



Obesity and obstetric complications are associated with rapid-cycling in Italian patients with bipolar disorder



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ABSTRACT

Background: Rapid cycling (RC) worsens the course of bipolar disorder (BD) being associated with poor response to pharmacotherapy. Previous studies identified clinical variables potentially associated with RCBD: however, in many cases, results were discordant or unreplicated. The present study was aimed to compare clinical variables between RC and non RC bipolar patients and to identify related risk factors.

Methods: A sample of 238 bipolar patients was enrolled from 3 different community mental health centers. Descriptive analyses were performed on total sample, and patients were compared in terms of socio-demographic and clinical variables according to the presence of RC by multivariate analyses of variance (MANOVAs, continuous variables) or χ^2 tests (qualitative variables). Binary logistic regression was performed to calculate odds ratios.

Results: Twenty-eight patients (11.8%) had RC. The two groups were not different in terms of age, age at onset, gender distribution, type of family history, type of substance use disorder, history of antidepressant therapy, main antidepressant, psychotic symptoms, comorbid anxiety disorders, suicide attempts, thyroid diseases, diabetes, type of BD, duration of untreated illness, illness duration, duration of antidepressant treatment and GAF scores. In contrast, RC patients had more often a history of obstetric complications ($p < 0.05$), obesity ($p < 0.05$) and a trend to hypercholesterolemia ($p = 0.08$). In addition, RC bipolar patients presented more frequently lifetime MDMA misuse ($p < 0.05$) than patients without RC.

Discussion: Findings from the present study seem to indicate that obesity and obstetric complications are risk factors for the development of RC in BD. In addition, lifetime MDMA misuse may be more frequent in RC bipolar patients.

1. Introduction

Bipolar disorder (BD) is a condition that affects about 2.4% of the adult population (Merikangas et al., 2011) according to a broader definition and when applying DSM-IV criteria. Variations in lifetime prevalence between countries (e.g. United States and India) have been explained in the light of differences in social structure and consequently in BD diagnosis (Merikangas et al., 2011). If BD is not promptly treated, it is associated with severe disability and a high risk of chronicity (Angst et al., 2002). Several factors have been associated with poor prognosis in bipolar patients including early onset (Baldessarini et al., 2012), long duration of untreated illness (DUI) (Altamura et al., 2010, 2015), lifetime history of psychotic symptoms (Østergaard et al., 2013) and rapid cycling (RC, i.e. ≥ 4 mood episodes in the prior year) (Suppes et al., 2005). RC subtype has been observed

in about 16% of bipolar patients (Kupka et al., 2003), although this clinical presentation is transient in most subjects (Bauer et al., 2008). Thus, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA, 2013) (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatry Association, 2013) continues to include “rapid cycling” as a course specifier for patients with bipolar I disorder or bipolar II disorder, rather than an illness subtype. In addition, RC bipolar patients have been found to show a worse response to pharmacotherapy, often requiring poly-therapies for long-term clinical stabilization (Schneck et al., 2004; Buoli et al., 2014).

Several clinical variables have been associated with RC course in BD, including: antidepressant treatment (particularly with tricyclic antidepressants) (Altshuler et al., 1995; Azorin et al., 2008), long duration of illness (Azorin et al., 2008) and of untreated illness (Kupka

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et al., 2005), early age at onset and childhood onset (Kupka et al., 2005; Holtzman et al., 2015), female gender (Kupka et al., 2003), bipolar II subtype (Kupka et al., 2003; Dell'Osso et al., 2015), comorbid hypothyroidism (Kupka et al., 2003; Azorin, 2008) and obesity (Galvez et al., 2014). The greater clinical severity of RCBD might reflect underlying biological vulnerabilities in these patients. Of note, a recent study reported higher IL-6 and IL-18 plasma levels, reflecting, therefore, a more prominent inflammatory response in hypomanic/manic RC bipolar patients compared to patients without RC (Munkholm et al., 2015).

In many cases, past studies, investigating clinical variables associated with RCBD, have reported discordant results (e.g. regarding the effect of antidepressant treatment) (Amsterdam et al., 2015) or they have not been replicated (e.g. regarding the role of inflammatory factors in causing RC) (Munkholm et al., 2015). In some important instances, the direction of causality between RC course and clinical variables remains unclear. For example, it remains to be established whether antidepressant treatment causes RC (Wehr, et al., 1988) or whether the prescription of antidepressants is the consequence of more frequent treatment-resistant major depressive episodes in RC patients than in non-RC ones (Calabrese et al., 2001). In light of these observations, purpose of the present research was to compare RC versus non-RC bipolar patients in terms of socio-demographic and clinical variables with the aim to confirm/disconfirm previous data or to find new possible associations in a substantial sample of patients with BD. We hypothesize that RC patients have a more severe course of illness, as showed by outcome variables such as medical comorbidity or higher rates of suicide attempts, and that praecox insults (such as derived from obstetric complications) may be predictive of RC.

2. Methods

A sample of 238 patients was enrolled from 3 different community mental health centers affiliated to the Department of Psychiatry of the University of Milan. The study was cross-sectional and patients, from longer monitored at the community health centers, back to 1997. Patients had a diagnosis of BD (type I or type II) according to DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatry Association, 2013). RC was defined as the presence of at least 4 mood episodes in the prior year according to DSM-5 criteria. Diagnoses were made by expert psychiatrists, who had regularly followed up the selected patients. The diagnoses were made by the same psychiatrist for a single patient and they were reviewed in 2013 according to DSM-5 criteria. In case of hospitalization of the patients no changes in the diagnosis were made by psychiatrists working in inpatient clinic. Clinical information were extrapolated through a retrospective review of the clinical charts, Lombardy database and, if necessary, through clinical interviews with patients and their relatives. Collected data included the following socio-demographic and clinical variables: gender, age, family history for psychiatric disorders, age at onset, duration of untreated illness (DUI), duration of illness, lifetime substance use disorder and type of substance use disorder, last pharmacological treatment (in case of poly-therapies the compound at the highest doses and taken for the longest period of time), poly-therapy, history of antidepressant treatment, type of main antidepressant (taken for the longest time), total duration of antidepressant treatment, Global Assessment of Functioning (GAF) scale score, history of psychotic symptoms, comorbid anxiety disorders, history of suicidal attempts, history of obstetrical complications, comorbid thyroid diseases, comorbid diabetes, presence of hypercholesterolemia, obesity before the onset of rapid cycles, type of BD, number and type of mood episodes in the last year. Obesity was defined as a Body Mass Index (BMI) ≥ 30 . The severity of obesity was classified according to BMI as light ($\geq 30 < 35$), intermediate ($\geq 35 < 40$) or severe (≥ 40) (World Health Organization Criteria). An obstetric complication was considered as the presence of a score of 2 (definite

complication) in one of any item of the Lewis-Murray Scale (Lewis and Murray, 1987; Buoli et al., 2016). Hypercholesterolemia was defined as total cholesterol serum levels > 200 mg/dl or treatment with statins in the last year. We considered the presence of thyroid diseases in case of pharmacotherapy for thyroid dysfunction (e.g. hormone replacement therapy) or abnormal Thyroid-Stimulating Hormone (TSH) levels in the last year. Finally, the comorbidity with diabetes was recorded in case of hypoglycemic therapy (both insulin and oral hypoglycemic compounds) or alterations in glycated hemoglobin in the last year. Fasting glycaemia and total cholesterol serum levels are screened at least once a year in bipolar patients afferent to our clinic.

Exclusion criteria were the following: 1) patients who had not been examined in the last 12 months (due to the inability to definitively establish the presence of prior year RC); 2) patients whose clinical information were incomplete; 3) patients with a diagnosis of dementia, mental retardation or other medical conditions (e.g., untreated endocrine disorders) associated with an increased risk of psychotic symptoms or causing medical conditions included in the analysis of the present study (e.g., untreated Cushing syndrome and diabetes/obesity).

With these criteria, 35% of the initially screened patients ($n=366$) were excluded ($n=128$). None of the patients had been previously treated by child neuropsychiatric services.

Descriptive analyses of the total sample were performed. The subgroups (divided according to the presence of RC) were compared by multivariate analyses of variance (MANOVAs) for continuous variables and Chi-Square tests for qualitative variables, corrected, when appropriate, by Bonferroni's tests. Finally, a binary logistic regression was performed considering presence of RC as dependent variable, and presence of obesity and history of obstetric complications as independent variables.

The level of statistical significance was set at $p < 0.05$. Statistical Package for Social Sciences (SPSS) for Windows (version 22.0) was used as statistical analysis program.

3. Results

3.1. Total Sample

The sample included 238 patients: 107 males (45%) and 131 females (55%). Twenty-eight patients (11.8%) had RC. No new diagnosis of diabetes, thyroid disease or hypercholesterolemia was done in the last year.

3.2. RC versus non-RC patients

Summary of statistics about demographic and clinical variables of the sub-groups of patients are reported in Table 1. Last main pharmacological treatments are reported in Table 2.

Twenty-two patients showed obesity before the onset of RC (12 light, 8 intermediate and 2 severe). Fourteen patients showed at least one obstetric complication (5 gestational age < 37 weeks; 2 complicated breech birth; 1 birthweight < 2000 g; 3 difficult forceps; 1 cord prolapse; 2 emergency caesarean delivery; 2 incubator > 4 weeks).

MANOVA model, comparing continuous variables of the two groups of patients, resulted to be valid (Wilks'lambda: $p < 0.05$).

RC versus non-RC patients over two times as frequently had obesity before the onset of RC (21.4% versus 7.6%, $\chi^2=5.56$, $df=1$, $p=0.03$), a lifetime history of obstetric complications (17.9% versus 4.3%, $\chi^2=8.22$, $df=1$, $p=0.02$) (Fig. 1), and a lifetime history of 3,4-methylenedioxy-methamphetamine (MDMA) misuse (7.1% vs. 0.05%, post-hoc analyses of type of lifetime substance use disorder: $p < 0.05$), and tended to more frequently have hypercholesterolemia ($\chi^2=3.48$, $df=1$, $p=0.08$). No differences were found between groups in relation to severity of obesity before the onset of RC ($\chi^2=0.58$, $df=2$, $p=1.00$). In contrast, BD patients divided according to the presence/absence of RC were not significantly different in terms of age ($F=0.004$, $p=0.95$), age

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