ORIGINAL ARTICLE

An Assessment of the Independent Effects of Olanzapine and Risperidone Exposure on the Risk of Hyperlipidemia in Schizophrenic Patients

Carol E. Koro, PhD; Donald O. Fedder, DrPH; Gilbert J. L'Italien, PhD; Sheila Weiss, PhD; Laurence S. Magder, PhD; Julie Kreyenbuhl, PhD; Dennis Revicki, PhD; Robert W. Buchanan, MD

Background: The newer antipsychotic agents exhibit a superior safety profile compared with conventional antipsychotic agents in terms of extrapyramidal symptoms. Previous studies have suggested an association between olanzapine treatment and hyperlipidemia. We evaluated this association using a large health care database.

Methods: The study was derived from the England and Wales–based General Practice Research Database, composed of 3.5 million subjects followed up between June 1, 1987, and September 24, 2000. A total of 18 309 individuals diagnosed as having schizophrenia were identified. A 6:1 matched nested case-control design was used. Conditional logistic regression was used to derive adjusted odds ratios (ORs), controlling for sex, age, and other medications and disease conditions influencing lipid levels. Antipsychotic drug exposure was defined as the receipt of at least 1 prescription for an antipsychotic medication within the 3 months before the date of diagnosis of hyperlipidemia.

Results: There were 1268 incident cases of hyperlipidemia in the cohort, matched to 7598 control subjects. Olanzapine use was associated with nearly a 5-fold increase in the odds of developing hyperlipidemia compared with no antipsychotic exposure (OR, 4.65; 95% confidence interval [CI], 2.44-8.85) ($P<.001$) and more than a 3-fold increase compared with those receiving conventional agents (OR, 3.36; 95% CI, 1.77-6.39) ($P<.001$). Risperidone was not associated with increased odds of hyperlipidemia compared with no antipsychotic exposure (OR, 1.12; 95% CI, 0.60-2.11) ($P=.72$) or conventional antipsychotic exposure (OR, 0.81; 95% CI, 0.44-1.52) ($P=.52$).

Conclusions: We observed a strong association between olanzapine exposure and hyperlipidemia in schizophrenic patients. The possible metabolic consequences of olanzapine use should be given serious consideration by treating physicians.

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From the Schools of Pharmacy (Drs Koro, Fedder, L'Italien, and Weiss) and Medicine (Drs Magder, Kreyenbuhl, and Buchanan), University of Maryland, Baltimore; Bristol-Myers Squibb, Pharmaceutical Research Institute, Wallingford, Conn (Dr L'Italien); MEDTAP International, Bethesda, Md (Dr Revicki); and the Maryland Psychiatric Research Center, Catonsville (Dr Buchanan).

IN RECENT decades, several new antipsychotic agents exhibiting improved mechanisms of action compared with conventional antipsychotic agents have been widely adopted in the clinical treatment of schizophrenia. The clearest advantage of the newer antipsychotic agents is the reduction of extrapyramidal adverse effects.[1] However, the new-generation antipsychotic agents are associated with a different spectrum of adverse effects, including weight gain,[2] alterations in glucose metabolism,[3-5] and elevations of blood cholesterol and lipid levels.[2,6] Most of these observations are based primarily on case reports[7-9] and 1 small comparative study.[6] If these associations were confirmed in larger studies, one might conclude that the nutritional and metabolic effects of the new-generation antipsychotic agents are as serious as the extrapyramidal effects seen with conventional antipsychotic agents.[10] For example, lipid elevations have been unequivocally associated with an increased risk for cardiovascular events, such as myocardial infarction and stroke, in general populations.[11-14] More recently, the US Adult Treatment Panel III guidelines[15] recommend aggressive modification of lipid levels to reduce cardiovascular risk.

Previous studies have suggested that olanzapine use is associated with the development of hyperlipidemia. A report by Sheitman et al[7] found that olanzapine treatment resulted in marked increases in triglyceride levels for some patients. Another cohort study[8] of 25 olanzapine-treated patients demonstrated an increase in mean fasting triglyceride levels of 37% over baseline at 12 weeks. Melkersson et al[16] found increased rates of hypertriglyceridemia and hypercholesterolemia among olanzapine-treated schizophrenic patients at 5 months. One comparative study by Meyer[6] demonstrated increases in total cholesterol levels by 24 mg/dL (0.62 mmol/L) and fasting triglyceride levels by

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88 mg/dL (0.99 mmol/L) in 47 patients after 1 year of olanzapine treatment. Among a nongeriatric subset, the increases were 31 mg/dL (0.80 mmol/L) and 105 mg/dL (1.19 mmol/L) for cholesterol and triglyceride levels, respectively. Meyer[17] also reported 14 cases of severe hypertriglyceridemia at levels exceeding 600 mg/dL (7.74 mmol/L) in 12 olanzapine- and 2 quetiapine fumarate–treated patients.

In contrast, there is no evidence of an association between risperidone use and hyperlipidemia in the literature. Ghaeli and Dufresne[9] reported decreases in triglyceride levels after patients switched from clozapine to risperidone. The Meyer study[6] demonstrated no clinically significant increase in total cholesterol level and only modest increases in fasting triglyceride level (30 mg/dL [0.34 mmol/L], $P = .03$) compared with baseline for the 47 risperidone-treated patients.

Last, there is no evidence that schizophrenia itself is associated with an increased risk of hyperlipidemia. In fact, low cholesterol levels have been found in some schizophrenic patients.[18,19] Modai et al[18] showed that patients with schizophrenia had significantly lower cholesterol levels than patients with unipolar depression. Boston et al[20] demonstrated that cholesterol levels were significantly lower among treatment-resistant patients vs responsive patients. However, lifestyle factors may increase the risk of lipid abnormalities in patients with schizophrenia.[21-23]

The association between treatment with newer antipsychotic agents, particularly olanzapine, and incident hyperlipidemia warrants a more scientifically comprehensive examination. Given that other factors, such as concomitant medications, disease conditions, and the unhealthy lifestyle of schizophrenic patients, may contribute to the development of hyperlipidemia, it is important to explore these associations in data sources that contain information on these potential confounders. For this study, we used the General Practice Research Database (GPRD) to quantify the risk of hyperlipidemia associated with exposure to various antipsychotic agents, including conventional and atypical agents (olanzapine and risperidone).

METHODS

STUDY POPULATION

The GPRD is a computerized medical database, containing data collected from approximately 400 general medical practices in England and Wales. In 1996, the GPRD included more than 6% of the total population.[24] Continuous information has been collected from most of the practices for more than 10 years, giving a total experience of more than 30 million patient-years of observation.[25] The present study population was defined as individuals with a record of a physician diagnosis of schizophrenia registered with medical practices that submitted data to the GPRD between June 1, 1987, and September 24, 2000. The information for the present study was derived from the patient registration record, the medical record, the prevention record, and the detailed prescription record of the GPRD.

COHORT DEFINITION

Patient eligibility begins from the time that "up-to-standard" data are provided to the GPRD. Up to standard refers to data recording that reaches an appropriate standard for use in research. However, all previous diagnoses and treatments are recorded in the medical record. Eligibility criteria for this study included a diagnosis of and treatment for schizophrenia recorded at any time in the medical and treatment records. For patients identified as having schizophrenia before up to standard medical records, the start of the study period is defined as the date when the practice began submitting up to standard data for the patient up to the date when the patient transferred out, died, or provided the last data submission to the GPRD. For all other patients, the start of the study period is defined as the earliest date of diagnosis with schizophrenia. To be eligible for the present study, patients must have contributed at least 3 months of up to standard data.

For the cohort analysis, the incidence rates were calculated from the number of patients who developed hyperlipidemia within 3 months of exposure to the drug of interest, divided by the person-time exposure for the drug of interest. The person-time exposure is calculated from the number of prescriptions of the drug of interest divided by 12 (the typical prescription in the GPRD is written for 1 month).

SELECTION OF CASE AND CONTROL SUBJECTS

Cases

Incident cases of hyperlipidemia were defined as the earliest date of a diagnosis of (by medical code) or treatment for (by drug code) hyperlipidemia, occurring at least 3 months after the beginning of the patient's study period. Issued prescriptions were used as a proxy for drug exposure. The date of hyperlipidemia diagnosis is defined as the index date. A diagnosis of hyperlipidemia was defined as an Oxford Medical Information System diagnostic code or a Read medical code for an increased cholesterol or triglyceride level in the medical record. Treatment of hyperlipidemia was defined as a prescription written for any of the following medications: acipimox, atorvastatin calcium, bezafibrate, cerivastatin sodium, cholestyramine resin, ciprofibrate, colestipol hydrochloride, fenofibrate, fluvastatin sodium, gemfibrozil, inositol niacinate, ispaghula husk, niacin, pravastatin sodium, simvastatin, or Ω-3 marine triglycerides (fish oils). To ensure that the hyperlipidemia cases were incident, the medical and prescription records were checked for any record of a diagnosis of or treatment for hyperlipidemia before the start of the subject study period. If there was a record of hyperlipidemia before the start of the study period, then these patients were excluded. All remaining patients must have contributed at least 3 months of up to standard data between the start of the study period and the index date. Patients identified as cases must not have obtained a prescription for lipid-lowering agents within these 3 months, otherwise they are excluded for being prevalent cases. Prescriptions in England and Wales are usually dispensed with a 1-month supply of medication and, therefore, 3 months is sufficient time to assess treatment before the index date. The use of a 3-month window period as opposed to a longer period avoids the exclusion of hyperlipidemia cases who contributed no more than 3 months of data.

Controls

For each patient defined as a case, 6 controls with study periods at least as long as the study period of the case were matched by age at index date (±5 years), sex, and index date. All controls who met the matching criteria were assigned a random number using SAS statistical software (SAS Institute Inc, Cary, NC) procedures. Then, the 6 controls for each case were selected at random from the pool of eligible controls. Controls were selected from patients with a diagnosis and treatment of

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schizophrenia who did not have a diagnosis or treatment of hyperlipidemia during or before the study period. Control patients were assigned the same index date as the case patients to whom they were matched. Furthermore, the start of the study period of the controls was truncated to match the start of the study period of the cases. Therefore, by definition, the study periods were the same for cases and controls.

ANTIPSYCHOTIC DRUG EXPOSURE

Antipsychotic drugs were classified as conventional agents (depot and/or nondepot), olanzapine, risperidone, and other newer drugs, including amisulpride, remoxipride, and sertindole. There were no patients undergoing quetiapine and clozapine therapy because the latter must be initiated during hospitalization.[26] There are no other restrictions on the use of atypical antipsychotic agents in England and Wales.

All prescriptions written by the general practitioner for the treatment of schizophrenia between the start of the study period and the index date were abstracted. The dates of all antipsychotic prescriptions within the study period were compared with the index date. Exposure wasdefined as the receipt of at least 1 prescription for an antipsychotic agent within the 3 months before the index date. Nonexposed subjects are those who did not have a prescription for an antipsychotic agent within the 3 months before the index date.

STATISTICAL ANALYSES

All analyses were conducted using SAS statistical software for personal computers, version 7.0 (SAS Institute Inc). The primary study design was a case-control analysis nested within a cohort of schizophrenic patients. To account for the matched study design, the effect of exposure to the different antipsychotic agents on the odds of hyperlipidemia development was modeled using conditional logistic regression.[27] Unadjusted incidence rates for hyperlipidemia were also calculated from the cohort experience.

Two reference groups were used to estimate the odds of hyperlipidemia development among those exposed to olanzapine, risperidone, and conventional antipsychotic agents. The first referent group included all individuals prescribed no antipsychotic medications within the 3 months before the index date. The second referent group included individuals prescribed conventional antipsychotic medications within the 3 months before the index date. In both comparisons, individuals were divided into mutually exclusive categories of antipsychotic exposure. In addition, patients exposed to 2 or more antipsychotic agents from 2 or more different classes within the 3-month period before the index date were grouped into a combination antipsychotic exposure category.

In addition to the matching variables, the analyses were adjusted for prescription of other drugs known to affect the risk of hyperlipidemia, including β-adrenergic blockers, thiazide diuretics, combination β-blockers and thiazide diuretics, corticosteroids, female sex hormones (estrogens and progestins), and valproate sodium.[28] Disorders associated with secondary hyperlipidemia, including hypothyroidism and diabetes mellitus, were also adjusted for in the analysis.[28]

RESULTS

Between June 1, 1987, and September 24, 2000, 20 865 subjects were diagnosed as having schizophrenia and received treatment for schizophrenia. Of these subjects, 1429 (7%) contributed less than 3 months of follow-up and were excluded. Another 1127 (5%) who were diagnosed as having or were treated for hyperlipidemia before the start of their study period were also excluded, leaving 18 309 subjects (88%) available for study. The study population was almost equally divided between men and women, with a mean ± SD age of 51 ± 20 years (**Table 1**). Of the 18 309 subjects in the cohort, 85% received at least 1 prescription for nondepot conventional antipsychotic medications during the follow-up period; 22%, for depot conventional antipsychotic medications; 5%, for olanzapine; 8%, for risperidone; and 3%, for other newer antipsychotic agents.

Table 1. Descriptive Statistics of the Overall Cohort and the Case and Control Patients*

Variable	Overall Cohort (N = 18 309)	Case Patients (n = 1268)	Control Patients (n = 7598)
Age, y			
<20	447 (2)	3 (<1)	11 (<1)
20-44	7404 (40)	333 (26)	2041 (27)
45-65	5400 (29)	506 (40)	2985 (39)
>65	5058 (28)	426 (34)	2561 (34)
Sex			
Male	9002 (49)	822 (65)	4925 (65)
Female	9307 (51)	446 (35)	2673 (35)
Exposure to antipsychotic drugs at any point during follow-up†			
Conventional drugs			
Nondepot	15 505 (85)	1054 (83)	5696 (75)
Depot	4067 (22)	273 (22)	1608 (21)
Olanzapine	853 (5)	23 (2)	65 (<1)
Risperidone	1453 (8)	34 (3)	205 (3)
Other newer agents	501 (3)	15 (1)	91 (1)

*Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding.
†Categories are not mutually exclusive.

COHORT ANALYSES

During a mean ± SD follow-up of 4.07 ± 2.80 years, a total of 1269 hyperlipidemia cases (7%) were identified; 205 case identifications were based on a diagnosis of hyperlipidemia only, 1171 on treatment for hyperlipidemia, and 107 on a diagnosis and on treatment for hyperlipidemia. Among all antipsychotic-treated schizophrenic patients, the incidence rate of hyperlipidemia was 17.04 per 1000 person-years. Women had a higher incidence rate (21.6 per 1000 person-years; 95% confidence interval [CI], 20.14-23.10) of hyperlipidemia compared with men (12.3 per 1000 person-years; 95% CI, 11.21-13.49). The incidence rate of hyperlipidemia within 3 months of a prescription was 26.6 per 1000 person-years for olanzapine (95% CI, 17.15-41.19), 11.5 per 1000 person-years for risperidone (95% CI, 7.41-17.81), and 18.5 per 1000 person-years for conventional antipsychotic medications (95% CI, 17.30-19.82). Olanzapine-exposed subjects exhibited a 40% increase in the risk of hyperlipidemia compared with those exposed to conventional antipsychotic medications (risk ratio, 1.4; 95% CI, 0.92-2.22). The increase in the risk of hyperlipidemia in subjects prescribed olanzapine compared with those pre-

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Table 2. Comparison of Patients Exposed to Olanzapine and Risperidone Within 3 Months of the Index Date With Patients Not Exposed to Antipsychotic Agents Within the Risk Period*

Antipsychotic Drug Exposure†	Case Patients (n = 1268)‡	Control Patients (n = 7598)‡	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)§	*P* Value
No antipsychotic agents	413 (33)	3089 (41)	. . .	. . .	. . .	. . .
Olanzapine	16 (1)	27 (<1)	4.52 (2.38-8.60)	<.001	4.65 (2.44-8.85)	<.001
Risperidone	12 (<1)	79 (1)	1.13 (0.60-2.11)	.71	1.12 (0.60-2.11)	.72
Antipsychotic agents						
Conventional drugs	807 (64)	4320 (57)	1.40 (1.23-1.59)	<.001	1.38 (1.22-1.57)	<.001
Other newer drugs	5 (<1)	17 (<1)	2.19 (0.80-5.95)	.13	2.04 (0.75-5.60)	.16
Combination drugs‖	15 (1)	66 (<1)	1.68 (0.94-3.00)	.08	1.63 (0.91-2.91)	.01

*The referent was patients not taking antipsychotic agents. OR indicates odds ratio; CI, confidence interval; and ellipses, data not applicable.
†Categories are mutually exclusive.
‡Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding.
§Adjusted for age, sex, index year, length of follow-up, β-blockers, combination β-blockers and thiazide diuretics, corticosteroids, thiazide diuretics, female sex hormones, valproate sodium, hypothyroidism, and diabetes mellitus.
‖A separate category was created for patients exposed to more than one antipsychotic agent and included in the model.

Table 3. Comparison of Patients Exposed to Olanzapine and Risperidone Within 3 Months of the Index Date With Patients Exposed to Conventional Antipsychotic Agents Within the Risk Period*

Antipsychotic Drug Exposure†	Case Patients (n = 1268)‡	Control Patients (n = 7598)‡	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)§	*P* Value
Conventional antipsychotic agents	807 (64)	4320 (57)	. . .	. . .	. . .	. . .
Olanzapine	16 (1)	27 (<1)	3.24 (1.71-6.15)	<.001	3.36 (1.77-6.39)	<.001
Risperidone	12 (1)	79 (1)	0.81 (0.43-1.51)	.50	0.81 (0.44-1.52)	.52
Other newer antipsychotic agents	5 (<1)	17 (<1)	1.57 (0.58-4.26)	.38	1.48 (0.54-4.04)	.45
None of the above agents	413 (33)	3089 (41)	0.72 (0.63-0.81)	<.001	0.72 (0.64-0.82)	<.001
Combination antipsychotic agents‖	15 (1)	66 (<1)	1.20 (0.68-2.14)	.53	1.18 (0.66-2.10)	.58

*The referent was patients taking conventional antipsychotic agents. OR indicates odds ratio; CI, confidence interval; and ellipses, data not applicable.
†Categories are mutually exclusive.
‡Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding.
§Adjusted for age, sex, index year, length of follow-up, β-blockers, combination β-blockers and thiazide diuretics, corticosteroids, thiazide diuretics, female sex hormones, valproate sodium, hypothyroidism, and diabetes mellitus.
‖A separate category was created for patients exposed to more than one antipsychotic agent and included in the model.

scribed conventional antipsychotic medications was 8.1 per 1000 person-years.

NESTED CASE-CONTROL STUDY

A total of 1268 hyperlipidemia cases were matched to 7598 controls. One case could not be matched and was excluded. Table 1 details the demographic characteristics for the matched cases and controls. The mean ± SD age for the cases and controls was 56 ± 16 years.

The prevalences of conventional antipsychotic prescriptions and risperidone were similar in the cases and controls, whereas olanzapine prescribing was 2.1 times higher among the cases compared with the controls. **Table 2** summarizes the odds ratios and 95% CIs for the development of hyperlipidemia in individuals exposed to the different antipsychotic agents compared with patients not receiving antipsychotic agents. Compared with no antipsychotic exposure, olanzapine significantly increased the odds of hyperlipidemia, followed by conventional antipsychotic medication exposure, but not risperidone exposure. As shown in **Table 3**, exposure to olanzapine was associated with a significant increase in the odds of hyperlipidemia compared with conventional antipsychotic medications, whereas risperidone was again not associated with an increased odds of hyperlipidemia compared with conventional agents. The **Figure** summarizes the odds ratios for olanzapine and risperidone exposure relative to the 2 comparison groups.

COMMENT

Our analyses demonstrate an increased risk of hyperlipidemia among olanzapine-treated patients, adjusted for demographic risk factors and concomitant medications and disorders. Subjects prescribed olanzapine exhibited more than a 3-fold increase in the odds of developing hyperlipidemia compared with subjects prescribed conventional antipsychotic medications, and olanzapine exposure was associated with a nearly 5-fold increase in the odds of developing hyperlipidemia compared with schizophrenic patients not prescribed antipsychotic agents. Conventional antipsychotic exposure was also associated with an increased odds of developing hyperlipidemia, although to a lesser extent than olanzapine. In contrast, exposure to risperidone was not associated with an increased odds of hyperlipidemia in any of the models. These results corroborate the association of olanzapine with elevated lipid levels seen in several case studies[7,8,16] and 1

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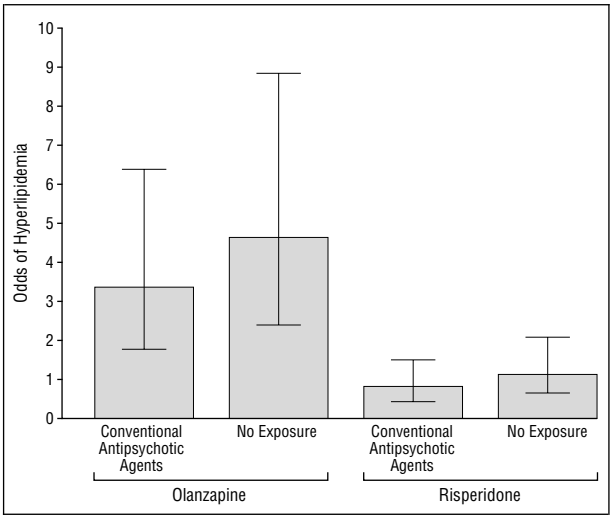
comparative study.[6] However, to our knowledge, the magnitude of effect seen in this study has not been observed previously. Similarly, the observation of no association between risperidone use and hyperlipidemia is consistent with other reports[6,9] from the literature.

The clinical relevance of cholesterol and triglyceride elevations has been repeatedly demonstrated for general populations,[11-14] and therapies focus on aggressive interventions to modify lipid levels.[15,29] The British, the European, and, more recently, the US Adult Treatment Panel III guidelines have quantified the risk for cardiovascular events associated with an increased cholesterol level; these guidelines recommend lifestyle and pharmacological therapies to reduce risk. Hypertriglyceridemia was also shown to be a strong risk factor for ischemic heart disease independent of other major risk factors, including high-density lipoprotein cholesterol level.[30] In addition, the spectrum of cardiovascular risk factors defined as the metabolic syndrome or syndrome X has also received considerable attention among clinicians in recent years.[31] The clinical relevance of the syndrome is related to the combination of morbid factors that results in diabetes mellitus and subsequent cardiovascular disease. Furthermore, many of the risk factors associated with the metabolic syndrome, such as obesity, impaired glucose homeostasis, and dyslipidemia, including hypertriglyceridemia, may be exacerbated by exposure to olanzapine.

The increased risk of hyperlipidemia among subjects prescribed olanzapine in the present analysis raises serious questions about the risk-benefit ratio for olanzapine use among schizophrenic patients. This is particularly true because schizophrenic patients also tend to exhibit other major risk factors for cardiovascular events, such as smoking,[23] a sedentary lifestyle,[32] diabetes mellitus,[33-36] and weight gain.[2]

There are several limitations to the present study. Antipsychotic drug exposure was inferred from automated prescription data, and it is not possible to determine whether patients actually obtained or consumed the prescribed medication. Patient-specific data are limited to those recorded in the automated database. However, one study[37] showed that 95% of all known GPRD prescriptions and 74% of all consultations were recorded in the computer records compared with 42% and 75% in written records, respectively. There is no direct information on the severity of schizophrenia, race, social class, or weight gain. We are, thus, unable to adjust for the potential confounding effect of these variables. It was not possible to study the association between clozapine and hyperlipidemia, because clozapine therapy must be initiated during hospitalization[26]; this information is not available.

Surveillance bias is a possibility if olanzapine-treated patients were more likely to have lipid tests ordered than patients receiving other newer or conventional antipsychotic agents. If this were so, then the proportion of patients undergoing laboratory tests would be higher in olanzapine-treated patients vs others. We examined this issue by measuring the proportion of patients undergoing lipid tests within 3 months before the index date using the GPRD prevention and medical records. We found no differences in the percentage of patients treated with olanzapine, risperidone, and conventional agents who had a plasma lipid or cholesterol test ordered. Furthermore, we calculated the number of patients for whom a test for cholesterol or lipid levels was ordered within 6 months of their first prescription for antipsychotic agents. Again, there were no differences in the proportion of tests ordered according to specific agent. These data indicate that physicians were not more likely to monitor the lipid levels of patients taking the newer antipsychotic agents.



Adjusted odds of hyperlipidemia in patients exposed to olanzapine and risperidone relative to different comparison groups. Data, given as odds ratios and 95% confidence intervals, were adjusted for age, sex, index year, length of follow-up, β-blockers, combination β-blockers and thiazide diuretics, corticosteroids, thiazide diuretics, female sex hormones, valproate sodium, hypothyroidism, and diabetes mellitus.

The diagnosis of hyperlipidemia included a diagnosis of increased cholesterol or triglyceride levels. Because of lack of laboratory data on high- or low-density lipoprotein cholesterol, total cholesterol, and triglyceride levels, it was not possible in this study to determine which specific lipoprotein fraction is elevated.

A recent study by Primatesta and Poulter[38] found that at least 25% of English adults have adverse lipid profiles; of these adults, only 2% use a lipid-lowering agent. Among those treated, only 10% are effectively controlled to target low-density lipoprotein cholesterol levels.[38] The prevalence of obesity among schizophrenic patients suggests that they are at considerable risk for hypercholesterolemia.[31] Brown et al[23] found that the schizophrenic patient's diet is typically higher in fat and lower in fiber compared with the general population. In addition, compliance with lipid-lowering therapy may prove more problematic in these patients. Therefore, the effect of antipsychotic drug therapy on the odds of hyperlipidemia observed in this study may be underestimated.

It can be concluded from this study that exposure to olanzapine is associated with clinically important increased odds of hyperlipidemia, after adjusting for other factors, in schizophrenic patients. The potential cardiovascular consequences of olanzapine therapy, and its association with the metabolic syndrome, warrant serious consideration of its risk-benefit ratio by treating physicians.

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Corresponding author: Carol E. Koro, PhD, School of Pharmacy, University of Maryland, 506 W Fayette St, Suite 201, Baltimore, MD 21201 (e-mail: ckoro001@umaryland.edu).

REFERENCES

1. Kane JM. Pharmacologic treatment of schizophrenia. *Biol Psychiatry.* 1999;46:1396-1408.
2. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999;156:1686-1696.
3. Popli AP, Konicki PE, Jurjus GJ, Fuller MA, Jaskiw GE. Clozapine and associated diabetes mellitus. *J Clin Psychiatry.* 1997;58:108-111.
4. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. *Biol Psychiatry.* 1998;44:778-783.
5. Hendersen DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schenfeld DA, Goff DC. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry.* 2000;157:975-981.
6. Meyer JM. A retrospective comparison of lipid, glucose, and weight changes at one year between olanzapine- and risperidone-treated inpatients [abstract]. *Biol Psychiatry.* 2001;49:536.
7. Sheitman BB, Bird PM, Binz W, Akinli L, Sanchez C. Olanzapine-induced elevation of plasma triglyceride levels. *Am J Psychiatry.* 1999;156:1471-1472.
8. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry.* 1999;60:767-770.
9. Ghaeli P, Dufresne RL. Elevated serum triglycerides with clozapine resolved with risperidone in four patients. *Pharmacotherapy.* 1999;19:1099-1101.
10. Lieberman JA, Golden R, Stroup S, McEvoy J. Drugs of the psychopharmacological revolution in clinical psychiatry. *Psychiatr Serv.* 2000;51:1254-1258.
11. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. *Ann Intern Med.* 1971;74:1-12.
12. Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease, and death: the Framingham study. *Arch Intern Med.* 1981;141:1128-1131.
13. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham study. *JAMA.* 1986;256:2835-2838.
14. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. *Lancet.* 1986;2:933-936.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
16. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 2000;61:742-749.
17. Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol.* 2001;21:369-374.
18. Modai I, Valevski A, Dror S, Weizman A. Serum cholesterol and suicidal tendencies in psychiatric inpatients. *J Clin Psychiatry.* 1994;55:252-254.
19. Boston PF, Dursun SM, Reveley MA. Cholesterol and mental disorder. *Br J Psychiatry.* 1996;169:682-689.
20. Boston PF, Dursun SM, Reveley MA. Serum cholesterol and treatment resistance in schizophrenia. *Biol Psychiatry.* 1996;40:542-543.
21. Saugstad LF, Odegard O. Mortality in psychiatric hospitals in Norway 1950-1974. *Acta Psychiatr Scand.* 1979;59:431-447.
22. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. *Br J Psychiatry.* 1993;163:183-189.
23. Brown S, Birtwistle J, Poe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychol Med.* 1999;29:697-701.
24. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet.* 1997;350:1097-1099.
25. Lawson DH, Sherman V, Hollowell J, for the Scientific and Ethical Advisory Group. The General Practice Research Database. *QJM.* 1998;91:445-452.
26. *British National Formulary 38.* London, England: British Medical Association, Pharmaceutical Society of Great Britain; 1999.
27. Kleinbaum G. Analysis of matched data using logistic regression. In: *Logistic Regression: A Self-learning Text.* New York, NY: Springer Publishing Co Inc; 1994:60-81.
28. Schaefer EJ. Diagnosis and management of lipoprotein disorders. In: Rifkind BM, ed. *Drug Treatment of Hyperlipidemia.* New York, NY: Marcel Dekker Inc; 1991:17-52.
29. British Cardiac Society, British Hyperlipidemia Association, and British Hypertension Society. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart.* 1998;80(suppl 2):S1-S29.
30. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation.* 1998;97:1029-1036.
31. Grundy MS. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation.* 1997;95:1-4.
32. Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Hyland B. Cardiovascular risk factors for people with mental illness. *Aust N Z J Psychiatry.* 2001;35:196-202.
33. McKee HA, D'Arcy PF, Wilson PJ. Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharm.* 1986;11:297-299.
34. Tabata H, Kikuoka M, Kikuoka H, Bessho H, Hirayama J, Hanabusa T, Kubo K, Momotani Y, Sanke T, Nanjo K, Higaehl Y, Miyamura K. Characteristics of diabetes mellitus in schizophrenic patients. *J Med Assoc Thai.* 1987;70(suppl):90-93.
35. Mukherjee S, Decina P, Bocola V, Saracini F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry.* 1996;37:68-73.
36. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. *Schizophr Bull.* 1996;22:421-430.
37. Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis on a general practice computer system. *BMJ.* 1993;307:32-34.
38. Primatesta P, Poulter NR. Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey. *BMJ.* 2000;321:1322-1325.

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