European Psychiatry 29 (2014) 134–141

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Original article

Psychoeducation and cognitive-behavioral therapy for patients with refractory bipolar disorder: A 5-year controlled clinical trial

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ARTICLE INFO

Article history:
Received 18 September 2012
Received in revised form 29 October 2012
Accepted 4 November 2012
Available online 28 December 2012

Keywords:
Refractory bipolar disorder
Combined therapy
Pharmacological treatment
Psychoeducation
Cognitive-behavioral model
Long-term follow-up

ABSTRACT

Objective: The aim of this research, which represents an additional and longer follow-up to a previous trial, was to evaluate a 5-year follow-up study of a combined treatment (pharmacological + psychoeducational and cognitive-behavioral therapy) as compared with a standard pharmacological treatment in patients with refractory bipolar disorder.
Method: Forty patients were randomly assigned to either an Experimental group–under combined treatment — or a Control group — under pharmacological treatment. Data were analyzed by analysis of variance (ANOVA), with repeated measures at different evaluation time points.
Results: Between-group differences were significant at all evaluation time points after treatment. Experimental group had less hospitalization events than Control group in the 12-month evaluation ($P = 0.015$). The Experimental group showed lower depression and anxiety in the 6-month ($P = 0.006$; $P = 0.019$), 12-month ($P = 0.001$; $P < 0.001$) and 5-year ($P < 0.001$, $P < 0.001$) evaluation time points. Significant differences emerged in mania and misadjustment already in the post-treatment evaluation ($P = 0.009$; $P < 0.001$) and were sustained throughout the study (6-month: $P = 0.006$, $P < 0.001$; 12-month: $P < 0.001$, $P < 0.001$; 5-year: $P = 0.004$, $P < 0.001$). After 5-year follow-up, 88.9% of patients in the Control group and 20% of patients in the Experimental group showed persistent affective symptoms and/or difficulties in social-occupational functioning.
Conclusions: A combined therapy is long-term effective for patients with refractory bipolar disorder. Suggestions for future research are commented.

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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 with residual symptoms [25,31], rapid cycling [20] and suicide attempts [19,22], despite receiving appropriate treatment with mood stabilizers. Furthermore, even without presentation of rapid cycling, these patients may suffer frequent relapses and experience severe difficulties in their social-occupational functioning. This situation is significantly associated with elevated total healthcare costs [23].

Refractory bipolar disorder is a rather frequent finding in patients with this disorder. In a recent study, patients followed-up for 18 months after resolution of their episodes, remained symptomatic for one third of the follow-up period and were three times more days depressed than manic or hypomanic [11]. Other studies reported that up to 40% of patients with bipolar disorders continued to show subsyndromal symptoms after recovery [24,44]. In this context, euthymic patients were found to progress better and to report higher quality of life than patients with subsyndromal symptoms [32]. In an earlier study, we found that receiving combined therapy, experiencing fewer previous hospitalizations and having higher self-esteem were the most influencing factors for a favorable progression of refractory bipolar disorder [18].

Current pharmacological treatments fail to control the course of about half the cases of bipolar disorder [40]. Recent reviews of studies based on psychoeducational and cognitive-behavioral therapy for bipolar disorder [21,43] evidenced that both psychoeducation and cognitive-behavioral therapy were most effective treatments for preventing recurrence in patients under pharmacological therapy [5,8,21].

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0924-9338/$ – see front matter. Published by Elsevier Masson SAS.
http://dx.doi.org/10.1016/j.eurpsy.2012.11.002

In a recent study, a group of patients receiving standard treatment for bipolar disorder was compared with a group additionally receiving psychoeducation as an adjunctive therapy, for a 5-year follow-up period. Patients receiving adjunctive psychoeducation therapy experienced fewer recurrence episodes and shorter periods with acute symptoms, and needed shorter hospital stay [10]. A further long-term benefit of psychological adjunctive therapy is that, compared to conventional therapy, it is less costly and more effective [38].

In the last few years, structured psychological therapies that combine both types of procedure (psychoeducation and cognitive-behavioral therapy) are being increasingly adopted [28,34,35,37]. While psychoeducation has proven effective on bipolar disorder [10] both for preventing manic and depressive episodes, studies reported that cognitive-behavioral therapy is especially useful in the treatment and prevention of depression [6,41]. Thus, combining both therapies was expected to be especially helpful. Studies on other severe mental diseases like schizophrenia, suggested that enhancing patients' insight into the disease through psychoeducation without providing clues to reduce depressive symptoms could entail certain risk [1]. However, in a long-term study, participants who received cognitive-behavioral therapy in addition to psychoeducation experienced 50% fewer days of depressed mood over the course of 1 year and less antidepressant increases as compared with the group of psychoeducation alone [46].

Earlier we reported the results of a pilot study on this issue, though with a reduced number of patients [15,16]. More recently, we presented a study on the evaluation of short-term and medium-term (1 year) efficacy of a psychological intervention program that combined psychoeducation with cognitive-behavioral therapy, applied as a complement to pharmacological therapy with a group-based approach, for patients with refractory bipolar disorder [17]. We also proposed that incorporating such a psychological program to standard clinical practice in Mental Health Centers of our Community could help reducing the burden and associated costs of these patients on the Health Services.

However, no evidence of the long-term effectiveness of such a program is available, an important issue in view of the chronic nature of this type of mental disease. Some researchers reported that the effectiveness of psychological interventions decreased over the time [7,30], while others demonstrated persistent efficacy [10].

The main aim of this study was to evaluate the effectiveness of a psychological program for patients with refractory bipolar disorder, taking into account global affective symptoms and adaptation to daily life as therapeutic failure/success, in a 5-year follow-up study. We also examined, as a secondary aim, specific clinical differences regarding anxiety, depression, mania, misadjustment and recent hospitalizations, between a group of patients receiving standard treatment for bipolar disorder and a group additionally receiving psychoeducation and cognitive-behavioral therapy as an adjunctive therapy.

2. Method

2.1. Participants

Participants were outpatients diagnosed with refractory bipolar disorder in the Grand Canary healthcare area, who were managed at the Center for Mental Health of Las Palmas, during 2005 and 2006. All of these patients were under pharmacological treatment, prescribed on an individual basis, mainly consisting of a mood stabilizer (predominantly lithium); some of them also received antipsychotics and/or benzodiazepines. Inclusion criteria were:

- patient meeting the DSM-IV-TR [2] criteria for type I bipolar disorder for at least 2 years;
- history of severe or unfavorable progression of the disease despite adequate pharmacological treatment, defined as two or more relapse events in the preceding year, suicide attempts, persistent affective symptoms (for a period of at least 3 months) 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 (Misadjustment Scale [IS]score > 14);
- patient euthymic or with subsyndromal symptoms at the beginning of the study (BDI > 7; YMRS > 6);
- patient not receiving psychotherapy (individual or group-based);
- age between 18 and 65 years.

Patients with poor medication adherence, according to the doctor or relatives' report, were excluded.

Forty patients were recruited for this study. All of them completed the treatment during the follow-up period except for two control patients who died during the first year (one by suicide and one by heart attack); none of them met the criteria to diagnose a 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 randomly assigned to either the Experimental or the Control group. Subjects in the Experimental group received psychotherapy in addition to conventional drug treatment, while those in the Control group only received conventional drug treatment. Patients in the Control group did not receive psychotherapy during the 5 years of the study.

Independent measures corresponding to each subject were evaluated at five different time points: immediately before treatment (baseline), immediately after the termination of the treatment (post-treatment), in a follow-up visit 6 months after the termination of treatment (6 months), in a follow-up visit 12 months after the termination of treatment (12 months) and in a follow-up visit 5 years after the termination of treatment (5 years).

The researchers in charge of evaluating the subjects were blinded to their treatment.

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 hospitalization events as well as possible improvements in daily functioning and anxiety in both groups of patients.

2.3. Assessment measures

Patients underwent a semi-structured individual interview (Structured Clinical Interview for DSM-IV-TR Axis Disorders-Patient Version; SCID-P) [13] at the beginning of the study, aimed at confirming the diagnosis of a bipolar disorder I or II, according to the DSM-IV-TR criteria. During the interview, subjects were asked to describe their symptoms, the history of their disorder, the treatments they had received and the degree to which they perceived their disorder to be disabling for daily life.

During each evaluation visit, the researcher (blinded to patients' treatment) administered the following questionnaires: Beck's Depression Index (BDI) [4,42], Young Mania Rating Scale (YMRS) [2,9,45], State Trait Anxiety Inventory (STAI-S) [39] and Misadjustment Scale (IS) [12]. In all of these scales, lower scores indicate better outcomes. These tools are described in detail elsewhere [15].

2.4. Treatment groups

2.4.1. Experimental group (pharmacological treatment plus psychotherapy)

Patients assigned to this group participated in a psychological intervention program in addition to their conventional pharmacological treatment. The psychological program consisted of an initial psychoeducation session about their disorder, followed by an explanation of the relationship between thoughts, activities, physical feelings and mood, and about 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 in detecting distorted thoughts and using the process of cognitive restructuring. Finally, for the purpose of consolidating the treatment and in an attempt to prevent relapse, participants were trained in problem solving and improvement of self-esteem. 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 the 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 levels of anxiety, to improve their repertoire of social skills and assertiveness control, to help them controlling their mood by shifting thoughts and getting involved 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 therapist's guide manual included in Lam et al. [27]. This psychological intervention program — based on a cognitive-behavioral model — consisted of 20 weekly sessions of 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 a psychiatrist.

2.4.2. Control group (pharmacological treatment)

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

2.5. Statistical analysis

In a first analysis, the baseline characteristics of both groups were compared.

Analysis of the results of STAI-S was based on numerical scores, while the results of BDI, YMRS and IS were analyzed both numerically and categorically for the purpose of comparing the proportion of subjects 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, i.e. admissions to hospital during the previous 6 months, was established before every evaluation session.

Continuous variables were expressed as mean with standard deviation/typical error or range values. Variables were compared both within- and between-groups at different evaluation time points by using ANOVA, 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 time points, by using the Pearson's Chi^2 test.

Effect size analysis, based on the Cohen's d (continuous variables) and Chuprov's T-square (proportions) tests, was used to estimate clinical differences.

3. Results

3.1. Descriptive characteristics at baseline

Table 1 shows the descriptive characteristics at baseline for both groups. As expected for a study with a random-design, no significant between-group differences were found in terms of: proportion of males and females, number of prior hospitalization events, number of recent hospitalization events, use of lithium or other mood stabilizers, adherence measured by the clinician in charge of the patient, and results of the questionnaires. Thus, the results of subsequent repeated measures analysis were expected to be unbiased. Patients' mean age was 41 years ($\pm$ 10.76). Seventy-five percent of patients in each group had persistent affective symptoms (depression rather than mania symptoms) and/or severe difficulties in social-occupational functioning. The rest of patients had experienced two or more relapse events 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 and Control group at different evaluation time points:

- in the post-treatment evaluation, 80% of Control patients and 45% of Experimental patients showed these symptoms (difference reached statistical significance $X^2 = 5.227$, $P = 0.022$, $T^2 = 0.131$);
- in the 6-month evaluation, 80% of Control patients and 40% of Experimental patients were affected (difference also significant $X^2 = 6.667$, $P = 0.010$, $T^2 = 0.167$);
- in the 12-month evaluation, 83.3% of Control patients and only 30% of Experimental patients were affected (difference significant $X^2 = 10.90$, $P = 0.001$, $T^2 = 0.287$);
- in the 5-year evaluation, 88.9% of Control patients and only 20% of Experimental patients showed symptoms (difference also significant $X^2 = 18.034$, $P = 0.001$, $T^2 = 0.475$).

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

Table 2 shows the differences between Experimental and Control groups in terms of the measured variables, at the different evaluation time points: in the post-treatment evaluation, the

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)	0.10	0.752
Age[d]	41.30 (10.76)	43.35 (11.48)	39.25 (9.85)	−1.21	0.233
Age of onset[d]	30.05 (10.82)	29.75 (11.5)	30.35 (9.5)	0.18	0.858
Duration of disorder[c]	13.68 (5–25)	13.35 (6–25)	14.01 (5–24)	0.46	0.649
No. previous episodes[c]	10.75 (2–18)	11.10 (2–17)	10.40 (3–18)	0.40	0.693
No. prior hospitalizations[c]	2.18 (0–20)	2.30 (0–20)	2.05 (0–20)	−0.23	0.822
No. 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)	0.44	0.507
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)	1.11	0.292
Misadjustment Scale					
≤ 14[b]	22 (55.0)	9 (45.0)	13 (65.0)		
>14[b]	18 (45.0)	11 (55.0)	7 (35.0)	1.62	0.204
Persistent affective symptoms and/or severe misadjustment					
With symptoms[b]	30 (75.0)	15 (75.0)	15 (75.0)		
Without symptoms[b]	10 (25.0)	5 (25.0)	5 (25.0)	0.00	1.000

[a] Due to the sample size, the Chi^2 test and the t Student test were used for comparisons between categorical and numerical variables.
[b] n (%).
[c] Mean (range).
[d] Mean (standard deviation).

number of recent hospitalizations tended to be higher for Control than for Experimental patients ($t = 2.03$, $P = 0.056$); by the 12-month evaluation, this difference reached statistical significance ($t = 2.71$, $P = 0.015$) thus evidencing that patients in the Experimental group needed less hospitalizations than those in the Control group; in the 5-year evaluation, the number of hospitalizations was higher for the Control group, though not significantly ($t = 1.68$, $P = 0.109$).

Anxiety and depression related symptoms followed a similar trend, with Control patients showing worse outcome. Although differences were not significant in the post-treatment evaluation (STAI-S: $t = 1.92$, $P = 0.062$; BDI: $t = 1.54$, $P = 0.131$), they reached significance in the 6-month (STAI-S: $t = 2.46$, $P = 0.019$; BDI: $t = 2.91$, $P = 0.015$), 12-month (STAI-S: $t = 6.50$, $P < 0.001$; BDI: $t = 3.81$, $P = 0.001$) and 5-year evaluations (STAI-S: $t = 8.46$, $P < 0.001$; BDI: $t = 6.71$, $P < 0.001$).

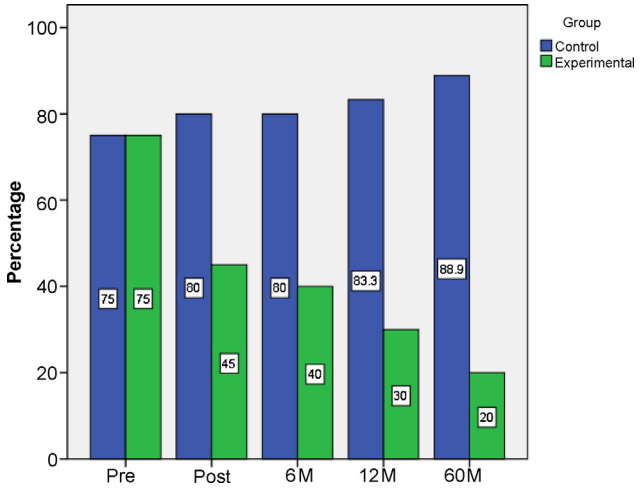

Fig. 1. Percentage of patients with persistent affective symptoms and/or with important maladaptation.

Mania and misadjustment symptoms were milder in Experimental than in Control patients at all evaluation time points: post-treatment (YMRS: $t = -0.72$, $P = 0.009$; IS: $t = 5.67$, $P < 0.001$); 6-month (YMRS: $t = 3.10$, $P = 0.006$; IS: $t = 7.01$, $P < 0.001$); 12-month (YMRS: $t = 4.49$, $P < 0.001$; IS: $t = 11.98$, $P < 0.001$); and 5-year (YMRS: $t = 3.28$, $P = 0.004$; IS: $t = 7.88$, $P < 0.001$).

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

Table 3 shows within-group differences in the measured variables. Observations were compared at the indicated evaluation time points.

No significant differences were found in the number of hospitalization events throughout the study for the Experimental group, while it increased significantly for the Control group ($F = 6.881$, $P = 0.018$).

Symptoms of anxiety, depression and misadjustment showed similar patterns, namely they decreased significantly for the Experimental group (STAI-S: $F = 23.586$, $P < 0.001$; BDI: $F = 33.329$, $P < 0.001$; IS: $F = 49.530$, $P < 0.001$) and increased significantly for the Control group (STAI-S: $F = 22.45$, $P < 0.001$; BDI: $F = 7.056$, $P = 0.017$; IS: $F = 49.530$, $P = 0.001$) throughout the study.

Mania symptoms increased significantly for the Control group (YMRS: $F = 12.321$, $P = 0.003$), while remained unchanged for the Experimental group (YMRS: $F = 3.124$, $P = 0.093$).

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

Values	Pretreatment		Post-treatment		6 months		12 months		5 years	
Scales	Mean (sd)	*t* (*P* value)[c]	Mean (sd)	*t* (*P* value)[c]	Mean (sd)	*t* (*P* value)[c]	Mean (sd)	*t* (*P* value)[c]	Mean (sd)	*t* (*P* value)[c]
No. recent hospitalizations										
Control group	0.40 (0.82)	1.53 (0.139)	0.25 (0.55)	2.03 (0.056)	0.30 (0.66)	1.61 (0.121)	0.39 (0.61)	2.71 (0.015[a])	1.06 (2.24)	1.68 (0.109)
Experimental group	0.10 (0.31)		0.00 (0.00)		0.05 (0.22)		0.00 (0.00)		0.02 (0.49)	
	d = –0.62		d = –0.64		d = –0.49		d = –0.91		d = –0.62	
Anxiety (STAI-S)										
Control group	16.80 (8.66)	–1.39 (0.172)	22.35 (12.24)	1.92 (0.062)	26.35 (13.94)	2.46 (0.019[a])	32.78 (11.97)	6.50 (< 0.001[b])	28.44 (8.92)	8.46 (< 0.001[b])
Experimental group	21.30 (11.57)		16.00 (11.93)		16.50 (11.27)		8.85 (10.72)		8.80 (5.05)	
	d = 0.55		d = –0.53		d = –0.78		d = –2.10		d = –2.71	
Beck Depression (BDI)										
Control group	11.25 (9.06)	0.07 (0.942)	12.70 (10.28)	1.54 (0.131)	14.85 (10.16)	2.91 (0.006[a])	13.72 (10.47)	3.81 (0.001[b])	17.61 (6.75)	6.71 (< 0.001[b])
Experimental group	11.05 (8.11)		8.60 (5.95)		6.80 (7.03)		3.80 (4.87)		4.30 (5.46)	
	d = –0.02		d = –0.50		d = –0.94		d = –1.29		d = –2.18	
Mania Scale (YMRS)										
Control group	1.85 (2.70)	–0.72 (0.477)	3.75 (4.68)	2.85 (0.009[a])	5.40 (6.92)	3.10 (0.006[a])	6.39 (5.83)	4.49 (< 0.001[b])	10.39 (11.40)	3.28 (0.004[a])
Experimental group	2.50 (3.01)		0.65 (1.27)		0.55 (1.10)		0.20 (0.52)		1.45 (1.99)	
	d = 0.22		d = –1.04		d = –1.21		d = –1.95		d = –1.33	
Misadjustment Scale										
Control group	12.70 (7.95)	–1.00 (0.323)	14.85 (6.22)	5.67 (< 0.001[b])	15.50 (6.04)	7.01 (< 0.001[b])	17.22 (4.809)	11.98 (< 0.001[b])	19.00 (7.14)	7.88 (< 0.001[b])
Experimental group	15.10 (7.17)		4.65 (5.11)		3.45 (4.75)		1.90 (2.65)		4.40 (3.48)	
	d = 0.32		d = –1.80		d = –2.23		d = –4.11		d = –2.72	

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] Bonferroni correction for multiples comparisons.

Table 3
Within-group differences throughout the study.

	Control group						Experimental group					
Scales	Pre	Post	6 M	12 M	5Y	F (*P* value)	Pre	Post	6 M	12 M	5Y	F (*P* value)
No. prior hospitalizations	2.06	2.28	2.61	3.00	4.06	6.881 (0.018[a])	2.30	2.30	2.35	2.35	2.50	6.86 (0.144)
Anxiety (STAI-S)	16.80	22.35	26.35	32.78	28.44	22.45 (<0.001[b])	21.30	16.00	16.50	8.85	8.80	23.589 (<0.001[b])
Beck Depression (BDI)	11.25	12.70	14.85	13.72	17.61	7.056 (0.017[a])	11.05	8.60	6.80	3.80	4.30	33.329 (<0.001[b])
Mania Scale (Young)	1.85	3.75	5.40	6.39	10.39	12.321 (0.003[a])	2.50	0.65	0.55	0.20	1.45	3.124 (0.093)
Misadjustment Scale	12.70	14.85	15.50	17.22	19.00	15.620 (0.001[a])	15.10	4.65	3.45	1.90	4.40	49.530 (<0.001[b])

[a] $P < 0.05$.
[b] $P < 0.001$.

4. Discussion

As far as we know, this is the first study to show such long-term maintained efficacy of a combined pharmacological plus psychoeducation and cognitive-behavioral therapy program in subjects with refractory bipolar disorder. Patients with refractory bipolar disorders, who present persistent and significant affective symptoms (depression rather than mania symptoms) despite appropriate pharmacological treatment generate the highest burden on the healthcare system, while showing the worst outcomes in terms of disease progression and chronicity [14,36]. Inclusion of euthymic patients and patients with subsyndromal symptoms was based on the reality of daily clinical practice [32]. Up-to-date, well-controlled studies including patients with bipolar disorders with a history of unfavorable progression are rather scarce. We postulate that the present research study contributes to evaluate the possible benefits of a combined therapy and to study the progression of refractory disorders in patients under standard therapy. Thus, it offers a good ecological validity.

The psychological program applied in this study was based on psychoeducation and cognitive-behavioral therapy, some of the most studied therapeutic approaches in this field [21,34,35]. Long-term randomized controlled trials published up-to-date, either included psychoeducation only [10] or follow-up periods shorter than 5 years [3,29]. We decided to use group therapy because it facilitated the application of the therapy and reduced its associated costs.

Combined treatment proved better than pharmacological treatment in relieving mania, depression and anxiety symptoms after 6 months and in producing better adjustment to everyday life upon termination of treatment. These benefits were maintained after 5 years. During these 5 years, patients did not receive any other psychological treatment or support. Furthermore, although the number of hospitalization events increased significantly for the Control group, it remained unchanged for the Experimental group throughout the 5-year follow-up period. No subjects failed to comply with the treatment or were lost to follow-up, except for two control patients who died in the first year (one by suicide and one by a heart attack). The reason why no participant left the group and no study patient lost to follow-up was probably related to an active commitment of therapist to patients. Thus, psychological therapy, applied as a complement to pharmacological therapy, seemed to be attractive to 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 psychological intervention, which may have contributed to the marked differences between groups, thus supporting the efficacy of a psychological treatment in terms of improving the evolution of bipolar disorders. Psychological treatment helps patients to learn how to better manage their illness.

Up-to-date evidence supports the view that pharmacological treatments available are necessary though not sufficient to treat refractory bipolar disorders successfully. The few published studies conducted with patients with bipolar disorders with a history of unfavorable progression [26,34,35], showed that combined therapy reduced the number of episodes, hospitalizations and symptoms, and improved social functional capacity. Such improvements were sustained during 1-year follow-up [3,28]. Our results agree with these studies, and further evidence a new aspect: not only is the improvement sustained, but also the evidence of positive effects increased in several areas over the time.

In contrast with our results, Scott et al., in 2006 [37], found no differences in patients with a refractory bipolar disorder, who were treated with psychotherapy. However, their sample comprised a combination of acute patients and patients in remission; moreover, 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, because this therapy might be ineffective in that situation; furthermore, the pharmacological treatment should be prescribed according to clinical guidelines by psychiatrists with expertise in the management of these difficult-to-treat patients. Lam et al., 2005 [29], found that cognitive therapy had no significant effect in reducing relapse over an 18-month study period and that additional booster sessions were necessary. Our psychological intervention program included psychoeducation, anxiety-control techniques, cognitive restructuring, activities planning, a social skill program, a problem-solving program and a self-esteem improvement program. In turn, Meyer and Hautzinger, in 2012 [33], did not find any differences in relapse rates over a 24-month study between cognitive-behavior therapy (CBT) and supportive therapy (ST) of equal intensity and frequency, suggesting that certain shared characteristics (e.g. information, systematic mood monitoring) might explain the effects of psychosocial treatment for bipolar disorder. Changes over time were observed in some variables, they were not differentially associated with CBT or ST. Their results also suggest that a higher number of prior episodes, a lower number of therapy sessions and a diagnosis of bipolar II disorder are associated with a shorter time before relapse.

In our earlier pilot study conducted with a reduced population sample [16], we found significant differences between the group under combined treatment and the group under pharmacological treatment in the 12-month evaluation but not in earlier evaluations. That treatment included some psychoeducation although not in a structured fashion. More recently, we reported differences already in the post-treatment evaluation, which were even larger in the 6-month and 12-month evaluations [17]. Such difference in the outcome of both studies may be accounted for by the intensity of the applied psychological treatment (13 sessions in the first study, 20 in the later one) and the size of the sample (20 subjects in the first study, 40 subjects in the later one). In this study, we found the program to be still effective by the 5-year evaluation. Thus, unlike other studies [29], our results support the view that the benefits of a psychological treatment do not dissipate over time.

Anyway, there are some limitations in this study. It would have been interesting to have more information (for example, the

recurrences or time to recurrence) about the whole sample in the period between the 12-month and 5-year assessments. These measures would have offered a more comprehensive idea of the trajectory of the clinical course of the illness. Further research should take this limitation into account.

We postulate that this study evidences the long-term benefits of a psychological treatment and opens new research lines. Further studies with larger sample sizes, where additional variables are evaluated, such as the number of days admitted to hospital or the adherence to medication, are needed. Additionally, research lines focused on the evaluation of the different components of the psychological program (psychoeducation and cognitive-behavioral therapy) or comparing psychoeducation alone with more structured psychological programs, would be helpful and enriching. A further step to this issue would address the effectiveness of psychological programs applied to patients' relatives/caretakers.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

The work presented in the manuscript "Psychoeducation and cognitive-behavioral therapy for patients with refractory bipolar disorder: A 5-year controlled clinical trial" by the authors Ana González Isasi, Enrique Echeburúa, José María Limiñana and Ana González-Pinto, has been entirely funded by the Servicio Canario de Salud. Therefore, the funding source is the same public institution where the work has been performed.

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