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Research paper

Onset polarity in bipolar disorder: A strong association between first depressive episode and suicide attempts

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ABSTRACT

Background: The role of onset polarity (OP) in patients with bipolar disorder (BD) has been increasingly investigated over the last few years, for its clinical, prognostic, and therapeutic implications. The present study sought to assess whether OP was associated with specific correlates, in particular with a differential suicidal risk in BD patients.

Methods: A sample of 362 recovered BD patients was dichotomized by OP: depressed (DO) or elevated onset (EO: hypomanic/manic/mixed). Socio-demographic and clinical variables were compared between the subgroups. Additionally, binary logistic regression was performed to assess features associated with OP.

Results: DO compared with EO patients had older current age and were more often female, but less often single and unemployed. Clinically, DO versus EO had a more than doubled rate of suicide attempts, as well as significantly higher rates of BD II diagnosis, lifetime stressful events, current psychotropics and antidepressants use, longer duration of the most recent episode (more often depressive), but lower rates of psychosis and involuntary commitments.

Limitations: Retrospective design limiting the accurate assessment of total number of prior episodes of each polarity.

Conclusions: Our results support the influence of OP on BD course and outcome. Moreover, in light of the relationship between DO and a higher rate of suicide attempts, further investigation may help clinicians in identifying patients at higher risk of suicide attempts.

1. Introduction

Bipolar disorder (BD) is responsible for a chronic burden and a significantly increased suicide risk, compared with the general population (Simon et al., 2007).

Recently, renewed interest has emerged on the role of predominant polarity over the course of BD and use of polarity index as a long-term course specifier, with meaningful therapeutic and prognostic implications (Carvalho et al., 2014). Moreover, in a recent review, depressive predominant polarity has been associated with depressive onset (DO), delayed BD diagnosis, diagnosis of BD II, and a higher rate of suicidal behaviors, whereas manic predominant polarity has been related to earlier onset, first manic/psychotic episode, and an increased rate of substance abuse (Carvalho et al., 2014).

However, to date, only limited evidence is available in relation to DO versus elevated (EO) onset polarity (OP) and their biological, socio-demographic, and clinical correlates (Azorin et al., 2011). For instance, OP appears to cluster in families (Kassem et al., 2006) and has been increasingly investigated for its potential role over BD course, outcome, prognosis, and impact on clinical and therapeutic decision-making (Daban et al., 2006).

Furthermore, like for other clinical variables addressed in previous studies from our group (Dell'Osso et al., 2016a, 2016b), the assessment of OP may contribute to distinguish more homogeneous subgroups of bipolar patients (Daban et al., 2006), leading to more targeted interventions (Forty et al., 2009).

Indeed, several studies over the last decades have supported the association between OP and selected clinical variables, such as long-term predominant polarity (Turvey et al., 1999; Perugi et al., 2000; Perlis et al., 2005; Kassem et al., 2006; Vieta et al., 2009), polarity at relapse (Calabrese et al., 2004), rapid cycling (Perugi et al., 2000), number of episodes and suicide attempts (Perlis et al., 2005), comor-

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bidity with other psychiatric disorders (e.g., anxiety) (Azorin et al., 2011), lifetime psychotic symptoms (Daban et al., 2006), chronic severity of illness, and treatment response (Haag et al., 1987; Maj et al., 1989).

Importantly, several studies reported that suicide risk was robustly associated with DO (Perris and d'Elia, 1966; Roy-Byrne et al., 1985; Perugi et al., 2000; Perlis et al., 2005). This has very substantial clinical relevance, since approximately 30% of individuals with BD attempt suicide in their lifespan (Chen and Dilsaver, 1996), most often during depressive episodes (Goldberg and Ernst, 2002) and dysphoric mania (Rihmer and Kiss, 2002).

Prior research on OP has been frequently limited by being restricted only to BDI patients (Forty et al., 2000; Perlis et al., 2005; Kassem et al., 2006; Azorin et al., 2011), focusing on the impact of first manic or psychotic episodes, mainly conducted with inpatients (who likely over-represent the diagnosis of mania) (Sipos et al., 2001; Tohen et al., 2003), and not including onset with mixed features (Forty et al., 2000; Perlis et al., 2005; Daban et al., 2006; Kassem et al., 2006).

Thus, the present study aimed to assess demographic and clinical associates of OP in a large sample of recovered Italian bipolar I and II patients. The inclusion of BDII patients in our study sample was intended to make it more representative of the real-world population of bipolar patients, providing new insight in the field. We hypothesized that OP might be significantly related with specific socio-demographic and clinical correlates, in particular that DO might be associated with an increased risk of suicidal behavior.

2. Methods

2.1. Subjects

The study sample consisted of 362 recovered BD patients, primarily referred to the University Department of Mental Health at the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico in Milan, Italy. We also included patients who sought evaluation and treatment at outpatient and community-based psychiatric services, in order to obtain a more representative BD phenomenology of the Northern Italian population. All subjects provided written informed consent to have their clinical charts and medical records used for research purpose.

2.2. Assessment

Participants were assessed by psychiatrists or residents in psychiatry with specific training in mood disorders, with the Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, APA, 2000) (SCID I and II - First et al., 1997, 2002), in order to ascertain Axis I/II diagnoses of mood disorders and comorbid psychiatric conditions. To enhance diagnostic specificity, individuals with BD Not Otherwise Specified were not included in the study sample, so that all participants had BD I or BD II. If patients had a comorbid psychiatric disorder, BD had to be the disorder primarily affecting their everyday functioning, quality of life, and help seeking. Individuals with mental retardation, neurological disorders, mental illnesses associated with an organic basis, or other disabling medical conditions were excluded.

Data was gathered from patients and their relatives, and derived from available clinical records. Socio-demographic variables included: age, gender, education, current employment, and lifetime occupational functioning impairment, co-habitation, and marital status. Clinical variables included: diagnosis, age at onset (i.e., age of first mood episode of any polarity), duration of BD, duration of untreated BD illness (DUI), OP, most recent episode duration and polarity, lifetime number of psychiatric hospitalizations, involuntary commitments, suicide attempts, family history of psychiatric disorders, lifetime occurrence of psychosis, current subthreshold symptoms, history of stressful life events (e.g., catastrophes, serious accidents or illnesses, death of a loved one, significant relationship breakup, financial problems, pregnancy), psychiatric/medical comorbidity, and psychosocial rehabilitation, which includes community-based interventions to improve social/working skills, reduce functional disability, and improve quality of life (Barbato, 2006). Moreover, the Global Assessment of Functioning (GAF) (Hall, 1995) was administered after the resolution of the most recent syndromal mood episode (to exclude potential mood episode-related bias), in order to evaluate patient's current level of global functioning. Current pharmacological treatment was recorded, focusing in particular on the use of antidepressants, mood stabilizers, and antipsychotics, in mono- and poly-therapy.

All patients were grouped according to OP, defined as DO or EO (i.e., hypomanic/manic/mixed first episode). Only subjects able to specifically provide the above OP information were included in our analyses.

2.3. Statistical analyses

For continuous parameters, the DO and EO subgroups were compared using corrected Multivariate Analysis of Covariance (MANCOVA), with polarity of first episode as the independent variable and current age as covariate (to exclude its potential influence when analyzing other clinical parameters). The MANCOVA model proved to be valid (Wilks' lambda test, $p < 0.001$). For categorical parameters, the DO and EO subgroups were compared using Chi-square tests, with Bonferroni post-hoc analysis. A two-tailed significance threshold was set at $p < 0.05$.

Furthermore, to assess potential confounders, binary logistic regressions were performed to investigate significant relationships between OP (dependent variable) and other variables (included as covariates). Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 22.

3. Results

3.1. Socio-demographic and clinical characteristics

Tables 1, 2 show, respectively, socio-demographic and clinical data of the entire sample and the DO and EO subgroups.

Overall 46/362 patients (13%) were excluded from our original sample due to inadequate information about OP. DO compared with EO was more common (binomial test, $p < 0.05$). With respect to socio-demographic variables, patients with DO compared with EO had significantly older current age ($F=10.8$, $p=0.001$) and were significantly more often female ($\chi^2=7.4$, $df=1$, $p=0.008$), but less often single ($\chi^2=8.4$, $df=3$, $p=0.04$) and unemployed ($\chi^2=5.9$, $df=2$, $p=0.05$).

With respect to clinical variables, BD I was the most common diagnosis in both DO and EO (62.6% and 86.6%). However, patients with DO vs EO had significantly higher rates of BD II ($\chi^2=22.3$, $df=1$, $p < 0.001$), lifetime suicide attempts ($\chi^2=4.7$, $df=1$, $p=0.03$), lifetime stressful events ($\chi^2=5.5$, $df=1$, $p=0.02$), longer duration of the most recent episode ($F=5$, $p=0.03$) - more often depressive ($\chi^2=6.8$, $df=1$, $p=0.01$) - as well as more current psychotropic drugs ($F=6.4$, $p=0.01$) and antidepressants use ($\chi^2=13.6$, $df=1$, $p < 0.001$).

In contrast, DO vs EO had lower rates of lifetime psychotic symptoms ($\chi^2=30$, $df=1$, $p < 0.001$) and lifetime involuntary commitments ($\chi^2=10.3$, $df=1$, $p=0.001$) as well as less lifetime involuntary commitments ($F=10.5$, $p=0.001$).

Fig. 1 shows clinical variables with significant difference between the two subgroups. Patients with DO vs EO had no significant difference for any other demographic or clinical parameter in Table 1.

3.2. Logistic regression analysis/Correlates of OP

The variables found to be significant after MANCOVAs were