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Research paper

Impact of predominant polarity on long-term outcome in bipolar disorder: A 7-year longitudinal cohort study

Gabriel Okawa Belizario*, Michelle Silva, Beny Lafer

Bipolar Disorder Research Program (PROMAN), Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Rua Dr. Ovidio Pires de Campos, 785 - 3° andar / Ala norte / Ceapesq/ Sala 4, Sao Paulo, SP 05403-010, Brazil

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ABSTRACT

Introduction: Recent studies suggest that Predominant Polarity (PP) may be an important specifier of Bipolar Disorder (BD), establishing distinct groups of patients and providing a potential tool for tailored treatment. PP has been associated to various clinical variables present in the course of the disorder, including deficits in cognitive functioning, suicide attempts, hospitalizations and response to pharmacological treatment. However, most published studies are retrospective and cross-sectional, frequently relying on patients´ ability to recall past information, which may often be inaccurate.

Methods: Participants were recruited from the outpatient clinic of the Bipolar Disorder Research Program at the Institute of Psychiatry of the University of São Paulo. Baseline clinical and demographic variables were collected using a semi-structured questionnaire and the SCID-CV. Longitudinal data were collected through medical records, mood charts, and mood symptom scales conducted throughout a 7-year follow-up period.

Results: Manic Predominant Polarity (MPP) was associated with a significantly higher number of hospitalizations, suicide attempts, and episodes with psychotic symptoms throughout the 7-year observed period in comparison to Depressive Predominant Polarity (DPP) and Indefinite Predominant Polarity (IPP) patients. Moreover, baseline PP was significantly associated with 7-year PP, with 67% of patients maintaining their PP both at baseline and after the 7-year follow-up period.

Limitations: The present study is limited due to the statistically small sample size, although, to our knowledge, it is the largest longitudinal study conducted in this topic, and the unequally distributed frequency of patients´ visitations, which may have created intervals of unobserved periods within the follow-up period.

Discussion: The results revealed PP to be an important specifier for predicting the course of the disorder. Overall, MPP was significantly associated with variables indicative of a worse outcome, suggesting that greater attention to preventive treatment should be addressed to this subgroup. Lastly, baseline PP was significantly associated with 7-year observed PP, suggesting that patients tend to remain within the same PP throughout the course of the disorder.

1. Introduction

Bipolar Disorder (BD) is a severe and recurrent psychiatric disorder identified by periodic episodes of depressive and manic symptomatology. It affects approximately 2.4% of the population (Merikangas et al., 2011) and is associated with the highest suicide rate among psychiatric disorders (Goldstein et al., 2012).

The BD diagnosis is often accompanied by specifiers intended to further detail the course of the disorder and provide predictive tools for treatment. Specifiers included in the DSM-5 (American Psychiatric Association, 2013) are divided into two categories: 1) specifiers defining the current episode, which include the presence of psychotic, mixed, melancholic, atypical and catatonic features, and 2) specifiers defining recurrent episodes (course of the disorder), which include rapid cycling, peripartum onset and seasonal patterns (American Psychiatric Association, 2013). Recent studies have suggested Predominant Polarity (PP) as an important course specifier of the disorder, establishing distinct groups of patients and providing another tool for tailored treatment (Carvalho et al., 2015; Colom et al., 2006; Rosa et al., 2008). PP consists of three categories: 1) Manic

Abbreviations: BD, Bipolar Disorder; PP, Predominant Polarity; MPP, Manic Predominant Polarity; DPP, Depressive Predominant Polarity; and IPP, Indefinite Predominant Polarity

* Corresponding author.
E-mail addresses: gabrielokawabelizario@gmail.com (G.O. Belizario), michellesilva.enf@gmail.com (M. Silva), benylafer@gmail.com (B. Lafer).

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Predominant Polarity (MPP), 2) Depressive Predominant Polarity (DPP), and 3) Indefinite Predominant Polarity (IPP). There are currently two established definitions of the specifier (Colom et al., 2015): the Barcelona proposal (Colom et al., 2006), which requires participants to present at least two-thirds (2/3) of lifetime episodes of one polarity in order to be included into either the MPP or the DPP categories, and the Harvard proposal (Baldessarini et al., 2012), which instead requires participants to present a simple majority of episodes of one polarity for inclusion in either category.

PP has been associated with various clinical variables correlated with the course of the disorder. DPP has been associated with higher numbers of suicide attempts, depressive onset and comorbid anxiety disorders (Azorin et al., 2015; Colom et al., 2006). MPP has been associated to higher rates of substance abuse, psychotic symptoms, and hospitalizations, earlier onset of symptoms, and manic/psychotic onset (Carvalho et al., 2014; Popovic et al., 2014). A systematic review of 16 articles, conducted by García-Jiménez and colleagues (García-Jiménez et al., 2017), found MPP to be associated with a manic onset, drug consumption prior to onset, and a better response to antipsychotics and mood stabilizers. The same study also found DPP to be associated with a depressive onset, more relapses, prolonged episodes, greater suicide risk, and a later diagnosis of BD. PP has also been associated with therapeutic regiments. Recent studies have associated PP to the Polarity Index (PI), which aims to provide a guide to clinicians for choosing pharmacological treatments by characterizing medications as either having anti-manic (>1) or anti-depressant (<1) prophylactic properties (Gnanavel, 2015; Popovic et al., 2014). MPP patients are more often treated and present better responses to positive PI medications (anti-manic stabilization packages) while DPP are more often treated with medications presenting a negative PI (anti-depressive stabilizations packages) (Popovic et al., 2012; Carvalho et al., 2015). Finally, a recent study found PP to be associated with cognitive impairments, in which MPP patients demonstrated significantly poorer performances in various neuropsychological domains when compared to DPP and IPP patients, and healthy controls (Belizario et al., 2017). However, most published studies investigating PP are retrospective, often employing a cross-sectional design unable to determine causality.

The present study´s primary focus is on associations between PP and longitudinal clinical variables, hypothesizing that DPP patients should present significantly higher numbers of total episodes and suicide attempts, and MPP patients should present higher numbers of hospitalizations and psychotic symptoms throughout the 7-year follow-up. The secondary hypotheses, concerning associations between PP and baseline clinical and demographic variables, investigated whether MPP is associated to BD type 1, comorbid substance abuse/dependence, and an earlier onset of symptoms, and also tested whether DPP is associated to BD type 2, a delayed diagnosis of BD, and comorbid anxiety disorders. Lastly, although we found no literature regarding IPP patients, the study hypothesized that this subgroup should present results positioned in between MPP and DPP patients´ results.

2. Methods and materials

Participants were recruited from the outpatient clinic of the Bipolar Disorder Research Program (PROMAN) at the Institute of Psychiatry of the Hospital das Clinicas of the University of São Paulo Medical School. Inclusion criteria required participants to be between 18 and 60 years of age, reside in the city of São Paulo and present a diagnosis of BD, type 1 or 2, accordingly to the DSM-IV-TR´s requirements. Patients presenting schizoaffective disorder were excluded from the study.

We followed the Barcelona Predominant Polarity Classification and PP was calculated from the reported number of episodes and their respective polarities at baseline, requiring participants to demonstrate at least two-thirds (2/3) of lifetime episodes of one polarity in order to be included in either the MPP or DPP groups. Patients presenting a lower proportion of episodes of either polarity were assigned to the IPP group.

Baseline clinical and demographic variables were collected using a semi-structured interview developed by the Brazilian Bipolar Research Network and the SCID-CV (First et al., 1996). Longitudinal data was collected through medical records, mood charts, and mood symptom scales completed throughout the 7-year follow-up period. All participants have signed an informed consent form authorizing the usage of their data for research purposes.

The study employed an ANOVA for parametric continuous variables, the Kruskal-Wallis test for non-parametric continuous variables, and a Chi-square test for categorical variables, in order to investigate the presence of significant differences between groups for both baseline and longitudinal variables. Normality was determined through the Kolmogorov-Smirnov test. Lastly, a binary logistic regression was employed to investigate the association between baseline and the 7-year observed PP. The statistical analyses were conducted using the IBM SPSS 21.0 Statistical Package and an alpha level of 0.05 (two-tail) defined significance.

3. Results

The study included 87 participants in total, 23 males and 64 females (27% and 73% respectively), with an average age of 49.19 (SD = 9.67) years old and 12.31 (SD = 3.67) years of schooling at baseline. The sample was divided into 3 groups: (1) 25 MPP patients, (2) 42 DPP patients, and (3) 20 IPP patients. Univariate analysis of demographic variables (Table 1) revealed significant differences between groups only for gender ($p = 0.026$), with females being more prevalent in the DPP group. Age ($p = 0.694$), years of schooling ($p = 0.791$) and income (0.605) revealed no significant differences between groups.

Results regarding the primary hypotheses (Table 2), which included longitudinal variables collected during the 7-year follow-up, revealed significant differences in the total number of manic ($p < 0.001$), hypomanic ($p = 0.031$) and depressive ($p < 0.001$) episodes, number of suicide attempts ($p = 0.001$) and hospitalizations ($p < 0.001$), and number of episodes with psychotic symptoms ($p < 0.001$). A Bonferroni correction for multiple comparisons suggested an adjusted alpha level of 0.005, maintaining the significant results previously found by the ANOVA except for the number of hypomanic episodes. An LSD post-hoc for pairwise comparisons found a significant higher number of manic ($p = 0.001$), suicide attempts ($p < 0.001$), episodes with psychotic symptoms ($p = 0.001$) and hospitalizations ($p < 0.001$) in MPP patients in comparison with DPP patients. DPP patients presented a significant higher number of depressive episodes ($p = 0.001$) in comparison to IPP patients, and MPP patients presented a significant higher number of manic episodes ($p < 0.001$), hospitalizations ($p < 0.001$), suicide attempts ($p = 0.003$) and episodes with psychotic symptoms ($p = 0.001$) in comparison to IPP patients.

Further univariate analysis (Table 3) regarding baseline clinical variables revealed significant differences between groups for type of BD ($p = 0.015$), age of first depressive episode ($p = -0.029$), age of BD diagnosis ($p = 0.038$), number of lifetime hospitalizations ($p = 0.005$), and presence of psychosis in the first episode ($p = 0.025$). However,

Table 1
Demographic variables between groups.

Variables	MPP (n = 25)	DPP (n = 42)	IPP (n = 20)	*p*-value
Age*	47.75 (11.17)	49.77 (9.34)	49.75 (10.52)	0.694
Gender (male)**	11 (46)	6 (15)	6 (30)	**0.026**
Years of Schooling*	12.6 (3.38)	12.38 (3.68)	11.85 (4.08)	0.791
Income (Brazilian real)*	1111.54 (1616.86)	1112.66 (1367.22)	1545.15 (2200.87)	0.605

MPP: mania predominant polarity; DPP: depressive predominant polarity; IPP: indefinite predominant polarity

* ANOVA test – Mean (SD)

** Chi-square test – N (%)