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Research report

How effective is a psychological intervention program for patients with refractory bipolar disorder? A randomized controlled trial

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ABSTRACT

Background: The aim of this research was to evaluate the short-term and long-term efficacy of a combined treatment (pharmacological + psychoeducational and cognitive-behavioral therapy) as compared with a standard pharmacological treatment in patients with refractory bipolar disorder.
Method: 40 patients were randomly assigned to one of the following: Experimental group under combined treatment, and Control group under pharmacological treatment. We used an analysis of variance (ANOVA), including one or two factors, with repeated measures at different evaluation times: baseline, post-treatment, 6-month follow-up and 12-month follow-up.
Results: We found significant between-group differences at all evaluation times after the treatment. The experimental group showed less hospitalizations than the control group in the 12-month evaluation ($p=0.007$) as well as lower rates of depression and anxiety in the 6-month valuation ($p=0.015$; $p=0.027$) and the 12-month evaluation ($p=0.001$; $p<0.001$). Significant differences in relation to mania and inadaptation emerged in the post-treatment evaluation ($p=0.004$; $p<0.001$) and were sustained throughout the study ($p=0.002$, $p<0.001$; $p<0.001$, $p<0.001$). Analysis of within-group differences in the Experimental group showed reduction of mania ($p<0.001$), depression ($p=0.001$), anxiety ($p=0.003$) and inadaptation ($p<0.001$) throughout the study; while in the Control group, it showed increased numbers of hospitalizations ($p=0.016$), as well as higher rates of mania ($p=0.030$), anxiety ($p<0.001$) and inadaptation ($p=0.003$).
Conclusions: Our results suggest that a combined treatment is effective in patients with refractory bipolar disorder. Suggestions for future research are commented on.

1. Introduction

Patients with a refractory bipolar disorder (resistant to treatment and with a history of unfavorable progression) frequently have a poor prognosis; they usually present residual symptoms (López et al., 2001a; Judd et al., 2008), rapid cycling (González-Pinto et al., 2002) and suicide attempts (González-Pinto et al., 2001; González-Pinto et al., 2006), in spite of an appropriate treatment with mood stabilizers. Furthermore, even without presentation of rapid cycling, these patients may suffer frequent relapses and have severe difficulties in their social-occupational functioning. All this is connected with elevated healthcare costs (González-Pinto et al., 2009).

After remission of episodes, 40% of bipolar disorder patients continue to have subsyndromal symptoms, with 32% of them presenting depressive symptoms, and the remainder, presenting hypomanic symptoms or mixed

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symptoms (Judd et al., 2002; Yatham et al., 2005). Euthymic patients progress better than those with subsyndromal symptoms (Mansell et al., 2005) and have a better quality of life.

Medical and psychiatric co-morbidity, psychotic symptoms in manic or mixed episodes, subsyndromal clinical pattern, early onset and high level of anxiety (Williams et al., 2008), as well as low level of pre-morbid functional capacity, are predictors of an unfavorable prognosis of the disorder (Tohen et al., 1992; Keck, 2006).

Current pharmacological treatments fail to control the course of bipolar disorder in half of the cases (Stahl, 2002). According to Prien and Potter (1990), lithium is ineffective in between 20% and 40% of bipolar patients due to inadequate responses or side effects. In other cases, the ineffectiveness of pharmacological treatment is due to patients' failure to comply with it, which entails additional risk of suicide.

In the 1990s, complementary psycho-social treatments aimed at patients resistant to standard treatments were developed (Prien and Potter, 1990; Rothbaum and Astin, 2000; Swartz and Frank, 2001).

Recent reviews of the psycho-educational and cognitive-behavioral studies conducted in the field of bipolar disorder (González-Pinto et al., 2004), evidenced that both psycho-education and cognitive-behavioral therapy were the most effective treatments for preventing recurrence in patients under pharmacological therapy (Becoña and Lorenzo, 2003; González-Pinto et al., 2004; Colom and Vieta, 2004). More recently, structured psychological therapies that combine both types of procedures have been adopted (Lam et al., 2003; Miklowitz et al., 2007a, b; Scott et al., 2006). We have reported an earlier pilot study on this issue, although with a reduced number of patients (González Isasi et al., 2003; González Isasi et al., 2010).

The aim of the present study was to evaluate the short-term and long-term efficacy of a psychological intervention program that combines psycho-education and a cognitive-behavioral therapy, as a complement to the pharmacological therapy, in a group-based treatment for patients with refractory bipolar disorder. Additionally, we propose that incorporation of such a psychological program into the standard clinical practice of the Mental Health Centres of the Community could reduce the burden that these patients place on the Health Services, and consequently, the health-care costs.

2. Method

2.1. Participants

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

Inclusion criteria were: a) patient meeting the DSM-IV-TR diagnostic criteria (American Psychiatry Association, 2000) for type I or type II bipolar disorder, for at least 2 years; b) history of severe or unfavorable progression of the disease despite adequate pharmacological treatment, defined as two or more relapses in the preceding year, suicide attempts, persistent affective symptoms despite appropriate drug treatment (Beck's Depression Index—BDI score>7; Young Mania Rating Scale—YMRS score>6) or severe difficulties in social-occupational functioning (Inadaptation Scale—IS score>14); c) euthymic or with subsyndromal symptoms at the beginning of the study (BDI>7; YMRS>6); d) patient not receiving any psychotherapy (individual or group); and e) aged 18 to 65 years.

We recruited forty patients, who met the inclusion criteria; all of them completed the treatment during the follow-up period; none of them met the criteria necessary to diagnose depressive or hypomanic or manic episode at the beginning of the study. All patients gave their informed consent to participate in this randomized clinical trial. This research was approved by the Hospital's Ethics Committee.

2.2. Study design

The sample size was calculated for 5% confidence level, 90% power, 0.75 success proportion in the experimental group, 0.20 success proportion in the control group, and 15% approximate failure; the resulting sample size was approximately 20 subjects per group.

Subjects were assigned to the Experimental or the Control group on a random basis. Subjects in the Experimental group received psychotherapy, while those in the Control group did not. However, since all patients were under standard drug treatment (similar drugs at individualized doses), the resulting treatments were: Experimental group, under psychotherapy plus drug treatment, and Control group, only under drug treatment.

Independent measures corresponding to each subject were evaluated at four different time points: immediately before treatment (baseline), immediately after the termination of treatment (post-treatment), in a follow-up visit 6 month after the termination of treatment (6-month) and in a follow-up visit 12 month after the termination of treatment (12-month).

The researchers in charge of evaluating the subjects were blind to the treatment that each subject had been assigned to.

This study was designed for between-group comparison of the proportions of patients with persistent affective symptoms and/or severe difficulties in their social-occupational functioning, during the follow-up period, and for analyzing the number of hospitalizations as well as possible improvement in daily functioning and anxiety in patients from both groups.

2.3. Assessment measures

A semi-structured individual interview (Structured Clinical Interview for DSM-IV-TR Axis Disorders—Patient Version; SCID-P) (First et al., 2002) 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. During the interview, the subjects described their symptoms, history of the disorder, received treatment and degree to which they perceived their disorder to be disabling in their daily life.

During every evaluation visit, the researcher—who was blind to the patient's treatment—administered the following questionnaires: Beck's Depression Index (BDI) (Beck et al., 1979; Spanish version by Vázquez and Sanz, 1997), Young Mania Rating Scale (YMRS) (Young et al., 1978; Spanish version by Colom et al., 2002), State Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970; Spanish version by Seisdedos) and Inadaptation Scale (IS) (Echeburúa et al., 2000). For all these scales, lower scores mean better results. These tools have been described in detail elsewhere (González et al., 2003).

2.4. Treatment groups

2.4.1. Experimental group (pharmacological treatment plus psychotherapy)

Patients assigned to this group attended a psychological intervention program consisting of an initial psycho-education session about their disorder, followed by an explanation of the relationship between thoughts, activities, physical feelings and mood, as well as on identifying and monitoring early warning symptoms in order to deal with them. Subsequently, they were trained in the use of anxiety-control techniques (relaxation and breathing, self-instructions and cognitive distraction), sleep hygiene habits and planning gratifying activities. Later on, they were trained to detect distorted thoughts and to use the process of cognitive re-structuring. Finally, for the purpose of consolidating treatment changes and in an attempt to prevent relapse, participants were trained in problem-solving and self-esteem improvement. In addition, a program of social skills (assertiveness, non-verbal communication, conversational skills, giving and receiving compliments, giving and receiving criticism and asking for favors) was introduced from the second session on, and was part of every therapy session until the end of treatment. The objectives of the psychological intervention program were to enhance patients' understanding of their disorder, to reduce the number of hospitalizations, to reduce their anxiety levels, to improve their repertoire of social skills and assertiveness control, to help them control their mood by shifting thoughts and enhancing involvement in enjoyable activities, to enhance their self-esteem and to improve their adaptation to daily life by learning problem-solving strategies.

The cognitive therapy used in this research was based on the manualized therapist's guide included in Lam et al. (1999). 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 two subgroups of 10 subjects each.

Two weeks elapsed between patients consent and the beginning of the psychological intervention program. As mentioned, all patients in this group were under individualized psychoactive drug(s) treatment (mood stabilizers, antipsychotics and/or benzodiazepines) adjusted by the psychiatrist.

2.4.2. Control group (pharmacological treatment)

Patients assigned to the control group only received individualized psychoactive drug(s) treatment (mood stabilizers, antipsychotics and/or benzodiazepines) adjusted by the psychiatrist. Patients regularly visited the psychiatrist once per month approximately, although the psychiatrist provided support when necessary.

2.5. Statistics

The first analysis of data consisted in comparing the baseline characteristics of both groups.

Analysis of the STAI-S results was based on numerical scores. Results of BDI, YMRS and IS were analyzed numerically as well as categorically for the purpose of comparing the proportion of people with persistent depression or mania symptoms (BDI score>7; YMRS score>6) and/or severe difficulties in social-occupational functioning (IS score>14) in both groups during the follow-up period. The number of recent hospitalizations was defined for each evaluation session, as the number of hospitalizations within the 6 months previous to that session.

Continuous variables were expressed as means with standard deviations/typical errors or range values. Variables were compared both within and between groups at different evaluation times, by using an ANOVA design, including one or two factors, both with repeated measures. Categorical variables were expressed as number of cases and proportions and were compared between groups, at different evaluation times, by using the Fisher's Exact test.

3. Results

3.1. Descriptive characteristics at baseline

Table 1 shows the descriptive characteristics at baseline for both groups. As expected for a random-design, no between-groups significant differences were found in terms of: proportion of females and males proportion (even when females were much more abundant in the sample), number of prior hospitalizations, number of recent hospitalizations, use of lithium or other mood stabilizers, adherence impression measured by the clinician that treated the patients and results of the questionnaires. Thus, results of the subsequent repeated measures analysis were expected to be unbiased. Patients' mean age was 41 years old ($\pm$10.76). 75% of patients in each group had persistent affective symptoms (symptoms of depression rather than symptoms of mania) and/or severe difficulties in social-occupational functioning; while the remainder had suffered two or more relapses during the previous year.

3.2. Between-group differences in persistent affective symptoms and/or difficulties in social-occupational functioning

Fig. 1 shows the percentage of patients with persistent affective symptoms (BDI>7; YMRS>6) and/or difficulties in social-occupational functioning (IS>14) in the Experimental group and the Control group, at the different evaluation times. In the post-treatment evaluation 80% of Control patients and 45% of Experimental patients met these criteria, a difference that was statistically significant ($p=0.048$). In the 6-month evaluation, 80% of Control patients were still affected while the proportion of affected Experimental patients decreased to 40%; difference also significant ($p=0.022$). In the 12-month evaluation, 83.3% of Control

Table 1
Description of sample and baseline characteristics.

	Total	Experimental group ($N=20$)	Control group ($N=20$)	Statistics [a]	p value
Gender					
Male [b]	21 (52.5)	11 (55.0)	10 (50.0)		
Female [b]	19 (47.5)	9 (45.0)	10 (50.0)	–	0.752
Age [d]	41.30 (10.76)	43.35 (11.48)	39.25 (9.85)	−1.21	0.233
Number of prior hospitalizations [c]	2.18 (0–20)	2.30 (0–20)	2.05 (0–20)	−0.23	0.822
Number of recent hospitalizations [c]	0.25 (0–3)	0.10 (0–1)	0.40 (0–3)	1.53	0.134
Scales at baseline					
STAI-S [d]	19.05 (10.34)	21.30 (11.57)	16.80 (8.66)	−1.39	0.172
Beck depression					
≤7 [b]	14 (35.0)	8 (40.0)	6 (30.0)		
>7 [b]	26 (65.0)	12 (60.0)	14 (70.0)	–	0.741
Mania rating scale					
≤6 [b]	36 (90.0)	17 (85.0)	19 (95.0)		
>6 [b]	4 (10.0)	3 (15.0)	1 (5.0)	–	0.605
Inadaptation scale					
≤14 [b]	22 (55.0)	9 (45.0)	13 (65.0)		
>14 [b]	18 (45.0)	11 (55.0)	7 (35.0)	–	0.341
Persistent affective symptoms and/or severe inadaptation					
With symptoms [b]	30 (75.0)	15 (75.0)	15 (25.0)		
Without symptoms [b]	10 (25.0)	5 (25.0)	5 (25.0)	–	1.000

[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 (range).
[d] Mean (standard deviation).

patients and only 30% of Control patients were affected, with differences again significant ($p=0.001$).

3.3. Between-group differences in the main variables throughout the study

Table 2 shows the differences in the measured variables between the Experimental and the Control group at the different evaluation times.

In the post-treatment evaluation, the number of recent hospitalizations tended to be higher for the Control group than for the Experimental group ($p=0.037$). In the 12-month evaluation, such difference reached statistical significance ($p=0.007$) thus evidencing that patients in the experimental group needed less hospitalizations than those in the control group, in the long term.

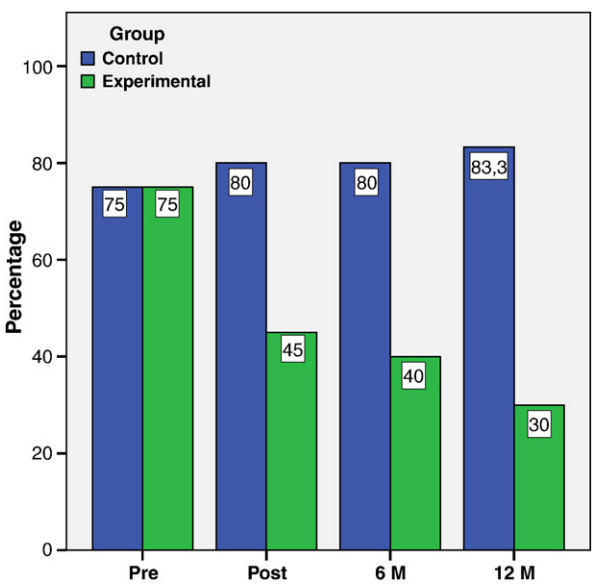

Fig. 1. Percentage of patients with persistent affective symptoms and/or with important inadaption.

Symptoms related to anxiety and depression showed a similar tendency, with worse progression for patients in the control group. Although differences were not significant in the post-treatment (STAI-S: $p=0.077$; BDI: $p=0.176$), they were significant in the 6-month evaluation (STAI-S: $p=0.027$; BDI: $p=0.015$) and the 12-month evaluation (STAI-S: $p<0.001$; BDI: $p=0.001$).

Mania and inadaptation symptoms were milder for patients in the Experimental group than for those in the Control group already in the post-treatment evaluation (YMRS: $p=0.004$; IS: $p<0.001$), in the 6-month evaluation (YMRS: $p=0.002$; IS: $p<0.001$) and in the 12-month evaluation (YMRS: $p<0.001$; IS: $p<0.001$).

3.4. Within-group differences in the main variables throughout the study

Table 3 shows within-group differences in the measured variables corresponding to each group. Observations were compared at the evaluation times indicated.

The Experimental group showed no significant differences in the number of hospitalizations throughout the study. However, the number of hospitalizations in the Control group increased significantly during this period ($p=0.016$).

Symptoms of anxiety, mania and inadaptation showed similar patterns: they reduced significantly for the Experimental group (STAI-S: $p=0.003$; YMRS: $p<0.003$; IS: $p<0.0010$), and increased significantly for the Control group (STAI-S: $p<0.001$; YMRS: $p=0.030$; IS: $p=0.003$) throughout the studied period.

Table 2
Between-group differences at the different evaluation time points.

Values scales	Pretreatment Mean (te)	(*p* value) [a]	Postreatment Mean (te)	(*p* value) [a]	6 months Mean (te)	(*p* value) [a]	12 months Mean (te)	(*p* value) [a]
Number recent hospitalizations								
Control group	0.39 (0.15)		0.28 (0.09)		0.33 (0.12)		0.39 (0.10)	
Experimental group	0.10 (0.14)	(0.164)	0.00 (0.09)	(0.037) *	0.05 (0.11)	(0.089)	0.00 (0.09)	(0.007) *
Anxiety (STAI-S)								
Control group	17.50 (2.43)		23.05 (2.82)		26.05 (3.00)		32.78 (2.67)	
Experimental group	21.30 (2.30)	(0.264)	16.00 (2.67)	(0.077)	16.50 (2.85)	(0.027) *	8.85 (2.53)	(<0.001) **
Beck depression (BDI)								
Control group	11.06 (2.07)		12.44 (2.02)		14.06 (2.05)		13.72 (1.89)	
Experimental group	11.05 (1.97)	(0.998)	8.60 (1.92)	(0.176)	6.80 (1.95)	(0.015) *	3.80 (1.79)	(0.001) **
Mania scale (Young)								
Control group	2.06 (0.68)		4.06 (0.81)		5.89 (1.17)		6.39 (0.95)	
Experimental group	2.50 (0.65)	(0.641)	0.65 (0.77)	(0.004) *	0.55 (1.11)	(0.002) *	0.20 (0.90)	(<0.001) **
Inadaptation scale								
Control group	12.44 (1.63)		14.78 (1.34)		15.00 (1.29)		17.22 (0.90)	
Experimental group	15.10 (1.54)	(0.245)	4.65 (1.27)	(<0.001) **	3.45 (1.22)	(<0.001) **	1.90 (0.85)	(<0.001) **

* $p<0.05$.
** $p<0.001$.
[a] Bonferroni correction for multiples comparisons.

Table 3
Within-group differences throughout the study.

		Control group					Experimental group				
		Pre	Post	6 M	12 M	*F* *p* value	Pre	Post	6 M	12 M	*F* *p* value
Scales	Number of prior hospitalizations	2.06	2.78	2.61	3.00	0.016*	2.30	2.30	2.35	2.35	0.330
	Anxiety (STAI-S)	17.50	23.06	26.06	32.78	<0.001**	21.30	16.00	16.50	8.85	0.003*
	Beck Depression (BDI)	11.06	12.44	14.06	13.72	0.589	11.05	8.60	6.80	3.80	0.001*
	Mania Scale (Young)	2.06	4.06	5.89	6.39	0.030*	2.50	0.65	0.55	0.20	<0.001**
	Inadaptation Scale	12.44	14.78	15.00	17.22	0.003*	15.10	4.65	3.45	1.90	<0.001**

* $p<0.05$.
** $p<0.001$.

Symptoms of depression showed significant reduction in the Experimental group ($p=0.001$) and remained unchanged in the Control group ($p=0.589$).

4. Discussion

The interest of this study lies in the choice of patients with a refractory bipolar disorder, who present persistent and significant affective symptoms (symptoms of depression rather than symptoms of mania) in spite of receiving appropriate pharmacological treatment. These patients generate the highest demand for healthcare, while showing the worst progression of the disease and the highest chronicity (Gazalle et al., 2007; Piccinni et al., 2007). Depressive morbidity exceeds manic morbidity both in patients with chronic bipolar disorder (Judd et al., 2002) and in first bipolar patients (Baldessarini et al., 2010).

Up to now, well-controlled studies including patients with a bipolar disorder with a history of unfavorable progression are rather scarce. However, inclusion of euthymic patients and patients with subsyndromal symptoms has been based on the daily reality of the clinical practice (Mansell et al., 2005). Comparing a group of patients under combined treatment with a group under standard pharmacological treatment contributes, not only to evaluate the possible advantage of a combined therapy, but also to study the progression of the refractory disease in patients under a standard treatment. Thus, this study offers a good ecological validity.

The psychological program applied in this study was based on psycho-education and cognitive-behavioral therapy—the most consolidated therapeutic approaches in this field (González-Pinto et al., 2003; Miklowitz et al., 2007a, b). We chose a format of group therapy, because this facilitates its application and reduces associated costs.

The combined treatment has proved to be better than the pharmacological treatment in reducing hospitalizations after a year of treatment, in relieving manic, depressive and anxiety symptoms after 6 months of treatment and in producing better adaptation to everyday life upon termination of treatment. No subjects failed to comply with the treatment or were lost to follow up, except for two control patients who died during the follow-up period. Thus, the psychological therapy, as a complement to the pharmacological treatment, was attractive for patients, effective in producing good results and efficient for application due to its short duration and group-based format. The standard treatment consisted of medication prescription without psycho-education. This may have contributed to the marked differences between groups, however evidencing the efficacy of a psychological treatment in improving the evolution of bipolar disorders.

Evidence supports the view that a pharmacological treatment is necessary but not sufficient in treating refractory bipolar disorder successfully. In the few studies conducted with patients with a bipolar disorder with a history of unfavorable progression (Lam, 2006; Miklowitz et al., 2007a, b) combined therapy was found to reduce the number of episodes, hospitalizations and symptoms, and to improve social functional capacity. Such improvements were sustained during one-year follow-up (Lam et al., 2003; Ball et al., 2006). Our study supports those results, and evidences a new aspect: not only is the improvement sustained, but also increased in several areas over time.

By contrast to our results, Scott et al. (2006) found no differences in patients with a refractory bipolar disorder, who were treated with psychotherapy. However, their sample included a combination of acute patients and patients in remission; furthermore, some of them were not under pharmacological treatment. It is our view that patients should not be in the manic or hypomanic phase at the time psychotherapy is applied, since in that situation the therapy may be ineffective.

In our earlier pilot study with a reduced population sample (González Isasi et al., 2010) we found significant differences between the group under combined treatment and the group under pharmacological treatment, in the 12-month evaluation but not in the previous evaluations. However, the treatment in that study included some degree of psycho-education though not structured. In the present study, differences emerged in the post-treatment evaluation and were found to be higher in the 6-month and 12-month evaluations. Such a variation in the results of both studies may be accounted for a more intensive psychological treatment (13 sessions in the previous study; 20, in the current one) and the use of a larger sample (20 subjects in the previous study; 40 subjects in this one).

This study opens up new lines of research, although it also evidences some restrictions: it would be advisable in future studies to increase the sample size and to extend the follow-up period since, according to Lam et al. (2005), the benefits of a psychological treatment may dissipate after one-year follow-up. It would be convenient in the future to accurately describe medication use in the two groups because the final improvement may be mediated by more intensive medication management or better medication adherence. Further research lines

could address the evaluation of each of the components of the psychological program (psycho-education and cognitive-behavioral therapy) or other psychological approaches (behavioral experiments or exposure techniques), as well as the possible additive effect of setting up a psycho-education program for relatives who live with the patients.

Conflict of interest

This manuscript reports original material, which has not been published previously and is not being considered for publication elsewhere. There is no commercial or financial conflict of interest concerning this article.

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