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## Long-term efficacy of a psychological intervention program for patients with refractory bipolar disorder: A pilot study

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### ABSTRACT

The aim of this research was to test the long-term efficacy of combined standard treatment (pharmacotherapy and adjunctive psychosocial treatment based on a cognitive-behavioral model) compared with standard drug treatment for patients with recurrent bipolar disorder. Twenty patients selected according to DSM-IV-TR criteria were randomized to 1) combined treatment or 2) control treatment. A multigroup experimental design with repeated assessment measures (pre-treatment, post-treatment, 6-month follow-up, and 12-month follow-up) was used. Results of the repeated measurement analysis showed a significant increment in scores of Global Activity Functioning within the combined treatment group during the follow-up, which was not observed in the control treatment group. Therefore, the effectiveness of psychotherapy tends to increase with time, and this improvement is not significant until 12 months of follow-up.

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### 1. Introduction

Drug treatments studied to date have not been able to control the course of bipolar disorder in half of the cases (Stahl, 2002). Therefore, new adjunctive psychosocial therapies have begun to be developed in view of the relatively poor outcome in many cases, given the presence of significant subsyndromal symptoms that persist beyond the acute stage of the disorder and the persistence of psychosocial deficits (Prién and Potter, 1990; Rothbaum and Astin, 2000; Swartz and Frank, 2001).

Psychosocial interventions as an adjunctive therapy to drug treatment aim to increase compliance with medical treatment, decrease relapse/recurrence and re-hospitalization rates, and improve the quality of life of both patients and their families. Such interventions also seek to reinforce patients' social and occupational functioning, as well as to develop their abilities to deal with socio-occupational stressors (Craighead and Miklowitz, 2000; Huxley et al., 2000).

Psychoeducational and cognitive-behavioral studies conducted on bipolar disorder have recently been reviewed (González-Pinto et al., 2003). Both approaches have been shown to be effective treatments in

preventing new recurrences in patients with bipolar disorder who are receiving drug therapy (Becoña and Lorenzo, 2003; Lam et al., 2003; Colom and Vieta, 2004; Mansell et al., 2005; Vieta et al., 2005; Scott et al., 2007). Interpersonal and social rhythm therapy appear to offer another approach to the management of bipolar I disorder, particularly with respect to prophylaxis of new episodes (Frank et al., 2005).

The objective of this study was to assess the efficacy of this treatment approach as an adjunctive treatment to pharmacotherapy, provided as group therapy to patients with a previously recurrent course of illness over a 1-year follow-up period. The short-term results have been described elsewhere (González et al., 2003) and showed significant improvement at the 6-month follow-up in most treated patients (80% in the experimental group, 70% in the control group), but there was no significant difference between the two therapeutic modes. The program contains psychoeducation, identification and monitoring of early warning symptoms, training in social skills, conflict resolution, restructuring of cognitive distortions, work on self-esteem, and planning of enjoyable activities.

### 2. Method

#### 2.1. Participants

The study group comprised patients with bipolar disorder in the Álava healthcare catchment area who sought treatment at the Department of Psychiatry (outpatient department or day hospital) of Santiago Apóstol Hospital in Vitoria between 2002 and 2003. All were receiving drug treatment, mainly consisting of a mood stabilizer (predominantly lithium) and, in some cases, antipsychotics and/or benzodiazepines.

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**Table 1**  
Description of sample and baseline characteristics.

|   |                     | Total       | Intervention group | Control group | Statistics <sup>a</sup> | P     |
|---|---------------------|-------------|--------------------|---------------|-------------------------|-------|
| Gender                                  | Male <sup>b</sup>   | 6 (30)      | 2 (20)             | 4 (40)        | –                       | 0.628 |
|   | Female <sup>b</sup> | 14 (70)     | 8 (80)             | 6 (60)        |                         |       |
| No. prior hospitalizations <sup>c</sup> |                     | 1.5 (0–17)  | 2 (0–9)            | 1 (0–17)      | 48.5                    | 0.908 |
| Age <sup>d</sup>                        |                     | 38.5 (7.48) | 36.9 (8.29)        | 39.2 (6.83)   | 46.5                    | 0.820 |
| <i>Scales at baseline</i>               |                     |             |                    |               |                         |       |
| GAF <sup>d</sup>                        |                     | 71.1 (13.3) | 70.3 (14.07)       | 71.9 (13.2)   | 46.5                    | 0.819 |
| RAS <sup>d</sup>                        |                     | –2.8 (21.8) | –3.2 (19.4)        | –2.4 (25.09)  | 45.0                    | 0.739 |
| BDI                                     | ≤18 <sup>b</sup>    | 16 (80)     | 8 (80)             | 8 (80)        | –                       | 1.000 |
| BDI                                     | >18 <sup>b</sup>    | 4 (20)      | 2 (20)             | 2 (20)        |                         |       |
| YMRS                                    | ≤6 <sup>b</sup>     | 17 (85)     | 9 (90)             | 8 (80)        | –                       | 1.000 |
| YMRS                                    | >6 <sup>b</sup>     | 3 (15)      | 1 (10)             | 2 (20)        |                         |       |

Abbreviations. GAF, Global Assessment of Functioning; RAS, Rathus Assertiveness Schedule; BDI, Beck Depression Inventory; YMRS, Young Mania Rating Scale.

<sup>a</sup> Due to the sample size, the Fisher test and the Mann–Whitney test were used for comparisons between categorical and numerical variables.

<sup>b</sup> n (%).

<sup>c</sup> Median (range).

<sup>d</sup> Mean (standard deviation).

The study inclusion criteria were as follows: a) DSM-IV-TR diagnosis of type I or type II bipolar disorder made at least 2 years before; b) severe or bad prior course despite adequate pharmacological treatment, defined as two or more relapses in the preceding year, rapid cycling, psychiatric hospitalizations in the previous 12 months, suicide attempts, need for treatment with combined stabilizing treatments and/or electroconvulsive therapy in the previous year, unscheduled psychiatric consultation in the previous year or severe difficulties in social-occupational functioning during the preceding year; c) euthymic or with subsyndromal depressive symptoms at the beginning of the study; and d) aged 18 to 50 years.

Twenty patients satisfied the entry criteria, and all of them completed treatment during the follow-up period. All patients gave their informed consent to take part in this randomized clinical trial.

2.2. Study design

Randomized assignment to an experimental group or a control group was carried out, and independent measures were analyzed in the pretreatment, posttreatment, 6-month follow-up, and 12-month follow-up time points. Assessment was done by investigators without knowledge of treatment assignment. All patients were undergoing standard drug treatment (similar drugs with individualized doses). Hence, the resulting modalities were the following: a) an experimental group with psychotherapy combined with drug treatment and b) a control group with only drug treatment. The study was designed to allow the comparison of the proportion of patients without relapses (mania and/or depressive episodes) during the follow-up period between the two groups, and to analyze the improvement in daily functioning and in quality of life in both groups.

2.3. Assessment measures

A semi-structured individual interview (Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Patient Version; SCID-P) (First et al., 2002) was conducted at the beginning of the study to confirm the diagnosis of bipolar disorder I or II according to

DSM-IV-TR diagnostic criteria. During the interview, the subjects described the symptoms they experienced, the history of the problem, the treatment received, and to what degree they found the disorder incapacitating in their daily life.

The following questionnaires were administered by a blind investigator at all evaluation visits: Beck Depression Inventory (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), Rathus Assertiveness Schedule (RAS) (Rathus, 1973; Spanish translation by Echeburúa, 1995), and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000; Spanish translation, Masson, 2000). For the first two scales, the lower the score, the better; for the third and fourth scales, the higher the score, the better. The instruments have been described in detail elsewhere (González et al., 2003).

2.4. Treatment modalities

2.4.1. Combined treatment group (drug treatment and psychotherapy)

The patients assigned to this group began with a session of psychoeducation about their disorder, followed by an explanation of the relationship between thoughts, activities, physical feelings and mood, and about how to identify and monitor early warning symptoms and how to deal with them. Secondly, they were exposed to anxiety control techniques (relaxation and breathing, self-instructions and cognitive distraction), educated about sleep hygiene, and taught how to plan gratifying activities. Later on, they were taught to detect irrational thoughts and to use the process of cognitive restructuring. Finally, to consolidate treatment changes and in an attempt to prevent relapses, participants underwent training in problem-solving and improvement of self-esteem. In addition, from the second session on, a program of social skills (assertiveness, non-verbal communication, conversational skills, giving and receiving compliments, giving and receiving criticism, and asking for favours) was introduced and constituted one part of every therapy session throughout the treatment. Its objectives were to enhance the patient's understanding of the disorder, to lower anxiety levels, to improve their repertoire of social skills and assertiveness control, to control mood by shifting thoughts and enhancing involvement in enjoyable activities, to enhance self-esteem, and to better adapt to daily life by learning problem-solving strategies. Cognitive therapy used in this research is based on the therapist's manual included in Lam et al. (1999). This psychosocial treatment was therefore based on a cognitive-behavioral model, and consisted of 13 sessions that lasted 1.5 h with a weekly frequency, which were led by a resident in clinical psychology assisted by psychiatric nurses. All patients attended the sessions together. The time elapsed between the patient's consent and the beginning of treatment was 2 weeks. Likewise, all patients in this group received individual treatment with psychoactive drug(s) (mood stabilizers, antipsychotics and/or benzodiazepines) adjusted by the psychiatrist.

2.4.2. Control group

Patients assigned to the control group only received treatment with psychoactive drug(s) (mood stabilizers, antipsychotics and/or benzodiazepines), likewise adjusted on an individual basis by the psychiatrist.

2.5. Statistics

Data analysis began with a comparison of the relevant characteristics between the two groups at baseline. Of the four scales considered, the GAF and the RAS were analyzed on the basis of numerical scores, but the other two were analyzed categorically because the focus was to compare the proportion of people with severe depressive symptoms (BDI score > 18) and/or with moderate mania (YMRS score > 6) in both groups over the follow-up period. For the continuous variables, mean and standard deviation or median and range values were provided depending on the characteristics of the data, and the Mann-Whitney test was performed for between-group comparisons. For the categorical variables, the number of cases and the

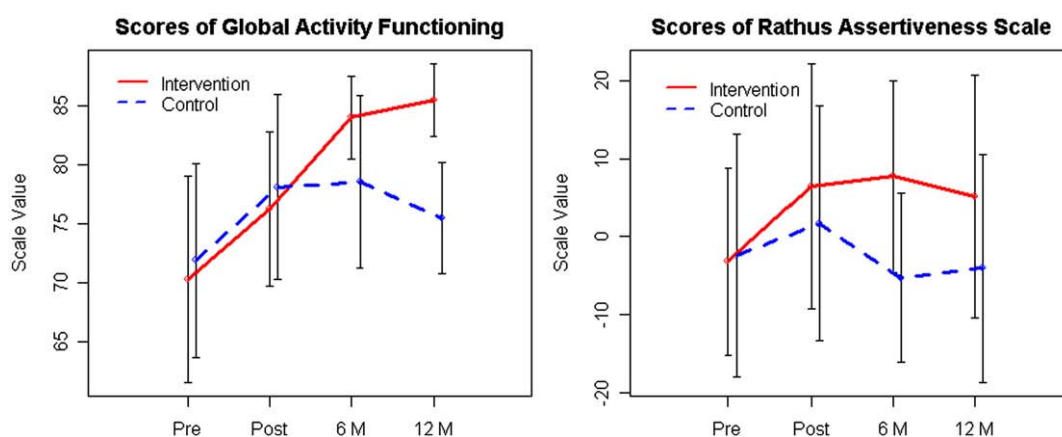


Fig. 1. Evolution of the scores during the follow up for the two groups.

**Table 2**  
Estimation of the repeated measures model for the two scales.

|                           | Group                 | Pretreatment       | Posttreatment      | 6 months           | 12 months          | Between subjects | Wilks Time | Wilks Time*group |
|---------------------------|-----------------------|--------------------|--------------------|--------------------|--------------------|------------------|------------|------------------|
| GAF                       | Control               | 71.9 ( $P<0.001$ ) | 78.1 ( $P<0.001$ ) | 78.5 ( $P<0.001$ ) | 75 ( $P<0.001$ )   | $P=0.347$        | $P=0.317$  | $P=0.032$        |
| Intervention <sup>a</sup> | I. group <sup>a</sup> | -1.6 ( $P=0.796$ ) | -1.9 ( $P=0.718$ ) | 5.5 ( $P=0.201$ )  | 10 ( $P=0.003$ )   |                  |            |                  |
| RAS                       | Control               | -2.4 ( $P=0.739$ ) | 1.7 ( $P=0.832$ )  | -5.3 ( $P=0.386$ ) | -4.1 ( $P=0.602$ ) | $P=0.461$        | $P=0.655$  | $P=0.547$        |
|                           | Intervention          | -0.8 ( $P=0.937$ ) | 4.8 ( $P=0.672$ )  | 13 ( $P=0.140$ )   | 9.2 ( $P=0.410$ )  |                  |            |                  |

<sup>a</sup> Values and  $P$ -values in the independent lines are estimates of the constant parameters in the control group, whereas values in the intervention group are estimates of the differences between the two groups.

proportion for each category were provided, and the Fisher Exact test was performed to study the association of these variables between the two groups at baseline.

Fisher Exact tests were used to compare the proportion of patients that suffered from severe depression and moderate mania between the two groups after 1 year of treatment. With the same objective but adjusting for baseline depressive and mania characteristics, logistic models were fitted including group and baseline categorical values as explanatory variables.

To evaluate the evolution of the patients and compare it between the two groups, repeated measures ANOVA was carried out using the GAF and the RAS, and the hypothesis of no time effects and no differences between groups was tested. Our interest here was to compare changes in GAF and RAS scores over time in the two groups, and with this aim the Wilks lambda test for time and for the group by time interaction was computed.

Finally, in a complementary analysis, the four scales were further evaluated with a most widely used method to assess of clinical significance proposed by Jacobson and Truax (1991) and compared with other approaches in Aitkins et al. (2005). This method uses pretherapy and posttherapy data to render classifications. More precisely, it consists of two steps; the first defines a cutoff point that separates the "functional population" from the "dysfunctional population", while the second one compares the individual's change from pretherapy to posttherapy to the standard error of measurement for the outcome, referred to as the Reliable Change Index (RCI). These two steps are used to classify individuals into one of four categories including recovered (passed cutoff and RCI in the positive direction), improved (passed RCI but not cutoff), unchanged (has passed neither criterion) or deteriorated (has passed RCI in the negative direction). For this study, we have used cutoff A, which defines the functional population as those with posttherapy scores above (or below, depending on the scale's direction) the pretherapy mean score by at least 2 standard deviations, and we assumed an internal consistency of 0.9. Details of the method can be found in Aitkins et al. (2005).

Statistical analyses were performed using both SAS version 9.1. and R version 2.4.0.

### 3. Results

#### 3.1. Descriptive characteristics at baseline

Table 1 shows the descriptive characteristics at baseline. As expected given the randomness of the design, no statistical differences were found among the two groups in terms of the proportion of females, although there are many more females than males in the sample. The number of prior episodes and the scale measures at baseline were not statistically different either, and therefore the results of the repeated measures analysis are expected to be unbiased. Patients had a mean age of almost 40 years old ( $\pm 7.48$ ) and had subsyndromal depressive symptoms of severe intensity in 20% of the cases in both groups.

#### 3.2. Depression and mania relapses

The proportion of patients with severe symptoms in the control group remained stable (20% at baseline and at the end of the follow-up period), whereas in the intervention group, it fell 10% (from 20% to 10%). The difference was not statistically significant due to the sample size (Fisher Exact  $P$  value = 1.000 and logistic model  $P$  value = 0.561 after correction for baseline values), with an odds ratio of 0.46 indicating non-significant double odds of relapses in the control group.

Regarding the Young mania categories, the proportion of people with moderate symptoms diminished in the control group from 20% to 10%, whereas in the intervention group, it fell from 10% to 0%, so that non-significant results are derived ( $P = 1.000$  for both unadjusted and adjusted for baseline).

#### 3.3. Repeated measures ANOVA

Fig. 1 shows the evolution of the two scales considered during the follow-up period. It can be seen that the variability for the measurements at each time point is high, and we do not expect big differences among the two groups due to the small sample size. However, it is important to highlight the fact that both scales seem to have a good evolution in those patients from the intervention group, which is not clearly observed in the control group. Results of the repeated measures ANOVA (Table 2) corroborate our findings. In particular, differences among mean GAF scores at the end of the follow-up are about 10 points ( $P=0.003$ ), but such a big difference is not observed in the previous time point, where it was about 5 points ( $P=0.201$ ). This finding suggests that both groups seem to improve in daily life functioning at the beginning of the follow-up period, but the improvement is more marked and lasts longer in the intervention group, as indicated by the significant group by time interaction ( $P=0.032$ ). Regarding the RAS, the mean profile plots suggest a slightly better evolution within the intervention group, with the highest mean differences obtained at 6 months (about 13 points,  $P=0.140$ ). However, this difference is not augmented as time goes by, and neither the effect of time nor the group by time interaction is statistically significant ( $P=0.655$  and  $P=0.547$ , respectively).

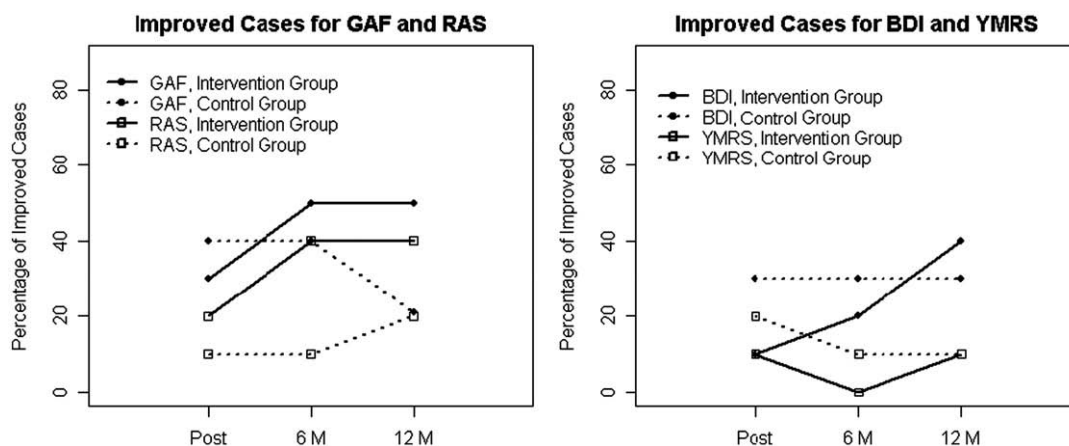


Fig. 2. Percentage of people classified as improved cases using clinical significance methodology.

### 3.4. Clinical significance assessment results

Assessment of clinical significance classified subjects into four categories, but to facilitate the presentation, the first two and the last two categories have been combined. Fig. 2 shows the proportion of people in the category of “improved or recovered” for the control and the intervention group derived from the four scales at each time point. It can be seen that the intervention group (solid line) appears superior to the control group (dashed line) for all scales except for the YMRS, where similar results are found. Moreover, it is in the last time point where differences are greatest. Furthermore, it seems that the GAF score reveals the greatest differences, with 50% of the intervention group showing improvement as compared with 20% of the control group. Similarly, the RAS showed that 40% of the intervention group improved compared with 20% of the control group. These results agree with those derived following the classical statistical significance approaches.

## 4. Discussion

The main finding of this research is the efficacy of a psychosocial intervention, based on a cognitive-behavioral model, as an add-on treatment in patients with refractory bipolar disorder. The effect is seen in quality of life and in long-term follow-up (12 months). The use of psychosocial therapy in resistant bipolar disorder in combination with psychoactive drugs has received scant attention to date, with very few long-term controlled studies. Efficacy trials suggest that structured psychological therapies may significantly reduce recurrence rates of major mood episodes in individuals with bipolar disorders (Lam et al., 2003; Miklowitz et al., 2007a,b). The research done by Lam (2006) included a homogeneous remitted group treated with mood stabilizers and with history of frequent relapses in the preceding 5 years. Although in a study done by the team of Scott et al. (2006) there were no differences in efficacy between treatment and control groups, the therapy was carried out in a naturalistic setting including acute and remitted patients (Scott et al., 2006). It is possible that the differences between the findings of Scott et al. and the findings of Lam and Miklowitz and their associates, as well as our own research, reflect the inclusion of acute patients in the study of Scott and associates. Psychological treatments may be a good option for selected severe patients, but only when manic and hypomanic symptoms are remitted and if psychopharmacological treatment is adequate. In fact, in a recent meta-analysis, psychological treatments have better results when the patients included are remitted from acute episodes (Scott et al., 2007). In our study only subsyndromal depressive symptoms were allowed to be present at study entrance, and no patients with a diagnosis of bipolar depression were included in the study. Nevertheless, it has recently been reported that bipolar depression improves with psychological techniques added to psychopharmacological treatment (Miklowitz et al., 2007b). In our study, we considered it important to include patients with subsyndromal symptoms because depressive symptoms commonly appear when a severe bipolar disorder has remitted (Judd et al., 2002).

We want to emphasize the importance of psychopharmacological treatment in bipolar disorder when a psychological treatment is going to be applied. Indeed, in the study done by Scott et al., there were some patients who, in this naturalistic design, were not taking psychopharmacological treatment. It is clear that psychoactive drugs are absolutely needed in this clinical syndrome, although they are probably not enough, at least in treatment-resistant cases. The addition of a type of psychological therapy that has demonstrated its effectiveness in preventing relapse in other disorders, such as depression or anxiety disorders (*cf.* Echeburúa et al., 2006), and applying it in group format, appears to be an attractive option (Becoña and Lorenzo, 2003; Ramírez-Basco and Thase, 1997). Nevertheless, using only cognitive therapy for these patients is not a good option, as the efficacy of pharmacological approaches has been well established

for bipolar disorder. Ultimately, it is a matter of testing a new treatment option (combined therapy) for a disorder that negatively affects the patient's quality of life and that tends to become chronic, hence generating many consultations with medical services. The effectiveness of combined treatment over the longer term also needs to be evaluated.

The psychosocial program tested in this study sought to teach skills that lead to improved patient understanding of the illness, an increased repertoire of social skills, mood control by shifting thoughts and involvement in enjoyable activities, improvement in self-esteem, enhanced adaptation to daily life and decreased levels of anxiety.

The main hypothesis of the study (i.e. that psychotherapy adds value to benefit obtained by psychoactive agents alone) is not completely confirmed. Around 80%–90% of the patients did not present overall symptoms for the diagnosis of a depressive, manic or mixed episode as part of bipolar disorder during the 12-month follow-up. Nonetheless, the experimental group demonstrated greater improvement in quality of life than the control group. Since this was not the case at the 6-month follow-up, it can be concluded that the effectiveness of psychotherapy tends to increase with time, as observed in other studies of bipolar disorder (Colom et al., 1998) and even of resistant schizophrenia (Sensky et al., 2000).

Although these findings are preliminary, psychotherapy conducted in a group format seems both effective and efficient, at least with respect to quality of life, and it can easily be implemented in the setting of a mental health center or day hospital. Moreover, the patients were very satisfied with it and felt that it had served to improve their adaptation to daily life, and that it should last longer.

A larger and better controlled study design is needed in future research and, depending on the mood instability found in this type of patients, more continuous follow-up visits and more specific variables for this disorder are required. It would also be a good idea to design a longer and more specific psychological treatment for this disorder, to get patients more actively involved in performing household chores and to evaluate the degree of compliance with treatment prescriptions, as well as to perfect the assessment instruments that were used (Vázquez, 1995). Since all patients in the sample were euthymic or with subsyndromal symptoms, a new area of research would be to confirm that subjects euthymic at the beginning of treatment have better outcome than those with syndromal symptoms (Mansell et al., 2005).

In conclusion, a psychological treatment based on a cognitive-behavioral model added to pharmacotherapy is effective in improving quality of life in refractory bipolar patients, but it does not reduce their relapse rate. Its efficacy is not apparent in the medium term (6 months), but appears in the long term (12 months).

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