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Predictors of good outcome in patients with refractory bipolar disorder after a drug or a drug and cognitive-behavioral treatment

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Abstract

Objective: The objective of the present research study was to analyze the variables involved in the favorable prognosis of patients with refractory bipolar disorder after a drug or a drug and cognitive-behavioral treatment.
Methods: A sample of 40 patients was divided into 2 groups: (1) combined drug plus psychoeducational and cognitive-behavioral treatment or (2) drug treatment only (control group). We used a multigroup design with repeated measures at different times (baseline, posttreatment, 6-month follow-up, and 12-month follow-up) to evaluate the following variables: age, sex, number of hospitalizations, type of treatment, mania (Young Mania Rating Scale, or YMRS) and depression (Beck Depression Index, or BDI) symptoms, subsyndromal symptoms (BDI >7; YMRS >6), global suffering index, general index of social ability, self-esteem (Rosenberg scale), inadaptation (inadaptation Scale), anxiety (State-Trait Anxiety Inventory), quality of life (Global Activity Functioning), and health (European Quality of Life Scale). We considered favorable prognosis for subjects without persistent affective symptoms (BDI <7; YMRS <6) and/or without relevant difficulties in adaptation (Inadaptation Scale <14) in a 12-month follow-up.
Results: A binary logistic regression showed that the type of treatment (combined therapy corresponded to better progression), the number of prior hospitalizations (fewer hospitalizations corresponded to better progression), and self-esteem (higher self-esteem corresponded to better prognosis) were statistically significant.
Conclusions: The type of treatment, the number of prior hospitalizations, and the level of self-esteem were the most influencing factors for a favorable progression of refractory bipolar disorder. Differently from other studies, no significant influences of age, sex, subsyndromal symptoms, anxiety, and depression symptoms on the prognosis of refractory bipolar disorder were observed in our study.

1. Introduction

Patients with a refractory bipolar disorder (resistant to treatment and with a history of unfavorable progression), despite proper treatment attempts with mood stabilizers, frequently have a gloomy prognosis: residual symptoms [1], rapid cycling [2], and suicide attempts [3,4]. However, the evolution of such cases is actually influenced by a number of different factors.

According to several studies about the progression of bipolar disorder, medical and psychiatric comorbidity between episodes, psychotic symptoms in manic or mixed episodes, subsyndromal symptoms between episodes [5], and low premorbid functionality are predictors of unfavorable prognosis [6]. Similarly, previous occurrence of mixed episodes, subsyndromal depressive symptoms, and previous hospitalizations [7] are predictors of poor evolution of bipolar disorder. The occurrence of subsyndromal symptoms together with deterioration of verbal memory and executory functions may be predictors of unfavorable prognosis [8,9]. Recent life events and supportive interpersonal relationship predict the likelihood of onsets and recurrence of bipolar

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mood episodes [10]. Private self-consciousness predicts the likelihood of onset too, but not the number of episodes [11].

Anyway, all these variables are rather heterogeneous. Thus, failure to comply with the treatment [12], drug abuse [13], anxiety [14,15], early onset of the bipolar disorder [16,17], rapid cycling [18], mixed presentation [19], mood-incongruent psychotic symptoms [20], expressed emotion [21,22], and initial or long-term depression symptoms [23-25] are factors associated to poor prognosis: high hospitalization rates, suicide behavior, poor psycho-social functioning, and chronicity.

In earlier studies [26-28], we demonstrated the positive effects of a combined treatment (psychoeducational and cognitive-behavioral therapy + drug therapy) on the evolution of patients with a refractory bipolar disorder. In the present randomized study—conducted with a larger sample of patients—we evaluated different sociodemographic and clinical variables that may influence the prognosis of patients with a history of unfavorable progression of bipolar disorder.

This study is focused on predictors of good outcome in the treatment of refractory bipolar patients. These patients have been chosen because often they do not respond to usual treatment approaches, and further research about the predictors of outcome is required. The aim of this study was to determine the most important elements in relation to good prognosis, as well as the type of treatment that improves the progression of the condition, to improve the clinical utility of the intervention programs.

2. Methods

2.1. Participants

The studied group consisted of patients with a refractory bipolar disorder in the Grand Canary health care catchment area, managed at the Center of Mental Health located in Las Palmas during 2005 and 2006. All patients were under pharmacologic treatment (Table 1) mainly consisting of a mood stabilizer (predominantly lithium). Antipsychotics and/or antidepressants were also administered in some cases.

Inclusion criteria were as follows: (*a*) patient diagnosed with a type I or type II *Diagnostic and Statistical Manual and Mental Disorder, Fourth Edition, Text Revision* (DSM-IV-TR) bipolar disorder for at least 2 years; (*b*) patients with history of severe or unfavorable progression of the disorder despite adequate pharmacologic treatment (patients with poor medication adherence were excluded), defined as frequent relapses with rapid cycling course and suicide attempts in the preceding year with additional poor functional outcome (Inadaptation Scale [IS] score >14), or persistent affective symptoms (Beck's Depression Index [BDI] score >7; Young Mania Rating Scale [YMRS] score >6) and severe difficulties in social-occupational functioning (IS >14); (*c*) patients who were euthymic or with subsyndromal symptoms at the beginning of the study (BDI >7; YMRS >6); and (*d*) patients aged 18 to 65 years. Patients with current manic, hypomanic, or depressive episode according to *DSM-IV-TR* were excluded from the study because they are unable to attend group psychological therapy.

The preselection was carried out with 50 patients. Forty patients who met the inclusion criteria were finally recruited: all of them completed the treatment during the follow-up period; none of them met the criteria necessary to diagnose a depressive or hypomanic or manic episode at the beginning of the study. All participants gave their informed consent to participate in the study. This research was approved by the hospital's ethics committee.

2.2. Assessment measures

A semistructured individual interview (Structured Clinical Interview, SCID-P) was conducted at the beginning of the study for the purpose of verifying patients' diagnosis of bipolar disorder I or II according to the *DSM-IV-TR* diagnostic criteria.

Multiple demographic and psychological variables (age, sex, number of previous hospitalizations, number of recent hospitalizations, type of received treatment, previous subsyndromal symptoms, global suffering index, general index of social ability, self-esteem, depression and mania symptoms, anxiety, inadaptation, quality of life, and health) were evaluated for predictive value of therapeutic success/failure.

The researcher administered the following questionnaires: Symptom Checklist-90-Revised (SCL-90-R) [29], Scale of Social Skills [30], Scale of Self-esteem [31], BDI [32], YMRS [33], State-Trait Anxiety Inventory [34], IS [35], Scale of Global Activity Functioning [36], and Questionnaire European Quality of Life Scale [37]. These tools have been described elsewhere [26].

2.3. Study design and analysis

The original study was a randomized clinical trial where subjects were assigned to either the experimental group (under psychotherapy plus drug treatment) or the control group (only under drug treatment), to study the differential effectiveness of both therapeutic modalities. The experimental group showed a lower rate of depression and anxiety symptoms and less hospitalizations than the control group [28].

Table 1
Pharmacologic treatment received for patients

Pharmacologic treatment	Group	
	Control	Experimental
Lithium salts + atypical antipsychotics	10	11
Lithium salts + atypical antipsychotics + lamotrigine	4	4
Valproate + atypical antipsychotics	2	1
Valproate + antidepressants	1	2
Lithium salts + valproate	3	2

This current study was based on a correlational design. In this case, all patients were included in only a group (n = 40) with enough power for statistical analysis.

The cognitive-behavioral therapy used in this research was based on the manualized therapist's guide included in Lam et al [38]. This psychological intervention program—based on a cognitive-behavioral model—consisted of 20 weekly sessions lasting 1.5 hours each, led by a clinical psychologist assisted by psychiatric nurses. Patients in the experimental group underwent psychotherapy in 2 subgroups of 10 subjects each. The psychological intervention program comprised psychoeducation about the disorder; explanation of the relationship between thoughts, behavior, physical feelings, and mood; training in the use of anxiety-control techniques (relaxation and breathing, self-instructions, and cognitive distraction); sleep hygiene habits; planning of gratifying activities; training to detect distorted thoughts and to use the process of cognitive restructuring; training in problem-solving and self-esteem improvement; and a program of social skills.

Pharmacologic treatment included individualized psychoactive drug(s) treatment (mood stabilizers, antipsychotics, and/or antidepressants) adjusted by the psychiatrist. Patients regularly visited the psychiatrist once per month approximately, although the psychiatrist provided support when necessary.

Independent variables were measured for each subject at 4 different times (pretreatment, posttreatment, and 6- and 12-month follow-up). The researchers in charge of evaluating the subjects were blind to the treatment that each subject had been assigned to.

We performed a binary logistic regression (backward stepwise regression) of all the independent variables assessed at baseline, to evaluate their influence on therapeutic success/failure. We considered favorable prognosis for subjects without persistent affective symptoms (BDI <7; YMRS <6) and without relevant difficulties in their social-occupational functioning (IS <14) at the 12-month follow-up.

3. Results

3.1. Descriptive characteristics at baseline

No between-group significant differences were found in terms of sex (even when female subjects were much more abundant in the sample), number of prior hospitalizations, and results of the questionnaires. Thus, results of the subsequent repeated measures analysis were expected to be unbiased. Patients' mean age was 41 years (SD, ±10.76; Table 2). In total, 75% of the patients had subsyndromal symptoms, defined as more than 7 in the BDI or more than 6 in YMRS and severe difficulties in social-occupational functioning (IS score >14), and 25% had frequent relapses with rapid cycling course and suicide attempts with additional poor functional outcome (IS >14).

3.2. Variables predictive of therapeutic success/failure

Table 3 shows the results of the binomial logistic regression of the 3 selected variables (type of treatment, number of prior hospitalizations, self-esteem). Previously,

Table 2
Description of sample and baseline characteristics

	Total	Experimental group (n = 20)	Control group (n = 20)	Statistics[a]	*P*
Sex					
Male[b]	21 (52.5)	11 (55.0)	10 (50.0)		
Female[b]	19 (47.5)	9 (45.0)	10 (50.0)	–	.752
Age (y)[c]	41.30 (10.76)	43.35 (11.48)	39.25 (9.85)	−1.21	.233
No. of prior hospitalizations[d]	2.18 (0-20)	2.30 (0-20)	2.05 (0-20)	−0.23	.822
No. of recent hospitalizations[d]	0.25 (0-3)	0.10 (0-1)	0.40 (0-3)	1.53	.134
Scales at baseline					
STAI-S[c]	19.05 (10.34)	21.30 (11.57)	16.80 (8.66)	−1.39	.172
Beck Depression					
≤7[b]	14 (35.0)	8 (40.0)	6 (30.0)	–	.741
>7[b]	26 (65.0)	12 (60.0)	14 (70.0)		
Mania Rating Scale					
≤6[b]	36 (90.0)	17 (85.0)	19 (95.0)	–	.605
>6[b]	4 (10.0)	3 (15.0)	1 (5.0)		
Persistent affective symptoms and severe inadaptation					
With symptoms[b]	30 (75.0)	15 (75.0)	15 (25.0)	–	1.000
Without symptoms[b]	10 (25.0)	5 (25.0)	5 (25.0)		

STAI-S indicates State-Trait Anxiety Inventory state subscale.

[a] Due to the sample size, the Fisher test and the Student *t* test were used for comparisons between categorical and numerical variables.

[b] n (%).

[c] Mean (SD).

[d] Mean (range).

Table 3
Logistic regression of therapeutic success/failure at 12-month follow-up

		Variables according to logistic regression						
		B	E.T.	z	$P > \|z\|$	Exp(B)	95% CI	
							Inferior	Superior
Variables	Type of treatment	2.134	0.884	2.414	.021	8.449	1.494	47.782
	No. of admissions	0.101	0.048	2.104	.044	3.888	1.007	1.481
	Self-esteem	−0.059	0.024	−2.458	.019	0.943	0.899	0.989

(A) The logistic regression model can be expressed as:
P(Failure/Type of treatment (T*), No Admissions (A), Self-esteem (S)) = $\frac{e^{2.134(T) + 0.101(A) - 0.059(S)}}{1 + e^{2.134(T) + 0.101(A) - 0.059(S)}}$
*Variable "Type of treatment" is valued as 1 when there is drug treatment only, and 0 when there is combined psychotherapy plus drug treatment.

(B) Prediction of results

Real group	Predicted group		Corrected percentage
	Success	Failures	
Success: 17	13	4	76.5
Failures: 23	3	20	87.0

Percentage of correctly classified cases: 82.5%.

univariate analyses with all demographic and psychological variables indicated in the section of assessment measures were performed to select these 3 variables. These specific predictors were chosen according to their predictive power.

These 3 variables accounted for 82.5% of cases. Thus, it can be predicted that patients with only drug treatment, several hospitalizations, and low self-esteem have a high probability of therapeutic failure at the 12-month follow-up.

4. Discussion

The focus of this study is on the treatment of patients with refractory bipolar disorder because they often do not respond to usual treatment approaches, and so, it is convenient to determine the most important elements in relation to good prognosis. The variables with the highest significance levels in the prediction of prognosis were type of treatment, number of prior hospitalizations, and level of self-esteem. In particular, patients under combined therapy (drug treatment + cognitive-behavioral therapy) had better prognosis than did those under drug therapy only. The type of treatment was the most important predictive factor in the long-term outcome. Psychological treatments have demonstrated to be effective in bipolar disorder [39]. Nevertheless, there are some controversies about the effectiveness of cognitive therapy in those patients with refractory bipolar disorder, especially in those with frequent relapses [40]. Although we found that treatment was effective for these refractory patients, in agreement with a study by Rosa et al [7], our results showed that patients with fewer hospitalizations (namely, having fewer or milder episodes also) showed more favorable progression. However, in a systematic review [41], it is concluded that there is no clear evidence that the number of previous episodes moderated the effect of the psychological therapy.

Self-esteem appeared to be the most important predictor of change in depression across a 6-month follow-up [42]. In this sense, we found that patient's level of self-esteem also influenced the progression of the disorder, with lower scores corresponding to patients with poor prognosis. Although there is considerable evidence that bipolar disorder is characterized by unstable self-esteem rather than particularly high or low self-esteem [43], the finding of our study is related to a more stable self-esteem, measured when patients were euthymic or with subsyndromal symptoms.

Unlike other studies [14-17,25,44], variables of age, sex, psychiatric comorbidity, subsyndromal symptoms, and anxiety and depression symptoms were not significant in the prognosis of bipolar disorder with a history of unfavorable progression. Our hypothesis for this failure to replicate prior studies could be related to the small sample size and to the follow-up duration.

Our findings suggest for future research that certain factors influence therapeutic success in cases of refractory bipolar disorder. This study has some clinical implications. Patients with refractory bipolar disorder should benefit from a combined (drug and cognitive-behavioral) therapy, and it would be necessary to provide additional or more intensive therapy to patients with a high number of prior hospitalizations and to those with a more stable low self-esteem.

However, the main limitations of this study are related to the sample size and to the follow-up duration. Prognostic factors of outcome examined in a sample selected for participation in a randomized clinical trial can be somehow distorted. Further research, conducted with larger and nonbiased samples and longer follow-up, on variables involved in the progression of refractory bipolar disorder is necessary for the generalizability of the data to improve currently applied

therapeutic procedures. Another limitation is related to the representative value of the sample of patients included. It would be interesting to test if the predictors found in this study are also applicable to nonrefractory bipolar patients.

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