Journal of Affective Disorders 188 (2015) 319–323

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The role of comorbidities in duration of untreated illness for bipolar spectrum disorders

A. Murru [a], D. Primavera [b], M. Oliva [b], M.L. Meloni [b], E. Vieta [a,*], B. Carpiniello [b]

[a] Bipolar Disorders Unit, Institute of Neuroscience, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, c/Villaroel 170, esc. 12 pl. 0, 08036 Barcelona (ES), Catalonia, Spain

[b] Department of Public Health, Section of Psychiatry and Psychiatric Clinic, University of Cagliari, Via Liguria 13, 09127 Cagliari, Italy

ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form
2 September 2015
Accepted 5 September 2015
Available online 10 September 2015

Keywords:
Bipolar Disorder
Duration of Untreated Illness
DUI
Personality Disorders
Predominant Polarity

ABSTRACT

Background: Growing interest has been given to the construct of Duration of untreated illness (DUI) on the outcome of bipolar disorder (BD), due to its potentially modifiable nature. The aim of this study was to identify possible clinical correlates of DUI in a sample of BD patients.

Method: 119 BD spectrum patients included. DUI rate was calculated and dichotomized into short DUI and long DUI subgroups, cut-off 24 months. These subgroups were compared for socio-demographic and clinical variables. Significant results were included into direct logistic regressions to assess their impact on the likelihood of presenting with long DUI.

Results: Mean DUI ± SD was 75.6 ± 98.3 months. Short DUI subgroup comprised 56 (47.1%), long DUI 60 (52.9%) patients. Age at onset of BD was lower in the long DUI subgroup ($p=0.021$), illness duration longer ($p=0.011$). Long DUI subgroup showed significantly more comorbidity with Axis I ($p=0.002$) and personality disorders ($p=0.017$), less interepisodic recovery ($p<0.001$) and less Manic Predominant Polarity ($p=0.009$). Direct logistic regression as a full model was significant, correctly classifying 76.7% of cases. A unique statistically significant contribution was made by: Manic Predominant Polarity, Personality Disorder Comorbidity, and Total Changes in Medications.

Limitations: Partial retrospective data, cross sectional study.

Conclusions: DUI was longer than 24 months in half of the sample. Psychotic /Manic onset contributed to a quick diagnostic classification. Personality disorders in depressed patients could delay a correct diagnosis of BD, factors associated with an increased likelihood of BD must be considered. More research on personality disorder comorbidities is needed.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating illness, with an estimated population prevalence of 1–5%, and that often remains unrecognized for long periods (Berk et al., 2007; Merikangas et al., 2007). In the last fifteen years the problem of its correct diagnosis has been raised and addressed in clinical research, resulting in far-from-perfect awareness that yet fails to be translated into correct diagnostic assessments (Ghaemi et al., 1999; Hirschfeld, 2014).

BD can be misdiagnosed easily with other conditions and depending on the acute episode it is presenting with: manic and/or psychotic acute episodes may fail to be differentiated from other psychotic conditions, whilst on the other polarity BD may present itself with one or more acute depressions before (hypo)manic symptoms manifest (Altamura and Goikolea, 2008; Altamura et al., 2015; Faedda et al., 2015).

The onset of BD reportedly involves a major depressive episode in approximately half of BD type I patients, and three-quarters of BD type II patients (Baldessarini et al., 2013). Variable proportions of BD patients present two or more episodes of depression before manifesting a (hypo)manic or mixed episode, required for diagnosis of BD (Angst et al., 2011). The observed interval from an initial episode of depression to clinical diagnosis of bipolar disorder typically is from 5 to 15 years (Angst et al., 2005; Fiedorowicz et al., 2011).

The need to correctly identify patients bears the consequent need to reduce the latency to a proper evidence-based treatment. A major barrier to fully understanding the nature and size of diagnostic delay has been that published studies often failed to use consistent definitions of the phenomenon. Duration of Untreated Illness (DUI) is a clinical construct originally introduced to study schizophrenia and later extended to bipolar disorder and other conditions (Altamura et al., 2010b; Dell'osso and Altamura, 2010;

* Corresponding author. Fax: +34932275795.
E-mail address: EVIETA@CLINIC.UB.ES (E. Vieta).

http://dx.doi.org/10.1016/j.jad.2015.09.009
0165-0327/

Marshall et al., 2005). It is defined as the time elapsed between the onset of an illness and the first adequate pharmacological treatment, and has shown a predictor of outcome and clinical course across different psychiatric disorders (Altamura et al., 2010a; Penttilä et al., 2014).

In the case of BD, DUI calculated by subtracting the age of onset of the disorder and the age of first adequate pharmacological treatment (i.e. lithium, valproate, and atypical antipsychotics), according to international clinical guidelines (Grunze et al., 2013; Nivoli et al., 2012, 2011). DUI may provide a standard definition for the latency to appropriate treatment and this can help identifying related clinical factors that may be potentially modifiable.

1.1. Aims of the study

The objective of this study was to analyze demographical, clinical and therapeutic correlates of DUI in BD and its possible consequences on the course of illness, especially focusing on the clinical concept of Predominant Polarity. A secondary objective of this study was to create a model of characteristics clinically associated with short or long DUI.

2. Methods

2.1. Study design and sample

A cross-sectional study with some variables coming from a prospective assessment and others collected from a retrospective evaluation.

The sample of outpatients was recruited from those participating in the systematic follow-up of the Psychiatric Clinic of the University of Cagliari, which recruits patients from a catchment area of 75,000 inhabitants. Inclusion criteria comprised DSM-IV-TR diagnosis of Bipolar Disorder type I, type II, and NOS. Subjects must be of at least 18 years of age, and having signed written informed consent. As this was a naturalistic study, the treatment strategy and the frequency of visits were chosen by the treating psychiatrist on the basis of each patient's condition. Each patient received at least approximately 4 visits per year. Clinical histories were collected retrospectively from standardized clinical records routinely used in the community mental health center, as described by procedures suggested by the Association for Methodology and Documentation in Psychiatry (AMDP) (Conti et al., 1988; Guy and Ban, 1982) and applied in previous clinical studies (Carpiniello et al., 2002; Primavera et al., 2012). Data have been extracted between January 2012 and march 2014.

2.2. DUI definition

DUI was defined as the interval between the onset of the first mood episode of any polarity (American Psychiatric Association, 2000) and the first treatment with mood stabilizers that patients received at standard doses for an adequate period of time, according to currently available guidelines (Grunze et al., 2013; Nivoli et al., 2012, 2011). The assessment of the DUI was based on the clinical information derived from the diagnostic interview and on all additional information provided by patients, caregivers and clinical histories. Considering the intrinsic retrospective nature of DUI that makes it difficult for a patient to recall the exact latency between initial symptom presentations and actual diagnosis, patients were divided into two groups according to a DUI <2 years ($n=63$) and ≥ 2 years ($n=56$). This threshold was arbitrarily chosen on the basis of previous studies on bipolar disorder (Altamura et al., 2010a; Altamura et al., 2010b; Drancourt et al., 2013) and schizophrenia (Altamura et al., 2001).

2.3. Statistics

DUI rate was calculated, and after dividing patients into "short DUI" and "long DUI", comparisons between those groups were conducted: $\chi 2$ tests were used to compare categorical data, ANOVA 1-way for continuous variables. Statistically significant results were then included into direct logistic regressions to assess their impact on the likelihood that the patients would present with long DUI. All p values were two-tailed and statistical significance was set at $p<0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS v.20.0.0. for Windows®).

3. Results

A total of 119 individuals were included in the present study: 79 (66.4%) affected by BD type I, 34 type II (28.6%) and 5 BD NAS (4.2%). A total of 66 patients (55.5%) were female. Mean age $\pm$ SD in the sample was 52.24 ± 13.28, mean age at onset 28.54 ± 10.64, with an average duration of illness of 23.71 ± 11.34 years.

DUI showed a great variability and a non-normal distribution, with positive skew. Mean DUI $\pm$SD was 75.6 ± 98.3 months. Median DUI was 24 months (range 1–480). For statistical purposes, the sample was divided into a "short DUI" (DUI <2 year) and "long DUI" (DUI >2 year) subgroups. Following our assessment criteria 56 (47.1%), patients presented a short DUI and 60 (52.9%) patients a long DUI.

Socio-demographic differences were generally not statistically significant between DUI subgroups, with longer DUI BD patients more likely to be separated/divorced ($p=0.010$).

Age at onset of BD was lower in the long DUI subgroup ($p=0.021$), which also showed a longer illness duration ($p=0.011$). No significant differences in bipolar diagnostic subgroups were found among patients with long or short DUI. Clinical Differences were evidenced among the DUI subgroups. Long DUI subgroup showed significantly more comorbidity with Axis I ($p=0.002$) and personality disorders ($p=0.017$), less interepisodic recovery ($p<0.001$) and Manic Predominant Polarity ($p=0.009$), but higher total, hypomanic and depressive recurrences ($p=0.005$). Hospitalizations were more frequent in longer DUI subgroup ($p=0.012$) as well as changes in medication ($p=0.003$).

Results are presented in Table 1 and Table 2.

Direct logistic regression was performed to assess the contribution of a number of variables in explaining a short or long DUI. Included independent variables were: (1) *Comorbidity with axis I disorders*; (2) *Comorbidity with personality disorders*; (3) *Manic predominant polarity*; (4) *Age at onset;* (5) *Change in medication;* (6) *Total depressive* recurrences. (7) *Interepisodic remission.* The full model containing all predictors was statistically significant, $\chi^2=43.320$, $p<0.001$, explaining between 31.2% (Cox and Snell R square) and 41.6% (Nagelkerke R squared) of the variance in DUI status, and correctly classifying 76.7% of cases. Only three of the independent variables made a unique statistically significant contribution to the model: *Manic Predominant Polarity* ($p=0.041$), *Personality Disorder Comorbidity* ($p=0.047$), *Total Changes in Medications* ($p=0.032$). The strongest contributor was *Manic Predominant Polarity*, recording an odds ratio of 0.226. This indicated that patients presenting a manic predominant polarity were over ($1/0.226=4.424$) 4 times less likely to have a long DUI. The odds ratio for personality disorder comorbidity was 0.292, meaning that patients with personality disorder comorbidity were 3.424 times more likely to present a long DUI. The last significant unique contribution was *Total Changes in Medications*, recording an odds ratio of 1.151, meaning that patients with more frequent changes in medication were likely to be in the long DUI subgroup.