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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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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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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.