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ORIGINAL PAPER

# Modifiable and non-modifiable factors associated with functional impairment during the inter-episodic periods of bipolar disorder

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**Abstract** The chronic, long-term evolution of bipolar disorder (BD) requires a careful clinical characterization with prognostic implications in terms of symptom and functional control. The OPTHYMUM multicenter study was conducted in France with the objective of evaluating residual symptoms on overall functioning of BD patients during inter-episodic period. The aims of the present study were to identify the potentially modifiable (e.g., treatable) and non-modifiable variables associated with functional impairment during the inter-episodic periods of BD. Sample was divided into two groups according to level of functioning (adequate vs. impaired), based on the FAST scale total score. FAST cut-off for functional impairment is a score >11. The two subgroups were compared as per sociodemographic and clinical variables with standard univariate analyses, and a logistic regression model was created. The model as a whole contained independent non-modifiable factors (age, gender, BD type, illness duration) and modifiable factors (illness severity, predominant polarity, depressive and manic residual symptoms, comorbidities). The final model was statistically significant ($\chi^2 = 53.89$, $df = 5$, $p < 0.001$). Modifiable factors most strongly associated with functional impairment were manic predominant polarity (OR = 1.79, CI 95% 1.09–2.96, $p = 0.022$), residual depressive symptoms (OR = 1.30, CI 95% 1.18–1.43, $p < 0.001$) and illness severity (OR = 1.24, CI 95% 1.01–1.52, $p = 0.037$), whilst non-modifiable factor was illness duration (OR = 1.03, CI 95% 1.01–1.05, $p = 0.017$). Despite intrinsic and non-modifiable illness characteristics, a clinical-wise choice of treatment may help to improve control of manic relapses. Potential improvement of residual depressive symptoms may alleviate the functional burden associated with bipolar disorder.

**Keywords** Bipolar disorder · Inter-episodic periods · Functioning · Residual symptoms · Predominant polarity

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## Introduction

Bipolar disorder (BD) is a chronic condition historically thought to present a benign outcome between acute episodes [1]. This conviction was a pillar in differentiating BD from schizophrenia, together with a supposed absence of cognitive impairment and seemingly normal functioning between episodes [2]. Nonetheless, this diagnostic construct has been challenged in the last decades. Inter-episodic periods of illness in BD are associated with frequent persistence of residual symptoms, such as residual depressive symptoms, cognitive impairment or emotional dysregulation, which contribute to an increased

risk of recurrence and cause long-term disability in BD patients [3–5].

Despite modern treatments, a favorable outcome in BD patients is not always achieved, as the course of illness still involves multiple recurrences and impaired psychosocial functioning [6]. Notably, almost two-thirds of BD patients fail to achieve functional recovery during the inter-episodic period after 24 months from an acute admission, despite an evidence-based treatment that allows for a good syndromal recovery [7, 8]. A number of studies have addressed the levels of functioning and disability of people with BD [9]. However, while there is some standardization regarding diagnostic assessments, a wide variety of instruments has been traditionally used to assess functioning and disability, resulting in an extreme heterogeneity of measures and definitions for functioning [10].

The OPTHYMUM study [11, 12] was an observational multi-center, non-interventional study that evaluated the impact of residual symptoms on the functional outcome of a large sample of adult BD patients recruited during the inter-episodic period in France, and measured with a functioning scale (FAST, Functioning Assessment Short Test) presenting a set of different domains that contribute to comprehensively describe the burden of BD [13].

The gap between symptomatic remission and functional control of BD may recognize different concurring causes, some of which potentially improvable when properly identified.

The aims of the present study were to identify the potentially modifiable (e.g. treatable) and non-modifiable variables associated with functional impairment during the inter-episodic periods of BD.

## Materials and methods

### Study design and recruitment

The present study was based on a sample of 468 adult BD outpatients from a large multicenter, cross-sectional, non-interventional study conducted in France [11].

Patients were enrolled by psychiatrists in academic and non-academic hospital and office-based settings throughout France ($n = 97$; Ile-de-France region 22.7%, northwest regions 15.5%, northeast regions 12.4%, southeast regions 36.1%, southwest regions 13.4%) agreeing to participate to the study between April and October 2012. 46.4% of participating psychiatrists had a private practice, 38.1% worked in a public institution and 15.5% had a mixed practice.

During an initial 2-month period, the participating French psychiatrists could include their first six adult outpatients meeting the inclusion criteria.

Inclusion criteria were: (a) age 18 or older; (b) with a clinician-based diagnosis of BD type I or type II according to the DSM-IV-TR criteria [14]; (c) and in inter-episodic phase for at least 6 months (up to 5 years). Inter-episodic phase was defined on the remission criteria proposed by the International Society for Bipolar Disorder (ISBD) Task Force [15] as a Young Mania Rating Scale (YMRS) score <8 [16] and a Bipolar Depression Rating Scale (BDRS) score ≤8 [17].

Exclusion criteria were participation in a clinical trial.

The procedures followed in the study were approved by an independent national ethics committee (CPP Sud-Méditerranée IV) and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

### Measures and assessments

Clinical and sociodemographic data (i.e., age, gender, employment status, marital status, BD type, illness duration (since the first identified mood episode), predominant polarity (PP, defined as the tendency to relapse towards manic or depressive polarity in 2/3 of total episodes [18], overall illness severity of BD with the Clinical Global Impression Scale for BD (CGI-BP; [19]), anxiety disorder comorbidity, substance abuse or dependence were collected through patient interview [11]. All these variables were considered as non-modifiable factors, except predominant polarity, illness severity and psychiatric comorbidities. Pharmacological treatment was also recorded.

Depressive and manic residual symptoms were measured using the BDRS and the YMRS, respectively. The BDRS was designed to measure the severity of depressive symptoms in BD expressed by patients currently and during the past few days. It consists of 20 questions and total score range between 0 and 60. Higher scores indicate greater severity [17]. The YMRS was used to assess the severity of manic residual symptoms. The scale has 11 items and total score range also between 0 and 60. Higher scores indicate greater severity [16]. Depressive and manic residual symptoms, predominant polarity, illness severity and psychiatric comorbidities were considered as modifiable factors.

Psychosocial functioning was assessed during the interview using the FAST [13]. It is a valid and reliable instrument assessing functioning in BD patients. The FAST scale consists of 24 items that assess disability over the last 15 days in six specific areas: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The overall FAST score ranges from 0 to 72 points and higher scores indicate

**Table 1** Sociodemographic and clinical characteristics of patients ($N = 468$)

| Variable (yes listed) | *N* | % |
|---|---|---|
| Gender (female) | 276 | 59.0 |
| Employment | 227 | 48.5 |
| Married | 247 | 52.8 |
| Bipolar disorder, type I | 268 | 57.3 |
| Predominant polarity | | |
| Depressive | 265 | 56.6 |
| Manic | 149 | 31.8 |
| Not specified | 54 | 11.5 |
| Comorbidities | | |
| Anxiety disorders | 139 | 29.7 |
| Substance abuse or dependence | 69 | 14.7 |
| Medications | | |
| Lithium | 134 | 28.7 |
| Anticonvulsants | 235 | 50.2 |
| First-generation antipsychotics | 35 | 7.5 |
| Second-generation antipsychotics | 215 | 46.2 |
| Antidepressants | 183 | 39.1 |
| Benzodiazepines | 129 | 27.6 |
| Variable (quantitative) | Mean | SD |
| Age (years) | 47.7 | 12.5 |
| Illness duration | 17.6 | 10.7 |
| CGI-BD | 4.6 | 1.1 |
| Bipolar Depression Rating Scale | 4.4 | 2.4 |
| Young Mania Rating Scale | 1.8 | 1.9 |
| FAST | 12.1 | 10.0 |

*CGI-BD* Clinical Global Impressions Scale for Bipolar Disorder, *FAST* Functioning Assessment Short Test, *SD* standard deviation

greater disability. A threshold score above 11 indicates an overall functional impairment [13].

### Statistical analysis

The sample was divided into two groups according to the level of functioning, based on the FAST total score. Cut-off for functional impairment with the FAST is set as a total score higher than 11 [13]. Statistical comparisons between groups of patients were done using standard statistical tests: the Chi-square test for categorical variables and Student's *t* test or the Wilcoxon–Mann–Whitney test for continuous variables.

Variables were selected for inclusion in logistic regression modeling when significant at $p < 0.25$ in the univariate analysis, or when considered clinically relevant (e.g., age, gender). A stepwise-backwards logistic regression model was used to determine the predictive value of the non-modifiable factors (age, gender, BD type, illness duration,) and modifiable factors (illness severity, predominant polarity of BD, depressive and manic residual symptoms, comorbidities) on functional impairment.

The results are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed using the Statistical Package for the Social Sciences, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and the significance level was set at 5%.

## Results

The sample consisted of 468 euthymic BD patients. Sociodemographic and clinical characteristics of patients are presented in Table 1.

Forty-two percent ($n = 197$) of the patients presented poor overall functioning (FAST total score >11). These patients had longer illness duration ($p = 0.011$), more severe illness (CGI-BD score; $p < 0.001$) and significantly higher BDRS ($p < 0.001$) and YMRS ($p = 0.046$) scores (Table 2). Patients with functional impairment were more frequently diagnosed with BD type I, and presented significantly less frequently a depressive predominant polarity ($p = 0.046$). Manic predominant polarity was significantly more often associated with functional impairment ($p = 0.023$). Groups did not differ with respect to age and gender.

A multivariate logistic regression analysis was performed to assess the impact of modifiable and non-modifiable factors on the likelihood that patients presented a functional impairment as measured with FAST total score (Table 3). The final model was statistically significant ($\chi^2 = 53.89$, $df = 5$, $p < 0.001$). Modifiable factors most strongly associated with functional impairment compared to patients with adequate functioning were manic predominant polarity (OR = 1.79, CI 95% 1.09–2.96, $p = 0.022$), residual depressive symptoms (OR = 1.30, CI 95% 1.18–1.43, $p < 0.001$) and illness severity (OR = 1.24, CI 95% 1.01–1.52, $p = 0.037$), whilst non-modifiable factor was illness duration (OR = 1.03, CI 95% 1.01–1.05, $p = 0.017$).

## Discussion

The present study was aimed at identifying possible modifiable and non-modifiable factors associated to a worse functional outcome in a sample of BD type I and II patients during the inter-episodic periods.

Interestingly, in our study, BD diagnostic subtypes do not seem to have direct prognostic implications. This is in line with the finding that severity of depression is more

**Table 2** Non-modifiable and modifiable factors in functionally impaired and non-impaired patients according to FAST score

| Non-modifiable factors | FAST ≤11 ($n = 271$) | FAST >11 ($n = 197$) | $t$, $\chi^2$, $U$ | $p$ value |
|---|---|---|---|---|
| Age, mean (SD) | 47.0 (12.5) | 48.5 (12.5) | 1.29[a] | 0.198 |
| Gender (female), *n* (%) | 162 (59.8) | 114 (57.9) | 0.17[b] | 0.678 |
| Diagnostic type, *n* (%) | | | | |
| Bipolar type I | 145 (53.5) | 123 (62.4) | 3.72[b] | 0.054 |
| Bipolar type II | 126 (46.5) | 74 (37.6) | | |
| Illness duration (years), mean (SD) | 16.5 (10.4) | 19.1 (10.9) | 22.01[c] | 0.011 |
| Modifiable factors | | | | |
| Illness severity (CGI-BD), mean (SD) | 4.4 (1.1) | 4.9 (1.1) | 32.37[c] | <0.001 |
| Predominant polarity of BD, *n* (%) | | | | |
| Depressive | 164 (60.5) | 101 (51.3) | 3.97[b] | 0.046 |
| Manic | 75 (27.7) | 74 (37.6) | 5.14[b] | 0.023 |
| Not specified | 32 (11.8) | 22 (11.2) | 0.05[b] | 0.830 |
| Mood residual symptoms | | | | |
| Bipolar Depression Rating Scale, mean (SD) | 3.9 (2.3) | 5.1 (2.2) | 34.59[c] | <0.001 |
| Young Mania Rating Scale, mean (SD) | 1.6 (1.8) | 2.1 (2.0) | 29.50[c] | 0.046 |
| Comobidities | | | | |
| Anxiety disorders, *n* (%) | 74 (27.3) | 65 (33.0) | 1.77[b] | 0.184 |
| Substance abuse or dependence, *n* (%) | 39 (14.8) | 30 (15.9) | 0.10[b] | 0.748 |

*FAST >11* cut-off for impaired overall functioning, *BD* bipolar disorder, *CGI-BD* clinical global impression for bipolar disorder, *FAST* Functioning Assessment Short Test, *SD* standard deviation

[a] Student's *t* test (*t*)

[b] Chi-square test ($\chi^2$)

[c] Wilcoxon–Mann–Whitney test (*U*)

**Table 3** Stepwise-backward logistic regression model predicting functional impairment

| Predictive variables[a] | Wald | $p$ value | OR | 95% CI |
|---|---|---|---|---|
| Non-modifiable | | | | |
| Illness duration | 5.730 | 0.017 | 1.03 | 1.01–1.05 |
| Modifiable | | | | |
| Illness severity | 4.340 | 0.037 | 1.24 | 1.01–1.52 |
| Manic predominant polarity | 5.245 | 0.022 | 1.79 | 1.09–2.96 |
| Residual depressive symptoms | 28.847 | <0.001 | 1.30 | 1.18–1.43 |

[a] Variables included in the first step: age, gender, bipolar type, illness duration, predominant polarity (manic, depressive, not specified), illness severity, residual depressive symptoms, residual manic symptoms, anxiety disorders

predictive of outcome in BD type I and II patients, and that these subgroups may differ little in proneness to depressive states [20]. Also, contrary to what was thought in the past, approximately one-half of the patients with bipolar II disorder may present cognitive dysfunction and functional impairment [21].

In our sample, the concept of predominant polarity seemed able to better predict functional outcome. Significantly, more patients with depressive predominant polarity show little or no impairment in functioning measured with the FAST scale, whilst significantly more manic predominant polarity patients show some degree of functional impairment. Moreover, in our logistic regression, manic predominant polarity was the strongest factor associated with functional impairment. This seems in line with the findings that the number of manic relapses may have a long-term neuropsychological impact [22], and it may bear strong implications on the clinical management of BD [23]. For instance, patients with manic predominant polarity usually bear higher comorbidities with substance use and poor adherence to treatment [24, 25]. The impact of manic predominant polarity could be somehow softened by a careful assessment of adherence, the choice of adequate treatments and interventions aimed at targeting specifically manic relapses (e.g., treatment with high manic polarity index) [26–29].

The persistence of residual depressive symptoms also appears to be a modifiable factor significantly and strongly related to functional impairment both in our univariate analysis, and in the regression model. Residual depressive symptoms may contribute to impaired functioning and worse quality of life [3, 30, 31]. Albeit potentially modifiable, the therapeutic approach of these symptoms is complex, and historically poses a challenge in the case management of a BD patient [32]. Moreover, very few guidelines

provide recommendations on the management of residual depressive symptoms, such as the maintenance treatment combination [8].

Among the non-modifiable factors included in our logistic regression, only the illness duration was associated with functional impairment. However, it presented a small contribution to a worse functional outcome. It is commonly assumed that longer duration of illness leads to more pronounced clinical and pathological changes, including treatment refractoriness neuropathological changes and neuropsychological deficits [33, 34]. Today, the progressive conceptualization of BD as chronic and/or recurrent disorder takes somehow into account that longer periods of illness bear more recurrences, which strongly contribute to the overall final functioning of the patients [35, 36]. It is possible that in our predictive model the weight of illness duration contributed less to the model being modulated by the other predictors. This seems in line with the finding that functional outcome could be not function of illness duration, but rather of episode density (number of episodes/years of illness) which, together with other clinical features such as depressive residual symptoms, would be more useful in defining prognostic classes [30].

A substantial gap remains between what can be achieved by clinical actions and what patients and their relatives can expect from health care providers. A more precise diagnostic approach with strong prognostic implications will allow to better tailor specific treatments in the future, improving the burden of suffering associated with mental disorders [37].

In the short term, the inclusion of predominant polarity in the therapy decision-making process seems a feasible and clinical-wise decision that bears immediate diagnostic [38], clinical and therapeutic implications [39, 40].

The results from the present study should be interpreted with caution in light of several limitations. The cross-sectional design of the study did not allow analysis of the causal relationships between the different modifiable/non-modifiable factors and the psychosocial functioning. To facilitate the feasibility of the study, none objective cognitive evaluation of the patients has been performed. Cognitive factors may directly or indirectly contribute to psychosocial outcome in BD [41, 42]. Nonetheless, duration of illness and residual depressive symptoms, contemplated in the present study, seems associated with poor performance in executive function in BD [43], so that a role of cognitive dysfunction in patients with longer course of BD and persistent residual depressive symptoms may be inferred. Also, it must be considered that cognitive deficits could represent a therapeutic target which is partially independent from subsyndromal symptoms [35]. Moreover, confounding variables such as medications or current psychosocial treatment were not controlled for.

Prospective longitudinal studies, even if only for 1 year, with more accurate and repeated objective assessments, such as neurocognitive evaluation, might provide more information characterizing modifiable and non-modifiable factors associated with functional impairment on BD.

In conclusion, the burden of BD represents a major cause of concern from the perspective of patients and professionals alike. The efforts in better characterizing and defining BD populations are pointing towards a stratified, ideally personalized approach to the clinical and therapeutic management of BD. Despite the difficulties in controlling some intrinsic aspect of the illness, it is possible for clinicians to address properly improvable aspects like the overall illness severity and a careful evaluation of residual depressive symptoms. Patients presenting a tendency to predominantly relapse into mania may bear strong functional limitations. Yet, most of the treatment options we have today are actually more effective in containing this polarity of the illness. Last, it is possible that in future years the improvement of early detection and interventions for BD may somehow control with the illness duration, the most intrinsic and non-modifiable element, so that the illness progression may be hopefully interrupted or, at least, slowed down.

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**Compliance with ethical standards**

**Ethical statement** The procedures followed in the study were approved by an independent national ethics committee (CPP Sud-Méditerranée IV) and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

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