Hyperlipidemia in Persons Using Antipsychotic Medication: A General Population–Based Birth Cohort Study

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Background: Shortly after phenothiazines were introduced, they were found to elevate serum triglyceride and total cholesterol levels. During the past decade, an increasing body of literature has also documented this effect in atypical antipsychotics. Previous studies of antipsychotic-associated hyperlipidemias are based on clinical samples, mostly from case series. We studied the prevalence of hyperlipidemia in subjects who did and did not take antipsychotic medication in a prospective, general population–based birth cohort.

Method: The study sample consisted of 5654 members of the unselected Northern Finland 1966 Birth Cohort who participated in the 1997–1998 clinical examination at 31 years of age. Blood samples were taken after an overnight fast, and serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were determined. Health habits and other possible correlates for hyperlipidemia were assessed using a questionnaire. The sample was analyzed in 4 categories according to use of antipsychotic medication: (1) atypical, (2) typical, (3) atypical and typical (for the 3 antipsychotic categories, total N = 45), and (4) no antipsychotic medication (N = 5609). Nonparametric tests and multiple logistic regression analysis were used to measure the effect of antipsychotics on serum lipids.

Results: High lipid levels were found in persons treated with both atypical and typical medication (mean total cholesterol = 233 mg/dL, mean triglycerides = 163 mg/dL). Mean total cholesterol and triglycerides were also high in subjects who used only typical medication (215 mg/dL and 148 mg/dL, respectively). The prevalence of hypercholesterolemia, high LDL cholesterol, and hypertriglyceridemia was high in persons using antipsychotic medication (31.1%, 20.0%, and 22.2%, respectively) compared with persons not using such medication (12.2%, 10.2%, and 7.0%, respectively). After we adjusted for risk factors for hyperlipidemia (sex, diet, waist circumference, physical exercise, smoking, and alcohol consumption), the results of logistic regression analysis showed that in persons treated with antipsychotic medication the risk of hypercholesterolemia was 2.8 (95% CI = 1.4 to 5.6); of hypertriglyceridemia, 2.3 (95% CI = 1.0 to 5.4); and of high LDL cholesterol, 1.6 (95% CI = 0.7 to 3.5).

Conclusion: Lipid levels in subjects who used both atypical and typical medication and those who used only typical medication were high even in young age. As these persons are at special risk of hyperlipidemia, their lipid levels should be regularly monitored, and a cholesterol-lowering diet, as well as medication, should be considered. The results indicate an elevated risk of hyperlipidemia in persons using antipsychotic medication independent of the other risk factors assessed.

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The elevating effect of antipsychotics on serum lipids is well documented in several clinically based studies involving both typical[1,2] and atypical neuroleptics.[3–10] Patients with schizophrenia also show a tendency toward weight gain.[11,12] Previous studies of antipsychotic-associated hyperlipidemias are based on clinical samples; however, these are mostly from case series.

We compared total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels in persons who did and did not use antipsychotic medication in a prospective, geographically defined birth cohort at 31 years of age. In addition, we report the prevalence and risk of hyperlipidemia, taking into account several known risk factors for hyperlipidemia.

METHOD

The Northern Finland 1966 Birth Cohort is an unselected, general-population birth cohort ascertained

during mid-pregnancy. The cohort comprises 12,058 live-born children in the provinces of Lapland and Oulu with an expected delivery date during 1966.[13] Permission to gather data was obtained from the Ministry of Social Affairs and Health (Helsinki, Finland). The study was reviewed by the Ethics Committee of the Faculty of Medicine of the University of Oulu (Oulu, Finland).

In 1997, at the age of 31 years, 8463 of the members of the cohort who were living in northern Finland or in the area of the capital (Helsinki) were invited to participate in a clinical examination. After complete description of the study to the subjects, written informed consent was obtained. Of those invited, 5654 subjects (67%) participated in the present study and gave written informed consent.

The participants were asked to fast overnight before coming to the clinical examination, where their weight, height, and waist circumference were measured; body mass index (BMI) was calculated; and blood samples were taken.

Serum total cholesterol, HDL cholesterol, and triglyceride levels were determined by enzymatic methods using a Hitachi 911 Clinical Chemistry Analyzer. To translate SI units into conventional U.S. values, the following conversion factors were used: for converting mmol/L to mg/dL, cholesterol values were divided by 0.02586 and triglycerides were divided by 0.01129. LDL cholesterol was calculated using the Friedewald formula if serum triglyceride level was < 354.3 mg/dL[14]; if triglyceride level was ≥ 354.3 mg/dL, LDL cholesterol was determined by precipitating low-density lipoproteins with heparin, measuring cholesterol in the liquid phase, and subtracting it from total cholesterol. Hypercholesterolemia was defined as total cholesterol of ≥ 240 mg/dL; hypertriglyceridemia, as triglyceride level of ≥ 200 mg/dL; and high LDL cholesterol, as LDL of ≥ 160 mg/dL.[15]

The participants also completed a questionnaire including 89 items concerning, e.g., body weight and height, diet, physical exercise, smoking, alcohol consumption, and medication. In cases of incomplete answers, psychiatric medication treatment at the time of blood sampling was identified by referring to case records. None of the subjects using antipsychotic medication reported taking any lipid-lowering medication. Since nonfasting triglyceride values differ significantly from fasting values,[16] study subjects with nonfasting blood samples were excluded.

Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. In men, waist circumference of 100 cm and under was defined as normal and over 100 cm as obese, and in women, 90 cm was defined as the cutoff point.

Diet was classified as unhealthy when it included daily or almost daily consumption of sausages and consumption of rye bread or crisp bread, fresh vegetables and salads, and berries or fruit twice a week or less often, with 1 point being assigned for each of these items, so that a sum of 4 to 5 points indicated an unhealthy diet and 3 or fewer, a healthy diet.[17]

Subjects were considered smokers if they reported smoking at least occasionally, even if irregularly. Alcohol use questions measured the average frequency of consumption of beer, wine, and spirits during the last year and the usual amount of each consumed on 1 occasion. The amount of alcohol consumed per day was calculated, and the validity of questions was ascertained.[17] Subjects were thereby divided into light (≤ 15 g per day) and moderate (> 15 g per day) drinkers. Physical activity was recorded in 2 categories (regular vs. nonregular). Regular physical activity was defined as consisting of exercise at least 2 times per week that makes the person become breathless and sweat at least mildly.

Statistical Methods

Because data were nonnormally distributed, all comparisons were made using nonparametric tests. The significance of differences in serum lipid levels between the study groups according to antipsychotic medication was tested with nonparametric 1-way Kruskal-Wallis analysis of variance, and pairwise comparisons were tested with the Mann-Whitney U test.

The Pearson chi-square test was used to test the statistical significance of the relationship between antipsychotic medication use and hyperlipidemia. Multiple logistic regression analysis with adjustment for waist circumference (> 100 cm for men, > 90 cm for women/normal), diet (unhealthy diet: yes/no), smoking (yes/no), alcohol consumption (moderate/light drinkers), and physical activity (yes/no) was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Confounders were selected based on previous knowledge of the risk factors for hyperlipidemia. The statistical analyses were performed using SAS system version 8.2 for Windows (SAS Institute Inc., Cary, N.C.).

RESULTS

Forty-five subjects reported that they used antipsychotic medication (58% had a DSM-III-R diagnosis of schizophrenia, 13% had other psychosis, and 29% were without a hospital-treated diagnosis of psychosis), and 5609 reported that they did not. Of the 45 subjects using antipsychotic medication, 6 (13%) were using atypical antipsychotic medication; 32 (71%), typical; and 7 (16%), both atypical and typical.

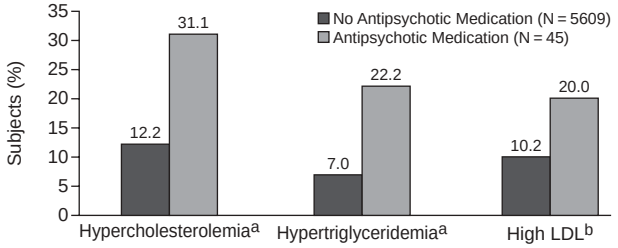
We found high lipid levels in persons who used both atypical and typical medication (mean total cholesterol = 233 mg/dL, mean triglycerides = 163 mg/dL). Mean total cholesterol and triglycerides were also high in the subjects who used only typical medication (215 mg/dL and 148 mg/dL, respectively) (Table 1).

Table 1. Serum Total Cholesterol, HDL and LDL Cholesterol, and Triglycerides According to Antipsychotic Medication[a]

	Atypical (N = 6)[b]		Typical (N = 32)[c]		Atypical and Typical (N = 7)[d]		No Antipsychotic Medication (N = 5609)		Atypical vs No Medication, p Value	Typical vs No Medication, p Value	Atypical and Typical vs No Medication, p Value
Variable	Median	Mean	Median	Mean	Median	Mean	Median	Mean			
Total cholesterol	212	206	214	215	240	233	193	196	.3066	.0071	.0234
HDL cholesterol	58	56	54	54	58	61	59	60	.6287	.0054	.8914
LDL cholesterol	133	126	124	132	147	140	87	104	.3226	.0064	.1016
Triglycerides	110	119	124	148	184	163	87	104	.4300	.0039	.0103

[a]Serum levels expressed as mg/dL.
[b]Medications were as follows: clozapine, N = 4; risperidone, N = 2.
[c]Medications were as follows: thioridazine, N = 7; perphenazine, N = 7; haloperidol, N = 4; chlorprothixene, N = 3; zuclopenthixol, N = 2; pericyazine, N = 1; chlorpromazine, N = 1; levomepromazine, N = 1; haloperidol and thioridazine, N = 1; perphenazine and chlorpromazine, N = 1; perphenazine and thioridazine, N = 2; haloperidol, thioridazine, and fluphenazine, N = 1; sulpiride, zuclopenthixol, and levomepromazine, N = 1.
[d]Medications were as follows: clozapine and haloperidol, N = 1; risperidone and thioridazine, N = 1; clozapine and thioridazine, N = 1; risperidone and chlorprothixene, N = 1; clozapine and thioridazine, N = 1; olanzapine and chlorpromazine, N = 1; risperidone and chlorpromazine, N = 1.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Figure 1. Prevalence of Hypercholesterolemia, Hypertriglyceridemia, and High LDL Cholesterol in Subjects Who Did and Did Not Use Antipsychotic Medication



[a]$p < .001$.
[b]$p = .03$.
Abbreviation: LDL = low-density lipoprotein.

Persons using antipsychotic medication had a higher prevalence of hypercholesterolemia (31.1%) and hypertriglyceridemia (22.2%) than those not using such medication (12.2% and 7.0%, respectively; $p < .001$ for both). In addition, high LDL cholesterol was more prevalent in subjects using antipsychotic medication (20.0%) than in those who were not (10.2%, $p = .03$) (Figure 1).

After adjusting for sex, diet, waist circumference, physical exercise, smoking, and alcohol consumption, which are risk factors for hyperlipidemia, the results of logistic regression analysis showed that in persons using antipsychotic medication the risk of hypercholesterolemia was 2.8 (95% CI = 1.4 to 5.6); of hypertriglyceridemia, 2.3 (95% CI = 1.0 to 5.4); and of high LDL cholesterol, 1.6 (95% CI = 0.7 to 3.5).

DISCUSSION

We found a high prevalence of hyperlipidemias in subjects using antipsychotic medication independent of other known risk factors for hyperlipidemia. The mechanism for the elevation in lipid levels is somewhat obscure, but it has been previously attributed to weight gain associated with use of these compounds. Accumulation of fat in the waist enhances release of free fatty acids in the liver and accelerates liver triglyceride synthesis and very-low-density lipoprotein secretion. Increases in free fatty acid concentrations may also inhibit metabolism of glucose, especially in muscle tissue, resulting in impaired glucose tolerance and type 2 diabetes.[18] In our study, however, the elevation was not related to weight or BMI, suggesting that other mechanisms may also contribute.

Atypical neuroleptics are potent antagonists at both 5-HT_{2A} and 5-HT_{2C} receptors, with the latter implicated in hyperphagia and the subsequent development of obesity and adult-onset diabetes; however, chronic 5-HT_{2C} blockade does not seem to directly induce hyperlipidemia.[5]

Although there are general recommendations on the treatment of hyperlipidemia,[15] there are no special recommendations for persons using antipsychotic medication. Diet and physical exercise are accepted strategies, but are not easy to carry out. Persons with lipid metabolism disorders can receive diet therapy and be treated with, for example, statins as well. Results of open trials show that triglyceride levels in patients who received gemfibrozil or pravastatin did not increase during treatment with olanzapine.[3] Most statins are metabolized through the cytochrome P450 3A4 enzyme, which may result in interactions with higher doses of second-generation antipsychotics such as clozapine, olanzapine, and quetiapine that also in part use this pathway.[19] Attempts can also be made to reduce the adverse effects of lipid metabolism disorders by means of treatment with low-dose acetylsalicylic acid medication. It is important to remember that even if the initial dosage to relieve an acute symptom episode exceeds the recommendations for the maintenance therapy, efforts should be made to reduce the dosage gradually. Because there may be a relationship between the dose of antipsychotic agent and weight gain,[20] the lowest effective dose should be used.

The number of persons using antipsychotic medication was limited, but, as far as we know, ours is the first

population-based study concerning lipid levels among subjects who do and do not use antipsychotic medication. Further studies are needed to confirm our findings regarding the differences between neuroleptics. Our longitudinal data are unique and extensive, representing a geographically well-defined and unselected general population. High rates of follow-up over 3 decades and the use of record linkage minimized selection, information, and recall biases. We wonder, however, if persons who were worried about their health (e.g., due to obesity or other risk factors for hyperlipidemia) were more likely to participate, with less motivated subjects inhibited from participation by factors like positive or negative symptoms.

Diet, alcohol consumption, and other health parameters were ascertained as part of the larger structured postal questionnaire, which study subjects returned at the clinical examination. This method is commonly used in Finnish population-based surveys of health behavior[21,22] and has been found to be valid.[23,24] In addition, to examine the validity of variables measuring unhealthy diet and alcohol consumption in the Northern Finland 1966 Birth Cohort, immediately after the health examination a subsample of 196 participating cohort members recorded for 7 days, all drinks, including alcohol beverages, and foods consumed, with amounts and a detailed description of the food/drink consumed. Food and drink records were compared with responses to questions in the questionnaire measuring alcohol use and diet and then analyzed with the SPSS computer program. The authors concluded that self-reported questions measuring alcohol use and unhealthy diet were sufficiently valid.[17]

In conclusion, we found high lipid levels in persons using antipsychotic medication. A recent study demonstrated that patients are infrequently monitored for dyslipidemias,[25] and schizophrenia sufferers have higher than expected mortality from diseases of the circulatory system.[26] The combination of conventional and atypical neuroleptics should be very carefully considered, and specifically in these cases lipid levels should be monitored regularly.

Finally, our findings highlight the importance of regular monitoring of lipid levels in persons using antipsychotic medication. If hyperlipidemia develops, lipid-lowering medication should be considered in addition to weight loss (5%–10%) if a patient is obese.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), fluphenazine (Prolixin, Permitil, and others), gemfibrozil (Lopid and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), pravastatin (Pravigard Pac, Pravachol), quetiapine (Seroquel), risperidone (Risperdal).

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