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A longitudinal mirror-image assessment of morbidity in bipolar disorder

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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

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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.

Table 1
Demographic and clinical variables at baseline.

	Mean (SD)/Median (Range)
Age	44.07 (13.06)/44 (20–65)
Years of education	13.31 (13.02)/12 (6–19)
Length of illness	15.36 (8.23)/16 (34)
Number of previous hypo/manic episodes	3.44 (2.92)/2 (1–15)
Number of previous depressive episodes	3.91 (2.44)/3 (0–12)
Gender (female), %	67.2
Clinical subtype (type I), %	50.0
History of hospitalizations, %	43,8
History of psychotic symptoms, %	48.4

comparisons, a Bonferroni correction was applied. Despite the asymmetric distribution of certain variables, results are also expressed as mean and standard deviation to improve understanding.

3. Results

Demographic and clinical variables at baseline are showed in Table 1. The period of follow-up was 80.08 (SD = 20.31, median = 74, range = 48–139) months during which patients experienced a mean of 3.14 (SD = 2.76, median = 2, range = 0–11) depressive episodes and 1.61 (SD = 1.83, median = 1, range = 0–7) hypo/manic episodes. On average, patients spent 77.9% of the follow-up euthymic, 16.8% with depressive symptoms, and 5.2% with hypo/manic symptoms. Likewise, 42 patients experienced at least three episodes during the follow-up and were considered to compare the length of the first and the last cycle. All patients received medications during the period of the study: 100% mood stabilizers (mean IFD score = 3.40, SD = 0.90), and 59.4% antipsychotics (mean IFD score = 2.21, SD = 0.84), 53.1% benzodiazepines (mean IFD score = 2.20, SD = 0.96), and 39.1% antidepressants (mean IFD score = 2.24, SD = 1.13).

There was a trend to a smaller amount of time spent with subclinical symptomatology during the second half of the follow-up period (Table 2). In contrast, there were no differences in terms of number of episodes or time spent with clinical symptoms between the first and second half of the follow-up period (Table 1). Likewise, there was no difference between the length of the first (mean = 43.98, SD = 36.29, median = 32, range = 9–200) and the last (mean = 62.60, SD = 55.55, median = 41, range = 13–256) cycle among the patients who suffered more than three episodes during the follow-up (Wilcoxon Signed Ranks Test $Z = -1.59$, $P = 0.12$).

Finally, as a secondary analysis, we searched the percentage of patients with a progressive clinical course based on the following criteria:

- decreased cycle length plus increased number of affective episodes or time spent ill during the follow-up;
- or increased number of affective episodes plus increased time spent ill during the follow-up.

The percentage of patients meeting these criteria was 21.9%. With the opposite criteria, 54.7% of patients had a decrease of morbidity during the follow-up period, while the remaining 23.4% had no increase or decrease in morbidity. There were no differences between clinical and demographic variables at baseline between these subgroups of patients (all Ps > 0.05).

4. Discussion

We used a mirror-image design with the aim of assessing whether each individual BD patient experienced increased morbidity along a follow-up period. In addition, we used a mixed sample of outpatients with BD types I and II to make it more representative of the total population of people with this disorder. Another strength of our study was that the measures of morbidity were evaluated through personal interviews at periods usually between 1–2 months, which minimize the risk of recall bias.

Considering our mirror-image design, it is not easy to determine which the best parameter to assess changes in morbidity is. Number of episodes per se might be an inappropriate measure, since it hides the increases in morbidity that may occur as a result of a longer duration of episodes or more severe subclinical symptoms (Fig. 2a and b). Likewise, the number of episodes could not reflect increases in morbidity that occurred as a result of increased severity of them (Fig. 2c). Similarly, although cycle length is a widely used measure, it has been shown to be an imprecise indicator of morbidity because it does not reflect how much time within any given cycle is spent in an affective episode [22]. Thus, a patient with stable cycle length could have increased morbidity due to a longer duration or severity of affective episodes or secondary to an extension of subclinical symptoms (Fig. 2d–e). Even more, taking into account the random or chaotic course described for BD [23], a shortening of the cycle in the context of a reduction in morbidity (Fig. 2f) cannot be ruled out. With these caveats in mind, we selected three measures to assess morbidity during a mean follow-up period longer than 6 years.

First, we assessed changes in the entire sample of patients comparing the three measures of morbidity in both halves of the

Table 2
Number of episodes and time spent ill along the two halves of the follow-up period.

	First Half of follow-up Mean (SD)/Median (range)	Second half of follow-up Mean (SD)/Median (raange)	Wilcoxon Signed-Rank Test
Number of episodes			
Depressive episodes	1.71 (1.74)/1 (0–8)	1.43 (1.52)/1 (0–5)	$Z = -1.43$, $P = 0.15$
Hypo/manic episodes	0.98 (1.18)/1 (0–5)	0.63 (0.94)/0 (0–4)	$Z = -2.65$, $P = 0.009$
Time spent ill (weeks)			
Total	40.16 (29.30)/34.5 (0–151)	29.20 (26.55)/24.5 (0–114)	$Z = -2.79$, $P = 0.005$
Subclinical depressive symptoms	19.28 (17.91)/15.5 (0–80)	12.42 (13.78)/8.5 (0–52)	$Z = -3.20$, $P = 0.001$*
Mild depressive symptoms	8.70 (10.21)/6.5 (0–46)	7.30 (9.66)/4 (0–47)	$Z = -1.00$, $P = 0.32$
Moderate depressive symptoms	2.13 (3.85)/0 (0–15)	2.16 (4.66)/0 (0–22)	$Z = -0.45$, $P = 0.96$
Severe depressive symptoms	0.55 (0.29)/0 (0–14)	0.17 (0.97)/0 (0–6)	$Z = -1.38$, $P = 0.17$
Subclinical hypo/manic symptoms	6.38 (8.84)/2 (0–38)	4.91 (8.80)/0 (0–38)	$Z = -2.15$, $P = 0.031$
Mild hypo/manic symptoms	2.47 (4.05)/1 (0–18)	2.03 (4.05)/0 (0–17)	$Z = -1.32$, $P = 0.18$
Moderate hypo/manic symptoms	0.58 (1.63)/0 (0–11)	0.34 (1.52)/0 (0–9)	$Z = -1.30$, $P = 0.19$
Severe hypo/manic symptoms	0.08 (0.37)/0 (0–2)	0.03 (0.25)/0 (0–2)	$Z = -1.63$, $P = 0.10$

* Significant after Bonferroni correction.

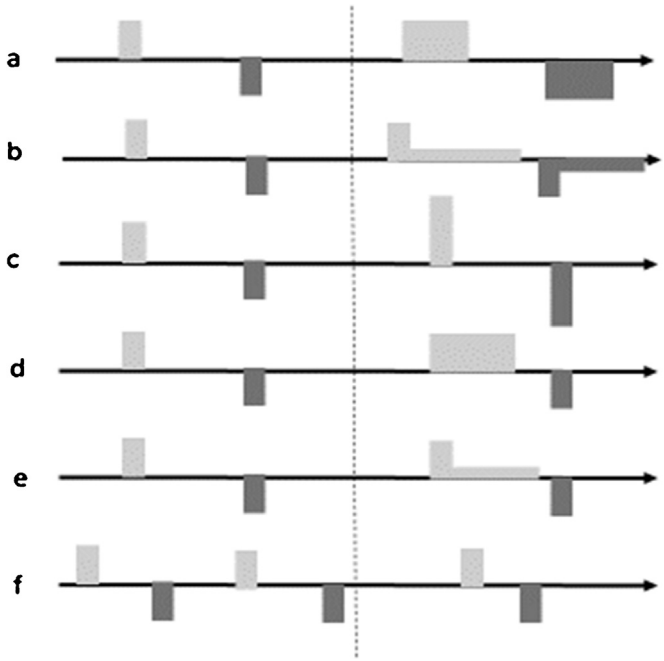

Fig. 2. Potential changes in morbidity using a mirror-image design: a: an increase in morbidity occurs as a result of longer duration of episodes; b: an increase in morbidity occurs as a result of more severe subclinical symptomatology; c: an increase in morbidity occurs as a result of greater severity of episodes (in a patient with stable cycle length); d: an increase in morbidity occurs as a result of longer duration of episodes in a patient with stable cycle length; e: an increase in morbidity occurs as a result of higher subclinical symptomatology in a patient with stable cycle length; f: a decrease in morbidity occurs in the context of a shortening of cycle length.

follow-up period. If there was an increase in morbidity throughout the course of BD, we should expect an increase in the number of episodes or time-spent ill, or a shortening in cycle length. However, the main finding of this study was that there was a trend to decrease in subclinical symptomatology and hypo/manic episodes during follow-up, while there were no changes in the other measures of morbidity considered. These results suggest that patients with BD as a group had a relatively stable clinical course over a follow-up period of about 6–7 years. Then, we performed a subgroup analysis and identified 21.9% of patients who showed consistent data of a worsening during follow-up. Contrarily, 54.7% of patients had a decreased morbidity during the follow-up period, while the remaining 23.4% had no increase or decrease in morbidity. These results agree with studies that report, on average, stability or slight improvement over the course of BD [22,23]. In contrast, our findings do not support the hypothesis of neuroprogression based on a progressive worsening of clinical course in BD [3,5,6]. The existence of a subgroup with a worsening clinical course is in line with some previous reports. A study that included patients with BD type I requiring hospitalization and assessed definitions of sensitization found a progressive course in 26.5% of the patients [28]. Another study reported that as many as 40% of hospitalized first-episode BD patients could have an apparently progressive illness during 5.7 years of follow-up [23]. Therefore, it would be possible that a subset, rather than the whole population of patients with BD, might have a progressive worsening of clinical course despite treatment.

As mentioned above, the long-term course of BD in terms of episode recurrences is highly heterogeneous. Similarly, functional outcome and neurocognitive performance have also shown high variability among patients with BD [29–32]. The interrelationship between these clinical and functional variables is currently well known, such that patients with more episodes show poorer cognitive performance [33], and patients with greater cognitive deficits have worse psychosocial functioning levels [26,34]. Accordingly, a recent study applied latent class analysis and identified two subtypes of bipolar patients: functionally and cognitively impaired multiepisode patients and functionally and cognitively preserved patients with low episode recurrence [35]. The preliminary results of our study suggest that overall morbidity/clinical course would be relatively stable among patients with BD. Similarly, neurocognitive performance also tended to be stable over time in early longitudinal studies [36]. If these preliminary results of clinical and cognitive stability in BD were confirmed by further studies, clinical staging models would be actually describing subgroups of patients according to the profile of their clinical course/neurocognitive functioning rather than the progression of the disorder at a particular point of time. In that case, forthcoming studies should explore whether these different subgroups or profiles are explained by the existence of a continuum of severity or different underlying pathophysiological processes [30,37].

Potential limitations of our study must be taken into account. First, we included patients with around 15 years of illness and seven previous affective episodes. Therefore, we cannot rule out that an increase in morbidity could have occurred in the early stages of illness prior to inclusion in this study. Nevertheless, both studies and sub-analyses conducted in first episode patients failed to find a progressive clinical course in BD [22,23]. Second, we included only patients with a follow-up period of more than 48 uninterrupted months, which could imply a potential selection bias. However, we compared the sample of patients included in this study with a random sample of patients of our database not included because they had a follow-up shorter than 48 months and there were no differences in any clinical or demographical variable at baseline (all $Ps > 0.05$, results available upon request). Moreover, our sample had a relatively benign course based on the shortest time spent ill compared with previous studies [38,39]. However, this might be a consequence of having included patients with strict criteria of euthymia because, otherwise, morbidity would have tended to increase in the first half of the follow-up period of the study. In contrast, this study was conducted with a clinical sample (or prevalence sample), which might tend to overestimate the morbidity of patients with BD

[40]. On the other hand, it could be argued that an average period of 6–7 years was not enough to bring out an increase in morbidity. Although we plan to extend the period of observation in the coming years, it is worth noting that to date there is a trend towards less morbidity over time. Finally, this was an observational study in which patients were under naturalistic conditions of treatment. Thereby, each psychiatrist conducted the treatment according to clinical guidelines and the treatment was monitored — but not controlled — during the study. Maintenance treatment could have modified the course of the disorder overshadowing a trend towards an increase in morbidity. Notwithstanding this limitation, actually it is not possible to conduct studies of unmedicated BD patients for extended periods. Studies in the pre-pharmacological era were also inconsistent regarding whether the clinical course of BD is progressive or not. More recent studies were naturalistic in nature, but while some of them were also monitoring treatment during the study [22,23], others were not [2,19]. This methodological discrepancy could have contributed to the inconsistent results observed in this field. Likewise, as in previous studies in this field, we did not control changes in factors that could affect clinical course such as psychosocial interventions or familiar support.

5. Conclusions

In summary, we found no evidence to support the hypothesis of a progressively worsening course of BD. However, this could be the case in a subset of patients regardless of treatment. Future research should focus on the possible clinical and pathophysiological differences between these subgroups of patients with BD.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

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