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Research paper

Duration of untreated illness and bipolar disorder: time for a new definition? Results from a cross-sectional study

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ABSTRACT

Background: We primarily aimed to explore the associations between duration of untreated illness (DUI), treatment response, and functioning in a cohort of patients with bipolar disorder (BD).
Methods: 261 participants with BD were recruited. DUI was defined as months from the first affective episode to the start of a mood-stabilizer. The functioning assessment short test (FAST) scores and treatment response scores for lithium, valproate, or lamotrigine according to the Alda Scale Total Score (TS) were compared between patients with short (<24 months) or long DUI. Differences in FAST scores among good (GR; TS≥7), poor (PR; TS=2-6), or non-responders (NR; TS<2) to each mood-stabilizer were analyzed. Linear regression was computed using the FAST global score as the dependent variable.
Results: DUI and FAST scores showed no statistically significant correlation. Patients with a longer DUI showed poorer response to lithium (Z=-3.196; p<0.001), but not to valproate or lamotrigine. Response to lithium (β=-1.814; p<0.001), number of hospitalizations (β=0.237; p<0.001), and illness duration (β=0.160; p=0.028) were associated with FAST total scores. GR to lithium was associated with better global functioning compared to PR or NR [H=27.631; p<0.001].
Limitations: The retrospective design could expose our data to a recall bias. Also, only few patients were on valproate or lamotrigine treatment.
Conclusions: Poor functioning in BD could be the result of multiple affective relapses, rather than a direct effect of DUI. A timely diagnosis with subsequent effective prophylactic treatment, such as lithium, may prevent poor functional outcomes in real-world patients with BD.

1. Introduction

Bipolar disorders (BD) begin in youth, with a mean age of onset of ~20 years (Carvalho et al., 2020). A delayed diagnosis of BD is not uncommon and might translate into a latency of almost 10 years before receiving adequate treatment (Drancourt et al., 2013). This diagnostic delay might be associated with illness-related factors, including previous depressive episodes, suicidal behavior, absence of a family history of BD among others (Tondo et al., 2014), while a timely diagnosis and treatment are keys to a favorable course of illness (Vieta et al., 2018b).

The time span from disorder onset to proper diagnosis and adequate treatment is defined as the duration of untreated illness (DUI) (Drancourt et al., 2013). DUI has been increasingly investigated in several psychiatric disorders as a possible predictor of illness course specifiers

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(Albert et al., 2019; Zhang et al., 2017), such as remission, response to treatment, symptomatic severity, and global functioning in psychoses (Jonas et al., 2020), but also in mood disorders (Galimberti et al., 2020), including BD (Buoli et al., 2021). Despite an improvement in diagnostic procedures concerning BD, a recent meta-analysis estimated that the mean DUI in BD is almost six years (Dagani et al., 2017). A longer DUI is associated with detrimental outcomes among people with BD, such as a poor treatment response (Joyce et al., 2016), more psychiatric comorbidities (Murru et al., 2015), and poor overall functioning (Altamura et al., 2010). Specifically, BD patients treated since their first episode may show better functional outcomes as compared to those treated at 6 and 12 months (Arrasate et al., 2014; Rosa et al., 2011). Coherently, a longer DUI in BD may translate into poor cognitive, occupational, and social functioning (Galimberti et al., 2020; Goldberg and Ernst, 2002). Unfortunately, the evidence on the relationship between longer DUI and worse overall functioning of BD patients is not conclusive (Berghöfer et al., 2008; Goldberg and Ernst, 2002; Kvitland et al., 2016; Oyffe et al., 2015).

The relationship between DUI in BD and poor treatment response has been outlined (Altamura et al., 2008), despite contrasting evidence (Baldessarini et al., 2007). Indeed, this association might underpin a spurious link as, for instance, lithium response negatively relates with the number of previous acute affective episodes, even when appropriately treated (Swann et al., 2000). Quite uniquely, lithium shows a neuroprotective effect including but not limited to BD (Berk et al., 2017; Moore et al., 2000; Velosa et al., 2020). It has been suggested that its timely introduction after an early detection might diminish neuroprogression (Berk et al., 2017; Michael Berk et al., 2017; Moore et al., 2000; Velosa et al., 2020).

In this study, we primarily aimed to explore the association between DUI, treatment response, and functioning in a cohort of patients with BD. We hypothesized that a longer DUI would lead to a worse response to mood-stabilizers which could, in turn, determine a worse global functioning. Secondarily, we aimed to explore the relationship between lithium treatment response and general functioning.

2. Methods

2.1. Study design and sample

A cross-sectional analysis of a large cohort of patients admitted to the Bipolar and Depressive Disorders Unit of the Hospital Clinic of Barcelona from October 2008 to March 2018. This specialized unit regularly follows more than 800 patients from a specific catchment area of Barcelona as well as tertiary patients from all Catalonia. All patients at intake to the program were assessed and screened for inclusion. The baseline assessment of each patient included the Hamilton Depression Rating Scale (HAM-D)(Hamilton, 1960), the Young Mania Rating Scale (YMRS) (Colom et al., 2002), and the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). Inclusion criteria were: 1) diagnosis of BD type I (BDI) or II (BDII) according to DSM-5 criteria (APA, 2013); 2) aged 18 or above; 3) presenting a FAST assessment during euthymia defined following consensus criteria (Tohen et al., 2009) (a score $\leq$8 on the HAM-D and $\leq$6 on YMRS of at least the 3 months); 4) treatment with lithium, valproate, or lamotrigine for more than 6 months; 5) written informed consent. Exclusion criteria were: 1) severe cognitive, motor, or visual impairment; 2) severe medical conditions requiring immediate hospitalization at baseline assessment. This study was approved by the local Ethics Committee.

2.2. Socio-demographic and clinical variable assessment

Socio-demographic and clinical variables were systematically collected using an ad-hoc schedule. Diagnoses were assessed using the Structured Clinical Interview for DSM-5 (SCID-I) (APA, 2013). Patients were asked about the number of lifetime depressive, manic or hypomanic episodes or presence of mixed features during the SCID-I. DSM-5 mixed features were defined by the presence of at least three symptoms of the opposite polarity compared with the current mood episode (APA, 2013). All patients enrolled were treated pharmacologically for BD by trained psychiatrists according to international guidelines (Verdolini et al., 2020; Yatham et al., 2018). A current pharmacological treatment refers to the baseline treatment of each patient, which was registered if maintained for at least 6 months. Complex polypharmacy was defined as a current use of four more psychotropic medication at once in each patients (Fornaro et al., 2016).

2.3. Duration of untreated illness

The assessment of the DUI was based on the clinical information derived by the diagnostic interview and on all the additional information provided by patients and close family members. Two different researchers (GF and CDM) independently extracted the specific information from the electronic clinical history of each patient. DUI was defined as the time (in months) from the referred onset of the first affective episode to the start of adequate treatment, as in previous studies (Drancourt et al., 2013). Adequate treatment is defined as the use of a mood stabilizer or antipsychotic at appropriate dosages and for an adequate time, in line with the most recent BD treatment guidelines (Verdolini et al., 2020; Yatham et al., 2018). Serum mood-stabilizers levels were periodically checked to monitor treatment adherence.

2.4. Functional assessment

All the participants were included with the most recent FAST (Rosa et al., 2007) score referred to a euthymic phase of at least 3 months, defined according to consensus criteria (Tohen et al., 2009). The FAST scale consists of 24 items related to six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Items are rated using a four-point scale, ranging from 0 (no difficulty) to 3 (severe difficulty). FAST scores range from 0 to 72, with higher scores indicating poor functioning (Rosa et al., 2007).

2.5. Treatment with mood-stabilizers

Treatment responses were evaluated using the "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" (Alda Scale) (Manchia et al., 2013), a widely used clinical measure of the long-term drug mood stabilization effect under naturalistic conditions. This scale measures the degree of improvement during the treatment (A score) addressing the change in the frequency and severity of mood symptoms and weighs clinical factors that might influence treatment response (B score). The total score (TS) is obtained by subtracting the B score from the A score; any negative score is reported as 0 (Grof et al., 2002). The A score goes from 0 (no change) to 10 (complete response), the B score from 0 (complete causal relation) to 10 (unlikely causal relation). The combined maximum score is 10 (which indicates the maximum response to treatment) and the minimum is 0 (no response to treatment).

The scale was originally developed to evaluate the clinical response to lithium and successively adapted to extend the evaluation to other prophylactic treatments commonly used in BD management, including valproate and lamotrigine (Garnham et al., 2007; Lee et al., 2020).

In the present study, we considered response to the current (with respect to the FAST score), prospectively administered adequate treatment with a mood-stabilizer (lithium, valproate, or lamotrigine).

2.3. Statistical analyses

The Kolmogorov-Smirnov test was used to assess whether continuous variables displayed a normal distribution. Patients were divided into

two groups according to DUI (short vs. long) according to previously used DUI cut-off of 24 months (Drancourt et al., 2013). These two groups were compared for socio-demographic and clinical characteristics with unpaired t-test with Bonferroni posthoc correction for continuous variables; for non-parametric distributions, a Mann-Whitney U-Test was used. Categorical data were analyzed with $\chi 2$ analysis. The association of the DUI with FAST scores and with Alda Scale Total Scores (TS) was assessed using Spearman's correlation tests. FAST scores were also correlated to the total number of lifetime affective episodes using Spearman's correlation test.

Three categorical variables were created to classify treatment response respectively to lithium, valproate, or lamotrigine in three groups based on Alda Scale TS: good responders (GR) (TS$\geq$ 7), poor responders (PR) (TS=2-6), non-responders (NR) (TS<2) (Manchia et al., 2013). Kruskal-Wallis H Tests with Bonferroni correction were then used to determine if FAST sub-scores and global scores statistically differed among the groups.

The FAST global score was used as a dependent variable in a linear regression model with DUI and other quantitative clinical variables associated with the FAST global score at bivariate analyses as independent variables, namely number of lifetime affective episodes, lifetime number of hospitalizations, Alda Scale TS for lithium, after controlling for illness duration.

Statistical analyses were performed using SPSS for PC (version 22) software. The level of significance was set at $p \leq 0.05$.

3. Results

3.1. Sample characteristics

The sample was composed of 261 individuals (134 women, 51.3%) with a diagnosis of BDI (N=201; 77%) or BDII (N=60; 23%), with a mean age of assessment of 42.38 years (SD±12.464). The mean DUI of the total sample was 34.40 months (SD±74.44). At the time of FAST administration, patients did not show any clinically relevant manic symptoms assessed by the YMRS (mean=1.14; SD±1.91) or depressive symptoms assessed by the HAM-D (mean=3.6; SD±3.1). Data on current pharmacological treatments are reported in Tables 1 and 2. In our sample, 17 patients (6.5%) reported a use four more psychotropic medication at once.

3.2. Clinical correlates of DUI and DUI relation with functioning

Patients were divided into two groups according to DUI (short vs. long) in accordance with a previously used DUI cut-off of 24 months (Drancourt et al., 2013).

One-hundred and seventy-two patients (65.9%) showed a DUI<24 months. Continuous and dichotomous variables were compared among the two groups (Table 1).

Patients with a longer DUI were more likely to have substance use ($\chi 2$= 6.291, p=0.012) and a seasonal pattern ($\chi 2$= 3.814, p=0.05), suffered more lifetime hypomanic episodes (Z=2.658, p=0.08), and showed an older age at baseline assessment (t=-2.335, p=0.02) and a longer duration of illness (t=4.766, p<0.001). Spearman's correlation tests showed no significant correlation between DUI and the FAST total score (Fig. 1) or subscores, HAM-D, or YMRS scores (Table 1). The FAST total score showed a significant correlation with the number of lifetime affective episodes (r=0.344, p<0001). Also, patients with a longer DUI showed lower Alda Scale TS for lithium, indicating a poorer response (Z=-3.196; p=0.001), but not for valproate or lamotrigine.

Linear regression was used to assess the ability of DUI to predict functioning measured as FAST global score, after controlling for illness duration. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity. The overall model fit was R2 = 0.217. Clinical variables with a single, statistically significant contribution were: Alda Scale TS

Table 1
Sociodemographic and clinical characteristics of the sample divided according to the Duration of Untreated Illness (total sample = 261).

	DUI < 2 Years (N=172; 65.9%)	DUI ≥ 2 Years (N=89; 34.1%)	t/Z/ χ2	p
Gender (N; %)				
Female	82; 47.7%	45; 50.6%		
Diagnosis (N; %)				
BDI	138; 80.2%	63; 70.8%		
BDII	34; 19.8%	26; 29.2%		
Age and illness duration (mean ± SD):				
Age at assessment	41.09±12.90	44.86±11.23	-2.335	.020
Age at onset	27.6±10.63	25.31±11.85		
Duration of illness (years)	14.02±11.00	20.00±10.297	4.766	.000
Number of DSM-IV-TR episodes, lifetime (mean ± SD):				
Depressive	6.36±8.63	7.84±10.41		
Manic	3.28±5.22	3.06±4.35		
Hypomanic	2.81±7.38	4.11±9.77	9.008	.008
Mixed	0.54±1.45	0.57±1.60		
Total	12.99±17.26	15.56±19.65		
Number of Psychiatric admissions, lifetime (mean ± SD):	1.88±2.24	1.95±2.70		
Clinical course variables, lifetime (N; %):				
Suicide attempts	68; 39.5%	30; 33.7%		
Aggressive behaviors	52; 35.1%	30; 44.1%		
Self-directed	11; 7.4%	9; 13.2%		
Hetero-directed	43; 29.1%	22; 32.4%		
Psychotic symptoms	283; 57.2%	42; 35.9%		
Rapid cycling	30; 17.5%	20; 22.5%		
Seasonality	15; 8.7%	15; 16.9%	3.814	.050
Substance use	37; 21.5%	32; 36%	6.291	.012
Predominant Polarity				
Depressive	35; 20.3%	18; 20.2%		
Manic	34; 19.8%	16; 18.0%		
Undetermined	93; 54.1%	53; 59.6%		
Scales assessments (mean ± SD):				
Alda Scale Total Score				
Lithium	4.25±2.5	3±2.3	2.690	.001
Valproate	4.25±2.4	3.8±2.6		
Lamotrigine	3±1.92	4.13±2.1		
HRSD total Score	3.63±3.2	3.59±2.9		
YMRS total Score	0.95±1.5	1.5±2.4		
FAST scores				
Autonomy	2.89±2.9	2.92±2.8		
Occupational	7.37±6.4	8.38±6.3		
Cognitive	5.23±3.8	5.47±3.6		
Financial	1±1.6	1.3±1.7		
Interpersonal	4.45±3.7	4.32±3.4		
Leisure	1.9±1.7	1.9±1.7		
Global Score	22.9±14.9	24.5±14.2		
Pharmacological treatment, baseline (N; %)				
Mood Stabilizers				
Lithium	126; 73.3%	60; 67.4%		
Valproate	20; 16.3%	20; 22.5%		
Lamotrigine	15; 8.7%	8; 9%		
Atypical Antipsychotics				
Aripiprazole	12; 15.8%	8; 14.5%		
Asenapine	3; 3.9%	3; 5.5%		
Clozapine	0; 0.8%	2; 1.2%		
Olanzapine	10; 13.2%	5; 6.3%		
Paliperidone	1; 1.4%	1; 1.9%		
Quetiapine	9; 11.8%	6; 10.9%		
Risperidone	12; 15.8%	13; 23.6%		
Ziprasidone	3; 2.3%	1; 1.8%		
Antidepressant				
SNRI	10; 13.2%	12; 21.8%		
SSRI	9; 11.8%	12; 21.8%		
TCA	3; 3.9%	1;1.9%		

Abbreviations: BD=Bipolar Disorder; DUI = Duration of Untreated Illness; N=number of cases; p=statistical significance; SD=standard deviation; HAM-D= Hamilton Depression Rating Scale; YMRS= Young Mania Rating Scale; FAST=Functioning Assessment Short Test; SNRI= Serotonin–norepinephrine reuptake inhibitors; SSRI= Selective Serotonin reuptake inhibitors; TCA=-Tricyclic Antidepressants.; χ2=Chi-square test; t=Independent Samples t-test; Z=Mann-Whitney U test

Table 2
Treatment response groups based on Alda Scale total score of different mood-stabilizers.

	Non-responders (TS < 2)	Poor-responders (TS = 2-6)	Good-Responders (TS ≥ 7)
Lithium (N; %)	41; 22%	112; 60%	33; 17%
Valproate (N; %)	10; 2.9%	27; 7.8%	11; 3.2%
Lamotrigine (N; %)	3; 13%	19; 82%	1; 4.3%

Abbreviations: *TS= Alda Scale Total Score*

for lithium [β=-1.814; 95% CI (2.5-0.9); p<.001], lifetime number of hospitalizations [β =.237, 95% CI (0.9-2.7); p<.001], and illness duration [β =.160, 95% CI (0.1-0.3); p=.028). DUI (β =-0.007, 95% CI (0.03-0.038); p=.599] and lifetime number of affective episodes (β = .045, 95% CI (0.15-0.1); p=.521] did not individually contribute to the model.

3.3. Effect of treatment response and functioning

The majority of patients in our sample were on treatment with lithium (N=186; 53.4%), followed by valproate (N=48, 13.8%) and lamotrigine (N=23; 6.6%). Treatment response to lithium, valproate or lamotrigine was classified into three groups (good-, poor- and non-responders) according to Alda Scale TS (Table 2).

Lithium good responders were compared with poor- and non-responders showing significantly lower scores (better functioning) in FAST global score [good-responders FAST=53.94, poor-responders FAST=95.91, non-responders FAST=119.57; H=27.631; 95% CI (21.03-24.97); p<.001] (see Fig. 2) and in each FAST domain [*Autonomy* (H=12.125; 95% CI (2.39-3.22); p=.002); *Occupational* (H=21.108; 95% CI (2.25-6.49); p<.001); *Cognitive* (H=23.912; 95% CI (4.74-5.78); p<.001); *Financial* (H=12.396; 95% CI (0.77-1.22); p=.002); *Interpersonal* (H=11.437; 95% CI (3.65-4.69); p=.003); *Leisure* (H=9.095; 95% CI (1.65-2.22); p=.011)]. FAST scores among good-, poor- and non-responders to valproate and lamotrigine did not show statistically significant differences.

4. Discussion

In our sample, BD patients with a longer DUI did not differ significantly in overall functioning when compared to the ones with a shorter DUI. Moreover, treatment response to lithium, but not to valproate or lamotrigine, was significantly associated with a shorter DUI and better global functioning. However, a longer DUI was associated with clinical variables linked to a worse longitudinal course of BD, implying more frequent relapses due to illness intrinsic and extrinsic factors, such as a seasonal pattern (Fico et al., 2021) and substance use (Woo et al., 2020) respectively.

The mean DUI in our sample (almost 3 years) is approximately half of the ones reported in previous studies (Buoli et al., 2021; Drancourt et al., 2013). This could be explained by the vast majority of our sample being represented by BDI patients, likely presenting a manic onset, and therefore showing a shorter latency in mood-stabilizers introduction compared with BDII (Morken et al., 2009). Indeed, a correct diagnosis with adequate treatment may be delayed by years in BDII due to the predominance of depressive symptoms (Goldberg and Ernst, 2002; Vieta, 2019).

Due to its potentially modifiable nature, it is not surprising that DUI has been a topic of clinical and research interest. A longer of DUI has

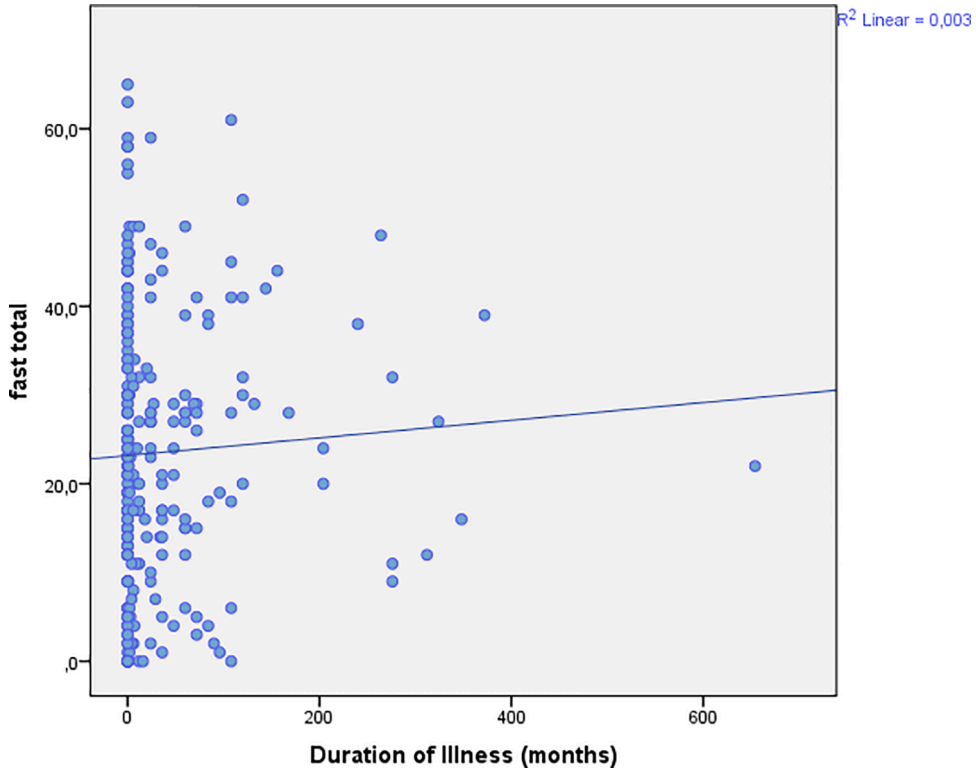

Fig. 1. Correlation plots. Spearman correlation of duration of untreated illness (DUI) expressed in months and Functional Assessment Short Test (FAST) total score in patients with bipolar disorder. Upper left corner with r, Spearman correlation coefficient and p, associated P-value.

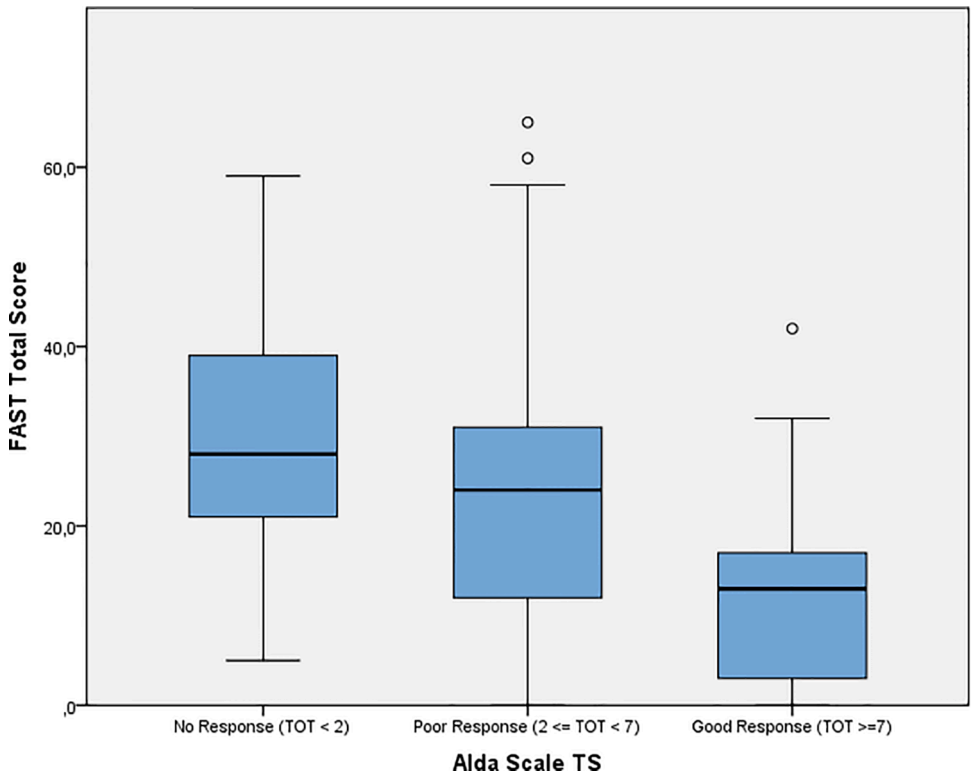

Fig. 2. Box-whisker plots showing Functional Assessment Short Test (FAST) total scores in non-responders (Alda Scale TS<2), poor-responders (Alda Scale TS=2-6) and good-responders (Alda Scale TS≥7) to Lithium. A Kruskal–Wallis test was performed between groups, and a statistically significant difference was accepted at $p<0.01$ by Bonferroni correction (*). Good-responders show significantly lower FAST scores, indicating better global functioning.

been strongly linked to worse treatment response, outcomes, and overall functional outcomes in schizophrenia (Amoretti et al., 2018; Murru and Carpiniello, 2018). Early intervention is also crucial in BD to improve patients' prognosis (Galimberti et al., 2020; Joyce et al., 2016), possibly reversing cognitive deficits and reducing gray matter volume changes (M Berk et al., 2017; Kozicky et al., 2016). Moreover, pharmacological and non-pharmacological treatments might work best in the earliest illness stages (Berk et al., 2011).

In our study, we did not find a significant association between DUI and functional outcomes. This apparently contrasts with previous evidence showing worse functional outcomes in BD patients with a longer DUI, but the same studies all shared an association between more lifetime affective episodes and longer DUI (Altamura et al., 2015; Drancourt et al., 2013). In our sample, patients in the DUI subgroups did not differ in terms of total affective episodes, and the latter highly correlated with worse functioning in bivariate analyses. This association was lost in the linear regression, likely due to a covering effect of illness duration, also strongly related to total affective relapses (Marzo et al., 2006).

DUI in psychoses is a measure of the active illness that marks the almost inevitable beginning of progressive structural changes in key brain areas (Malhi and Outhred, 2016). In mood disorders, the neuroprogression hypothesis suggest that mood relapses might promote cumulative neuronal damage, increasing brain susceptivity to further affective episodes (Berk et al., 2017). Recent evidence in major depression showed that microglial activation, which is a marker of neuroprogression, is greater in patients with longer DUI and shorter exposure to antidepressant treatment than in patients with shorter DUI and longer exposure to antidepressant treatment (Setiawan et al., 2018). Also, antidepressant treatment may reduce the microglial activation, preventing neuroprogression (Setiawan et al., 2018). On the other hand, neuroprogression in untreated BD is a possible but not inevitable clinical course, as the illness allostatic load seems to rely more on the number of acute affective episodes (Abé et al., 2020; Vieta et al., 2018a), of which DUI would just be a proxy, as well as other features such as subsyndromal inter-episodic symptoms of both polarities and specific neurocognitive deficits (Sanchez-Moreno et al., 2018). On the other hand, neuroprogression in untreated BD is a possible but not inevitable clinical course, as the illness allostatic load seems to rely more on the number of acute affective episodes (Abé et al., 2020; Vieta et al., 2018a), of which DUI would just be a proxy, as well as other features such as subsyndromal inter-episodic symptoms of both polarities and specific neurocognitive deficits (Sanchez-Moreno et al., 2018).

In conclusion, DUI in its current definition might be unfit for a direct translation into the clinical assessment of BD, as poor functioning in BD could be the result of multiple affective relapses in patients misdiagnosed or inappropriately treated, rather than a direct effect of DUI. In this perspective, the duration of untreated bipolar disorder (DUB) might be better represented by the duration of untreated affective episodes, expressed as total duration in months/weeks, rather than considering the duration of untreated illness as whole. However, further studies with larger samples should validate our preliminary hypothesis.

Our study highlights a novel significant association between DUI and treatment response to lithium, but not to valproate or lamotrigine. Whether or not treatment response in BD is influenced by illness progression is still a matter of debate. While some studies reported no effect of DUI on treatment response (Baldessarini et al., 2003), more recent studies indicate that a later start of a mood stabilizer is associated with increased lifetime suicide attempts and poor illness outcomes (Buoli et al., 2021). Also, short pre-lithium treatment illness duration was associated with good lithium response in a recent meta-analysis (Hui et al., 2019).

In our sample, treatment response to lithium was associated with better overall functioning, including cognitive functioning. Lithium is widely prescribed as a first-line treatment for bipolar disorder (Carvalho et al., 2020; González-Pinto et al., 2018). Furthermore, lithium long-term treated patients show increased volumes of cortico-limbic

structures and lithium showed a specific neuroprotective effect (Hozer et al., 2020; López-Jaramillo et al., 2017).

Previous evidence confirms the underlying network between lithium, neurocognition, and functioning in BD (Bonnín et al., 2010; Burdick et al., 2020; Malhi et al., 2016). Hence, the sooner lithium is started, the lower the impact on patients' functioning, likely due to a reduced number of relapses during the course of illness (Kessing, 2019), but also through the aforementioned lithium-induced neuroprotection. Further prospective studies should investigate the possible causal relationship between these variables.

Also, lithium seem to have a role in reducing the need for augmentation strategies in BD treatment, since the rates of complex polypharmacy in lithium-treated patients are lower compared the ones of patients treated with other mood-stabilizers (Fornaro et al., 2016).

Several limitations should be addressed for this study. First, the partially retrospective recollection of data could expose our data to recall bias. However, our study has been conducted on a real-world population of patients with BD, regularly followed in our specialized unit in a prospective follow-up, so that any baseline missing information can be reliably extracted during the follow-up. Indeed, various cohort studies on bipolar disorder provided crucial and reliable information on the course of the illness (Vieta and Angst, 2021). Secondly, we could not characterize the entangled relationship between DUI, treatment response, and functioning with causality, given the cross-sectional design. Lastly, we only considered patients receiving a specific mood-stabilizer, as suggested by international guidelines, but we excluded patients that only received antipsychotics, also considered as first-line in the treatment of BD, but mainly used as a combination therapy both in acute and maintenance treatment (Wingård et al., 2019).

5. Conclusions

According to our study and coherent with the neurobiological frameworks differentiating schizophrenia and BD, DUI as currently defined might not bear clinical validity in BD, whilst a definition of DUI incorporating the number of untreated affective episodes would warrant the prognostic implications that such a construct should provide. Nonetheless, a timely diagnosis with subsequently appropriate treatment may prevent poor functional outcomes of illness that may occur as a result of recurring major affective episodes.

Unique among mood stabilizers (Carvalho et al., 2021), lithium shows preventive effectiveness on symptomatic, episodic, and functional outcomes in bipolar illness.

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None.

Authorship

GF made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; formulated this article and wrote the first draft. CDM contribuited to acquisition of data, or analysis and interpretation of data. AM had been involved in drafting the manuscript and revising it critically for important intellectual content. EV read the first draft and added critical comments. All other authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Declaration of Competing Interest

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini with no financial or other relationship relevant to the subject of this article.

EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis and Takeda. GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck, unrelated to the present work. MM has received honoraria as CME speaker from Angelini. MA has no conflict of interest to declare. AGP has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, Takeda, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, and the European Framework Program of Research.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.07.062.

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