European Psychiatry xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Metabolic risk factors in schizophrenia and bipolar disorder: The effect of comedication with selective serotonin reuptake inhibitors and antipsychotics

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ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 30 March 2017
Accepted 1st April 2017
Available online xxx

Keywords:
Schizophrenia
Bipolar disorder
Psychopharmacology
Antidepressant
Antipsychotics

ABSTRACT

Background: The aim of this observational study was to investigate the relationship between metabolic factors and use of selective serotonin reuptake inhibitors (SSRIs) combined with olanzapine, quetiapine or risperidone.
Methods: Data from the Norwegian Thematically Organized Psychosis study, a cross-sectional study on 1301 patients with schizophrenia ($n = 868$) or bipolar disorder ($n = 433$), were analyzed. As exposure variables in the linear regression model were included the dose or serum concentration of SSRIs ($n = 280$) and of olanzapine ($n = 398$), quetiapine ($n = 234$) or risperidone ($n = 128$). The main outcome variables were levels of total cholesterol, low and high density lipoprotein (LDL and HDL) cholesterol, triglycerides and glucose.
Results: One defined daily dose (DDD) per day of an SSRI in addition to olanzapine was associated with an increase in total cholesterol of 0.16 (CI 0.01 to 0.32) mmol/L ($P = 0.042$) and an increase in LDL-cholesterol of 0.17 (CI 0.02 to 0.31) mmol/L ($P = 0.022$). An SSRI serum concentration in the middle of the reference interval in addition to quetiapine was associated with an increase in total cholesterol of 0.39 (CI 0.10 to 0.68) mmol/L ($P = 0.011$) and an increase in LDL-cholesterol of 0.29 (0.02 to 0.56) mmol/L ($P = 0.037$). There were no such effects when combined with risperidone.
Conclusions: The findings indicate only minor deteriorations of metabolic variables associated with treatment with an SSRI in addition to olanzapine and quetiapine, and none when combined with risperidone. These results suggest that SSRIs can be used in combination with antipsychotics, and that the possible increase in cardiovascular risk is negligible.

1. Introduction

Schizophrenia and bipolar disorder are mental disorders with serious implications for quality of life and overall health issues [1–6]. Patients suffer from a considerable physical health burden, with cardiovascular diseases as a main cause of early death [6–8]. Efficient treatment requires a series of measures, including use of psychotropic drugs, of which some are associated with metabolic adverse effects [9–11]. Concomitant drug treatment is often required due to the complex array of symptoms [12].

In schizophrenia, combining a selective serotonin reuptake inhibitor (SSRI) with an antipsychotic has been linked to improvement of negative symptoms beyond the effect exerted by the antipsychotic agent in monotherapy [13]. Although SSRIs are used to treat depressive and obsessive-compulsive symptoms

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http://dx.doi.org/10.1016/j.eurpsy.2017.04.001
0924-9338/

in schizophrenia as well, the limited data available prevents any definitive recommendations for their use in these cases [14].

In bipolar disorder, antidepressants are often administered for acute depression [15], but is generally discouraged as monotherapy due to the risk of switching to hypomania/mania, rapid cycling or increased suicidal ideation [16,17]. Co-medication with mood stabilizers or antipsychotic drugs is therefore recommended and consistent with practice guidelines [18–20]. These disorders as well as the use of antipsychotic drugs as such are linked to cardiovascular diseases [6–9,11,21]. The metabolic implications of SSRI augmentation of antipsychotic treatment should also be considered.

A few previous studies have addressed the metabolic adverse effects related to SSRIs and antipsychotics used in combination. Olanzapine and fluoxetine are the most frequently studied combination. A pooled analysis of data from five acute phase studies of patients with treatment resistant depression showed a significantly greater increase in total cholesterol when olanzapine and fluoxetine were combined, as compared to olanzapine monotherapy [22–26]. In contrast, in an 8-week double blind randomized controlled trial in bipolar disorder, non-significant increases in serum cholesterol, glucose and body weight were found in the olanzapine plus fluoxetine group compared to olanzapine alone [27]. Additionally, in a study of patients with bipolar depression, no differences in lipid levels were found between the olanzapine plus fluoxetine group and the olanzapine monotherapy group [28]. Finally, in a study based on the World Health Organization database for spontaneous reporting of adverse drug reactions, SSRIs were found to be a significant risk factor for glucose intolerance when administered in combination with clozapine, olanzapine and risperidone [29].

As there has been little effort toward addressing the risk of metabolic adverse effects when antipsychotics and SSRIs are used in combination, the aim of the present study was to investigate the metabolic effects of SSRIs in combination with antipsychotics in patients with schizophrenia or bipolar disorder. In order to relate the outcomes to the degree of exposure, the dose and the serum concentrations of SSRIs and antipsychotics were used as exposure variables.

2. Material and method

2.1. Subjects

The Thematically Organized Psychosis (TOP) Study at the University of Oslo in Norway consists of a sample of patients with schizophrenia spectrum and bipolar disorders recruited from the in- and outpatient wards of the university hospitals in Oslo. Inclusion criteria were meeting the DSM-IV criteria for schizophrenia or bipolar disorder, age from 18 to 65 years and being willing and able to give an informed consent of participation. Demographic data and information of pharmacological treatment were collected through interviews and medical records. Procedures of data collection and diagnostic and symptom assessment of the TOP study is thoroughly described elsewhere [30].

The Regional Committee for Medical and Health Research Ethics, South East Norway and the Norwegian Data Protection Agency approved the study. In total, 1301 patients were available at the time of the data extraction. Demographic characteristics of the patients are listed in Table 1 and are also described in further detail in a previous publication [31].

2.2. Variables

2.2.1. Outcomes

The serum levels of total cholesterol was the primary outcome variable, as it is considered one of the most important risk factors for cardiovascular disease [32]. Low density lipoprotein cholesterol (LDL-cholesterol), high density lipoprotein cholesterol (HDL-cholesterol), triglycerides, glucose, body mass index (BMI) and systolic and diastolic blood pressure were chosen as secondary outcome variables.

Fasting serum concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and glucose were analyzed at Department of Clinical Chemistry, Oslo University Hospital, using an Integra 800 instrument (Roche Diagnostics, Basel, Switzerland) according to standard methods. The height of each individual was measured with standard methods, body weight (with light clothes) was weighed on calibrated digital weights (Soehnle, Nassau, Germany), and BMI (kg/m^2) was thereafter calculated. A physician measured resting blood pressure manually, using a sphygmomanometer (Boso, Jungingen, Germany).

2.2.2. Exposure variables

To analyze comparable dosages of each drug, the daily dose for each patient was expressed in relationship to the defined daily dose (DDD) [33]. The following DDDs were applied: 10 mg for olanzapine, 400 mg for quetiapine, 5 mg for oral risperidone, 2.7 mg for intramuscular depot risperidone, 10 mg for escitalopram, 20 mg for citalopram, fluoxetine and paroxetine and 50 mg for sertraline. Thus, a patient using e.g. a daily dose of 10 mg citalopram was defined as using an SSRI dose 0.5 DDD per day.

Similarly, the measured serum concentration of each drug was divided by the middle value of the drug's reference interval [34], hereinafter referred to as the "reference serum concentration", to provide comparable concentration variables between different drugs. The middle values (reference intervals in parentheses) applied were 160 (65–255) nmol/L for olanzapine, 780 (260–1300) nmol/L for quetiapine, 95 (50–140) nmol/L for risperidone plus the active metabolite 9-hydroxyrisperidone, 142 (45–240) nmol/L for escitalopram, 240 (150–330) nmol/L for citalopram, 260 (35–490) nmol/L for sertraline, 1025 (400–1650) nmol/L for fluoxetine plus the active metabolite norfluoxetine and 225 (90–360) nmol/L for paroxetine [34]. The serum concentrations of all drugs were analyzed at the Department of Clinical Pharmacology, St Olav University Hospital by analytical methods described in detail previously [35,36].

2.3. Statistical analyses

The missing serum concentrations (numbers missing in parentheses) for the antipsychotics olanzapine ($n = 68$), quetiapine ($n = 39$) and risperidone ($n = 17$) and the SSRIs escitalopram ($n = 39$), citalopram ($n = 8$), sertraline ($n = 6$), fluoxetine ($n = 6$) and paroxetine ($n = 1$), were imputed with single imputation. The expectation maximization algorithm was applied separately for each substance, using the DDD, age and gender as predictors. The remaining missing values were imputed by multiple imputation. Seventy-seven variables were imputed, and we imputed 100 data sets as recommended by van Buuren [37]. The imputed data set included every variable used in the analyses as well as a group of variables thought to be supplementary predictors (numbers missing in parenthesis): height ($n = 96$), body weight ($n = 104$), heart rate ($n = 149$), Calgary Depression Scale for Schizophrenia score (CDSS) ($n = 402$) and use of snuff ($n = 61$). The variables used in the imputation were not transformed, as advocated by Rodwell et al. [38].

Linear regression was performed with total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, BMI and systolic and diastolic blood pressure as dependent variables, one at a time. Covariates were the antipsychotic drug (olanzapine, quetiapine, or risperidone), the SSRI and their interaction. Exposure was expressed as daily doses or serum concentrations

Please cite this article in press as: Fjukstad KK, et al. Metabolic risk factors in schizophrenia and bipolar disorder: The effect of comedication with selective serotonin reuptake inhibitors and antipsychotics. European Psychiatry (2017), http://dx.doi.org/10.1016/j.eurpsy.2017.04.001