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Metabolic Abnormalities Related to Treatment With Selective Serotonin Reuptake Inhibitors in Patients With Schizophrenia or Bipolar Disorder

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Objective: The aim of the present study was to examine the effect of selective serotonin reuptake inhibitors (SSRIs) on cardiovascular risk factors in patients with schizophrenia or bipolar disorder.

Method: We used data from a cross-sectional study on 1301 patients with schizophrenia or bipolar disorder, of whom 280 were treated with SSRIs. The primary outcome variable was the serum concentration of total cholesterol. Secondary outcome variables were low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglyceride and glucose levels, body mass index, waist circumference, and systolic and diastolic blood pressure.

Results: After adjusting for potential confounders, an SSRI serum concentration in the middle of the reference interval was associated with an increase of the total cholesterol level by 14.56 mg/dL (95% confidence interval (CI) 5.27–23.85 mg/dL, $P = 0.002$), the LDL cholesterol level by 8.50 mg/dL (CI 0.22–16.77 mg/dL, $P = 0.044$), the triglyceride level by 46.49 mg/dL (CI 26.53–66.46 mg/dL, $P < 0.001$) and the occurrence of the metabolic syndrome by a factor of 2.10 (CI 1.21–3.62, $P = 0.008$). There were also significant associations between the SSRI dose and total cholesterol and LDL cholesterol levels.

Conclusions: This study is the first to reveal significant associations between SSRI use and metabolic abnormalities in patients with schizophrenia or bipolar disorder. Although the effects were statistically significant, alterations were small. Thus, the clinical impact of the findings is most likely limited.

Key Words: antidepressants, selective serotonin reuptake inhibitors, metabolic abnormalities, schizophrenia, bipolar disorder, antipsychotics

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Patients with severe mental illnesses have a higher morbidity and mortality than the general population[1–4] mainly caused by the occurrence of cardiovascular diseases.[5,6] Patients with schizophrenia or bipolar disorder have an increased risk of metabolic disturbances,[7–11] which may be caused by factors associated with the underlying disease as such,[5,12] lifestyle factors, and treatment with psychotropic drugs of which antipsychotics and mood stabilizers are the groups most often studied.[13–15] Antidepressants are not the primary therapeutic agents for schizophrenia or bipolar disorder but are frequently used in these patient groups in clinical practice.[16,17]

According to a meta-analysis, use of antidepressants as a group does not increase the risk of metabolic disturbances in patients with depression.[18] However, several studies have revealed associations between use of selective serotonin reuptake inhibitors (SSRIs) and various elements of the metabolic syndrome, such as increased levels of total cholesterol[19–22] and low-density lipoprotein cholesterol (LDL cholesterol).[23,24] On the other hand, no consistent effects on high-density lipoprotein cholesterol (HDL cholesterol)[21,22,24] and triglyceride levels have been found.[22,24]

Two studies have examined the association between SSRI use and the occurrence of factors defining the metabolic syndrome, according to the National Cholesterol Education Program Adult Treatment Panel-III criteria.[25] In a general community cross-sectional health survey, Raeder et al[26] reported an association between the use of SSRIs and hypercholesterolemia and general and abdominal obesity. A prospective study in drug-naïve patients with generalized anxiety disorder reported a correlation between use of paroxetine and increases in body weight, body mass index (BMI), waist circumference, fasting glucose, total cholesterol, LDL cholesterol, and triglyceride levels.[27] Citalopram and escitalopram were associated with increased triglyceride levels, and sertraline with increased total cholesterol levels. In contrast, fluoxetine was associated with a reduction of body weight, total cholesterol, and triglyceride levels.

The effects of SSRIs on metabolic variables have been studied in patients with depressive and anxiety disorders, but to the best of our knowledge, there has not been published any such studies in patients with schizophrenia or bipolar disorders. We consider this an important topic because these patients due to their underlying disease have an increased risk of metabolic disturbances,[7–11] potentially making them even more susceptible for such adverse reactions caused by SSRIs.

The aim of the present study was to examine the effect of the SSRIs escitalopram, citalopram, sertraline, fluoxetine, and paroxetine on various cardiovascular risk factors in patients with schizophrenia or bipolar disorder.

MATERIALS AND METHODS

Subjects

The Thematically Organized Psychosis (TOP) study at the Oslo University in Norway provides a large, well-described

sample of patients with schizophrenia spectrum and bipolar disorders. Inclusion criteria consist of meeting DSM-IV criteria for schizophrenia or bipolar disorder, being 18 to 65 years, and being willing and able to give a written, informed consent of participation. A thorough description of the study has been published previously.[9] The TOP study is an ongoing study consecutively including new patients, and at the time of data extraction for the present study, 1301 patients were available (Table 1). The study was approved by the Regional Committee for Medical and Health Research Ethics South East, Norway and by the Norwegian Data Protection Agency. The presence of some cardiovascular risk factors in a subgroup of the TOP sample has been described earlier, primarily related to the type of the underlying disorder.[9]

Variables

As exposure variables for SSRI intake, the daily dose and the serum concentration of the drug were used. To be able to study SSRIs as a group, the daily dose for each subject was expressed as the number of defined daily doses (DDD) taken (10 mg escitalopram; 20 mg citalopram, fluoxetine, and paroxetine; and 50 mg sertraline).[28] The analyses of the SSRI serum concentrations were performed at the Department of Clinical Pharmacology, St. Olavs University Hospital by means of previously published analytical methods.[29] The concentrations of the various SSRIs were related to the reference interval of the respective drug[30] and expressed as the measured concentration of the SSRI divided by the middle value of the reference interval for the same drug, ie, 80 ng/mL (reference interval, 50–110 ng/mL) for citalopram, 48 ng/mL (reference interval, 15–80 ng/mL) for escitalopram, 310 ng/mL (reference interval, 120–500 ng/mL) for fluoxetine plus the active metabolite norfluoxetine, 75 ng/mL (reference interval, 30–120 ng/mL) for paroxetine, and 80 ng/mL (reference interval, 10–150 ng/mL) for sertraline. Because of the more definite metabolic effects reported after uses of paroxetine and fluoxetine,[22–24,26,27,31–33] subanalyses were performed after excluding these drugs.

The serum concentration of total cholesterol was chosen as the primary outcome variable because this is considered one of the most important factors related to cardiovascular health.[34] Secondary outcome variables were LDL cholesterol, HDL cholesterol, triglyceride and glucose levels, BMI, waist circumference, and diastolic and systolic blood pressure. Fasting serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose were analyzed at the Department of Clinical Chemistry, Oslo University Hospital according to standard methods using an Integra 800 instrument (Roche Diagnostics, Basel, Switzerland). Resting blood pressure was measured manually by a physician using a sphygmomanometer (Boso, Jungingen, Germany). Each individual's height and waist circumference was measured with standard methods, body weight was weighed on calibrated digital weights (Soehnle, Nassau, Germany) with light clothes on, and BMI (kg/m^2) was calculated accordingly.

The metabolic syndrome was defined as the presence of 3 or more of the following 5 variables surpassing predefined cutoff levels according to the National Cholesterol Education Program Adult Treatment Panel-III criteria[25]: waist circumference, HDL cholesterol levels, triglyceride levels, glucose levels, and blood pressure. When defining the occurrence of the metabolic syndrome, the medication criteria were not taken into account because there was only information available for psychotropic medications and not for drugs used for somatic conditions.

Statistical Analyses

Missing values were handled as follows: first, missing serum concentrations for the SSRIs (39 for escitalopram, 8 for citalopram, 6 for sertraline and fluoxetine, and 1 for paroxetine) were imputed by single imputation using the expectation

TABLE 1. Use of SSRIs Related to Demographic Variables, Diagnosis and Outcome Among 1301 Patients Included in the Study, Based on Complete Cases

	Numbers Missing	All Patients (N = 1301)	Patients Using SSRIs (N = 280)	Patients Not Using SSRIs (N = 1021)
Age (y)	0	31.7 (10.6)	31.4 (10.7)	31.8 (10.6)
Sex	0			
Males (n)		697 (53.6%)	130 (46.4%)	567 (55.6%)
Females (n)		604 (46.4%)	150 (53.6%)	454 (44.5%)
Diagnosis	0			
Bipolar disorder (n)		433 (33.3%)	111 (39.6%)	322 (31.5%)
Schizophrenia (n)		868 (66.7%)	169 (60.4%)	699 (68.5%)
Outcome				
Total cholesterol (mg/dL)	165	198 (41.8)	205 (44.1)	197 (41.0)
LDL cholesterol (mg/dL)	219	122 (37.1)	126 (40.6)	121 (36.0)
HDL cholesterol (mg/dL)	165	52.7 (16.4)	51.6 (16.5)	53.0 (16.4)
Triglycerides (mg/dL)	168	130 (93.9)	142 (101.9)	127 (91.2)
Glucose (mg/dL)	167	92.8 (20.4)	92.4 (20.4)	93.0 (20.4)
Waist circumference (in)	415	36.2 (5.7)	36.6 (6.2)	36.1 (5.6)
BMI (mg/m^2)	106	26.2 (5.0)	26.6 (5.2)	26.1 (15.6)
Systolic blood pressure (mm Hg)	99	121 (15.4)	120 (14.4)	121 (15.6)
Diastolic blood pressure (mm Hg)	103	77.6 (10.6)	77.4 (10.2)	77.7 (10.72)

In total, 280 patients (21.5%) were using SSRIs and 1021 (78.5%) were not. Values are mean (SD) or n (%) as appropriate. For variables related to symptom severity, lifestyle factors, and use of concomitant medication, see Supplementary Table A, Supplemental Digital Content 1, http://links.lww.com/JCP/A387.

maximization algorithm separately for each of the 5 substances using the number of DDD of the SSRI, age, and sex as predictors. Second, we used multiple imputation to handle other missing values. Sixty-two variables were imputed, and we imputed 100 data sets as recommended by van Buuren.[35] The imputed dataset consisted of variables included in the analyses (see Table 1 and Supplementary Table A, Supplemental Digital Content 1, http://links.lww.com/JCP/A387, where the numbers of missing values for each variable are also found). In addition, the following variables, which were considered additional predictors and were added to enhance the quality of the imputation, but were deemed redundant in the analyses (missing numbers in parentheses): height (n = 96), body weight (n = 104), heart rate (n = 149), Calgary Depression Scale for Schizophrenia (n = 402), use of snuff (n = 61), occurrence of diabetes (n = 0) and use of venlafaxine (n = 0), tricyclic antidepressants (n = 0), other antidepressants (n = 0), topiramate (n = 0), and amphetamine (n = 0). Analyses based on imputations with transformed variables gave implausible results and were discarded; we therefore imputed on untransformed variables as recommended by Rodwell et al.[36]

Linear regression was performed with total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, BMI, waist circumference, and systolic and diastolic blood pressure as dependent variables. Normality of residuals was assessed by visual inspection of Q-Q plots. The assumption of normality was violated in the case of triglycerides and glucose. Triglycerides were transformed logarithmically and glucose inversely. This provided practically the same results as regression with untransformed variables. All results are therefore presented for untransformed variables.

Potential confounders, listed in Supplementary Table B, Supplemental Digital Content 1, http://links.lww.com/JCP/A387, were added in separate analyses one at a time in a hierarchal manner and included in the final analysis. Results are presented unadjusted as well as adjusted for these confounders. A logistic regression was conducted to investigate the effects of SSRI doses and concentrations on the prevalence of metabolic syndrome, with the results presented as odds ratios (ORs).

Two-sided *P* values less than 0.05 were considered statistically significant, and 95% confidence intervals (CI) are reported when relevant. Analyses were performed in SPSS version 21 (IBM, Chicago, Ill).

RESULTS

Of the 1301 patients included, 280 (21.5%) used SSRIs: escitalopram (n = 154), citalopram (n = 51), sertraline (n = 40), fluoxetine (n = 25), paroxetine (n = 8), escitalopram and citalopram (n = 1), and escitalopram and sertraline (n = 1). Demographic and clinical characteristics of the patients are presented in Table 1 and Supplementary Table A, Supplemental Digital Content 1, http://links.lww.com/JCP/A387. In total, 76.4% of the patients treated with SSRIs and 72.7% of the patients not using SSRIs were prescribed antipsychotic drugs.

Results of regression analyses for total cholesterol level related to the dose and the serum concentration of the SSRIs are presented in Table 2. After adjusting for all potential confounders, for each DDD of an SSRI taken per day, the total cholesterol level was increased by 3.94 mg/dL (CI 0.35–7.50 mg/dL, $P = 0.032$). A serum SSRI concentration in the middle of the reference interval was associated with a 14.56 mg/dL (CI 5.27–23.85 mg/dL, $P = 0.002$) increase in total cholesterol level compared with an SSRI concentration of 0 (ie, not using any SSRIs). To visualize the results in absolute terms, the impact of SSRI use related to dose in a 30-year-old woman is presented in Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A388.

Associations with LDL cholesterol, HDL cholesterol, triglycerides, glucose, waist circumference, BMI, and blood pressure are presented in Table 3. The LDL cholesterol association was statistically significant for both SSRI dose and SSRI serum concentration after adjusting for potential confounders. In the cases of triglycerides, associations were significant when related to the SSRI serum concentration but not to the SSRI dose. Adding BMI as a covariate did not affect the outcome variables.

The SSRI serum concentration was significantly associated with occurrence of the metabolic syndrome (unadjusted OR 1.97, CI 1.12–3.27, $P = 0.008$; OR after adjustment for all potential confounders 2.10, CI 1.21–3.62, $P = 0.008$). In contrast, no significant association was found between SSRI dose and the metabolic syndrome (unadjusted OR 1.16, CI 0.79–1.40, $P = 0.100$; adjusted OR 1.16, CI 0.49–1.41, $P = 0.150$).

When excluding patients using fluoxetine and paroxetine, SSRI serum concentrations were still significantly associated with total cholesterol, LDL cholesterol, and triglyceride levels (Supplementary Table C, Supplemental Digital Content 1,

TABLE 2. Linear Regression With Serum Concentrations or Doses of SSRIs as Independent Variables, and Serum Levels of Total Cholesterol (in mg/dL) as Dependent Variable, in 1301 Patients With Bipolar Disorder or Schizophrenia

	Effect on Serum Cholesterol Level (mg/dL)					
	Related to SSRI Serum Concentration*			Related to SSRI Dose†		
	B	CI	*P*	B	CI	*P*
Unadjusted	13.50	3.93–23.07	0.006	3.63	0.00–7.27	0.050
Adjusted for age	13.71	4.56–22.86	0.003	4.02	0.54–7.50	0.024
Adjusted for sex	13.99	4.392–23.58	0.004	3.71	0.08–7.35	0.045
Adjusted for age and sex	14.55	5.83–23.71	0.002	4.18	0.70–7.66	0.019
Adjusted for all potential confounders‡	14.56	5.27–23.85	0.002	3.94	0.35–7.50	0.032

Results are presented as regression coefficients (B) with 95% CI and *P* values.

*The calculated effect is that represented by a serum concentration in the middle of the reference interval for each drug. For details, see "Materials and Methods" section.

†The calculated effect is that represented by a daily dose of 10 mg escitalopram, 20 mg citalopram, 20 mg fluoxetine, 20 mg paroxetine, or 50 mg sertraline.

‡Adjusted for all potential confounders. For details, see "Materials and Methods" section and Supplementary Table B, Supplemental Digital Content 1, http://links.lww.com/JCP/A387.

TABLE 3. Linear Regression With Serum Concentrations or Doses of SSRIs as Independent Variables and Serum Levels of LDL Cholesterol, HDL Cholesterol, Triglycerides, Glucose, Waist Circumference, BMI, or Blood Pressure as Dependent Variables, in 1301 Patients With Bipolar Disorder or Schizophrenia

		Unadjusted			Adjusted*		
Dependent Variable	**Independent Variable**	**B**	**CI**	***P***	**B**	**CI**	***P***
LDL cholesterol (mg/dL)	SSRI serum concentration†	6.19	−2.27–14.64	0.152	**8.50**	**0.22–16.77**	**0.044**
	SSRI dose‡	2.82	−0.39–5.99	0.083	**3.52**	**0.31–6.69**	**0.031**
HDL cholesterol (mg/dL)	SSRI serum concentration†	−1.98	−5.73–1.78	0.302	−3.30	−6.89–0.29	0.071
	SSRI dose‡	−1.08	−2.47–0.35	0.134	−1.12	−2.44–0.23	0.106
Triglycerides (mg/dL)	SSRI serum concentration†	**45.87**	**25.65–66.09**	**<0.001**	**46.49**	**26.53–66.46**	**<0.001**
	SSRI dose‡	**8.41**	**0.89–16.03**	**0.029**	6.38	−1.15–13.99	0.099
Glucose (mg/dL)	SSRI serum concentration†	−2.39	−6.84–2.06	0.293	−3.11	−7.59–1.37	0.173
	SSRI dose‡	−0.76	−2.41–0.92	0.379	−1.00	−2.70–0.70	0.248
Waist circumference (in)	SSRI serum concentration†	0.80	−0.49–2.09	0.225	1.06	−0.15–2.28	0.086
	SSRI dose‡	0.29	−0.15–0.73	0.201	0.33	−0.09–0.75	0.124
BMI (kg/m^2)	SSRI serum concentration†	0.77	−0.26–1.79	0.144	0.74	−0.27–1.75	0.151
	SSRI dose‡	0.28	−0.09–0.66	0.142	0.27	−0.11–0.64	0.161
Systolic blood pressure (mm Hg)	SSRI serum concentration†	−1.43	−4.69–1.84	0.392	−0.27	−3.38–2.83	0.863
	SSRI dose‡	−0.52	−1.71–0.68	0.397	−0.34	−1.49–0.81	0.563
Diastolic blood pressure (mm Hg)	SSRI serum concentration†	0.32	−1.95–2.58	0.784	0.84	−1.32–3.01	0.446
	SSRI dose‡	−0.06	−0.89–0.77	0.888	0.05	−0.75–0.85	0.906

Results are presented as regression coefficients (B) with 95% CI and *P* values. Statistically significant values are displayed in bold.

*Adjusted for all potential confounders. For details, see "Materials and Methods" section and Supplementary Table B, Supplemental Digital Content 1, http://links.lww.com/JCP/A387.

†The calculated effect is that represented by a serum concentration in the middle of the reference interval for each drug. For details, see "Materials and Methods" section.

‡The calculated effect is that represented by a daily dose of 10 mg escitalopram, 20 mg citalopram, 20 mg fluoxetine, 20 mg paroxetine, or 50 mg sertraline.

http://links.lww.com/JCP/A387). In addition, there were significant associations with waist circumference and BMI. Associations between the individual drugs citalopram, escitalopram, and sertraline and the metabolic variables are also presented in Supplementary Table C, Supplemental Digital Content 1, http://links.lww.com/JCP/A387.

DISCUSSION

In this naturalistic study of patients with bipolar disorder or schizophrenia, there were significant associations between SSRI serum concentrations and total cholesterol, LDL cholesterol, and triglyceride levels as well as the risk of the metabolic syndrome. We also found significant associations between SSRI dose and total cholesterol and LDL cholesterol levels.

Our results are mostly in line with previous findings related to SSRI treatment in patients with depression and anxiety.[19–24,26,27] In these studies, effects have been most consistent for total cholesterol and LDL cholesterol. In contrast, effects on triglyceride levels, body weight/BMI, and waist circumference vary across studies. The lack of significant effects on glucose levels and blood pressure in the present study is in line with the findings in previous studies.[26,27]

Subanalyses were performed to investigate potential differences in metabolic disturbances between the individual SSRIs. Paroxetine has been reported to be more strongly associated with metabolic abnormalities than other SSRIs[20,22–24,26,27] and fluoxetine has been found to have beneficial effects related to the metabolic syndrome.[27] We therefore reanalyzed data after excluding these drugs. Our findings for citalopram, escitalopram, and sertraline are partly consistent and partly inconsistent with the results from previous studies.[26,27] These differences can most likely be ascribed to methodological factors, including differences in study design (eg, related to inclusion criteria and follow-up strategies) and statistical issues, such as mass significance and type II errors. It therefore remains unclear whether the subgroup findings reflect true differences between specific SSRIs in various patient groups or are caused by small materials and statistical coincidences.

Some SSRIs have the potential to inhibit the metabolism of certain antipsychotic drugs, thereby increasing the concentration of the antipsychotic drug and possibly also enhancing its effect on metabolic variables. Such pharmacokinetic interactions are most prominent for fluvoxamine combined with clozapine/olanzapine, but exist also, eg, for fluoxetine/paroxetine plus risperidone and fluoxetine/paroxetine plus clozapine.[37] The effects we have found remained, in general, stable irrespective of the specific drug combinations studied. In addition, as numerous SSRI/antipsychotic combinations have been used, most of them with no interacting potential, we consider such an effect to be negligible at the group level. Further testing of possible interaction effects on metabolic variables between SSRIs and antipsychotics is an interesting issue but beyond the scope of this paper.

The fact that we have included the SSRI serum concentration as well as the SSRI dose as exposure variables is considered a strength. Because some effects were related both to SSRI dose and SSRI serum concentration and because the associations generally were stronger when applying the SSRI serum concentration as exposure variable, credibility is added to these associations. The SSRI serum concentration is held to be the criterion standard in terms of exposure because this variable more closely than the dose reflects a drug's pharmacological effect at the site of action in the body. The weaker associations shown by SSRI dose than by SSRI serum concentration are likely to be caused by a combination of variations in adherence and the considerable interindividual

variability in the pharmacokinetics of SSRIs, whereas the SSRI serum concentration bypasses these factors.

We also consider it being a strength that we have been able to include more than 1000 patients with extensive information available from each subject, thereby allowing us to adjust for an array of potential confounding factors. The most important factors with this respect include age, sex, diagnosis, lifestyle factors, concomitant treatment with other psychotropic drugs, and the occurrence of current and previous depression. Consequently, we consider our findings most likely being linked to the SSRI treatment as such.

The weaknesses of the present study are mainly related to its naturalistic and cross-sectional design. Most importantly, causality cannot be proven. Although we have adjusted for numerous potential confounding factors, residual confounding (eg, caused by somatic diseases, intake of nonpsychotropic medications, and dietary habits) cannot be excluded. The lack of information on concomitant pharmacological treatment for metabolic conditions (eg, cholesterol-lowering, antidiabetic, and antihypertensive drugs) is an important limitation, particularly related to the risk of misclassification of the metabolic syndrome. In contrast, we consider the risk of bias for the other metabolic variables due to lack of information on treatment with these drugs to be small because the frequency of such treatment would be expected to be similar among those treated and those not treated with SSRIs. Because treatment duration was not taken into consideration, we cannot rule out that some subjects very recently had commenced SSRI treatment. However, this factor would most likely cause an underestimation of the real associations because it could be assumed that the metabolic effects would develop through time.

In conclusion, the present study supports the hypothesis that SSRIs may cause metabolic disturbances. When related to the SSRI serum concentration, we revealed statistically significant but minor increases in total cholesterol, LDL cholesterol, and triglyceride levels as well as a modestly increased risk of the metabolic syndrome. Because of the limited magnitude of the alterations, the clinical impact of the findings is most likely small.

AUTHOR DISCLOSURE INFORMATION

Dr Andreassen has received speaker honoraria from GSK, Lundbeck, and Otsuka. Drs Fjukstad, Engum, Lydersen, Dieset, Steen, and Spigset have no financial interests to declare.

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