighted by six times the reciprocal of its frequency. The ICD-9 primary diagnostic groups include schizophrenia (295), major depression without psychotic features (296.2-296.3 except 296.24 and 296.34), major depression with psychotic features (296.24 and 296.34), bipolar disorder (296.0, 296.1, and 296.4-296.8), and other affective psychosis (296.9).

antipsychotic medications and each of the six currently available second-generation antipsychotic medications in relation to no antipsychotic medication treatment.

Method

Data were culled from statewide claims of the California Medicaid program (2001–2004). The study procedures were approved by the institutional review board of the New York State Psychiatric Institute.

The study cohort was first limited to patients ages 18 to 64 who received one or more claims for the treatment of schizophrenia (ICD-9:295) or an affective psychosis (ICD 296). Each patient was assigned on the basis of the number of claims to one of five diagnostic groups: 1) schizophrenia, 2) bipolar disorder, 3) major depressive disorder with psychotic features, 4) major depression without psychotic features, or 5) other affective psychosis.

Patients were excluded if they had medical conditions related to hyperlipidemia (16) or filled prescriptions for medications related to hyperlipidemia (17) before their index date, as defined. Medical conditions related to hyperlipidemia included hypothyroidism, nephrotic syndrome, cholecystitis, acute intermittent porphyria, anorexia nervosa, type 2 diabetes mellitus, obesity, malnutrition, Gaucher's disease, hepatitis, alcohol abuse/dependence, renal failure, sepsis, Cushing's syndrome, pregnancy, acromegaly, lipodystrophy, multiple myeloma, autoimmune disorders, monoclonal gammopathy, and orchidectomy. Medications related to hyperlipidemia included thiazide and loop diuretics, retinoids, protease inhibitors, anabolic steroids, androgens, androgen-estrogen combinations, second-generation oral progestogens, growth hormone, immunosuppressive agents, amiodarone, enzyme-inducing anticonvulsants, nonselective beta-blockers, and oral corticosteroids.

Cases were selected for an incident diagnosis of hyperlipidemia (ICD-9 codes 272.0–272.4) or a prescription for atorvastatin, cholestyramine, clofibrate, colesevelam, colestipol, fenofibrate, fluvastatin, gemfibrozil, lovastatin, pravastatin, or simvastatin. Patients with a previous hyperlipidemia diagnosis or antilipemic prescription during the preceding 180 days were excluded from the analysis. The first date of hyperlipidemia diagnosis or dispensed antilipemic medication was defined as the index date. Subjects with hyperlipidemia (cases) and comparison subjects (controls) were limited to patients who, during the 60 days before their index dates, either filled no antipsychotic medication prescriptions or filled two or more prescriptions of only one type of antipsychotic medication.

For each case, up to 6 comparison subjects that did not have a diagnosis or treatment of hyperlipidemia were selected matched by age, sex, race, and diagnostic group. Each comparison subject was weighted by six times the reciprocal of its frequency. Comparison subjects were assigned the same index date as the case to which they were matched.

A total of 13,133 cases were selected from an initial pool of 55,662 potential cases. Potential cases were excluded if they were prescribed a medication or treated with a medical condition related to hyperlipidemia (N=18,774, 33.7%), filled prescriptions for more than one type of antipsychotic medication (N=6,955, 12.5%), filled only a single prescription for an antipsychotic medication during the 60-day period (N=8,959, 16.1%), were eligible for California Medicaid benefits for less than 180 days before their index date (N=24,453, 44.0%), or had been treated for hyperlipidemia during the 180-day period before their index date (N=26,844, 48.2%). These eligibility criteria were not mutually exclusive. The selected 13,133 incident cases of hyperlipidemia were matched to 72,140 comparison subjects.

Antipsychotic medications were classified as aripiprazole, clozapine, olanzapine, quetiapine, ripseridone, ziprasidone, or a first-generation antipsychotic medication. Antipsychotic treatment was defined as the dispensing of more than one prescription for an antipsychotic medication within 60 days of the index date.

A case-control analysis was performed. The effect of treatment with each antipsychotic medication during the 60 days preceding the index date on the odds of developing hyperlipidemia was modeled with conditional logistic regression. The reference group included all patients prescribed no antipsychotic medications during the 60 days preceding their index date. Results are presented as odds ratios with 95% confidence intervals (95% CIs).

Results

A majority of the subjects with hyperlipidemia and comparison subjects were white (Caucasian) in race, and women outnumbered men in both groups (Table 1). The two groups were well matched in age (subjects with hyperlipidemia: mean=46.6 years [SD=10.5]; comparison subjects: mean=46.6 years [SD=10.7]). A great majority of the patients in each group were classified as having major depression without psychotic features, schizophrenia, or bipolar disorder (Table 1).

Over one-half of the cases (64.02%) were not treated with an antipsychotic medication during the 2 months before their index date. Among those who were treated with an antipsychotic medication, the most common medication was olanzapine (12.26%), followed by risperidone (8.86%). The subjects with hyperlipidemia were less commonly treated with quetiapine (6.09%), first-generation antipsychotic medications (3.97%), clozapine (2.79%), ziprasidone (1.40%), or aripiprazole (0.61%) (Table 2).

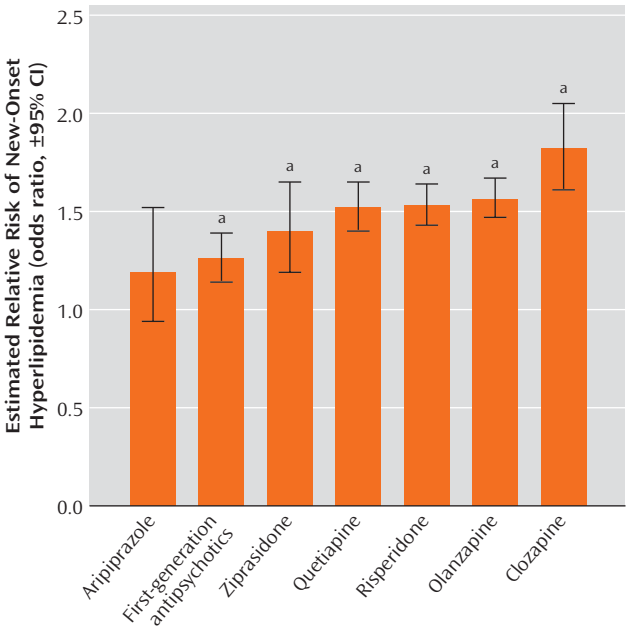
TABLE 2. Associations of Antipsychotic Medication Treatment With New-Onset Hyperlipidemia in Adults with Psychotic Disorders[a]

Variable	Subjects With New-Onset Hyperlipidemia (N=13,133)		Comparison Subjects (%) (N=72,140)[b]		Odds Ratio	95% CI
	N	%	N	%		
No antipsychotic medication	8,408	64.02	50,495	71.16	1.00 (reference)	
Aripiprazole	80	0.61	467	0.61	1.19	0.94–1.52
First-generation antipsychotics	521	3.97	2,947	3.88	1.26	1.14–1.39
Ziprasidone	184	1.40	898	1.19	1.40	1.19–1.65
Quetiapine	800	6.09	3,485	4.71	1.52	1.40–1.65
Risperidone	1,163	8.86	5,231	6.98	1.53	1.43–1.64
Olanzapine	1,610	12.26	7,097	9.53	1.56	1.47–1.67
Clozapine	367	2.79	1,520	1.94	1.82	1.61–2.05

[a] Data from 2001–2004 California Medicaid program.
[b] For comparisons with fewer than six control subjects per case, each control subject was weighted by six times the reciprocal of its frequency.

In the conditional logistic regression model, the patients with no antipsychotic medication treatment served as the reference group. Treatment with clozapine, risperidone, quetiapine, olanzapine, ziprasidone, and the first-generation antipsychotic medications, but not aripiprazole, was associated with a significantly greater risk of new-onset hyperlipidemia than treatment without an antipsychotic medication (Table 2, Figure 1).

FIGURE 1. Association of Antipsychotic Medication Treatment With New-Onset Hyperlipidemia in Adults With Psychotic Disorders



[a] Significantly different from no antipsychotic medication treatment (reference), p<.0.05.

Discussion

Across a range of antipsychotic medications, there was a significant association with increased risk of hyperlipidemia. First-generation antipsychotic medications and each of the second generation antipsychotic medications, except aripiprazole, posed a risk of hyperlipidemia that was significantly greater than the risk of no antipsychotic treatment. These findings extend earlier research concerning clozapine, olanzapine, and risperidone (5, 6, 8, 11, 14) to include relevant information regarding quetiapine, ziprasidone, and aripiprazole.

The magnitude of the odds ratio of hyperlipidemia for olanzapine (odds ratio=1.56) was considerably smaller than previously reported from an analysis of the U.K. General Practice Research Database (odds ratio=4.52) (11). One possible explanation for this discrepancy concerns a variation in underlying practice patterns. Whereas only a small proportion of the subjects in the U.K. study (3%) were treated with second-generation antipsychotic medications, a much larger proportion of cases in the current study (32%) were prescribed second-generation antipsychotic medications. It is possible that in U.K. general practice, treatment with olanzapine and other second-generation antipsychotic medications are reserved for especially severely ill patients who may have higher rates of smoking (18), obesity (19), physical inactivity (20), or other risk factors for hyperlipidemia that are common in severe mental illness but difficult to statistically control for in medical record based research. It is also possible that many U.S. physicians in the current study have become aware of the metabolic risks associated with olanzapine and are therefore relatively reluctant to prescribe it to their patients at high risk for developing metabolic abnormalities.

The current study has a number of limitations. First, antipsychotic treatment was measured with claims records rather than pill counts or electronic monitoring that might have yielded more accurate information. Second, no information was available concerning several well-known risk factors for hyperlipidemia, such as exercise level, diet, and body weight. Third, physicians may selectively prescribe antipsychotic medications partly on the basis of such risk factors and so attenuate observed associations between hyperlipidemia and some antipsychotic medications. Fourth, recorded diagnoses of hyperlipidemia and dispensed prescriptions of antilipemic medications probably underestimate the true incidence of hyperlipidemia in the

study population (21). Fifth, because the study was limited to Medicaid beneficiaries, the results may not generalize to other populations that may differ in their awareness and recognition of hyperlipidemia (22). Sixth, because the study included relatively few subjects prescribed aripiprazole, the results concerning this antipsychotic medication should be interpreted with caution. Finally, the study included only nonelderly adults who may differ from children and older adults in their metabolic response to antipsychotic medications and in their underlying risk factor structure for hyperlipidemia (23, 24).

We provide evidence that several antipsychotic medications may contribute to the development of hyperlipidemia. Because patients treated for medical illnesses and prescribed medications known to be associated with hyperlipidemia were excluded from these analyses, the observed relationships between antipsychotic medication treatment and the risk of hyperlipidemia are independent of these known risk factors. Patients with schizophrenia and related mental disorders are approximately twice as likely as the general population to die of cardiovascular disease (4). In addition to an increase in lipid disorders, patients with severe mental disorders also have elevated rates of diabetes, obesity, hypertension, physical inactivity, and smoking, although several of these associations are less clearly established for severe mood disorders than for schizophrenia (see reference 5). In light of these risk factors, primary prevention of the metabolic syndrome and cardiovascular disease is an important aspect of care of severe mental disorders. Our results suggest that physicians should give careful consideration to potential cardiovascular and metabolic consequences before prescribing an antipsychotic medication.

Received Nov. 9, 2005; revision received Jan. 11, 2006; accepted Jan. 30, 2006. From the Division of Clinical and Genetic Epidemiology, New York State Psychiatric Institute; the Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York; the Department of Social Work, University of Pennsylvania School of Medicine, Philadelphia; and Bristol-Myers-Squibb, Pharmaceutical Research Institute, Pharmaceutical Research Institute, Wallingford, Conn. Address correspondence and reprint requests to Dr. Olfson, Department of Psychiatry, Columbia University, NY State Psychiatric Institute, 1051 Riverside Dr., Unit 24, New York, NY 10032; mo49@columbia.edu (e-mail).

Dr. Olfson has been a consultant for Pfizer, Bristol-Myers-Squibb, Eli Lilly, and McNeil; has received grant/research support from Eli Lilly and Bristol-Myers-Squibb, and has served on the speakers/advisory boards for Janssen. He has also received grant support from the American Foundation for Suicide Prevention and the National Association for Research on Schizophrenia and Affective Disorders. Dr. Marcus has received grant/research support from McNeil and has been a consultant for Eli Lilly and Bristol-Myers-Squibb. Dr. Corey-Lisle, Dr. L'Italien, Ms. Tuomari, and Ms. Hines are employees of Bristol-Myers-Squibb.

This project was supported by a grant from Bristol-Myers-Squibb.

References

1. Domon SE, Webber JC: Hyperglycemia and hypertriglyceridemia secondary to olanzapine. J Child Adolesc Psychopharmacol 2001; 11:285–288
2. Nguyen M, Murphy T: Olanzapine and hypertriglyceridemia. J Am Acad Child Adolesc Psychiatry 2001; 40:133
3. Su KP, Shen WW, Huan SY: Lipid abnormalities induced by novel antipsychotic drugs. Drug Safety 2001; 24:1017–1018
4. Sheitman BB, Bird PM, Binz W, Akinli L, Sanchez C: Olanzapine-induced elevation of plasma triglyceride levels. Am J Psychiatry 1999; 156:1471–1472
5. Meyer JM: Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol 2001; 21:369–374
6. Gaulin BD, Markowitz JS, Caley CF, Nesbitt LA, Dufresne RL: Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999; 156:1270–1272
7. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC: Clozapine, diabetes mellitus, weight gain, and lipid abnormalities; a five-year naturalistic study. Am J Psychiatry 2000; 157:975–981
8. Meyer JM: A retrospective comparison of weight, lipid, and glucose changes between ripseridone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. J Clin Psychiatry 2002; 63:425–433
9. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002; 63:856–865
10. Melkersson KL, Holting A-L, Brismar KE: Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related disorders. J Clin Psychiatry 2000; 61: 742–748
11. Koro CE, Fedder DO, D'Italien GJ, Weiss S. Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW: An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59:1021–1026
12. Lund BC, Perry PJ, Brooks JM, Arndt S: Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001; 58:1172–1176
13. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA: Changes in glucose and cholesterol levels inpatients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003; 160:290–296
14. Food and Drug Administration Psychopharmacological Drugs Advisory Committee. Briefing document for Zeldox capsules. http://www.fda.gov.ohrms.dockets.ac.00.backgrd/3619b1a.pdf
15. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW: Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003; 28:182–192
16. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo D, Jameson JL (eds): Harrison's Principles of Internal Medicine, 16th Edition. New York, McGraw-Hill, 2005, p 2294
17. Mantel-Teeuvisse AK, Kloosterman JME, Maitland-van der See AH, Klungel OH, Posius AH, de Boer A: Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. Drug Safety 2001; 24: 443–456
18. Brown S, Birtwistle J, Poe L, Thompson C: The unhealthy lifestyle of people with schizophrenia. Psychol Med 1999; 29:697–701
19. Strassnig M, Brar JS, Ganguli R: Nutritional assessment of patients with schizophrenia: a preliminary study. Schizophr Bull 2003; 29:393–397
20. Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Nyland B: Cardiovascular risk factors for people with mental illness. Aust N Z J Psychiatry 2001; 35:196–202

21. Primesta P, Poulter NR: Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey. BMJ 2000; 321:1322–1325
22. Frontini MG, Srinivasan SR, Elkasabany A, Berenson GS: Awareness of hypertension and dyslipidemia in a semirural population of young adults: the Bogalusa heart study. Prevent Med 2003; 36:398–402
23. Stigler KA, Potenza MN, Posey DJ, McDougle CJ: Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance, and management. Paediatric Drugs 2004; 6:33–44
24. Barak Y: No weight gain among elderly schizophrenia patients after 1 year of risperidone treatment. J Clin Psychiatry 2002; 63:117–119