Predictors of recurrence during long-term treatment of bipolar I and II disorders. A 4 year prospective naturalistic study

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ABSTRACT

Despite the large number of treatments available for bipolar disorder (BD), more than one half of patients have a recurrence within 2 years, and over 90% experience at least one additional affective episode during their lifetime.

Methods: The aim of this study was to test the impact of a number of demographic and clinical features on the risk to recurrence in a real-world representative sample of 266 outpatients with BD-I or II treated in a naturalistic setting during a 4-years-follow-up period.

Results: We found that the number of episodes per year after study entry, compared to the number of episodes per year before study entry, significantly decreased and that about one third of patients had no recurrences during the observation period. The length of follow-up and the number of previous episodes, mainly depressive, predicted the risk of recurrence, while female gender, higher age at intake, and a higher frequency of past mixed episodes predicted a higher frequency of recurrences.

Limitations: The study had some limitations to consider: i.e. the risk of poor reliability of information on the previous course of illness or the naturalistic treatment during the follow-up.

Conclusions: Our study suggests that (a) an evidence-based long-term treatment, with regular follow-up visits could improve the course of disease and prognosis; (b) clinicians should carefully consider the presence of a high number of mixed episodes, to provide more targeted treatment strategies; (c) an appropriate use of anti-depressants in selected patients did not worsen the course of illness.

1. Introduction

Bipolar disorder (BD) is a common, highly disabling and recurrent illness, affecting 1–2% of the general population, that causes a lifelong burden in affected individuals (Goodwin and Jamison, 2007; Fagiolini et al., 2013). Treatment of this pleomorphic disease includes pharmacotherapy in combination with psychoeducational and/or psychological interventions (APA, 2002; Miklowitz and Scott, 2009; Fountoulakis et al., 2012).

Although in the last 2 decades important advances have been made in pharmacological and non-pharmacological treatments (Miklowitz and Scott, 2009; Fountoulakis et al., 2012; Goodwin et al., 2016) more than one half of patients with BD have a recurrence within 2 years, and over 90% experience at least one additional affective episode during their lifetime (Solomon et al., 1995).

In order to improve the prognostic ability of clinicians, and to help them select targeted treatments, a number of studies investigated the long-term predictors of relapses and recurrences in BD.

Several studies showed that the risk of relapse or recurrence is related to the number of previous episodes (Keller et al., 1987; Tohen et al., 1990; Altman et al., 2006; Perlis et al., 2006; De Dios et al., 2012), the persistence of residual symptoms (Keller et al., 1992; Judd et al., 2003; Altman et al., 2006; Perlis et al., 2006; De Dios et al., 2012; Cretu et al., 2016) or the poor sleep quality between episodes (De Dios et al., 2012; Cretu et al., 2016), psychiatric comorbidity (Tohen et al., 2003) such as lifetime anxiety, eating disorders or substance abuse disorder at study entry (Perlis et al., 2006), mixed onset (Tundo et al., 2015) mixed episodes in the past course (Dell’Osso et al., 2006; Berk et al., 2005; Vieta, 2005; González-Pinto et al., 2007; Peselow et al., 2016; Sportiche et al., 2017), poor adherence to pharmacological treatments or medication discontinuation by psychiatrists or by patients themselves (Keller et al., 1992; Fekadu, 2006; De Dios et al., 2012;...
Simhandl et al., 2014; Li et al., 2014), lack of family and social support, low educational level and not returning to work after episodes (Altman et al., 2006; De Dios et al., 2012; Li et al., 2014), antidepressants use in BD with rapid cycling course (El-Mallah et al., 2015). Nevertheless, other studies did not confirm the relationship between risk of relapse or recurrence and number of previous episodes (Fekadu et al., 2006; Simhandl et al., 2014), psychiatric comorbidity (Simhandl et al., 2014), polarity of first episode (Simhandl et al., 2014), marital status (proxy to family support) (Simhandl et al., 2014), education level (Fekadu et al., 2006) and antidepressant use in BD (Tohen et al., 2003; Fekadu, 2006).

The discrepancies in results could depend on the heterogeneity of inclusion criteria (patients with BD-I or BD-I and II, in-patients or outpatients or both), outcome definition, and follow-up duration (varying from 1 to 5 years).

Overall, the literature on predictors of relapses and recurrences during long-term treatment in BD disorder is limited and, at least in part, controversial.

In light of the clinical importance of the topic, this study aimed at complementing the results of previous controlled and naturalistic studies by investigating the impact of a number of demographic and clinical features on the risk to recurrence in a real-word representative sample of outpatients with BD-I or II treated in a naturalistic setting.

2. Material and methods

2.1. Subjects

We included consecutive patients recruited from January 2002 through January 2006 at the Section of Psychiatry, Department of Clinical and Experimental Medicine, University of Pisa, Italy and at the Istituto di Psicopatologia in Rome, Italy–two Italian centers specialized in mood and anxiety disorders. Patient enrolment criteria were age 18–65 years, meeting DSM IV criteria for BD-I or II (APA, 1994), and receiving prophylactic treatment for at least 8 months. Exclusion criteria were mood disorders induced by medical or neurological conditions.

2.2. Procedure

All subjects underwent initial diagnostic assessments by the study’s two senior psychiatrists (LM, AT) using the Structured Clinical Interview for DSM IV Axis I Disorders-Patient Version (SCID-I/P) (First et al., 1997) to interview all participants. The Semi-structured Interview for Mood Disorders (SIMD) (Cassano et al., 1988) was used to collect participants’ demographic and retrospective clinical data. SIMD had been developed to gather systematic information on family history, previous number and polarity of episodes, suicide attempts in current and previous episodes, and psychotic symptoms. Whenever possible, secondary clinical data, including information obtained from other informants as well as any available past medical records, were used to support patient information.

Diagnosis of manic, hypomanic, and depressive episode in BD-I and II, and of mixed episode in BD-I was made according to DSM-IV criteria (APA, 1994). As no official criteria are available for diagnosing mixed episodes in BD-II, we used Koukopoulos's criteria (Koukopoulos, 1999) that have been validated by Benazzi et al. (2004) and by Sani et al. (2014). According to these criteria, we defined mixed BD-II episode (or mixed depression) as a major depressive episode including three or more of the following eight additional symptoms: inner tension/agitation, racing or crowded thoughts, irritability or unprovoked feeling of rage, absence of signs of retardation, talkativeness, dramatic description of suffering or frequent spells of weeping, mood lability or marked reactivity, and early insomnia. A major depressive episode plus only psychomotor agitation, a condition usually named “agitated depression”, was diagnosed as depressive episode and not as mixed BD-II episode.

Longitudinal follow-up evaluation (LIFE) (Keller et al., 1987) was administered every 16 week during the follow-up period in order to collect data about recurrences and treatments.

All patients gave written informed consent for data collection and for their use in anonymous and aggregate form, and the local ethical committees approved the research project.

2.3. Treatment

First-line treatment was chosen by the senior clinicians (AT, LM) according to the international guidelines and clinical experience (First et al., 1996; American Psychiatric Association APA, 2002; Ghaemi, 2003), and included one mood stabilizer, mainly lithium or divalproex or carbamazepine. If patient response was inadequate, a combination of two mood stabilizers, mainly lithium plus one anticonvulsant was utilized. If necessary, mood stabilizer(s) were augmented with an anti-psychotic (acute manic or mixed episode or prevalent manic or mixed recurrences) or an antidepressant (acute depressive episode or prevalent depressive recurrences). The use of antidepressants followed specific guidelines consistent with those recently reported by Internation Society for Bipolar Disorders guidelines (Pacchiarotti et al., 2013: (a) serotonin–norepinephrine reuptake inhibitors and tri- and tetracyclics were prescribed only after other ADs had been tried; (b) patients with rapid cycling [DSM IV criteria (APA, 1994)], broadly defined mixed state (DSM IV and Koukopoulos criteria), high mood instability, and past (hypo)manic or mixed switch (Tohen et al., 2009) were excluded.

As routine practice at the two centers, pharmacological treatment was systematically implemented together with informal psychoeducation on BD, so information on the biological nature of disorder, the rationale for pharmacological treatment, the risk of relapse/recurrence, and the common recurrence triggers (stress, disregulation of rhythms, substance use/abuse, lack of treatment adherence) were given to patients and, whenever possible, to relatives.

2.4. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics Version 21.

Chi-square test was utilized to compare categorical variables. Independent-sample t-test and Mann-Whitney test (in case of non parametric variables) were used in the comparisons between patients with and without recurrences. Wilcoxon test was used to compare the frequency of episodes (number of episodes per year) before and after the study entry.

A multiple linear regression analysis was performed in order to identify the best predictors of the frequency of recurrences.

3. Results

The study included 266 patients, 153 (57.5%) with BD-I and 113 (42.5%) with BP-II. Patients were mostly female (n = 166, 62.4%), married (n = 120, 45.1%), and regularly employed (n = 187, 70.3%). The mean age was 37.9 (± 12.7) years, the mean length of the illness was 136.0 ± 116.6 months (median 108, mode 84).

During the follow-up (mean length 46.0 ± 27.5 months), 66.9% of patients were treated with lithium salts, 76.7% with anticonvulsants (valproate, carbamazepine or lamotrigine), 47.7% with lithium plus anticonvulsant, 3.4% with two or more anticonvulsants. In 13.9% of patients mood stabilizer(s) were augmented with an antipsychotics, in 41.7% with an antidepressant, and in 18.0% with an antipsychotic and an antidepressant. Comparison between patients with and without recurrences did not reveal any differences in the type of treatment.

Comparing the number of episodes per year before and after the study entry we found a significant reduction in the overall sample (1.63 ± 2.65 vs. 0.55 ± 0.69; p < .001) (Fig. 1). At the end of the
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