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Duration of untreated illness and suicide in bipolar disorder: a naturalistic study

A. Carlo Altamura · Bernardo Dell'Osso · Heather A. Berlin · Massimiliano Buoli · Roberta Bassetti · Emanuela Mundo

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Abstract The aim of this naturalistic study was to evaluate the potential influence of the duration of untreated illness (DUI)—defined as the time elapsed between the occurrence of the first mood episode and the first adequate pharmacological treatment with mood stabilizers—on the clinical course of bipolar disorder (BD). Three hundred and twenty outpatients ($n = 320$) with a DSM-IV diagnosis of BD—either Type I or Type II—were interviewed; their clinical features were collected and they were naturalistically followed-up for 5 years. At the end of the follow-up observation, the sample was subdivided into two groups: one group with a DUI $\leq$2 years ($n = 65$) and another group with a DUI >2 years ($n = 255$). The main demographic and clinical variables were analyzed and compared between the two subgroups of patients using chi-square tests for dichotomous variables or Mann–Whitney U tests for continuous variables. Patients with a longer DUI showed a higher frequency of suicide attempts ($Z = -2.11$, $P = 0.035$), a higher number of suicide attempters ($\chi^2 = 4.13$, $df = 1$, $P = 0.04$), and a longer duration of illness ($Z = -6.79$, $P < 0.0001$) when compared to patients with a shorter DUI. Moreover, patients with a longer DUI had a depressive first episode more frequently than patients with a shorter DUI ($\chi^2 = 11.28$, $df = 2$, $P = 0.004$). A further analysis performed dividing the total sample into two subgroups on the basis of a DUI of 6 years (corresponding to the median value of the DUI in the study sample) confirmed prior findings. Results indicate a potential association between a longer DUI and a worse outcome in BD, particularly in terms of suicidality, and confirm the clinical relevance of early diagnosis and pharmacological intervention with mood stabilizers in BD.

Keywords Bipolar disorder · Duration of untreated illness · Suicidality · Clinical course

Introduction

Several studies have investigated the duration of untreated illness (DUI)—defined as the time elapsed between the onset of an illness and the first adequate pharmacological treatment—as a predictor of outcome and clinical course across different psychiatric disorders. However, these studies have focused mostly on psychotic disorders [1, 19] and, only to a minor extent, on mood and anxiety disorders [11].

With regard to mood disorders, previous studies on major depressive disorder (MDD) reported that a longer DUI predicted persistence of depressive symptoms and chronicity [16, 24]. More recently, two naturalistic studies of our group suggested that a longer DUI may negatively influence the clinical course of MDD, having been associated with earlier age at onset, longer duration of illness, higher number of recurrences, and more frequent

A. C. Altamura · B. Dell'Osso (✉) · M. Buoli · E. Mundo
Department of Psychiatry, University of Milan,
Fondazione IRCCS Ospedale Maggiore Policlinico,
Mangiagalli e Regina Elena,
Via F. Sforza 35, 20122 Milan, Italy
e-mail: bernardo.dellosso@policlinico.mi.it

H. A. Berlin
Department of Psychiatry, Mount Sinai School of Medicine,
One Gustave L. Levy Place, Box 1230,
New York, NY 10029, USA

R. Bassetti
Department of Clinical Sciences L. Sacco,
Via G.B. Grassi 73, 20157 Milan, Italy

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comorbidity with Axis I disorders that have an onset later than that of MDD [3, 4].

Bipolar disorder (BD) is a major cause of disability, and the episodic and chronic nature of this mental illness, as well as the high comorbidity, often complicate the outcome of affected patients. A previous study by Goldberg and co-workers [14] reported that a delayed administration of mood stabilizer treatment in BD was related to an increased risk of suicidal behavior, poorer social adjustment, and more frequent hospitalizations. In addition, a recent study reported that an early age at onset of BD was associated with more severe clinical features and delayed treatment-seeking [26]. However, with respect to a possible influence of the DUI on treatment response in patients with mood disorders, some studies have found no difference between a short and a long latency to treatment in the final outcome of long-term treatments (lithium in particular) [9, 10].

Given that the onset of BD generally occurs in early adulthood or even in late childhood [12] and that bipolar patients often may wait several times before receiving a correct diagnosis and an adequate pharmacological treatment [14], the present naturalistic study was conducted to assess the potential influence of the DUI on the clinical course of BD. We considered the administration of mood stabilizers as the first pharmacological treatment.

Methods

The study sample consisted of 320 outpatients diagnosed with bipolar disorder—either Type I ($n = 128$) or Type II ($n = 192$)—according to DSM-IV-TR criteria [5]. All patients were assessed, interviewed, treated and followed-up for 5 years at the Mood Disorders Outpatient Clinic at the University Department of Psychiatry in Milan. Patients who had a complete clinical chart for the 5-year follow-up period were included in the study. Patients gave their informed written consent to be interviewed and to have the clinical information included in their charts and derived by diagnostic interview reviews.

For the purpose of this study, patients were divided into two groups according to a DUI $\leq$2 years ($n = 65$) and $>$2 years ($n = 255$). This threshold was arbitrarily chosen on the basis of previous studies on schizophrenia and MDD [1, 2, 18]. DUI was defined as the interval between the onset of the first mood episode of any polarity and the first treatment with mood stabilizers that patients received at standard doses for an adequate period of time, according to currently available guidelines [6, 17]. The assessment of the DUI was based on the clinical information derived from the diagnostic interview and on all additional information provided by patients and close family members. Patients who had undergone any kind of psychotherapy that was not associated with mood stabilizers were excluded from the study. These patients represented a small portion of the original sample.

Diagnostic interviews and clinical chart reviews were performed by trained psychiatrists, and diagnoses were assessed by administrating a semi-structured interview based on DSM-IV criteria (SCID-I) [13] and were made according to a best-estimate procedure. The interrater reliability of the diagnosis of BD and of the measure of the DUI was measured through an independent assessment of a randomly selected subsample of 20 patients by two other psychiatrists. The main demographic, clinical, and course variables of the sample were collected during clinical interviews with patients and relatives when available, as well as by reviewing the diagnostic interview data (SCID-I). These variables were as follows: gender, age, age at onset, age at the first mood-stabilizer treatment, age at the first pharmacological treatment, duration of illness, family history of psychiatric disorders in first-degree relatives, polarity of first mood episode, number of hospitalizations/follow-up, number of suicide attempts/follow-up, number of suicide attempters/follow-up, onset of rapid cycling course, and comorbidity with other Axis I or II disorders that had an onset before and after that of BD.

Mood stabilizer treatment included the following psychotropic compounds: lithium, anticonvulsants (i.e., valproate and carbamazepine) and atypical antipsychotics (i.e., quetiapine, olanzapine, and risperidone). To be considered adequate from a clinical point of view, each compound had to be administered for at least 12 weeks at standard dosages and, for lithium and valproate, in therapeutic plasmatic ranges (0.5–1.5 mEq/l and 50–150 μg/ml, respectively). During the follow-up observation, patients were assessed monthly with clinical interviews, at which point clinicians could modify patients' pharmacological treatments according to their clinical conditions.

At the end of the follow-up, the main demographic and clinical variables were compared between the two groups of patients defined by the DUI ($\leq$2 or $>$2 years). The Mann–Whitney U test was used to analyze the continuous variables, whereas a chi-square test was used for the dichotomous variables. In order to avoid potential bias created by separating the two subgroups on the basis of a DUI of 2 years (which might have caused an unbalanced distribution of subjects), further analyses were performed that divided the total sample into two subgroups on the basis of a DUI of 6 years ($\leq$6 or $>$6 years), which corresponded to the median value of the DUI in the study sample. Moreover, a logistic regression with DUI ($\leq$2 or $>$2 years; $\leq$6 or $>$6 years) as the independent categorical variable and the presence of suicide attempters or hospitalizations as dependent variables was performed to confirm chi-square test results. Finally, a χ^2 analysis was

performed to exclude the influence of mood stabilizer administration on the number of suicide attempters. For the statistical analyses, the alpha level of significance was set at 0.05 and was not adjusted. All statistical analyses were performed using the SPSS for Windows software (version 15.0).

Table 1 Demographic and clinical features of the total sample and of the two subgroups defined by the DUI (2 years)

Variables	DUI ≤2 years ($N = 65$)	DUI >2 years ($N = 255$)	Total sample ($N = 320$)	Statistics
DUI (mean, years)	1.34 (±0.62)	10.58 (±7.52)	8.7 (±7.68); median = 6	
Gender (males/females)	30 (46.1%) M, 35 (53.9%) F	110 (43.1%) M, 145 (56.9%) F	140 (43.8%) M, 180 (56.2%) F	$\chi^2 = 0.19$, $P = 0.677$
Age (years)	41.31 (±13.12)	47.15 (±12.53)	45.96 (±12.85)	***Z = −3.34, P = 0.001***
Age at onset (years)	32.05 (±12.13)	29.50 (±10.33)	30.02 (±10.75)	$Z = -1.38$, $P = 0.169$
Age of the first pharmacological treatment	32.52 (±11.92)	33.04 (±10.41)	32.94 (±10.72)	$Z = -0.75$, $P = 0.451$
Duration of illness (years)	9.25 (±7.22)	17.38 (±9.46)	15.73 (±9.62)	***Z = −6.79, P < 0.001***
Diagnosis (DSM-IV)				
BD I	32 (49.2%)	96 (37.6%)	128 (40.0%)	$\chi^2 = 2.90$, $P = 0.118$
BD II	33 (50.8%)	159 (62.4%)	192 (60.0%)	
Polarity of first mood episode				
Depressive	37 (56.9%)	197 (77.3%)	234 (73.1%)	***χ^2 = 13.4, P = 0.002***
Manic/hypomanic/mixed	28 (43.1%)	56 (22.7%)	86 (26.9%)	
Number of hospitalizations	1.15 (±1.94)	1.51 (±2.03)	1.44 (±2.01)	$Z = -1.44$, $P = 0.151$
Number of suicide attempters	8 (12.3%)	61 (23.9%)	69 (21.6%)	***χ^2 = 4.13, P = 0.04***
Number of suicide attempts	0.15 (±0.44)	0.40 (±0.86)	0.35 (±0.80)	***Z = −2.11, P = 0.035***
Presence of rapid cycling course	9 (13.8%)	44 (17.3%)	53 (16.6%)	$\chi^2 = 0.44$, $P = 0.579$
Family history				
Negative	26 (40.0%)	145 (56.9%)	171 (53.4%)	$\chi^2 = 5.98$, $P = 0.11$
Mood disorders	33 (50.8%)	94 (36.9%)	127 (39.7%)	
Schizophrenia	2 (3.1%)	6 (2.4%)	8 (2.5%)	
Anxiety disorders	4 (6.1%)	10 (3.8%)	14 (4.4%)	
Comorbidity before the onset of BD				
None	42 (64.6%)	177 (69.4%)	219 (68.4%)	$\chi^2 = 3.67$, $P = 0.894$
Substance abuse	8 (12.3%)	19 (7.5%)	27 (8.4%)	
Personality disorders	3 (4.6%)	11 (4.3%)	14 (4.4%)	
Panic disorder	7 (10.9%)	23 (9.0%)	30 (9.4%)	
Generalized anxiety disorder	0 (0.0%)	5 (2.0%)	5 (1.6%)	
Obsessive compulsive disorder	3 (4.6%)	13 (5.1%)	16 (5.0%)	
Eating disorders	1 (1.5%)	4 (1.6%)	5 (1.6%)	
Others	1 (1.5%)	3 (1.1%)	4 (1.2%)	
Comorbidity after the onset of BD				
None	56 (86.2)	207 (81.2%)	263 (82.2%)	$\chi^2 = 8.37$, $P = 0.301$
Substance abuse	3 (4.5%)	27 (10.6%)	30 (9.4%)	
Panic disorder	2 (3.1%)	14 (5.5%)	16 (5.0%)	
Others	4 (6.2%)	7 (2.7%)	11 (3.4%)	

The time risk for number of suicide attempts, number of suicide attempters and hospitalizations refer to the 5-year follow-up period

Standard deviations for continuous variables are shown in brackets

Variables with statistical significant differences between groups are in bold italics

Results

The entire sample showed a mean DUI of 8.7 ± 7.7 years before receiving a first pharmacological treatment with mood stabilizers.

Kolmogorov–Smirnov tests showed that the sample was not normally distributed with respect to age ($P < 0.0001$), age at onset ($P < 0.0001$), age at the first pharmacological treatment ($P = 0.002$), number of hospitalizations/follow-up ($P < 0.0001$) and number of suicide attempts/follow-up ($P < 0.0001$).

The main demographic and clinical variables for the two subgroups of patients (DUI ≤ or >2 years) are summarized in Table 1.

The two subgroups did not differ with respect to gender ($\chi^2 = 0.19$, $df = 1$, $P = 0.677$), age at onset ($Z = -1.38$, $P = 0.169$), age at the first pharmacological treatment (antidepressants or mood stabilizers) ($Z = -0.75$, $P = 0.451$), family history of psychiatric disorders in first-degree relatives ($\chi^2 = 5.98$, $df = 3$, $P = 0.110$), comorbidity with other Axis I or Axis II disorders *before* the onset of BD ($\chi^2 = 3.67$, $df = 8$, $P = 0.894$) and *after* the onset of BD ($\chi^2 = 8.37$, $df = 7$, $P = 0.301$), diagnostic subtype ($\chi^2 = 2.90$, $df = 1$, $P = 0.118$), onset of rapid cycling course ($\chi^2 = 0.44$, $df = 1$, $P = 0.579$), number of hospitalizations/follow-up ($Z = -1.44$, $P = 0.151$), and type of mood stabilizer administered during the follow-up period ($\chi^2 = 11.94$, $df = 8$, $P = 0.148$). However, patients with a longer DUI were significantly older ($Z = -3.34$, $P = 0.001$, $r = 0.19$) and showed a longer duration of illness ($Z = -6.79$, $P < 0.0001$, $r = 0.38$), a higher number of suicide attempts/follow-up ($Z = -2.11$, $P = 0.035$, $r = 0.12$), a higher number of suicide attempters/follow-up ($\chi^2 = 4.13$, $df = 1$, $P = 0.04$, $\Phi = 0.12$), and a greater frequency of depressive episodes at onset compared to patients with a shorter DUI ($\chi^2 = 13.40$, $df = 2$, $P = 0.002$, $\Phi = 0.21$). A higher probability of having suicide attempters in patients with a DUI >2 years was confirmed by logistic regression ($P = 0.046$) (Fig. 1).

Results did not change with DUI thresholds of ≤ or >6 years, except for the age at onset, comorbidity after the onset of BD, the onset of rapid cycling course, and the number of hospitalizations/follow-up periods (Table 2). Indeed, patients with a longer DUI (>6 years) showed an earlier age at onset ($Z = -2.10$, $P = 0.035$, $r = 0.12$), a higher frequency of rapid cycling course ($\chi^2 = 4.87$, $df = 1$, $P = 0.04$, $\Phi = 0.12$), a higher frequency of comorbidity with other psychiatric disorders after the onset of BD ($\chi^2 = 13.71$, $df = 7$, $P = 0.02$, $\Phi = 0.21$), especially with substance abuse ($P = 0.01$), and a higher number of hospitalizations/follow-up periods ($Z = -4.13$, $P < 0.0001$, $r = 0.23$). Of particular note is that a higher probability of having suicide attempters in patients with a DUI >6 years was confirmed by logistic regression ($P = 0.006$) (Fig. 2).

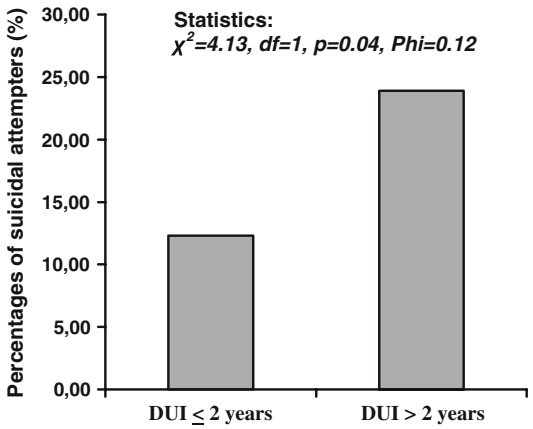

Fig. 1 Differences in suicide attempters in the two groups of patients divided according to a DUI ≤2 or >2 years

Finally, the type of mood stabilizer did not influence the number of suicide attempters ($\chi^2 = 11.54$, $df = 8$, $P = 0.16$).

Discussion

The main result of the present study is that bipolar patients with a longer DUI showed a higher number of suicide attempts and attempters during a follow-up observation of 5 years when compared to patients with a shorter DUI. In addition, patients with a longer DUI showed a higher frequency of depressive onset when compared to patients with a shorter DUI. Moreover, patients with a longer DUI were older and, understandably, showed a longer duration of illness. Maintaining the 2-year threshold for the DUI, we also found a greater frequency of depressive onset in subjects who experienced a longer DUI, whereas no such association was shown between a longer DUI and other clinical and demographic variables, such as age at onset, onset of rapid cycling course, number of hospitalizations/follow-up, and development of comorbidity with onset later than that of BD. Of specific relevance is that when the total sample was divided according to the median value of the DUI of 6 years, results on suicidality were confirmed, and patients with a longer DUI were also found to have a higher frequency of comorbidity with substance abuse and panic disorder following the onset of BD, as well as a higher frequency of rapid cycling course and hospitalizations/follow-up.

The relationship between BD and suicidality is well established, with recent studies also investigating a possible association between suicide attempts and neurobiological markers [7, 8, 21]. The risk for suicide among

Table 2 Demographic and clinical features of the two subgroups defined by the DUI (6 years)

Variables	DUI ≤6 years ($N = 159$)	DUI >6 years ($N = 161$)	Statistics
DUI (mean, years)	3.21 (+1.84)	14.12 (7.39)	
Gender (males/females)	73 (45.9%) M, 86 (54.1%) F	67 (41.6%) M, 94 (58.4%) F	$\chi^2 = 0.6$, $P = 0.5$
Age (years)	42.83 (±13.00)	49.06 (±11.95)	***Z = −4.37, P < 0.0001***
Age at onset (years)	31.47 (±11.31)	28.58 (±10.00)	***Z = −2.10, P = 0.035***
Age of the first pharmacological treatment	32.72 (±11.07)	33.15 (±10.39)	$Z = -0.73$, $P = 0.47$
Duration of illness (years)	11.22 (±8.44)	20.19 (±8.60)	***Z = −9.53, P < 0.0001***
Diagnosis (DSM-IV)			
BD I	65 (40.9%)	63 (39.1%)	$\chi^2 = 0.6$, $P = 0.5$
BD II	94 (59.1%)	98 (60.9%)	
Polarity of first mood episode			
Depressive	107 (67.3%)	127 (78.9%)	$\chi^2 = 0.1$; $P = 0.82$
Manic/hypomanic/mixed	52 (32.7%)	34 (21.1%)	
Number of hospitalizations	1.06 (±1.90)	1.81 (±2.06)	***Z = −4.13, P < 0.0001***
Number of suicide attempters	24 (15.2%)	45 (28.0%)	***χ^2 = 7.82, P = 0.006***
Number of suicide attempts	0.19 (±0.49)	0.51 (±0.99)	***Z = −3.04, P = 0.002***
Presence of rapid cycling course	19 (11.9%)	34 (21.1%)	***χ^2 = 4.87, P = 0.035***
Family history			
Negative	83 (52.2%)	88 (54.7%)	$\chi^2 = 0.99$, $P = 0.80$
Mood disorders	65 (40.9%)	62 (38.5%)	
Schizophrenia	3 (1.9%)	5 (3.1%)	
Anxiety disorders	8 (5.0%)	6 (3.7%)	
Comorbidity before the onset of BD			
None	109 (68.6%)	110 (68.3%)	$\chi^2 = 6.4$, $P = 0.62$
Substance abuse	18 (11.3%)	9 (5.6%)	
Personality disorders	5 (3.1%)	9 (5.6%)	
Panic disorder	13 (8.2%)	17 (10.5%)	
Generalized anxiety disorder	2 (1.3%)	3 (1.9%)	
Obsessive compulsive disorder	8 (4.9%)	8 (5.0%)	
Eating disorders	2 (1.3%)	3 (1.9%)	
Others	2 (1.3%)	2 (1.2%)	
Comorbidity after the onset of BD			
None	139 (87.4%)	124 (77.0%)	***χ^2 = 13.71, P = 0.02***
Substance abuse	8 (5.0%)	22 (13.7%)	
Panic disorder	6 (3.8%)	10 (6.2%)	
Others	6 (3.8%)	5 (3.1%)	

The time risk for number of suicide attempts, number of suicide attempters and hospitalizations refer to the 5-year follow-up period

Standard deviations for continuous variables are shown in brackets

Variables with statistical significant differences between groups are in bold italics

bipolar patients, in fact, is ≥20 times higher than that for the general population and is among the highest for any mental disorder [27], making it critical to assess whether suicidal behavior is predictable in this population. Understanding the origins of suicide in BD is the first step in preventing it. From this perspective, in a previous study Goldberg and Ernst [14] reported an association between a delay in the initiation of mood stabilizer treatment and an elevated risk of suicidal behavior, finding that bipolar patients with a longer DUI had a higher number of hospitalizations and poorer social functioning in the year. Furthermore, the authors found a mean lag-time from the onset of initial affective symptoms to the first mood stabilizer treatment of approximately 9.8 ± 9.4 years. This value is consistent with that found in the present study-sample, which shows a mean DUI of 8.7 ± 7.7 years.

With respect to the greater frequency of depressive onset exhibited in subjects with a longer DUI, it is noteworthy to

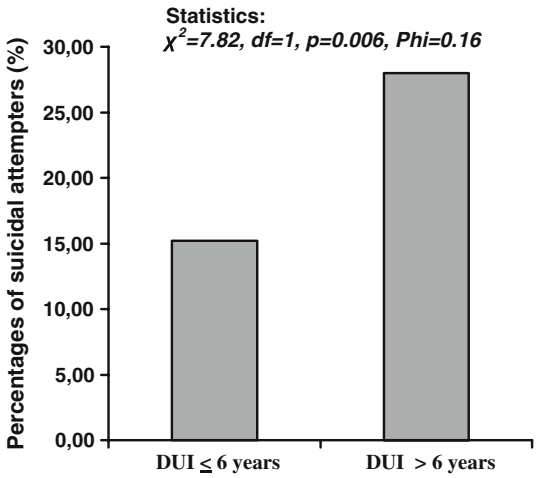

Fig. 2 Differences in suicide attempters in the two groups of patients divided according to a DUI ≤6 or >6 years

consider a similar result from a recent study assessing clinical differences between predominantly manic and depressed bipolar patients that placed a special focus on the time that patients remained undiagnosed [23]. Depressive polarity was associated with a longer delay in diagnosis (i.e., a longer DUI), and predominantly depressive patients tended to present a depressive onset of illness, longer duration of illness, and higher number of suicide attempts (as was found in the present study).

When taken as a whole, the cited studies and the present results, though preliminary, highlight the extent to which bipolar subjects may wait before receiving pharmacological treatment with mood stabilizers and suggest a potential association between depressive onset, higher number of suicide attempts, and a longer DUI in BD.

Indeed, when the DUI threshold was set at 6 years, a higher frequency of comorbidity with substance abuse and panic disorder following the onset of BD was found in the subgroup that had a longer DUI; this result is consistent with a recent study indicating that the comorbidity with anxiety disorders and substance abuse is a risk factor for suicide attempts in BD [25].

With respect to rapid cycling course and number of hospitalizations/follow-up, which were also more frequent in the group with a DUI >6 years, these data are consistent with the results of a recent trial on bipolar adolescents that indicated that a rapid cycling course in BD is predictive of higher levels of care [22]. In addition, a recent prospective study with Bipolar I patients showed that suicide risk is higher in patients who have had a greater number of past hospitalizations [15]. Another previous prospective study concluded that comorbidity with substance abuse in bipolar patients is predictive of hospitalization for suicidal ideation [20].

In conclusion, present preliminary results support the hypothesis of an association between a longer DUI and negative outcomes in BD. In terms of suicidality, a DUI longer than 2 years was associated with more suicide attempts and attempters/follow-up; moreover, when the DUI threshold was set at the median value (6 years), further factors associated with a poor clinical outcome were found, suggesting that a longer DUI yields a worse outcome. Of note, data on suicidality for both analyses were referred to the follow-up observation of 5 years and, therefore, reflect the same exposure time for the whole sample.

Some important clarifications and methodological limitations of the present study should be taken into account. First, the study was not designed to compare the efficacy of a specific compound (i.e., mood stabilizers or antipsychotics) in relation to DUI in the treatment of BD, but, rather, to assess the potential influence of the DUI on the long-term clinical course of BD. Second, retrospective assessment of the DUI required to ensure the reliability of the patient and other available information sources (e.g., close family members) in the collection of clinical data; in this regard, information about the onset of BD may not have been precise in some cases. Third, the present findings may have been biased by the decision to categorize the DUI into two groups (≤ or >2 years). It is possible that treating the DUI as a continuous variable might produce different results. However, when the threshold for the DUI was set at 6 years, results were similar and, indeed, even more robust. This suggests that the first few years of illness may play a crucial role in determining the global outcome. Finally, the reported findings may only apply to patients seeking treatment, and this population may not adequately represent the entire population of BD patients. In fact, access to mental health structures, treatment settings, and cultural attitudes may have been related to some patients' delays in receiving their first pharmacological treatment with mood stabilizers. In addition, it should be taken into account that large naturalistic studies, like the present one, that investigate the prognostic role of some variables in the outcome and clinical course of BD often report multiple associations with potential confounders, making it hard to establish what comes first.

Future studies focusing on the long-term effects of DUI on the clinical course of BD are needed in order to confirm the present preliminary results and to better define long versus short DUI.

Conflict of interest statement Prof. Altamura, Drs. Dell'Osso, Berlin, Buoli, Bassetti and Mundo do not have any affiliation or financial interest in any organization that might imply a conflict of interest.

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