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ORIGINAL ARTICLE

Pharmacological treatment and staging in bipolar disorder: evidence from clinical practice

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Objective: Staging models for medical diseases are widely used to guide treatment and prognosis. Bipolar disorder (BD) is a chronic condition and it is among the most disabling disorders in medicine. The staging model proposed by Kapczinski in 2009 presents four progressive clinical stages of BD. Our aim was to evaluate pharmacological maintenance treatment across these stages in patients with BD.
Methods: One hundred and twenty-nine subjects who met DSM-IV criteria for BD were recruited from the Bipolar Disorders Program at Hospital de Clínicas de Porto Alegre, Brazil. All patients were in remission. The subjects were classified according to the staging model: 31 subjects were classified as stage I, 44 as stage II, 31 as stage III, and 23 as stage IV.
Results: Patterns of pharmacological treatment differed among the four stages ($p = 0.001$). Monotherapy was more frequent in stage I, and two-drug combinations in stage II. Patients at stages III and IV needed three or more medications or clozapine. Impairment in functional status (Functioning Assessment Short Test [FAST] scale scores) correlated positively with the number of medications prescribed.
Conclusions: This study demonstrated differences in pharmacological treatment in patients with stable BD depending on disease stage. Treatment response can change with progression of BD. Clinical guidelines could consider the staging model to guide treatment effectiveness.

Keywords: Bipolar mood disorders; anticonvulsants; antidepressants; antipsychotics; diagnosis and classification

Introduction

Disease staging models have been historically important in improving health care, as they allow a more precise, comprehensive, and structured evaluation of the disease state and its progression. A more accurate evaluation of disease burden enables clarification of outcomes and prognosis and development of better treatment strategies. For years, staging models have been used in such areas as oncology, cardiology, hepatology, and pulmonology, helping clinicians in the decision-making process. In psychiatry, however, only recently has the issue of disease staging entered debate.[1,2]

Bipolar disorder (BD) is among the most disabling diseases,[3] not only due to episode-related dysfunction but mostly because of long-term impairment.[4] Data reporting different patterns of neuroprotective, inflammatory, and neuroanatomical biomarkers in the early and late stages of BD reinforce the longitudinal and progressive course of this disorder,[5-10] and are corroborated by clinical deterioration and neuroanatomical changes.

Different models for BD staging have been proposed.[11,12] They converge insofar as all describe a prodromal phase (i.e., stage 0,[11] latent stage[12]), followed by onset, recurrence, and, finally, chronicity, defining the later stages of the disease as more recurrent, treatment-resistant[11] and socially dysfunctional.[12]

While these staging models for BD have been considered theoretically, they must be validated and improved for clinical implementation. A study by Berk et al. pooled 12 BD studies and identified that those patients at the earliest stages of the illness had a more favorable response to treatment.[13] However, the pharmacological treatment profile of patients with BD across disease stages has yet to be characterized.

The perspective and implications of a progressive pattern have boosted research into development of staging models for BD.[11,12] The treatment of patients with multiple episodes may differ from that of patients with a smaller number of mood episodes. Stage I patients could be maintained on monotherapy, supplemented with close

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monitoring for treatment compliance and psychoeducation with a view to preserving cognitive status and social functioning. According to Reinares et al., patients at stage I derived more benefit from psychoeducation of their caregivers, as demonstrated by a longer time to recurrence.[14] However, patients at advanced stages have not shown evidence of significant benefits from caregiver psychoeducation, reinforcing the idea of different treatments for different stages of the illness. As treatment response could also change with progression of BD, many studies conducted to date have drawn attention to the fact that it would be helpful to incorporate a BD staging model into clinical guidelines, allowing treatment to be tailored according to the individual needs of each patient depending on their current stage.[12]

The objective of the present study was to evaluate pharmacological maintenance treatment in stable patients with BD classified in accordance with an established staging model[12] and thus determine whether there are empirical differences in pharmacological treatments across different stages. We hypothesized that treatment of BD patients in the early stages of illness (stage I and II) would be more reliant on monotherapy, whereas patients in the late stages (III and IV) would be more likely to be treated with combinations of three or more different drugs.

Methods

Subject selection

Two hundred and forty-three outpatients diagnosed with BD from the Bipolar Disorder Program at Hospital de Clínicas de Porto Alegre, state of Rio Grande do Sul, Brazil, were screened for this study. Of those, 129 patients met the inclusion criteria and entered the study. The inclusion criteria were: 1) age $>$ 18 years; 2) meeting DSM-IV-TR criteria for BD type I, according to the Structured Clinical Interview for DSM-IV-TR[15]; 3) meeting remission criteria, as assessed by the Young Mania Rating Scale (YMRS)[16] and the 17-item Hamilton Depression Rating Scale (HAM-D),[17] both scoring less than 7 points at least 1 month before assessment; 4) absence of comorbid mental retardation/severe intellectual disabilities; 5) absence of severe unstable medical comorbidities; 6) ability to comprehend and provide informed consent.

This study followed the ethical principles of the Declaration of Helsinki, and was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre. Patients were informed of the goals and procedures of the study, and were only included after signing an informed consent form.

Staging classification

Patients were classified on one of four clinical stages in accordance with the BD staging model described by Kapczinski et al.[12] To that end, a semi-structured interview was administered to each patient by two psychiatrists previously trained in the model. The clinicians collected data on course of illness, presence or absence of psychiatric comorbidities, subjective assessment of previous and present work activity, social interactions, and self-care. Even though functioning is an important aspect of BD staging, this variable was assessed separately, using the Functioning Assessment Short Test (FAST).[18] Patients were classified in clinical stages as follows: a) stage I, individuals who exhibit the same status in the interepisodic period as they did before the onset of BD (i.e., premorbid status); b) stage II, individuals whose interepisodic period is characterized by psychiatric comorbidities or residual symptoms that require changes in pharmacological treatment, but who are able to maintain daily activities; c) stage III, individuals who require occupational and social rehabilitation and face difficulties in their daily activities; and d) stage IV, individuals who are unable to maintain personal self-care and to live autonomously (Figure 1). Medical records were carefully checked, family and caregivers were interviewed, and the assistant clinician consulted in cases of inter-rater disagreement. The two psychiatrists were blinded to the results of clinical evaluation and functional assessment. This methodology has been used successfully in previous studies, and the authors were able to differentiate between patients in early vs. late stages of BD.[14,19]

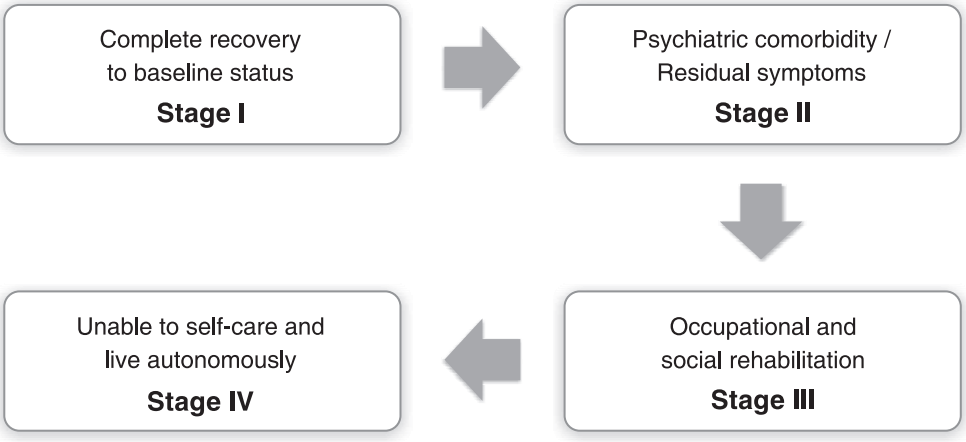

Figure 1 Four-stage clinical model proposed by Kapczinski et al.[12]

Clinical and pharmacological data

Data on sociodemographic and clinical variables were collected per research protocol. Information about pharmacological treatment prescribed was collected from the patient. An interview with the attending physician/psychiatrist and a chart review were then conducted to confirm all information. The chart review also endorsed stability of medication dosage, serum levels of mood stabilizers, and treatment adherence.

Statistical analysis

All statistical analyses were performed in SPSS version 19.0. The Kolmogorov-Smirnov test was used to assess normality of data distribution. Chi-square tests were used to analyze categorical data. Analysis of variance (ANOVA) with Tukey's post-hoc test was used for continuous, normally distributed variables.

Results

Among the 129 patients included in the study, 31 were classified as stage I, 44 as stage II, 31 as stage III, and 23 as stage IV. Groups did not differ regarding age, years of education, age at disease onset, family history of psychiatric disorders, marital status, or HAM-D and YMRS scores. As expected, however, patients at different stages had different numbers of mood episodes and psychiatric comorbidity and different patterns of work situation. Gender also differed significantly among groups, with a majority of female patients (see Table 1 for a detailed overview of subject characteristics). To assess possible group-to-group differences in characteristics, one-way ANOVA with Tukey's post-hoc test was performed and showed differences regarding age (I < IV = III = II; p = 0.049), illness duration (I = II < III = IV; p = 0.034), FAST (I = II = III < IV; p = 0.001), psychiatric comorbidity (I = II = IV < III; p = 0.044), and number of mood episodes (II > I = III = IV; p = 0.020).

Monotherapy consisted of using one mood stabilizer (MS; lithium or anticonvulsants), in therapeutic range, or an atypical antipsychotic (AA). Combination therapy always included at least one MS. Fifty percent of stage IV patients on monotherapy were receiving clozapine (8.7% overall).

There was no significant difference between the four clinical stages regarding use of lithium, AAs, benzodiazepines, or antidepressants. There were between-group differences in clozapine, anticonvulsant, and typical antipsychotic use. Clozapine was more frequently prescribed to stage IV patients, typical antipsychotics were more frequent in stages II and IV, and anticonvulsants were more frequent in stage III patients (Table 2).

Differences in pharmacological treatment patterns were observed across all four stages (ANOVA, p = 0.001). Monotherapy was more frequent in stage I. Two-drug combinations (i.e., MS plus AA) were more frequent in stage II, and patients at stages III and IV were more likely to require three-drug combinations or five or more agents. Interestingly, four-drug combinations were most frequent in stage II patients (Table 2).

Discussion

Regarding pharmacological treatment patterns, this study showed that stable stage I and II BD is associated with

Table 1 Sample characteristics

	Total (n=130)	Stage I (n=31)	Stage II (n=44)	Stage III (n=31)	Stage IV (n=24)	p-value	Post-hoc
Gender (male/female)	38/92	9/22	6/38	12/19	11/13	0.021*†	
Age, years	44.9±12.8	40.6±12.3	44.7±12.3	45.3±12.8	50.1±13.0	0.080‡	I < IV = III = II
Years of schooling	9.7±4.1	11.3±3.9	9.1±4.1	9.7±3.3	8.7±4.9	0.116‡	I = II = III = IV
Illness duration, years	16.9±12.8	10.5±7.3	16.9±14.1	19.1±12.3	22.4±13.5	0.003‡§	I < III = II = IV
Disease onset, age	27.9±12.6	31.1±11.8	27.8±13.9	26.2±11.3	27.6±13.0	0.638‡	I = II = III = IV
Number of mood episodes	16.0±23.8	6.6±6.3	23.1±16.3	14.8±14.7	16.9±12.8	0.035†‡	II > I = III = IV
Family history, %	49±50	50±51	50±50	48±51	43±51	0.995‡	I = II = III = IV
Psychiatric comorbidity, %	28±48	13±34	23±42	53±50	25±44	0.003‡§	I = II = IV< III
HAM-D	2.5±2.4	1.4±1.7	2.7±2.4	3.1±2.5	2.7±2.8	0.089‡	I = II = III = IV
YMRS	1.5±1.9	1.0±1.2	1.7±2.2	1.5±1.9	1.4±2.1	0.439‡	I = II = III = IV
FAST	24.9±15.8	17.0±12.7	20.1±10.1	25.6±13.9	41.1±15.8	0.001‡§	I = II = III < IV
Marital status							
Single	42 (32.6)	8 (25.8)	14 (32.6)	8 (25.8)	12 (50.0)	0.084*	
Married	62 (48.1)	19 (61.3)	17 (39.5)	20 (64.5)	6 (25.0)		
Divorced	19 (14.7)	2 (6.5)	10 (23.3)	2 (6.5)	5 (20.8)		
Widowed	6 (4.7)	2 (6.5)	2 (4.7)	1 (3.2)	1 (4.2)		
Work situation							
Employed	38 (32.8)	19 (67.9)	11 (19.7)	5 (17.9)	3 (13.0)	0.002*§	
Unemployed	37 (31.9)	4 (14.2)	16 (43.2)	9 (32.1)	8 (34.8)		
Retired	5 (4.3)	1 (3.6)	0	2 (7.1)	2 (8.7)		
On medical benefits	4 (3.4)	0	2 (5.4)	2 (7.1)	0		
On disability	25 (21.6)	1 (3.6)	6 (16.2)	8 (28.6)	10 (43.5)		
Student	7 (6.0)	3 (10.7)	2 (5.4)	2 (7.1)	0		

Data presented as mean ± standard deviation or n (%).
FAST = Functioning Assessment Short Test; HAM-D = Hamilton Depression Rating Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.
* Chi-square; † p-value significant at 0.05 level; ‡ ANOVA; § p-value significant at 0.01 level.

Table 2 Distribution of prescription patterns among stages of bipolar disorder (uncontrolled data)

	Stage I	Stage II	Stage III	Stage IV	p-value*
Number of patients on:					0.001
One drug	17 (13.2)	11 (8.5)	3 (2.3)	3 (2.3)	
Two drugs	7 (5.4)	14 (10.9)	10 (7.8)	6 (4.7)	
Three drugs	5 (3.9)	9 (7.0)	12 (9.3)	8 (6.2)	
Four drugs	2 (1.6)	10 (7.8)	5 (3.9)	4 (3.1)	
Five or more drugs	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.6)	
Number of patients on clozapine	0 (0.0)	0 (0.0)	1 (0.8)	4 (3.1)	0.002
Number of patients on:					
Lithium	20 (15.5)	28 (21.7)	14 (10.9)	12 (9.3)	0.321
Anticonvulsants	9 (7.0)	19 (14.7)	21 (16.3)	13 (10.1)	0.016
Atypical antipsychotics	10 (7.8)	20 (15.5)	14 (10.9)	11 (8.5)	0.606
Typical antipsychotics	3 (2.3)	10 (7.8)	8 (6.2)	10 (7.8)	0.039
Antidepressants	3 (2.3)	11 (8.5)	11 (8.5)	3 (2.3)	0.060
Benzodiazepines	3 (2.3)	12 (9.3)	5 (3.9)	8 (6.2)	0.097

Data presented as n (%).
* Chi-square.

monotherapy or use of two-drug combinations, whereas disease stages III and IV were more associated with combinations of three or more different drugs and with clozapine therapy. Clozapine seems important in avoiding polypharmacy among patients in stages III and IV. Despite the greater number of medications in those two groups, patients on clozapine therapy were using it as monotherapy or with an anticonvulsant. Data on pharmacological treatment patterns at later stages of BD suggest a better response to divalproex than to lithium in patients with a history of more episodes.[20] In treatment-resistant schizophrenia, clozapine yields more favorable results than any other antipsychotic,[21,22] but among treatment-resistant BD patients, its effectiveness is still unknown, which could pave the way for further research into clozapine therapy in BD.

Few studies have examined responsiveness to treatment at different stages of BD.[13,23] Berk et al. examined olanzapine clinical trials in symptomatic patients with BD and reported that patients with fewer than 10 previous episodes had fewer relapses to mania. In addition, patients with one to five previous episodes had fewer relapses to depression and a better response to treatment during acute episodes.[13] Although this study did not investigate different stages of illness, the number of previous episodes could be considered a good indicator for evaluation of disease progression, as patients who experience recurrent episodes are less resilient and have more neural dysfunction and greater functional impairment.[12,24] In a more classical study, Swann et al. assessed the antimanic effect of lithium, divalproex, and placebo according to the number of previous mood episodes. They found that a greater number of previous episodes was associated with poor antimanic response to lithium, but not to divalproex.[20]

Enough data from basic and translational research has mounted to endorse the concept of staging. Neurotrophins and anti-inflammatory biomarkers are known to be increased in patients who have experienced fewer episodes of BD (less than 3 years of BD and an average of three episodes) when compared to patients with more than 10 years of BD (average of 13 episodes), while TNF-α, an inflammatory biomarker, was increased in patients with more than 10 years of BD.[8,25] Differences in the redox system between the early and late stages of BD have also been observed. Glutathione reductase and glutathione S-transferase, markers of oxidative stress, were higher among patients with a history of fewer than three episodes as compared to patients with more than 10 episodes.[26]

Patients with BD exhibit progressive functional changes from stages I to IV.[19,27] Research on cognitive performance in BD also contributes to the idea of staging. Available data show that a higher number of mood episodes is associated with poorer neurocognitive performance, suggesting that the recurrence of mood episodes is associated with cognitive impairments, e.g., in executive function and episodic memory.[28] Tailored treatment approaches could also be used to meet patients' neuropsychological needs, preventing relapses and improving adherence.

The perspective of a progressive pattern of disease has boosted research into the development of staging models for BD.[11,12] As treatment response could change with disease progression, clinical guidelines could consider inclusion of the staging model to better guide treatment effectiveness. According to this model, management must be tailored to the individual needs depending on the current stage of the patient. Stage I patients could be maintained on monotherapy, supplemented with close monitoring of treatment adherence and psychoeducation, to preserve cognitive status and social functioning.

Patients in stage II showed higher rates of combination therapy in this sample, as compared with the other groups (Table 2). In the staging model, the main determinant for patient classification as stage II is symptomatology due to a comorbid disorder, despite stability of the mood disorder. Hence, we believe that, in these patients, the comorbid psychiatric disorder may have required changes in prescription. In stage III, complex regimens are often required, since cognitive and functional deterioration are present and patients exhibit more interepisodic dysfunction. The last stage of BD is associated with the worst prognosis, and daycare centers, occupational therapy, palliative care, and therapeutic accompaniment are commonly required.[12]

In other approach to this sample, as expected, early- and late-stage patients showed differences in functional status, as assessed by the FAST scale. Rosa et al., in a study of patients with first mood episode vs. multiple episodes, showed similar differences.[27] In further investigations, our group confirmed that the FAST scale is a good determinant to distinguish between stages, demonstrating progressive functional changes from stages I to IV.[19]

There are some limitations to the present study. Its cross-sectional design precluded direct examination of the course of pharmacological treatment in BD patients over time and their clinical progression. However, the study also has certain merits, including the sample consisting of stable patients and the fact that results were not confounded by age or years of education. Another important point is the fact that a validated instrument was used to evaluate functioning impairment.[18]

The BD staging model used in this study is growing in acceptance among researchers and clinicians. Assessing patients in euthymia allows correct evaluation of maintenance treatment, functioning, and, above all, accurate classification of staging. The limitations of this classification method notwithstanding, clinical practice has been empirically reinforcing the concept of staging. Of note, even in a naturalistic fashion, prescriptions in this study were in line with the most recent guidelines,[29] which should open discussion for the inclusion of BD staging in clinical practice guidelines.

Disclosure

The authors report no conflicts of interest.

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