Functional Outcome in the Middle Course of Bipolar Disorder

A Longitudinal Study

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Abstract: The aim of this study was to assess the long-term functional outcome of patients with bipolar disorder (BD). At baseline and after a follow-up period of at least 48 months, three measures of functioning were administered: psychosocial functioning (GAF), employment status (full-time, part-time, and unemployment/disability), and a self-reported measure of functional recovery. At baseline, patients with more than five previous affective episodes exhibited poorer outcomes on all measures of functioning than patients with less than five previous episodes. However, along a mean follow-up period of 77 months, measures of functioning tended to remain stable or improved slightly. These results highlight the limitation of studies comparing measures of functioning between patients with many and few episodes to evaluate functional outcome. Likewise, these preliminary results do not support the hypothesis that functional outcome deteriorates over the course of BD.

Key Words: Bipolar disorder, psychosocial functioning, neuroprogression, staging, long term

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Different models of clinical staging, in which illness features go through different stages from at-risk to more severe and disabling presentations, have been recently proposed for bipolar disorder (BD) (Berk et al., 2007; Kapczinski et al., 2009). Accordingly, BD began to be postulated as a neuroprogressive illness in subsequent reports (Berk, 2009; Berk et al., 2014; Gama et al., 2013; Kapczinski et al., 2014; Rodrigues et al., 2014).

One of the cornerstones of neuroprogression is the assumption that there is a worsening of functional outcome throughout the course of BD (Berk et al., 2014; Gama et al., 2013; Kapczinski et al., 2014; Rodrigues et al., 2014). This is based on studies such as that by Magalhães et al. (2012), which reported a relationship between a greater number of previous episodes and poorer functioning/quality of life both in cross-sectional and longitudinal (12 months) analyses. Similarly, Rosa et al. (2012) showed that BD patients who experienced their first episode had better functioning than patients with multiple episodes and stated that "functional impairment may be a consequence of enduring neurotoxicity of mood episodes and consequent neurostructural abnormalities." However, findings of this type of approach, comparing patients with many and few episodes, do not necessarily imply neuroprogression (Martino et al., 2016). Even if functional outcome were found to be stable in BD, patients with more severe forms of the disorder—*i.e.*, higher risk of recurrences from the beginning of illness—would have worse psychosocial functioning. Another study by Rosa et al. (2014) is usually cited as evidence of deterioration in functional outcome. In that study, patients in later stages of Kapczinski's staging model had worse results on the Functioning Assessment Short Test than patients in early stages. However, it might be difficult to infer a progressive decline in functional outcome from these results because the stages described by Kapczinski are partially defined on the basis of patients' functioning during euthymia. Contrarily, a longitudinal study reported that the occupational and residential statuses improved in BD patients between 6- and 48-month assessments after recovery from an episode of mania (Tohen et al., 1990).

Overall, although a worsening of functional outcome throughout the course of BD has been taken as evidence of neuroprogression in several reviews (Berk et al., 2014; Gama et al., 2013; Kapczinski et al., 2014; Rodrigues et al., 2014), the evidence is scarce and limited. Then, the aim of this preliminary report was to assess the long-term functional outcome of patients with BD under naturalistic conditions of treatment.

METHODS

Fifty-five 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, diagnosis of BD type I (BDI) or II (BDII) according to *DSM-IV* using the Structured Clinical Interview for *DSM-IV* (SCID) (First et al., 1996), a follow-up period 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 both at baseline and at the end of follow-up. Exclusion criteria were antecedent history of substance abuse/dependence, history of mental retardation, neurological disease, or any unstable clinical condition that could affect functional outcome. The study was approved by the Hospital Ethics Committee, and all subjects gave written informed consent for their participation after receiving a complete description of the study.

Clinical Assessment

Demographic and clinical information at baseline was obtained from clinical charts and direct patient interview. During the follow-up period, affective episodes (depressive and hypomanic/manic) based on *DSM-IV* criteria were documented.

Functional Assessment

All patients were evaluated at baseline (T1) and after at least 48 months of follow-up (T2)—when they were euthymic—with three simple measures of functional outcome: (1) General Assessment of Functioning (GAF) (*DSM-IV*)—the rater was instructed to use the GAF to assess functioning in the last month and not symptoms because other measures of mood symptoms were obtained at baseline and end of follow-up; (2) employment status—it was categorized as full-time, part-time, and unemployment/disability; and (3) functional recovery. This measure was conceptualized as a dichotomous variable (yes/no) based on the patient self-report to the question "have you reached the level of family, social and work functioning that you had before the onset of illness?"

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Data Analysis

Because most continuous variables such as GAF score or subclinical symptomatology were skewed, nonparametric tests were used. Differences at baseline between patients with more or less than five previous affective episodes were analyzed with the Mann–Whitney test for continuous variables and chi-squared test for categorical variables. Differences between T1 and T2 were analyzed as two related samples with the Wilcoxon signed-rank test for ordinal/continuous variables and McNemar or Marginal Homogeneity Test for categorical variables. Spearman's correlation coefficients were used to assess the relationship between GAF scores and number of affective episodes.

RESULTS

At study entry, patients had a mean age of 43.64 (standard deviation, SD = 12.62; median = 44; range = 43) years, 46.3% were BDI, and 53.7% BDII. Patients had a length of illness of 12.65 (SD = 6.87, median = 14.50, range = 29) years with 3.88 (SD = 1.89, median = 3, range = 8) previous depressive episodes and 2.76 (SD = 1.81, median = 2, range = 7) previous hypomanic/manic episodes. The period between baseline (T1) and the end of follow-up (T2) was 77.33 (SD = 18.42, median = 73, range = 73) months during which patients experienced a mean of 2.15 (SD = 2.26, median = 2, range = 9) depressive episodes and 1.02 (SD = 1.35, median = 0.50, range = 6) hypomanic/manic episodes. There were no differences between T1 and T2 in terms of subclinical symptoms or pharmacological exposure (Table 1).

First, we compared measures of functional outcome at baseline between patients with more ($n = 33$) or less ($n = 22$) than five previous affective episodes. Compared with patients with less than five previous affective episodes, those with more episodes showed worse psychosocial functioning [75.67 (SD = 9.19, median = 78.50, range = 40) *vs.* 85.00 (SD = 8.36, median = 90, range = 35), Mann–Whitney $Z = -3.17$, $p = 0.001$] and poorer employment status (unemployment/disability: 56.7% vs. 12.5%, part-time: 30.0 vs. 16.7%, full-time: 13.3 *vs.* 70.8%; $\chi^2 = 19.34$, $p < 0.001$). Likewise, patients with more previous affective episodes self-reported worse levels of functional recovery than patients with fewer episodes (56.7% *vs.* 85.0%, $\chi^2 = 4.42$, $p = 0.035$). Finally, baseline GAF scores were associated with the number of previous hypomanic/manic ($R = -0.46$, $p = 0.001$) and depressive episodes ($R = -0.30$, $p = 0.035$).

Then, we explored the changes in measures of functional outcome in each patient along the follow-up period. Overall, patients showed a better level of psychosocial functioning and functional recovery at the end of the follow-up period than at study entry (Table 1). Likewise, during the follow-up period, a trend towards improvement in employment status was observed although it did not reach statistical significance (Table 1). There was an association between GAF at T2 and the number of hypomanic/manic (Spearman's $R = -0.31$, $p = 0.027$) and depressive episodes ($R = -0.42$, $p = 0.002$) suffered during the follow-up period. However, changes in psychosocial functioning between T1 and T2 were not associated with the duration of follow-up of each patient (Spearman's $R = 0.13$, $p = 0.33$) or with the number of hypomanic/manic ($R = 0.11$, $p = 0.43$) or depressive ($R = -0.17$, $p = 0.22$) episodes experienced during this period. The same pattern of results was obtained when frequency of episodes (number of episodes for years of follow-up) was used instead of number of episodes.

DISCUSSION

During a mean follow-up longer than 6 years, patients with euthymic BD improved significantly their level of psychosocial functioning and employment status, and they tended to self-report a better rate of functional recovery. The improvement in psychosocial functioning is probably of little clinical relevance because there was an average change of less than three points in the GAF score. Overall, these results showed that the level of functioning remained stable or improved slightly during the follow-up period of the study. Therefore, these preliminary results do not support the hypothesis that functional outcome deteriorates over the course of BD as suggested in reports about staging and neuroprogression (Berk, 2009; Berk et al., 2014; Gama et al., 2013; Kapczinski et al., 2014; Rodrigues et al., 2014).

TABLE 1. Affective Symptoms, Pharmacological Exposure, and Functional Measures at Baseline and Follow-up

	Baseline (T1)	Follow-up (T2)	Test/Significance
HDRS, mean (SD)	1.65 (1.80)	1.78 (1.64)	
Median (range)	1 (6)	2 (5)	$Z = -0.39$, $p = 0.70$[a]
YMRS, mean (SD)	0.56 (1.02)	0.78 (1.22)	
Median (range)	0 (4)	0 (5)	$Z = -1.34$, $p = 0.18$[a]
Benzodiazepines (%)	29.6	35.2	$p = 0.25$[b]
Antidepressants (%)	50.0	37.0	$p = 0.12$[b]
Mood stabilizers (%)	96.3	92.6	$p = 0.50$[b]
Antipsychotics (%)	48.1	48.1	$p = 1.0$[b]
GAF score, mean (SD)	79.81 (9.92)	82.43 (8.96)	
Median (range)	80 (45)	85 (45)	$Z = -2.61$, $p = 0.009$[a]
Functional recovery (%)	57.42	70.4	$p = 0.039$[b]
Employment status (%)			
Unemployment/disability	37.0	22.2	$p = 0.056$[c]
Part-time	24.1	33.3	
Full-time	38.9	44.5	

HDRS indicates Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

[a]Wilcoxon signed-rank test.

[b]McNemar test.

[c]Marginal Homogeneity Test.

Another interesting finding was that when patients were categorized at baseline according to the number of previous affective episodes, those with higher number of previous episodes had poorer functioning in the three measures considered in this study compared with patients with lower number of episodes. These results, together with the absence of worsening during follow-up, highlight the limitation of studies comparing patients with many and few episodes to evaluate deterioration of functioning as evidence of neuroprogression in BD (Magalhães et al., 2012; Rosa et al., 2012, 2014). Moreover, psychosocial functioning at baseline was related to the number of previous hypomanic/manic and depressive episodes. Similarly, psychosocial functioning at the end of follow-up was related to the number of affective episodes suffered during the study period. On the contrary, the number of episodes occurred during the follow-up was not associated with changes in psychosocial functioning in that period. Together, these results suggest that patients with more episodes tended to be those with worst functioning and patients with fewer episodes those of better functioning over the whole follow-up, although with a relatively stable functional outcome in both cases.

Functional outcome is highly variable among individuals with BD; some patients have difficulties in achieving full functional recovery after syndromic remission, whereas other patients keep a high level of social and occupational functioning despite their illness. Accordingly, a recent cross-sectional study applied latent class analysis and identified two subtypes of bipolar patients with good and poorer functional outcome, although their long-term course was not tested (Reinares et al., 2013). The preliminary results of our study suggest that psychosocial functioning would be relatively stable among patients with BD. Similarly, neurocognitive performance, which is closely related to functional outcome (Jaeger et al., 2007; Martino et al., 2009; Reinares et al., 2013), was also found to be heterogeneous in BD (Burdick et al., 2014; Martino et al., 2014) and it tended to be stable over time in early longitudinal studies (Samamé et al., 2014). If these preliminary results about stability of functional outcome and neurocognition were confirmed in further studies, clinical staging models proposed for BD may be describing subgroups of patients according to the severity of their clinical course (good and poorer neurocognitive performance and functional outcome) rather than the progression of the disorder at a particular point of time. In that case, studies could explore whether these different subgroups are explained by the existence of a continuum of severity or different underlying pathophysiological processes (Martino et al., 2016).

Certain methodological limitations of our study should be taken into account. First, although the measures of functioning employed in this study—such as GAF or employment status—are widely used in the literature, they do not cover multiple domains of functioning. Therefore, future longitudinal research should employ more multidimensional measures of functioning. 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. There were no differences between these patient groups in any clinical or functional variables (all $ps > 0.05$, results available upon request). In addition, this study was conducted with a clinical sample (or prevalence sample) that might underestimate the level of functioning of the entire population of patients with BD. Moreover, we included patients with a mean duration of illness of 12.65 years and around six previous affective episodes. Therefore, we cannot rule out the possibility that any change in functioning may occur during the first years after the onset of the disorder, which could be the focus of future studies. Finally, a larger sample size would allow us to conduct a more efficiently stratified analysis (for example, good and poor psychosocial functioning level). Taken together, these results should be considered preliminary and be subject to further replication.

CONCLUSIONS

In summary, our findings bring preliminary evidence that functional outcome tends to be stable over time in the middle course of BD. Likewise, these results highlight the limitations of studies comparing measures of functioning between patients with many and few episodes to evaluate functional outcome. Further longitudinal studies are needed to improve our knowledge about functional outcome in BD.

DISCLOSURE

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The authors declare no conflict of interest.

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