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A longitudinal mirror-image assessment of morbidity in bipolar disorder

D.J. Martino [a,b,*], C. Samamé [a,b], E. Marengo [a], A. Igoa [a], M. Scápola [a], S.A. Strejilevich [a,c]

[a] Bipolar Disorder Program, Neuroscience Institute, Favaloro University, Solís 461, Buenos Aires, Argentina
[b] National Council of Scientific and Technical Research (CONICET), avenue Rivadavia 1917, Buenos Aires, Argentina
[c] Institute of Cognitive Neurology (INECO), Pacheco de Melo 1860, Buenos Aires, Argentina

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ABSTRACT

Background: Evidence about the clinical course of bipolar disorder is inconsistent and limited. The aim of this study was to assess changes in morbidity in patients with bipolar disorder along a mean follow-up period of 80 months.
Methods: Based on a mirror-image design, the follow-up period of each patient was divided into two halves. Then, three measures of morbidity — number of affective episodes, time spent ill, and cycle length — were recorded and compared between each half of the follow-up period.
Results: On average, there was a trend to a smaller amount of time spent with subclinical symptomatology during the second half of the follow-up period. In contrast, there were no differences in terms of number of episodes, time spent with clinical symptoms, or cycle length between the first and second half of the follow-up period. A subgroup analysis identified 21.9% of patients with consistent data of a worsening during follow-up.
Conclusions: The results suggest that, on average, there is stability or slight improvement of clinical morbidity over the course of BD. Then, worsening of the clinical course may be a feature of a subgroup of patients rather than an inherent characteristic of the disorder. These subgroups or patient profiles could represent an opportunity for further studies to assess clinical, pathophysiologic, and therapeutic features associated with them.

1. Introduction

The long-term course of bipolar disorder (BD) is highly heterogeneous: while some patients show few symptomatic periods, others experience many episodes and marked disability [1]. Notwithstanding this variability, it is usually assumed that a shortening of periods of wellness and a rising risk of future recurrences occur with each successive episode. In fact, the alleged progressive clinical course of the disorder is one of the cornerstones of the different models of clinical staging — in which illness features go through different stages from at-risk to more severe and disabling presentations — and neuroprogression recently proposed for BD [2–6].

The notion of a progressive clinical course of BD goes back on Kraepelin's original observations [7]: "... for the most part the disease shows the tendency later on to run its course more quickly and to shorten the intervals...". Some pioneering clinical and preclinical studies supported this view [8–11], while others, even in the pretreatment era, reported a random or highly variable course of illness [12–15]. These controversial findings might be related to some methodological issues. First, several studies were based on retrospective reports. Retrospective studies are subject to recall bias, with patients recalling recent affective episodes better than distant ones, which might contribute to an apparent rising risk of recurrences [16]. In addition, some of these previous studies were affected by another limitation: if patients who have multiple episodes have a constant high risk of recurrence from the beginning of the disease, these patients may have an increasing influence with each successive episode because they would represent a higher proportion of the remaining sample. This bias is usually called 'Slater's Fallacy' and could explain both the increasing risk of recurrences and the shortening of cycle length, which is the time between the onset of consecutive episodes [17,18].

More recent studies employed an extended Cox regression model to overcome this problem, a frailty model, in which patients

* Corresponding author at: Gurruchaga 2463, 1° C (C1425FEK) Ciudad Autónoma de Buenos Aires, Argentina. Tel./Fax: +5411 4833 2424.
E-mail address: diejmartino@gmail.com (D.J. Martino).

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with a large frailty value tended to have a high rate of recurrences after any episode, whereas patients with a small frailty value had a low rate of recurrences [19–21]. Kessing et al. [19] reported that the risk of recurrence increased very significantly with the number of previous episodes for all BD patients (younger, older, men, and women), but when the model was adjusted for frailty, statistical significance remained only for older women. Another study used a frailty model with a sample of unipolar and bipolar patients and found that the risk of recurrences increased with the number of episodes in the pooled sample of affective patients, but there was no association when the subgroup of patients having their first episode during the follow-up period was considered [20]. Finally, another study using a mixed sample of patients with major depressive disorder and BD (ICD-10) found that the rate of relapse (not recurrences) leading to hospitalization increased with the number of episodes in women but not in men [21]. In contrast, other authors who tested the hypothesis of cycle acceleration considering Slater's Fallacy and showed opposite results. On average, in a sample of patients with BD type I or schizoaffective mania, cycle length increased rather than decreased over a follow-up period of 10 years [22]. Likewise, in a sample of BD patients hospitalized for their first episode, the course was largely random or chaotic during a follow-up period of 6 years and only a minority of patients showed either cycle-acceleration or slowing, without changes in wellness intervals [23]. It is important to highlight that all these studies may have biased the samples towards more severe forms of BD type I requiring hospitalization.

Overall, evidence for progressive worsening of the clinical course of BD is inconsistent and limited and further research is needed. Therefore, this study employed a mirror-image design with the aim of exploring whether each individual patient experienced increasing morbidity along a follow-up period. This approach helps control between-patient heterogeneity in clinical course, as each subject is its own control.

2. Methods

Sixty-four subjects were consecutively selected from the outpatients population of the Bipolar Disorder Program of Favaloro University with the following inclusion criteria: age between 18 and 65 years old; diagnosis of BD type I or type II according to DSM-IV using Structured Clinical Interview for DSM-IV (SCID) [24]; a period of follow-up of more than 48 uninterrupted months in our Program, and euthymic (defined by Hamilton Depression Rating Scale ≤ 9 and Young Mania Rating Scale ≤ 8) for at least 8 weeks at baseline. Exclusion criteria were: history of substance abuse/dependence, history of mental retardation, neurological disease, or any unstable clinical condition (as hypothyroidism) that could affect the clinical course. The Hospital Ethics Committee approved the study and all subjects gave written informed consent for their participation after receiving a complete description of the study.

2.1. Clinical assessment

Demographical and clinical information at baseline was obtained from clinical charts. Average exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines during follow-up was assessed with the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) [25]. This scale provides a quantitative measure of current exposure to different groups of psychotropic medications in a 0–5 points range (0 = no medication, 1 = sporadic low dose, 2 = continued low dose; 3 = middle dose, 4 = high dose, and 5 = very high dose).

2.2. Morbidity assessment

Based on a mirror-image design, the follow-up period of each patient included in this study was divided into two halves. Then, two measures of morbidity usually documented for each patient treated in our program were retrospectively recorded in each of these halves with the aim of comparing the clinical course for each patient:

- affective episodes (depressive and hypo/manic) based on DSM-IV criteria;
- time spent ill documented at each visit (with intervals usually around 1–2 months) with a modified life charting technique rated by the treating psychiatrist on a weekly basis (Fig. 1).

This life chart technique was used in previous studies by our group [26,27] and was developed without the knowledge or purpose of the present work. In addition, cycle lengths (time between the onset of consecutive episodes) of the first and the last cycle were registered for patients with more than three episodes (at least two cycles).

2.3. Data analysis

The assumption of normality and homoscedasticity of each variable was analyzed with the Kolmogorov-Smirnov normality test and Levene's test respectively. Since most continuous variables such as number of episodes or time spent ill were skewed, non-parametric tests were used. Differences in cycle length and in morbidity measures between the two halves of the follow-up period of each patient were analyzed as two related samples with the Wilcoxon Signed Rank Test for ordinal/continuous variables and McNemar's Test for categorical variables. In order to decrease the risk of type I error due to several

	January				Etc.				
+4									Severe Mania (YMRS≥26)
+3									Moderate Mania (YMRS≥16 and <25)
+2									Mild Mania (YMRS≥9 and <15)
+1									Subclinical Mania (YMRS>4 and <8)
0									Euthymic (YMRS<4 and HDRS<4)
-1									Subclinical Depression (HDRS>5 and <9)
-2									Mild Depression (HDRS≥10 and <15)
-3									Moderate Depression (HDRS≥16 and <25)
-4									Severe Depression (HDRS≥26)

YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.

Fig. 1. Criteria for assigning mood state scores in life charts. YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.