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Abstract

Rationale

Metabolic syndrome (MetS) is common in patients with bipolar disorder, with a relative risk of 1.6–2 compared to the general population. The increased risk is believed to be due to unhealthy lifestyles and use of medications. Although antipsychotics and mood stabilizers have been associated with weight gain and MetS, the impact of antidepressants has not been comprehensively evaluated.

Objective

The objective of the study is to assess the risk of MetS in patients exposed to different types of antidepressants.

Methods

In this cross-sectional study, 294 patients with bipolar disorder were consecutively recruited. MetS was diagnosed according to NCEP ATP-III modified criteria. Antidepressants used by the patients were classified according to the usual nomenclature (SSRI, TCA, SNRI, and other antidepressants) and a pharmacodynamic classification taking into account histamine 1-receptor (H1-R) affinity.

Results

Use of antidepressants in general was not associated with MetS (prevalence ratio [PR], 1.08; 95% confidence interval, 0.73 to 1.62; $p = 0.70$). However, subjects using H1-R high-affinity antidepressants ($N = 15$) showed a substantial increase in the prevalence of MetS (PR, 2.17; 95 % confidence interval, 1.24 to 3.80; $p = 0.007$). When we included the inhibition constant (Ki) as a continuous covariate in the models, we found an inverse association between Ki and prevalence of MetS ($p = 0.004$).

Conclusion

We observed for the first time in a clinical setting that a pharmacodynamic-based classification of antidepressants could be more useful than the traditional one to predict the risk of MetS in patients with bipolar disorder.

Clinical consequences may be relevant. However larger studies are warranted to generalize these results.

Keywords

Antidepressant Affinity Histamine Metabolism Cardiovascular

Introduction

Antidepressant use in bipolar disorder (BD) is controversial due to inconclusive data regarding their efficacy and the potential of inducing manic switch and cycle acceleration (APA 2002; Ostacher 2006; Pacchiarotti et al. 2013). However, despite these concerns, antidepressants are frequently employed by physicians that face the complex problems of dealing with bipolar depression (Haeberle et al. 2012; Sussman et al. 2012).

Metabolic abnormalities are common in patients with BD, with a relative risk for metabolic syndrome (MetS) and type 2 diabetes of 1.6–2 in patients with BD compared with the general population (Murray et al. 2009; Vancampfort et al. 2013, 2015a). Patients with BD, especially during depressive phases, are inactive, often eat unhealthy food, smoke more cigarettes (Bly et al. 2014; Fagiolini et al. 2008; Vancampfort et al. 2015b), do not take care of themselves, and do

not attend medical checkups (Bradford et al. 2008), by all these reasons increasing the risk for metabolic and eventually cardiovascular disease. These patients also take several medications, such as mood stabilizers, antipsychotics, and antidepressants. This complex medication regimen very often increases weight, adding to the overall risk.

Although it is well known that treatment with atypical antipsychotics (Centorrino et al. 2012; Cerit et al. 2010; Stubbs et al. 2015; Vancampfort et al. 2013) and at a lesser extent mood stabilizers (Yumru et al. 2006) cause weight gain and metabolic abnormalities, there are reports that also antidepressants may increase risk factors for cardiovascular morbidity (Maina et al. 2004; McIntyre et al. 2006). For instance, a systematic review recently highlighted the association between use of antidepressants and new onset type 2 diabetes (Barnard et al. 2013). Although this association found in earlier case-control studies may be explained by confounding (e.g., patients treated with antidepressants have higher rates of diabetes because of underlying depression), recent well-conducted prospective studies are confirming the independent association between diabetes and antidepressants (Wu et al. 2014).

Besides hyperglycemia and diabetes, MetS has been inconsistently associated with antidepressant use: several studies failed to find an association between MetS and use of antidepressants (Cardenas et al. 2008; Garcia-Portilla et al. 2010; Godin et al. 2014; Salvi et al. 2012), while only a recent study found that patients with BD and schizophrenia affected by MetS were more frequently treated with antidepressants, with an odds ratio of 2.24 (Bly et al. 2014). However, no study to date has specifically evaluated the prevalence of metabolic syndrome in patients exposed to different antidepressant medications.

Several studies have underlined that weight gain and metabolic issues during treatment with psychotropic medications might be caused by a central block of the H1 histamine receptor (H1-R). For instance, antipsychotics inducing weight gain in the short-term have a strong antihistaminergic activity, while affinity to the muscarinic or the 5HT2c receptor could not predict increase in weight (Kroeze et al. 2003). Also, a recent study found an association between antihistaminergic antidepressants and disturbances in glucose homeostasis resulting in hyperglycemia (Derijks et al. 2008a). H1-R blockade might cause such metabolic anomalies due to counteracting the central anorexigenic effects of histamine (Jørgensen et al. 2007) or increasing adipose tissue deposition (He et al. 2013).

The aim of this study is to assess the prevalence of MetS in patients with bipolar disorder exposed to different types of antidepressants. In particular, we investigated whether the prevalence of MetS is affected by the H1-R affinity of antidepressants.

Methods

Data collection

The study has a cross-sectional design and involves patients consecutively admitted to the Mood and Anxiety Disorders Outpatient Unit of the University of Turin (Italy), from April 2008 to May 2012. All patients with a diagnosis of BD type I and II, NOS, or cyclothymia (DSM-IV TR) were asked to participate. Potential participants were thoroughly explained with study aims and procedures and had to give their written consent before participation. Exclusion criteria were age ≤18, pregnancy or postpartum, and refusal to consent participating in the study. All subjects were of Caucasian Italian origin. General socio-demographic characteristics were collected for each subject. The following clinical characteristics were also collected: duration of illness, number of previous manic/depressive episodes, and history of lifetime suicide attempt. We also administered, as a part of our routine clinical assessment, the Clinical Global Impression-Bipolar Disorder (CGI-BP). Lifestyle characteristics were also collected: we obtained data about smoking status (yes/no), alcohol consumption (yes/no), and physical exercise (yes/no). Physical exercise was defined by the presence of either any structured activity (e.g., gym, sport activities) or walking at least 30 min per day.

At study entry, weight, height, waist circumference, and blood pressure were measured. A blood draw for routine blood exam was performed; at the time the blood was drawn, patients had fasted for the previous 10 h. Blood exams included glucose, total cholesterol, triglycerides, and HDL-c. MetS was diagnosed according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria (Grundy et al. 2005), where metabolic syndrome is defined by any three of the following: (1) abdominal obesity characterized by waist circumference ≥102 cm for men and ≥88 cm for women, (2) triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides, (3) high-density lipoprotein cholesterol (HDL-c) <40 mg/dL for men and <50 mg/dL for women or drug treatment for reduced HDL-c, (4) blood pressure ≥130 mmHg or ≥85 mmHg or treatment for hypertension, or (5) fasting glucose ≥100 mg/dL or drug treatment for elevated glucose.

Use of psychotropic medications at the time of interview was assessed. Antidepressants were classified using different strategies. First, we classified the antidepressants according to the usual nomenclature: selective serotonin reuptake inhibitors (SSRI—citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressants (TCA—amitriptyline, clomipramine, nortryptiline, trimipramine), serotonin-norepinephrine reuptake inhibitors (SNRI—duloxetine, venlafaxine), and other antidepressants (bupropion, mirtazapine, reboxetine). Second, we classified the antidepressants according to their H1-R affinity.

H1-R affinity was assessed using their inhibition constant (Ki), a measure of the binding affinity of the ligand (antidepressant) for its receptor. Ki is the concentration of the ligand in which the receptor is occupied for 50 % by the ligand; thus, the lower the value of Ki, the higher is the affinity of the ligand for the receptor. Values of Ki for all antidepressants were mainly obtained from Derijks et al., which derived Ki values from the Psychoactive Drug Screening Program (PDSP) Ki database, employing not only Ki values coming from experiments with cloned human cell lines but also human receptors from the brain tissue, (frontal) cortex, choroids plexus tissue, striatum tissue, cortical membranes, and platelets (Derijks et al. 2008b). Ki value for the antidepressant trimipramine was directly taken from the PDSP database: the value had been obtained from human cortical membranes. We also used Derijks et al.'s cluster categorization to dichotomize antidepressants in H1-R low affinity and H1-R high affinity (2008b). According to the employed classification, all SSRIs plus venlafaxine, duloxetine, and clomipramine, which all show high affinity for the 5-HT reuptake transporter with little or no affinity for one or more other binding sites, belong to the first cluster. Amitriptyline, imipramine, and trimipramine, with high affinity for reuptake transporters, serotonergic 5HT3, histaminergic H1, muscarinic M3, and alpha-1 receptors are grouped in the second cluster. The third cluster comprises maprotiline, nortriptyline, mianserin, and mirtazapine which all show high affinity for the histamine H1 receptor and 5-HT2c receptor and less affinity for the 5-HT reuptake transporter. Finally, the fourth cluster comprises trazodone, reboxetine, and bupropion, identified as a group with no specific similarities to the others (Derijks et al. 2008b). Since we were only interested in H1 receptor affinity of antidepressants, we grouped together clusters 2 and 3 (in our sample, amitriptyline, imipramine, nortriptyline, trimipramine, and mirtazapine) including patients taking those medications in the H1-R high-affinity group, while patients taking SSRIs, clomipramine, venlafaxine, duloxetine, reboxetine, and bupropion, were included in the H1-R low affinity group. When more than one antidepressant was prescribed to a patient, the subject was classified according to the medication with the highest H1-R affinity.

Statistical analysis

Subject characteristics were summarized as mean and SD for continuous variables and as percentages for categorical variables. It has long been recognized that the odds ratio estimated via logistic regression can substantially overestimate the relative risk in cross-sectional studies where the outcome is common (Thompson et al. 1998). For this reason, different authors advocated for the use of prevalence ratios (PR) in these cases (Zou 2004; Petersen and Deddens 2008). A commonly used method to model PR is through modified Poisson regression models for binary data with

robust estimate of the variance (Zou 2004; Petersen and Deddens 2008; Diacinti et al. 2010). In the present study, we used this approach to investigate the association between use of different types of antidepressants and prevalence of MetS, after adjusting for possible confounders. Three different sets of analyses were conducted. We first used the usual classification (SSRI, TCA, SNRI, and other antidepressants) to assess whether any class of antidepressants was associated with an increased prevalence of MetS. Second, we used the pharmacodynamic classification of Derijks et al. to test our hypothesis that only H1-R high-affinity antidepressants were associated with MetS (2008b). Finally, we directly modeled the effect of H1-R affinity on MetS using the specific values of Ki of the different antidepressants. Consistent with the approach proposed by Kroeze, values of Ki were log-transformed before being included in the model and a maximum Ki of 10,000 nM was used for low-affinity interactions (Kroeze et al. 2003). Analyses were performed using Stata 12 Software (Stata Corp, College Station, TX, USA).

Results

Of 328 patients with BD consecutively admitted to our unit, 16 refused to consent, 11 were below 18 years of age, and 7 were pregnant at the time of interview. Thus, 294 patients with BD were finally recruited. After the exclusion of five patients that had missing values in some of the variables, the main analyses were conducted on 289 subjects. Among the patients included in the study, 62 % were females. Their mean age was 50 years. Table 1 shows the socio-demographic and clinical characteristics of patients stratified by type of antidepressant treatment; of 160 patients exposed to antidepressants, 15 (9.4 %) were taking H1-R high-affinity antidepressants. The characteristics of patients in the three groups were largely similar (Table 1). Notably, the prevalence of metabolic syndrome was almost identical (24 %) among patients not taking antidepressants and those treated with H1-R low-affinity antidepressants (Table 2). On the other hand, the prevalence of metabolic syndrome was substantially higher (53 %) among patients treated with H1-R high-affinity antidepressants (Table 2, Fig. 1).

Results of the regression models are reported in Table 3. Use of any class of antidepressants was not associated with an increased prevalence of MetS (PR, 1.08; 95 % confidence interval [CI], 0.73 to 1.62; *p* value, 0.70) (Table 3). Also, when patients were classified according to the usual nomenclature of antidepressants, we did not observe any association with MetS (Table 3). However, compared with patients not exposed to antidepressants, use of H1-R high-affinity antidepressants was associated with a substantial increase in the prevalence of MetS (PR, 2.17; 95 % CI, 1.24 to 3.80; *p* value, 0.007) (Table 3). Notably, no difference was observed between subjects not taking antidepressants and those taking H1-R low-affinity antidepressants (PR, 0.96; 95 % CI, 0.63 to 1.46; *p* value, 0.85). Results did not substantially change when possible confounders such as age, sex, exposure to antipsychotics and mood stabilizers, duration of illness, smoking status, alcohol consumption, and physical exercise were included in the model (Table 3). Finally, since the association was based on a small sample size of patients taking H1-R high antidepressants, we decided to include the inhibition constant (Ki) as a continuous covariate in the model, finding an inverse association between Ki and prevalence of MetS ($p = 0.004$), corresponding to a direct association between H1-R affinity and MetS (Fig. 2). The continuous model estimated a prevalence ratio exceeding 2 for antidepressants such as amytriptiline, trimipramine, mirtazapine, and nortryptiline.

Discussion

Patients with BD display high rates of metabolic abnormalities and MetS, and this is also due to the complex pharmacological regimen that these patients are prescribed, with combination pharmacotherapy being the rule more than the exception in BD (Zarate and Quiroz 2003). Although the role of antipsychotics, particularly second generation such as olanzapine and quetiapine, has been unveiled by extensive research, the impact of antidepressant use had not been

comprehensively evaluated so far. Nevertheless, antidepressants are widely prescribed to BD patients, both during acute depressive phases of the illness and during maintenance phases (Haeberle et al. 2012; Sussman et al. 2012).

In the present study, we did not find an association between use of antidepressants as a whole and prevalence of MetS. However, when we classified the antidepressants according to their affinity for the H1-receptor, a statistically significant association emerged between H1-R high-affinity antidepressants and prevalence of MetS. To our knowledge, this is the first time that this is observed in a clinical setting.

Our results are consistent with those from previous studies, which did not find an association between metabolic syndrome and use of antidepressants (Cardenas et al. 2008; Garcia-Portilla et al. 2010; Godin et al. 2014; Salvi et al. 2012); indeed, antidepressants taken as a whole are a group of quite heterogeneous molecules, and it is possible that gathering together medications with such different pharmacological profiles might have concealed the differences of the specific drugs in causing MetS. Also, when antidepressants were clustered according to the usual nomenclature (SSRI, TCA, SNRI, and other antidepressants), we could not find an association between any specific class and the prevalence of MetS. In a large study conducted on around 3000 Canadian women, obesity was consistently associated with use of TCA but not SSRI (Grundy et al. 2014). The authors concluded that "the increased risk of obesity among depressed women taking antidepressants supports a role for these medications as an intermediate between depression and obesity". However, it is likely that not all TCA exert their metabolic effects to the same extent: most of our patients treated with TCA were administered with clomipramine, whose H1-R affinity is not as high as the other TCA, further enforcing the accuracy of the pharmacodynamic-based classification in predicting such effects.

Weight gain has been repeatedly linked with antihistaminergic activity of several medications. For instance, a study used results from published RCT to link short-term weight gain induced by second generation antipsychotics with their receptor binding profiles: the authors found that only H1 antihistaminergic activity could strongly predict weight gain (Kroeze et al. 2003). In particular, clozapine and olanzapine, which have the highest affinity for H1 receptor, were the antipsychotics associated with the highest weight gain. In more recent years, Derijks et al., employing the described pharmacodynamic classification for antidepressants, found higher fasting glucose levels in patients taking antidepressants with high antihistaminergic activity (Derijks et al. 2008a).

A classification of antidepressants based on pharmacological profiles is supported by other findings that explain the neurobiological basis of anti-H1 induced weight gain: an experimental study found that 4 weeks of treatment with amitryptiline and mirtazapine led to an increase in leptin plasma levels and weight gain, while treatment with paroxetine and venlafaxine did not (Schilling et al. 2013). According to the authors, leptin resistance (shown by increase in leptin levels ineffective in controlling weight) could be explained by the antihistaminergic effect of such compounds, interfering on hypothalamic nuclei integrating signals relevant for energy balance. Additionally, blocking of hypothalamic H1 receptors by second-generation antipsychotics may also contribute to fat accumulation by decreasing lipolysis in some tissues but increasing lipogenesis in white adipose tissue (He et al. 2013). All these researches support the utility of classifying medications according to the H1-receptor binding profile.

Our study has several potential limitations. Cross-sectional studies are known to have important drawbacks. In particular, as the information on exposure and disease status is assessed at the same moment in time, reverse causation cannot be definitely ruled out in this type of studies. However, it is unlikely that reverse causation constitutes an issue in the present study: there is no reason to expect that having a diagnosis of MetS increases the probability of a patient of being subsequently treated with H1-R high-affinity antidepressants. On the contrary, medications known for their potential to induce weight gain and metabolic abnormalities, such as mirtazapine and tricyclics, are usually less prescribed to patients at risk for cardiometabolic disease. This is expected to translate in a possible underestimation of the association between H1-R high-affinity antidepressants and MetS.

As in any observational study, it is not possible to rule out the possibility that the results are due unmeasured confounding. However, in our study, the distribution of measured risk factors for MetS was very similar among patients using H1-R high-affinity antidepressants, those using H1-R low-affinity antidepressants, and subjects not taking antidepressants at all (Table 1). Notably, adjustment for possible confounders such as age, sex, use of antipsychotic drugs, use of mood stabilizers, smoking, alcohol, and physical exercise did not substantially change the estimate of the association between use of H1-R high-affinity antidepressants and prevalence of MetS.
Misclassification is unlikely to be a major issue in our study, as the assessment of exposure and disease status was based on objective information. Classification of disease status was based on internationally accepted and standardized criteria (Grundy et al. 2005). H1-R affinity of the different antidepressant was based on NIH database and previously published data. Any possible misclassification is thus expected to be non-differential and would thus result in an attenuation of the association. The small proportion of non-respondents and the fact that the study was based on consecutively recruited patients makes selection bias unlikely as well.
A further limitation is that, although metabolic abnormalities are also due to unhealthy food habits (Bly et al. 2014), we did not systematically investigate the dietary habits of the patients included in the study; it would be worthwhile to investigate in future studies the association between use of antihistaminergic medications and the consumption of unhealthy food.
Finally, another limitation resides in the small number of patients taking high H1-R affinity antidepressants. Since the majority of our patients taking antidepressants were treated with SSRIs, the H1-R high-affinity group was rather limited in size, and this affected the precision of the estimates and the generalizability of our results. Clearly, this observation should be replicated in a larger sample. However, it is reassuring that the association with MetS held also when H1-R affinity was modeled as a continuous variable (Fig. 2). This makes unlikely that the observed association was due to specific characteristics of few individuals in the H1-R high-affinity group.
In conclusion, our study showed in a clinical setting that antidepressants displaying high antihistaminergic activity may play a significant role in inducing metabolic syndrome in patients with BD. Therefore, we suggest that clinicians look at medications' pharmacodynamic profile more than merely at the class before deciding which treatment is more appropriate for a specific patient, in order to prevent the occurrence of metabolic syndrome.
In a recent paper, several opinion leaders in the field of clinical psychopharmacology state that, albeit classification should help the clinician in making the correct decision, ultimately leading to improved adherence, "current psychiatric drug classification fails to serve any of these purposes" (Zohar et al. 2014). The authors conclude that an updated nomenclature, based on current knowledge on neurotransmitter function, receptor affinities, and side effects, should be adopted for psychotropics. Our study adds evidence on the utility of a psychopharmacologic-based classification of antidepressants, which in our opinion would help reduce the risk for metabolic abnormalities in these at-risk patients.

Conflict of interest

The authors declare that they have no competing interests.

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