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ORIGINAL ARTICLE

Association between duration of untreated bipolar disorder and clinical outcome: data from a Brazilian sample

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Objective: Bipolar disorder (BD) is often left untreated for long periods, and this delay in treatment correlates with unfavorable prognosis. The present study sought to assess the magnitude of duration of untreated bipolar disorder (DUB) in Brazil. We hypothesized that DUB would be longer in Brazil than in developed countries, and would be associated with poor clinical outcomes.
Methods: One hundred and fifty-two psychiatric outpatients were evaluated for BD diagnosis, demographics, DUB, and clinical outcomes.
Results: The mean age and mean DUB were, respectively, 38.9±10.8 and 10.4±9.8 years. An extended DUB was associated with early onset of BD ($p < 0.001$), depression as first mood episode ($p = 0.04$), and presence of BD in a first-degree relative ($p = 0.012$). Additionally, a longer DUB was associated with poorer clinical outcomes, such as elevated rates of rapid cycling ($p = 0.004$) and anxiety disorders ($p = 0.016$), as well as lower levels of current full remission ($p = 0.021$).
Conclusion: As DUB may be a modifiable variable, better medical education regarding mental health, more structured medical services, and population-wide psychoeducation might reduce the time between onset and proper management of BD, thus improving outcome.

Keywords: Community mental health; mood disorders; bipolar disorder; outpatient psychiatry; chronic psychiatric illness

Introduction

Bipolar disorder (BD) carries a major social burden[1-3] and is associated with the highest expenditures among all mental disorders.[4] This condition tends to be chronic, and persons with BD experience high rates of work impairment, suicidal behavior, and hospitalization.[3,5-7] The evidence available from developed countries suggests that BD usually goes untreated for long periods, and that this delay in treatment correlates with an unfavorable prognosis.[8-11] However, the concept of duration of untreated bipolar disorder (DUB) is still understudied,[8] especially in developing countries.

DUB is formally defined as the interval between onset of BD and first pharmacological treatment with a mood stabilizer.[9] Some features of BD are associated with a longer DUB, such as having depression as the first mood episode and earlier onset of BD.[8,10] An extended DUB has been found to correlate with poor clinical outcomes, such as increased rates of suicidal behavior, a higher number of mood episodes, and increased social difficulties.[10,12] In Italy, Altamura et al. found a mean DUB of 8.7 years and an association between extended DUB and high numbers of suicide attempts, a higher percentage of suicide attempters, and a longer duration of BD.[8] In France, Drancourt et al. found an average DUB of 9.6 years and a correlation of extended DUB with more mood episodes, more suicidal behavior, and a trend toward more severe mood instability.[10] In Australia, McCraw et al. addressed the association between DUB and social functioning, and suggested that longer periods between onset of BD and its proper treatment were associated with more employment problems and higher social costs.[12] Although DUB may be a modifiable variable amenable to reduction through interventions,[13] to the best of our knowledge, there are no data regarding DUB in developing countries.

The fact that DUB has never been evaluated in a developing country is worrisome, as mental health care in these regions is usually less effective than in developed countries[14] and, as a result, DUB might be longer and produce more negative social impacts. The objective of the present study is to assess the magnitude of DUB in Brazil, a major developing country.[15] Our hypothesis is that DUB would be longer in this society than in developed nations, and would be associated with poor clinical outcomes.

Methods

Sample

Our sample consisted of 152 outpatients with a well-characterized diagnosis of BD – 134 (88.2%) with subtype

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I and 18 (11.8%) with subtype II – recruited from the Bipolar Disorder Program (PROMAN) at Hospital das Clínicas, School of Medicine, Universidade de São Paulo. During their first visit at the unit, each patient completed self-assessment questionnaires. Research-trained psychiatrists conducted the semi-structured interviews for this study.

The inclusion criteria were: 1) a formal DSM-IV diagnosis of BD, as assessed by the Structured Clinical Interview for DSM-IV (SCID); 2) age 18 to 65 years; 3) at least 5 years of schooling; and 4) absence of neurological disorders or severe physical illness.

Measurements

BD diagnosis

The diagnostic instrument used for BD diagnosis was the Portuguese version of the SCID.[16] This questionnaire has been properly translated and validated, and has demonstrated an excellent weighted kappa coefficient, good reliability for main disorders formerly placed in "axis 1," and high inter-rater reliability.[16]

Duration of untreated bipolar disorder (DUB)

DUB was calculated as the interval between first mood episode and first pharmacological treatment with a mood stabilizer,[9] defined as any of the first-line medications for maintenance treatment of patients with BD listed in the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[3]

Demographics and clinical outcomes

Data on age, gender, race, and years of schooling was collected from all participants. The clinical features and outcomes of BD, as well as comorbidities, were investigated using a standardized protocol and information from the SCID. Familial mood antecedents were collected by research-trained psychiatrists through the standardized questionnaire developed by the Brazilian Bipolar Research Network. The variables evaluated were: age at onset of BD, age at use of first mood stabilizer, duration of BD, presence of rapid cycling, current full remission, lifetime psychotic symptoms, number of psychiatric hospitalizations, polarity of first mood episode, presence of first-degree relative with BD, number of suicide attempts, lifetime prevalence of anxiety disorders, and lifetime prevalence of alcohol-use disorder.

Additionally, we divided our demographic variables and clinical outcomes into 1) factors that preceded BD diagnosis (gender, race, age at onset of BD, polarity of first mood episode, and presence of first-degree relative with BD) and 2) factors that occurred after BD diagnosis or with unknown chronology (age, years of schooling, age at use of first mood stabilizer, duration of BD, presence of rapid cycling, current full remission, lifetime psychotic symptoms, number of psychiatric hospitalizations, number of suicide attempts, lifetime prevalence of anxiety disorders, and lifetime prevalence of alcohol-use disorder). This categorization may provide additional information regarding any causal relationship between these variables and DUB.

Statistical analysis

First, we analyzed the distribution of continuous variables using the Kolmogorov-Smirnov test. Then, we tested for association between DUB and each of the demographic/clinical variables of interest, by performing a correlation analysis to assess the relationship between DUB and other continuous variables. Pearson's and Spearman's coefficients were used, respectively, for normally distributed and nonparametric continuous variables. The Mann-Whitney *U* test was used to evaluate associations between DUB and categorical variables. The level of significance was set at $p = 0.05$.

Ethical issues

This study was approved by the Ethics Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. All subjects participated voluntarily and provided written informed consent. The study was performed in compliance with the principles of the Declaration of Helsinki.[17]

Table 1 Demographics and clinical variables of subjects with BD (n=152)

Variable	
Demographic variables	
Factors that occurred before BD diagnosis	
Gender	
Male	51 (33.6)
Female	101 (66.4)
Race	
White	109 (71.7)
Nonwhite	43 (28.3)
Factors occurring after BD diagnosis*	
Age	38.9±10.8
Formal education, years (n=150)	11.7±3.7
Clinical variables	
DUB, years	10.4±9.8
Factors occurring before BD diagnosis	
Age at onset, years	23.1±9.4
Polarity of first episode (n=120)	
Mania or hypomania	39 (32.5)
Depression	81 (67.5)
First-degree relative with BD (n=132)	31 (23.5)
Factors that occurred after BD diagnosis	
Age at use of first mood stabilizer, years	33.6±10.1
Duration of illness, years	15.7±11.0
Rapid cycling (n=148)	15 (10.1)
Current full remission (n=151)	41 (27.2)
Lifetime psychotic symptoms	105 (69.1)
Number of psychiatric hospitalizations	3.0±11.8
Number of suicide attempts (n=146)	1.1±1.9
Lifetime anxiety disorder	74 (49.0)
Lifetime alcohol-use disorder	29 (19.2)

Data expressed as mean ± standard deviation or n (%). The number of subjects evaluated for each variable is n=152 unless otherwise stated.
BD = bipolar disorder; DUB = duration of untreated bipolar disorder; SD = standard deviation.
* Factors with unknown chronology were considered to have occurred after BD diagnosis.

Results

The mean age and mean DUB of the sample were, respectively, 38.9±10.8 and 10.4±9.8 years. The median DUB was 7 years (range, 0-43). With respect to current mood status, 50% of participants were euthymic, 36.2% presented with major depressive disorder, 8.5% presented with symptoms suggestive of mixed episodes, and 5.3% were experiencing hypomanic states. Table 1 presents descriptive statistics on the participants' demographics and clinical outcomes.

An extended DUB was associated with early onset of BD, presence of a first-degree relative with BD, and depression as first mood episode. Additionally, a longer DUB was associated with poorer clinical outcomes, such as elevated rates of rapid cycling and anxiety disorders, as well as lower rates of current full remission. The main results of the analysis of association between DUB and demographic/clinical variables are displayed in Table 2.

Discussion

This was the first study to evaluate the magnitude of DUB and the association between this parameter and clinical variables in a developing country.

Our most relevant findings were: 1) the mean DUB was long (10.4 years); 2) specific clinical features were associated with an extended DUB; and 3) a longer DUB correlated with poorer clinical outcomes.

The mean DUB in this study was longer than those reported in research studies conducted in developed countries.[8-10] The exception was a study performed by McCraw et al. in Australia, in which the average DUB was

Table 2 Association between DUB and demographic/clinical variables of subjects with BD (n=152)

Variable	DUB (mean ± SD) or correlation coefficient	p-value
Demographic variables		
Factors that occurred before BD diagnosis		
Gender		
Male	DUB = 12.3±11.6	0.383
Female	DUB = 9.5±8.6	
Race		
White	DUB = 11.0±10.2	0.361
Nonwhite	DUB = 8.9±8.5	
Factors that occurred after BD diagnosis*		
Age	P-coef. = 0.472	< 0.001
Formal education, years (n=150)	S-coef. = -0.060	0.464
Clinical variables		
Factors occurring before BD diagnosis		
Age at onset, years		
Polarity of first episode (n=120)	S-coef. = -0.445	< 0.001
Mania or hypomania	DUB = 6.1±9.3	0.004
Depression	DUB = 13.2±9.4	
First-degree relative with BD (n=132)		
Yes	DUB = 14.3±10.5	0.012
No	DUB = 9.3±9.4	
Factors occurring after BD diagnosis		
Age at use of first mood stabilizer in years	S-coef. = 0.381	< 0.001
Duration of illness	S-coef. = 0.809	< 0.001
Rapid cycling (n=148)		
Yes	DUB = 18.1±11.9	0.004
No	DUB = 9.7±9.2	
Current full remission (n=151)		
Yes	DUB = 7.9±8.9	0.021
No	DUB = 11.5±10.0	
Lifetime psychotic symptoms		
Yes	DUB = 10.5±9.7	0.939
No	DUB = 10.2±10.1	
Number of psychiatric hospitalizations	S-coef. = -0.082	0.322
Number of suicide attempts (n=146)	S-coef. = -0.015	0.860
Lifetime anxiety disorder		
Yes	DUB = 12.1±9.9	0.016
No	DUB = 9.0±9.7	
Lifetime alcohol-use disorder		
Yes	DUB = 14.1±12.7	0.102
No	DUB = 9.5±8.8	

The number of subjects evaluated for each variable is n=152 unless otherwise stated.
BD = bipolar disorder; DUB = duration of untreated bipolar disorder, in years; P-coef. = Pearson's coefficient (used for normally distributed variables); S-coef. = Spearman's coefficient (used for nonparametrically distributed variables); SD = standard deviation.
* Factors with unknown chronology were considered to have occurred after BD diagnosis.

Table 3 Findings and methodological characteristics of studies that evaluated the concept of DUB

	This study	McCraw[12]	Drancourt[10]	Altamura[8]
Country	Brazil	Australia	France	Italy
Sample size	n=152	n=173	n=501	n=320
Age, years	39.8±10.8	38.1±11.4	42.3±13.9	46.0±12.8
Male	33.6	38.2	41.7	43.8
Female	66.4	61.8	58.3	56.2
BD subtype I	88.2	14.5	83.4	40.0
BD subtype II	11.8	85.5	16.6	60.0
DUB, years	10.4±9.8	18.0±11.7	9.6±9.7	8.7±7.7
Main clinical outcomes associated with longer DUB	More rapid cycling Less current remission More anxiety disorder	More employment difficulties More social costs due to mood episodes	More suicidal behaviour Early onset of BD More mood episodes	More suicidal behavior
Recruitment	Bipolar outpatient clinic	Depression clinic	General psychiatric outpatient clinic	Mood disorders outpatient clinic

Data expressed as mean ± standard deviation or percentages, unless otherwise stated.
BD = bipolar disorder; DUB = duration of untreated bipolar disorder.

18 years. However, this Australian study used a sample with a disproportionally large percentage of subjects with BD subtype II (85.5%).[12] As this subtype tends to feature a significantly longer DUB than BD subtype I,[8-10,12] the longer DUB was expected. Table 3 presents some results and methodological characteristics of prior studies that evaluated the concept of DUB. The longer DUB in our study may represent the poorer structure of general primary health services and, especially, mental health services in Brazil when compared to developed countries.[18,19] The lack of an efficient public health approach may delay first contact with medical professionals and, consequently, delay a correct diagnosis of BD.[20]

We found that specific clinical features of BD were associated with a longer DUB. Patients who developed BD at a younger age and presented with depression as the first mood episode tended to have an extended DUB. Studies conducted in the developed world reported similar findings.[8,10]

However, our study was the first to observe that the presence of a first-degree relative with a diagnosis of BD was associated with a longer DUB. This may be a result of the social stigma associated with BD.[21] Stigmatization associated with BD has been increasingly studied and seems to be a complex phenomenon, including personal and population-wide elements.[21,22] A longitudinal study conducted by Perlick et al. suggested that subjects with BD who expressed concerns with stigma during acute episodes demonstrated poorer social adjustment.[23] In this context, individuals who, during their lives, observed the "social consequences" of a relative with this condition might try to avoid medical care and a possible BD diagnosis. Personal and familial psychosocial interventions may decrease the subjective stigma (also known as internalized stigma) and facilitate early treatment of affected family members. Community psychoeducational programs, in turn, might reduce stigma in the general population.

An extended DUB was also associated with markers of severity such as rapid cycling, lower rates of current full remission, and high rates of comorbid anxiety disorders. Although a clear causal relationship between longer periods without treatment and these poor clinical outcomes cannot be inferred, the neuroprogressive nature of BD may be a possible explanation.[24-26]

Some limitations of our study are worth noting. First, this was a cross-sectional study, in which DUB and other clinical variables were evaluated retrospectively. Implications include the possibility of recall bias, which may affect the completeness or accuracy of information. The fact that 50% of our sample presented with current mood symptoms may also reduce the precision of the information regarding degree of cognitive impairment. Furthermore, we are not able to establish a robust interrelationship of cause and effect among the different variables; longitudinal studies would better evaluate causality. Second, our sample consisted of treatment-seeking patients and, therefore, the impact of DUB may be underestimated, which also limits the possibility of generalizations at the population level. Nonetheless, the results obtained in this study may be considered clinically useful.

Future studies on DUB are still needed, especially in developing countries. Additionally, further research could analyze the pathophysiology of the association between longer DUB and poorer outcomes. The present study did not investigate the relationship between DUB and specific BD subtypes (BD I, BD II, etc.). Future studies to do so would help advance our understanding of the relationship between longer DUB and adverse clinical outcomes.

As DUB may be a modifiable variable,[13] better medical education regarding mental health and, particularly, the psychopathological characteristics of BD may improve correct diagnosis of this condition. In addition, more structured medical services and population-wide psychoeducational interventions may also reduce the time between onset and proper management of BD[4] and, thus, improve outcomes.

Disclosure

The authors report no conflicts of interest.

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