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

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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 12,688 incident cases of hyperlipidemia in the cohort, matched to 75,986 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.
ton et al20 demonstrated that cholesterol levels were higher than patients with unipolar depression. Bos-

peripidemia warrants a more scientifically comprehen-

 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 al18 showed that pa-

The association between treatment with newer anti-

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 schizophre

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METHODOLOGY

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 pa-

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 re-

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 prescrip-

SELECTION OF CASE AND CONTROL SUBJECTS

Cases

For each patient defined as a case, 6 controls with study peri-

Controls

For each patient defined as a case, 6 controls with study peri-

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. 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 was defined 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. 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. Disorders associated with secondary hyperlipidemia, including hypothyroidism and diabetes mellitus, were also adjusted for in the analysis.

**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, 1,429 (7%) contributed less than 3 months of follow-up and were excluded. Another 1,127 (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.

**COHORT ANALYSES**

During a mean ± SD follow-up of 4.07 ± 2.80 years, a total of 1,269 hyperlipidemia cases (7%) were identified; 205 case identifications were based on a diagnosis of hyperlipidemia only, 1,171 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 (93% 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 1. Descriptive Statistics of the Overall Cohort and the Case and Control Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Cohort (n = 18,309)</th>
<th>Case Patients (n = 1266)</th>
<th>Control Patients (n = 7098)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>447 (2)</td>
<td>3 (&lt;1)</td>
<td>11 (&lt;1)</td>
</tr>
<tr>
<td>20-44</td>
<td>7404 (40)</td>
<td>333 (26)</td>
<td>2841 (27)</td>
</tr>
<tr>
<td>45-65</td>
<td>5400 (29)</td>
<td>506 (40)</td>
<td>2985 (39)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>5058 (22)</td>
<td>426 (34)</td>
<td>2561 (34)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9002 (49)</td>
<td>822 (65)</td>
<td>4925 (65)</td>
</tr>
<tr>
<td>Female</td>
<td>9307 (51)</td>
<td>446 (35)</td>
<td>2673 (35)</td>
</tr>
<tr>
<td>Exposure to antipsychotic drugs at any point during follow-up†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondepot</td>
<td>15,505 (85)</td>
<td>1054 (83)</td>
<td>5696 (75)</td>
</tr>
<tr>
<td>Depot</td>
<td>4067 (22)</td>
<td>273 (22)</td>
<td>1608 (21)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>853 (5)</td>
<td>23 (2)</td>
<td>65 (&lt;1)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1453 (8)</td>
<td>34 (3)</td>
<td>205 (3)</td>
</tr>
<tr>
<td>Other newer agents</td>
<td>501 (3)</td>
<td>15 (1)</td>
<td>91 (1)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding.
†Categories are not mutually exclusive.
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 56.6 ± 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.

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*  

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

*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*  

<table>
<thead>
<tr>
<th>Antipsychotic Drug Exposure†</th>
<th>Case Patients (n = 1268)‡</th>
<th>Control Patients (n = 7598)§</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)§</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional antipsychotic agents</td>
<td>807 (64)</td>
<td>4320 (57)</td>
<td></td>
<td>.</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>16 (1)</td>
<td>27 (&lt;1)</td>
<td>3.24 (1.71-6.15)</td>
<td>&lt;.001</td>
<td>3.36 (1.77-6.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Risperidone</td>
<td>12 (1)</td>
<td>79 (1)</td>
<td>0.81 (0.43-1.51)</td>
<td>.50</td>
<td>0.81 (0.44-1.52)</td>
<td>.52</td>
</tr>
<tr>
<td>Other newer antipsychotic agents</td>
<td>5 (&lt;1)</td>
<td>17 (&lt;1)</td>
<td>1.57 (0.58-4.26)</td>
<td>.38</td>
<td>1.48 (0.54-4.04)</td>
<td>.45</td>
</tr>
<tr>
<td>None of the above agents</td>
<td>413 (33)</td>
<td>3089 (41)</td>
<td>0.72 (0.63-0.81)</td>
<td>&lt;.001</td>
<td>0.72 (0.64-0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Combination antipsychotic agents†</td>
<td>15 (1)</td>
<td>66 (&lt;1)</td>
<td>1.20 (0.68-2.14)</td>
<td>.53</td>
<td>1.18 (0.86-2.10)</td>
<td>.58</td>
</tr>
</tbody>
</table>

*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.

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.
comparative study. 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 from the literature.

The clinical relevance of cholesterol and triglyceride elevations has been repeatedly demonstrated for general populations, and therapies focus on aggressive interventions to modify lipid levels. 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. Hypertriglycerideremia 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. 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. 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 hypertriglycerideremia, 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, a sedentary lifestyle, diabetes mellitus, and weight gain. 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 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; 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.

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 Primatesa and Poulter 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. The prevalence of obesity among schizophrenic patients suggests that they are at considerable risk for hypercholesterolemia. Brown et al 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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REFERENCES