Research paper

Clinical correlates of acute bipolar depressive episode with psychosis

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ABSTRACT

Background: Psychotic bipolar depressive episodes remain remarkably understudied despite being common and having a significant impact on bipolar disorder. The aim of this study is to identify the characteristics of depressed bipolar patients with current psychosis compared to those without psychosis.

Methods: We used baseline data of a comparative effectiveness study of lithium and quetiapine for bipolar disorder (the Bipolar CHOICE study) to compare demographic, clinical, and functioning variables between those with and without psychotic symptoms. Of the 482 participants, 303 (62.9%) were eligible for the present study by meeting DSM-IV criteria for an acute bipolar depressive episode. Univariate analyses were conducted first, and then included in a model controlling for symptom severity.

Results: The sample was composed mostly of women (60.7%) and the mean age was 39.5 ± 12.1 years. Psychosis was present in 10.6% (n=32) of the depressed patients. Psychotic patients had less education, lower income, and were more frequently single and unemployed. Psychosis was also associated with a more severe depressive episode, higher suicidality, more comorbid conditions and worse functioning. Most group differences disappeared when controlling for depression severity.

Limitations: Only outpatients were included and the presence of psychosis in previous episodes was not assessed.

Conclusion: Psychosis during bipolar depressive episodes is present even in an outpatient sample. Psychotic, depressed patients have worse illness outcomes, but future research is necessary to confirm if these outcomes are only associated with the severity of the disorder or if some of them are independent of it.

1. Introduction

Psychosis is a frequent feature in bipolar disorder (BD) (Goghari and Harrow, 2016; Østergaard et al., 2013) and is associated with worse prognosis, lower rates of recovery (Goghari and Harrow, 2016; Solomon et al., 2010) and shorter time to first recurrence (Pallaskorpi

et al., 2015) including first episode patients (Tohen et al., 2003). Most studies of psychotic symptoms in BD focus on psychotic mania, because psychotic symptoms are more common in manic episodes (Altamura et al., 2015; Mantere et al., 2004). However, psychosis is also frequent in bipolar depressive episodes. According to Fountoulakis et al. (2016), the prevalence of psychosis in bipolar depression could be as high as 66% in historical descriptions. More recent studies report lower but still significant prevalence: 10.4% for a current episode (Mantere et al., 2004) and 10–28% for lifetime bipolar depressive episodes (Frankland et al., 2015; Goes et al., 2007; Rosenthal et al., 1980). Moreover, major depressive episodes with psychosis are more frequent (Frankland et al., 2015; Goes et al., 2007; Zaninotto et al., 2015) and more recurrent (Mitchell et al., 2001) in BD than in unipolar depression. First episodes of psychotic depression in 30% of cases are likely to switch diagnosis to bipolar disorder (Tohen et al., 2012). Psychotic depression is also associated with a more frequent history of suicidality (when compared to psychotic manic or mixed episodes) (Dell'Osso et al., 2000) and a reduction of gray matter volume in the dorsolateral prefrontal cortex and in the insula (Radaelli et al., 2014) further highlighting the potentially negative impact of psychosis during bipolar depressive episodes.

Despite the prevalence and possible impact of psychosis in bipolar depression, the differences between psychotic and nonpsychotic depressive episodes are understudied. To date, only one study compared psychotic (N=59) with nonpsychotic (N=176) outpatient bipolar depression (Benazzi, 1999). This study enrolled highly selective patients, or only those in an outpatient private practice of the author, and assessed only a limited number of features. The aim of the current study was to build upon Benazzi's data to compare acutely depressed bipolar patients with and without current psychosis from the Bipolar **C**linical **H**ealth **O**utcomes **I**nitiative in **C**omparative **E**ffectiveness (Bipolar CHOICE) study sample (Nierenberg et al., 2016) in terms of demographic characteristics, clinical presentation and functioning.

2. Methods

The Bipolar CHOICE study was an 11-site, 6-month randomized comparative effectiveness study that compared lithium, a classic mood stabilizer, to quetiapine, a second-generation antipsychotic, each with adjunctive personalized treatments (APTs [i.e., evidence-based, guideline-informed treatment based on illness course, treatment history, and current symptomatology]) in bipolar disorder. For a detailed description of the study design see Nierenberg et al. (2014). The study protocol was approved by the IRB and managed individually at the 11 sites. Participants provided written informed consent before starting any study-related procedure. The Bipolar CHOICE study was registered on ClinicalTrials.gov (identifier: NCT01331304).

2.1. Participants

The sample of this study is diverse and generalizable. The Bipolar CHOICE study was designed with limited inclusion and exclusion criteria in order to maximize generalizability. Eligible patients diagnosed with bipolar disorder I or II in any symptomatic mood state entered the study with at least mild symptoms of bipolar disorder (Clinical Global Impressions-Bipolar Version [CGI-BP] score ≥3 (Spearing et al., 1997). Potential participants were excluded from the study if they had any contraindication to lithium or quetiapine (e.g., pregnancy, prior hypersensitivity, severe renal disease, or lack of treatment response after an adequate trial), were currently in crisis such that hospitalization or more acute care was necessary, were currently taking lithium or quetiapine, or were unable to comply with study requirements. Data from the baseline assessment of enrolled patients were used, but only patients presenting with a depressive episode at study entry were included for the present study.

2.2. Assessments

Clinical interviewers obtained demographic information (e.g., employment and disability status, household income, educational background, and marital status), family psychiatric history, number of previous hospitalizations, suicide attempts, and age at illness onset.

2.2.1. Diagnosis and symptom severity

Lifetime and current diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), including bipolar disorder and other psychiatric comorbidities, were established at the screening visit with the electronic Mini-International Neuropsychiatric Interview (eMINI-PLUS) (Sheehan et al., 1998). The eMINI-PLUS was also used to assess current suicidality. Symptom severity was assessed by the CGI-BP and the Bipolar Inventory of Symptoms Scale (BISS) (Bowden et al., 2007; Gonzalez et al., 2008), a structured interview that yields an overall severity score with subscales specific to mania and depression. The BISS also identifies five domains of behavioral psychopathology (i.e., depression, mania, psychosis, irritability and anxiety) (Thompson et al., 2010).

Items of the psychotic domain of the BISS were used to define the presence of psychotic symptoms (i.e., itens 41-Persecutory Ideas; 42-Delusions; 43-Hallucinations; and 44-Impaired Insight). Patients were considered psychotic if a delusion or hallucination was definitely present; that is, there was a score of 4 on item 41 (persecutory ideas), a score greater than or equal to 2 on items 42 (delusions) or 43 (hallucinations), or a score of 3 or 4 on item 44 (impaired insight).

2.2.2. Functioning

Overall functioning was measured with the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 2000). The LIFE-RIFT comprises an overall score as well as four subscales characterizing the extent to which current psychopathology impacts: (1) work (i.e., employment, household, student); (2) relationships (i.e., spouse, children, other relatives, friends); (3) overall life satisfaction; and (4) recreation. Higher LIFE-RIFT scores indicate greater functional impairment.

2.3. Statistical analysis

Data were analyzed using SPSS 20.0. Univariate analyses were performed using student t-tests for continuous variables with a normal distribution and Mann-Whitney U-tests for continuous variables with non-normal distribution. Categorical variables were compared using the chi-square (χ^2) test or Fisher's Exact test when indicated. To adjust observed associations for depression severity, a multivariate analysis was performed using a logistic regression model with psychosis being the dependent variable. All variables for which a statistically significant difference was observed in the univariate analyses were included as predicting variables. The severity variable used in this model was the depression subscale of the BISS. This subscale was selected because it does not include the BISS itens that were used to define psychosis. All tests were two-tailed and a p-value < 0.05 was considered statistically significant, with no adjustment for multiple comparisons, given the exploratory nature of these analyses.

3. Results

Three hundred and three patients (62.9%) out of the 482 total sample presented with a major depressive episode at the time of enrollment. There were more women (60.7%; n=184) than men and the mean age was 39.45 ± 12.1 years. BD I was more frequent (64.7%; n=196) than BD II (35.3%; n=107). Among the depressed patients, 32 (10.6%) also presented with psychotic symptoms. Paranoid delusion was present in 2 patients (0.7%), any delusion in 17 patients (5.6%),