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Editorial

SEVERE MENTAL ILLNESSES AND METABOLIC SYNDROME: THE NEED FOR MORE AWARENESS AND BETTER CARE

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Mental disorders are a group of heterogeneous illnesses which include depression, bipolar affective disorder, schizophrenia and other psychoses, dementia, intellectual disabilities and developmental disorders including autism. According to the World Health Organization (WHO) severe mental illnesses (SMI) such as depression, schizophrenia, or bipolar disorder affect hundreds of millions of individuals [1]. Globally, an estimated 350 million people suffer from depression, about 60 million have bipolar affective disorder, and about 21 million have schizophrenia [1].

Mortality rates in people with schizophrenia are 2 to 3-fold higher than in general population and the life expectancy is decreased with approximately 20 years [2]. The main causes of premature death are suicide, cancer, and cardiovascular disease [3]. Several categories of factors contribute to the reduced life expectancy in patients with schizophrenia and other SMI [3,4]: suboptimal lifestyle choices including unhealthy diet, low or no physical activity, excessive smoking and alcohol consumption; higher prevalence of comorbid conditions such as diabetes, cardiovascular disease and cancer; side effects of antipsychotic drugs (weight gain, glucose intolerance and new-onset diabetes, hyperlipidemia); late diagnosis and insufficient treatment of physical illnesses; risk of suicide and accidents.

Prevalence of metabolic syndrome in severe mental illnesses

In patients with SMI, the prevalence and relative risk (RR) of modifiable cardiovascular risk factors were found to be higher than in the general population [5]. Obesity affects 45–55% of people with schizophrenia (RR=1.5–2), diabetes 10–15% (RR=2), hypertension 19–58% (RR=2–3) and dyslipidemia 25–69% (RR≤5). Two to three times more patients with schizophrenia are smokers (50-80%). The reported prevalence of metabolic syndrome (MetS) ranges from 37 to 63%, with a relative risk of 2-3.

Several meta-analyses examining the prevalence of metabolic syndrome in severe mental illnesses have been recently published [6-8]. In schizophrenia and related disorders, the overall rate of MetS was 32.5% (95% confidence interval [CI] = 30.1%–35.0%), and no significant differences were seen according to definitions of

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MetS, in inpatients vs. outpatients, or by country of origin. Males and females had similar rates of MetS: 34.8% (95% CI = 29.2%–40.6%) and 34.8% (95% CI = 29.5%–40.3%) respectively. The illness duration had the strongest influence on MetS rates, while age only modestly influenced the presence of metabolic syndrome [6]. In patients with bipolar disorder [7], the prevalence of MetS was 37.3% (95% CI=36.1-39.0) with higher rates compared with the general population groups (odds ratio=1.98; 95% CI=1.74-2.25). Interestingly, significant differences were observed among regions where the study took place, with the highest rates in New Zealand and Australia. The rate of MetS in patients with major depressive disorder was found to be 30.5% [95% CI 26.3-35.1] with an odds ratio (OR) of 1.54 (95% CI 1.21-1.97) when compared with age- and gender-matched controls [8]. Antipsychotic use was significantly associated with higher MetS prevalence, while age, gender, smoking, geographical area where the study took place, use of antidepressant, coexistence of other psychiatric co-morbidities, and median year of data collection were not.

When examined together in a meta-analysis including 52,678 individuals [9], patients with SMI had a MetS prevalence of 32.6% (95% CI: 30.8%-34.4). At direct comparisons, no significant difference in MetS prevalence was found between schizophrenia and bipolar disorder, or between bipolar disorder and major depressive disorder. In a regression model, age and body mass index were significant moderators of the relationship between SMI and MetS.

Antipsychotic agents, metabolic syndrome and metabolic syndrome components

The association between use of antipsychotic drugs and metabolic syndrome is well-established. In patients with schizophrenia, those using no medication had a reported MetS prevalence of 20.2% when Adult Treatment Panel (ATP) III criteria were used [6]. Using the same criteria (ATP III), the rate of MetS was 51.9% for clozapine users, 28.2% for olanzapine users, and 27.9% for those using risperidone [6]. The same association was found in bipolar disorder [7]. MetS was significantly more prevalent in patients treated with antipsychotics (45.3%) than in patients not using antipsychotics (32.4%). Overall, patients with SMI treated with any antipsychotic medication had a significantly higher risk for MetS compared to antipsychotic-naïve participants. The risk was significantly higher with clozapine and olanzapine than with other antipsychotics (with no significant difference between the two drugs) and significantly lower with aripiprazole than with other antipsychotics, except vs. amisulpride [9].

Antipsychotics-associated weight gain

Numerous studies and meta-analyses examined the short or long-term effects of antipsychotic drugs on weight changes. In an older analysis [10], the average weight change over a 10-week period of antipsychotics use ranged from a reduction of 0.39 kg with molindone and 0.74 kg with placebo to increases of 0.04, 2.10, 2.92, 3.19, 4.15, and 4.45 kg with ziprasidone, risperidone, sertindole, thioridazine, olanzapine, and clozapine, respectively.

A recently published meta-analysis [11] examined weight changes during antipsychotics use in more depth, using as outcomes changes in body weight and in body mass index (BMI), and proportion of subjects with clinically relevant weight gain (defined as >7% weight increase) or clinically relevant weight loss (>7% weight loss). As well, these changes were examined as a function of exposure to antipsychotics in drug-naive patients. The main findings were that almost all antipsychotics showed an increase in body weight, BMI and proportion of patients

with a clinically relevant weight gain with increased duration of use. Fewer antipsychotics (amisulpride, aripiprazole and ziprasidone) had weight neutral effects with duration of use. More important, an increase of mean weight gain and BMI with duration of use was seen in drug-naïve subgroup. The proportion of clinically relevant weight loss was around 10% for all studies, except aripiprazole which showed clinically relevant weight loss in around 15% of users.

Weight changes associated with use of antipsychotic drugs are related to their effect on different modulators of appetite and of energy balance [4]. Compared with conventional antipsychotics, olanzapine and clozapine rapidly increase leptin concentrations during the first 2 weeks after treatment and this increased level is maintained for several months [12]. In another study, it was found that olanzapine significantly decreased and risperidone significantly increased adiponectin concentrations as compared with healthy controls [13]. Ghrelin, an orexigenic hormone, decreases in the first phase of antipsychotic treatment and increases after longer exposure [14].

Antipsychotics-associated dyslipidemia

Use of second generation antipsychotics is associated with disturbances in lipid metabolism, leading to increased levels of LDL cholesterol and triglycerides and decreased levels of HDL cholesterol [15]. It is thought that most of lipid abnormalities are related to weight gain in the course of antipsychotic treatments and to obesity-induced insulin resistance [4], but a direct effect of these drugs on lipid metabolism cannot be excluded.

Antipsychotics-associated Dysglycemia and type 2 diabetes

Patients with schizophrenia have higher prevalence of glucose metabolism imbalances and type 2 diabetes than subjects in the general population [16] and the risk varies among different antipsychotics. In a recent study comparing clozapine with other antipsychotics [17], after a mean follow-up period of 12 years there was a significant difference in new-onset diabetes between clozapine users and the control group (21.7% vs. 8.4%), but biases in the clozapine group could not be completely excluded.

The link between dysglycemia and antipsychotic drugs could be weight gain and insulin resistance, but direct effects of olanzapine and clozapine on beta-cell insulin secretion have also been suggested [18].

In line with current knowledge [19], second generation antipsychotics are classified according to risk of weight gain and incident diabetes into three categories:

Lowest risk: aripiprazole, lurasidone, and ziprasidone

Moderate risk: asenapine, iloperidone, paliperidone, quetiapine, and risperidone

Highest risk: clozapine and olanzapine

Implications for clinical practice

Given the high risk for MetS in patients with SMI, scientific societies issued recommendations for a systematic metabolic screening in this category of patients [20,21]. Weight and body mass index should be assessed at baseline, every week for the first 6 weeks, at 12 weeks, at 1 year, and then annually; waist circumference at baseline and then annually; tobacco use at baseline; blood pressure, fasting glucose, glycated hemoglobin A1c (HbA1c), fasting lipid panel at baseline, at 12 weeks and 1 year, and then annually.

Despite clear recommendations and general recognition that SMI are associated with high cardiovascular risk, a recent meta-analysis of 48 studies conducted between 2000 and 2011 in five countries [22] revealed that routine screening for metabolic risk factors was

generally low. Only blood pressure and triglycerides were measured in more than 50% of patients (69.8 and 59.9%, respectively). Cholesterol, blood glucose and weight were measured in 41.5, 44.3 and 47.9% of cases. Lipids and HbA1c were monitored in only less than 25%.

In order to overcome the metabolic risk associated with use of antipsychotic drugs, several recommendations have been offered to clinicians treating patients with SMI [19]. Whenever possible, antipsychotic drugs with low risk of adverse metabolic effects should be chosen. A recent meta-analysis found that antipsychotics have similar efficacy, except for clozapine, which performed better in refractory psychosis [23]. Nevertheless, it should be acknowledged that in individual cases the use of an antipsychotic with higher metabolic risk can be necessary to maintain psychiatric stability. Antipsychotic polypharmacy should be minimized whenever possible and switching antipsychotic medication from a high-risk to a lower-risk antipsychotic can have metabolic benefits [19]. The last recommendation is based on the results of a randomized clinical trial [24] in which weight loss and decreases in lipid parameters (non-HDL cholesterol and triglycerides) significantly improved in those who were changed to a lower-risk drug (aripiprazole) as compared with patients kept on the higher-risk drug (risperidone, olanzapine, or quetiapine).

Use of concomitant medication to counteract the metabolic side-effects of antipsychotic drugs seems to be a reasonable option [19]. In a meta-analysis of randomized clinical studies [25], it was shown that metformin was the most extensively studied drug with regard to effects on body weight. Its use was associated with -3.17 kg mean difference of body weight compared to placebo. Effects of other drugs such as topiramate, sibutramine, aripiprazole, and reboxetine on body weight were also superior to placebo. Metformin and rosiglitazone improved insulin resistance, and aripiprazole, metformin, and sibutramine decreased blood lipids. However, no long-term studies are yet available regarding hard clinical endpoints (eg, development of diabetes), and the long-term data on risk-benefit ratio from adding metformin is missing [19].

High-risk medications (olanzapine and clozapine) should only be used in patients with serious illness. Lifestyle modifications and frequent monitoring of metabolic factors should be integrated as a routine part of clinical management [19-21], although frequent monitoring did not reduce the rate of new-onset diabetes in this subgroup of patients.

New-onset diabetes should be managed according to general guidelines. Diabetes self-management and support should be offered to patients with diabetes and concomitant psychosis and drugs with lower risk of hypoglycemia can be considered [19-21].

Interventions to increase awareness of metabolic risk and to encourage healthy lifestyle choices have been proven to have beneficial effects in patients with SMI [26]. The Control of Metabolic and Cardiovascular Risk in Patients with Schizophrenia and Overweight (CRESSOB) study was a 12-month, observational, naturalistic study including 403 patients from 109 community mental health clinics of Spain [27]. The patients were asked about health-related behaviors (such as smoking, diet and exercise) and were offered general recommendations to prevent cardiovascular risk and metabolic syndrome. After the 12-month study period, all parameters had significant decreases (weight, waist circumference, BMI, blood glucose, total and LDL cholesterol, triglycerides) and HDL cholesterol significantly

increased. As well, a significant reduction in the percentage of smokers and in the risk of heart disease at 10 years was obtained.

In conclusion, severe mental illnesses are associated with higher risk of metabolic syndrome and its consequences as compared to general population. A collaborative care model is needed in order to reduce the burden of premature morbidity and mortality in this group of patients. Careful consideration should be given to metabolic effects of antipsychotic agents. Better choices of pharmacological interventions, regular monitoring of metabolic factors and adapted lifestyle interventions are effective strategies leading to better care and better outcomes in severe mental illnesses.

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