

A Randomized Trial on the Efficacy of Group Psychoeducation in the Prophylaxis of Recurrences in Bipolar Patients Whose Disease Is in Remission

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Background: Studies on individual psychotherapy indicate that some interventions may reduce the number of recurrences in bipolar patients. However, there has been a lack of structured, well-designed, blinded, controlled studies demonstrating the efficacy of group psychoeducation to prevent recurrences in patients with bipolar I and II disorder.

Methods: One hundred twenty bipolar I and II outpatients in remission (Young Mania Rating Scale score <6, Hamilton Depression Rating Scale-17 score <8) for at least 6 months prior to inclusion in the study, who were receiving standard pharmacologic treatment, were included in a controlled trial. Subjects were matched for age and sex and randomized to receive, in addition to standard psychiatric care, 21 sessions of group psychoedu-

cation or 21 sessions of nonstructured group meetings. Subjects were assessed monthly during the 21-week treatment period and throughout the 2-year follow-up.

Results: Group psychoeducation significantly reduced the number of relapsed patients and the number of recurrences per patient, and increased the time to depressive, manic, hypomanic, and mixed recurrences. The number and length of hospitalizations per patient were also lower in patients who received psychoeducation.

Conclusion: Group psychoeducation is an efficacious intervention to prevent recurrence in pharmacologically treated patients with bipolar I and II disorder.

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THE INCREASING evidence of the efficacy of the pharmacologic treatment of bipolar disorders has sometimes led clinicians to forget psychological interventions as an adjunctive treatment. Other possible reasons for this negligence are the several methodological pitfalls present in most of the studies on psychological interventions in bipolar disorders.^{1,2} The design of class A trials on psychosocial interventions with bipolar patients deserves high priority.³

The psychoeducative approach has been performed by many clinicians for decades, but the first studies on its efficacy did not appear until recent years. To date, only the study of Perry and colleagues⁴ on individual psychoeducation included a control group, single-blind design, and provided results on efficacy measured as a decrease in the number of recurrences. On the contrary, most of the seminal studies on the issue reported only data on indirect measures of efficacy, generally regarding a change in patients' attitudes toward medication.^{5,6} A third group of studies was performed using less restrictive methods.^{7,8}

One of the first well-structured group interventions specifically designed for bi-

polar disorders was the "Life Goals Program."⁹ This form of group psychotherapy, when used as a part of a multimodal program, has proven to decrease emergency department use and costs. The program's efficacy is being tested in an ongoing multisite randomized controlled trial.^{10,11}

To our knowledge, ours is the first randomized blinded clinical trial comparing the efficacy of group psychoeducation with standard treatment. The treatment tested in this study combines 3 interventions that have shown some efficacy individually: early detection of prodromal symptoms,⁴ enhancement of treatment compliance,¹² and induction of lifestyle regularity,¹³ in a structured group intervention for euthymic bipolar outpatients receiving standard pharmacologic treatment.

METHODS

SUBJECTS

One hundred twenty patients fulfilling DSM-IV criteria for bipolar disorder type I or II, aged 18 to 65 years, were recruited from the bipolar I and II patients enrolled in the naturalistic prospective follow-up of the Bipolar Disorders Program of the Hospital Clinic at the University of

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Barcelona (Spain). Inclusion criteria were a lifetime diagnosis of bipolar disorder type I or II elicited by a trained psychiatrist (E.V. or A.B.); being euthymic (Young Mania Rating Scale [YMRS] score <6, Hamilton Depression Rating Scale [HDRS]-17 score <8) for at least 6 months; having sufficient data on the prior course of illness collected from a prospective follow-up of at least 24 months; and written consent to participate in the study. Exclusion criteria were DSM-IV Axis I comorbidity except for caffeine and nicotine dependence; mental retardation (IQ <70); organic brain damage; or deafness. Patients currently receiving any kind of psychotherapy or enrolled in any pharmacologic trial were also excluded.

STUDY DESIGN

This was a parallel 2-group (experimental and control) randomized, single-blind trial with 20 weeks of treatment and 2 years of follow-up, carried out in the Bipolar Disorders Program of the Hospital Clinic of Barcelona (Barcelona, Spain), whose research and ethics committee approved the study. This program merges clinical care, research, and education of residents and fellows, and is addressed primarily to the most severe bipolar I and II patients.

The study consisted of 2 phases: the treatment phase comprised 21 weeks of randomized treatment in which all patients received standard psychiatric care with standard pharmacologic treatment; patients were prohibited against visiting a psychologist outside the center. The experimental group received additional psychoeducation, and the patients assigned to the control group met every week in groups of 8 to 12 patients without special instructions from the therapist. This design was aimed to control the variability induced by the possible supportive effect of the group reunions themselves.

The follow-up phase comprised 2 years, during which all patients continued receiving standard treatment without psychological intervention and were assessed monthly for several outcome measures. After written informed consent was signed, patients were assessed at baseline and randomized, stratifying the groups by sex, age, and number of previous episodes. Randomization was made by a computerized random-number generator, ensuring restricted randomization. The preset sample size was 60 subjects per treatment group, with significance being set at $P = .05$.

TREATMENT

Standard Psychiatric Care (All Patients)

All patients were seen by 2 psychiatrists (E.V. or A.B.) every 4 weeks and were specifically told to go to the center whenever they felt any change in their mood or any other problem, such as insomnia. The psychiatrists had a minimum of 4 years of clinical and research experience in bipolar disorder.

Patients received pharmacologic treatment following the treatment algorithms of the Barcelona Bipolar Disorders Program. Psychiatrists were blinded as to the nature of the treatment given to the patients, who were told not to tell their psychiatrists if they were receiving psychoeducative treatment. The psychiatrist was not allowed to provide formal psychotherapy or specific psychoeducation.

Psychoeducation (Experimental Group)

Patients assigned to the experimental treatment received standard psychiatric care and were enrolled in a psychoeducative program¹⁴ composed of 21 sessions of 90 minutes, each aimed at improving 4 main issues: illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and life-

Table 1. Content of the Psychoeducative Program (Barcelona Bipolar Disorders Program)

1. Introduction
2. What is bipolar illness?
3. Causal and triggering factors
4. Symptoms (I): Mania and hypomania
5. Symptoms (II): Depression and mixed episodes
6. Course and outcome
7. Treatment (I): mood stabilizers
8. Treatment (II): antimanic agents
9. Treatment (III): antidepressants
10. Serum levels: lithium, carbamazepine, and valproate
11. Pregnancy and genetic counseling
12. Psychopharmacology vs alternative therapies
13. Risks associated with treatment withdrawal
14. Alcohol and street drugs: risks in bipolar illness
15. Early detection of manic and hypomanic episodes
16. Early detection of depressive and mixed episodes
17. What to do when a new phase is detected?
18. Regularity
19. Stress management techniques
20. Problem-solving techniques
21. Final session

style regularity. The program, a modification of some similar existing programs,^{9,15} was performed in an 8- to 12-patient group setting, conducted by 2 experienced psychologists (F.C. and A.M.A.) who had previous experience with bipolar patients (≥ 3 years) and specific education on group conduction. A preliminary study of 10 patients per group was performed both to ensure good training and to identify any potential problem with the program design.² The structure of each session consisted of a 30- to 40-minute speech on the topic of the day, followed by an exercise related to the issue (eg, drawing a life chart, writing a list of potential triggering factors), and a discussion. Participation was encouraged. **Table 1** presents the list of sessions in the psychoeducation treatment. The goals addressed by the group were (1) first-line goals: illness awareness; early detection of prodromal symptoms; and treatment compliance; (2) second-line goals: stress management; substance abuse avoidance; inducing lifestyle regularity; and preventing suicidal behavior; and (3) third-line goals: enhancing knowledge and coping with psychosocial consequences of past and future episodes; improving interpersonal and social interepisodic functioning; coping with subsyndromal, residual symptoms, and impairment; and increasing well-being and improving quality of life.

Control Group Procedures

In addition to standard pharmacologic treatment, patients assigned to the control group received an intervention consisting of 20 weekly group meetings of 8 to 12 patients with the same 2 psychologists (F.C. and A.M.A.). The psychologists tried not to give any psychoeducational feedback except for that necessary for patient interaction.

ASSESSMENTS

All subjects were assessed monthly by the study psychiatrists and every 2 weeks by a research assistant who had instructions to contact the psychiatrist if a recurrence was suspected. The psychiatrist and research assistant were blinded to treatment, and patients were requested not to reveal significant details.

All patients participating in this study had been enrolled in the prospective follow-up of the Bipolar Disorders Program

Table 2. Baseline Characteristics of the Sample*

	Control Group (n = 60)	Psychoeducation Group (n = 60)	Statistical Test	P Value
Sex			0†	>.99
Male	22 (36.7)	22 (36.7)		
Female	38 (63.3)	38 (63.3)		
Diagnostic subtype			0.96†	.32
Bipolar I	48 (80)	52 (86.7)		
Bipolar II	12 (20)	8 (13.3)		
Psychotic features	42 (70)	47 (78.3)	1.08†	.29
History of suicide attempts	19 (31.7)	21 (35)	0.15†	.69
Axis II comorbidity	22 (36.7)	15 (25)	1.91†	.16
Age at onset, mean ± SD, y	23.25 (7.55)	22.26 (6.69)	0.75‡	.45
Total No. of previous episodes, mean ± SD	8.81 (6.60)	10.31 (10.55)	-0.93‡	.35
No. of hospitalizations, mean ± SD	2.01 (2.12)	1.81 (1.78)	0.56‡	.57

*Data are given as number (percentage) of patients unless otherwise indicated.

†Fisher exact test; *df* = 1.

‡*t* Test.

of Barcelona for at least 2 years. This follow-up includes assessment of recurrences, symptom checking, and treatment registration, and is performed every 2 months. Baseline assessment includes the administration of the Structured Clinical Interview for DSM-IV (SCID I and SCID II), and also YMRS, HDRS-17, and the Holmes and Rahe inventory for stressful life events, which are also repeated every 2 months.

Psychiatric medication and reasons for changes were recorded. The number of hospitalizations, reasons for admission, and the total number of days that the patient remained hospitalized were also recorded. Compliance was assessed by the combination of a compliance-focused interview with the patient, a compliance-focused interview with significant first-degree relatives or a partner, and by plasma concentrations of mood stabilizers. This method has been extensively explained elsewhere.¹⁶

DEFINITION OF RECURRENCE

The primary outcome measure was recurrence. This was defined as the emergence of a new acute episode according to DSM-IV criteria and scores above or equal to 20 on the YMRS for manic recurrence; above or equal to 12 for hypomanic recurrence; above or equal to 17 on the HDRS-17 for depressive recurrence; and above or equal to 20 on the YMRS and 12 on the HDRS-17 for mixed recurrence.

PATIENT FLOW AND DROPOUT

One hundred twenty euthymic outpatients were recruited from the Bipolar Disorders Program of Barcelona. Sixty were randomly assigned to psychoeducation and 60 to the control group. Group rules, which were provided equally to both experimental and control subjects, included the possibility of group exclusion for those patients missing more than 5 sessions. Within the experimental group, 44 patients (73.3%) of 60 adhered to the psychoeducation. Sixteen patients (26.6%) withdrew from the group. Of these, 12 were followed up for 2 years. The 4 patients left were considered lost to follow-up after withdrawing from the psychoeducation group due to either a depressive (3 cases) or a manic episode (1 case). These episodes were included on the record of the experimental group on the corresponding condition but the patients were considered as missing for all other conditions.

Among the patients who did continue on the study after withdrawing from the psychoeducation group, the reasons for abandoning it were manic recurrence (7 patients), problems with the group time table (2 patients found a new job during the treatment phase and could not continue coming to the ses-

sions), consent withdrawal or nonacceptance of the group rules (1 patient), interpersonal problems with other group members (1 patient), and depressive recurrence (1 case).

Seven patients in the control group (11.6%) of 60 withdrew from the weekly meetings but continued with the psychiatrist visits, the pharmacologic treatment, and the follow-up phase procedures. The reasons for discontinuing among the control group were manic episode (4 cases), major depression (1 case), and nonattendance or nonacceptance of group rules (2 cases). Thus, the total number of patients who withdrew was higher among the experimental group ($P < .05$). If we consider discontinuation as withdrawing because of reasons other than recurrence, there were no differences (4 discontinuations [7%] vs 2 [3%]; $\chi^2 = 0.4$, $P = .40$). There were no significant differences in the number of sessions not attended: patients in the control group did not attend a mean \pm SD of 3.75 \pm 0.87 sessions compared with 3.38 \pm 1.16 sessions in the treatment group.

BASELINE CHARACTERISTICS OF TREATMENT GROUPS

There was no significant difference between the 2 groups regarding the baseline variables, as presented in **Table 2**. Each group was finally formed by 38 women and 22 men with a similar number of previous episodes.

As for the diagnostic subtype, 48 patients (80%) of 60 included in the control group were diagnosed as having bipolar I, and 12 (20%) as having bipolar II disorder. The psychoeducation group had a similar distribution: 52 (86.7%) of 60 bipolar I and 8 bipolar II patients. Regarding subtype, this difference between the composition of the 2 groups was not significant with a 95% confidence interval.

No difference was found between the 2 groups with respect to polarity of the first episode (most frequently depressive), presence of psychotic features (70% in the control group vs 78% in the treatment group), history of suicide attempts (32% vs 35%), Axis II comorbidity (37% vs 25%), family history of any psychiatric disorder (68% for both groups), seasonal pattern (15% vs 27%), or past rapid cycling (7% vs 13%). There were no significant differences between groups regarding the baseline pharmacotherapy.

DATA ANALYSIS

Recurrence-free curve analysis was performed using the Kaplan-Meier survival analysis. Comparison of baseline characteristics of the sample was made by a χ^2 test for categorical vari-

Table 3. Number of Patients Who Relapsed During the Treatment and the Follow-up Phase

	Treatment Phase		χ^2	P Value	Follow-up Phase		χ^2	P Value
	Control Group, No. (%)	Psychoeducation Group, No. (%)			Control Group, No. (%)	Psychoeducation Group, No. (%)		
Any recurrence	36 (60)	23 (38.3)	5.63	.01	55 (91.7)	40 (66.7)	11.36	<.001
Mania or hypomania	20 (33.3)	12 (21.1)	2.21	.13	45 (75)	28 (49.1)	8.34	.003
Mania	9 (15)	8 (14)	0.02	.88	28 (46.7)	18 (31.6)	2.78	.09
Hypomania	13 (21.7)	4 (7.1)	4.88	.02	30 (50)	18 (32.1)	3.80	.05
Mixed episode	13 (21.7)	7 (12.5)	1.70	.19	27 (45)	11 (19.6)	8.45	.003
Depression	19 (31.7)	8 (13.6)	5.56	.01	43 (71.7)	24 (40.7)	11.61	<.001

ables such as sex, diagnostic subtype, polarity of first episode, history of rapid cycling, seasonal pattern, psychotic features, history of suicide attempts, Axis II comorbidity, and type of treatment received using the Fisher z test when needed and the *t* test for quantitative variables. The separate analysis at follow-up of the number of patients who relapsed for each condition was by a χ^2 test. The comparison of the mean number of recurrences during the treatment and the follow-up phase was made using the Mann-Whitney *U* test. Statistical significance was set for all cases at $P < .05$.

RESULTS

NUMBER OF RECURRENCES

During the treatment phase, 36 subjects (60%) in the control group fulfilled criteria for recurrence (mania, hypomania, mixed episode, or depression) compared with 23 (38%) in the psychoeducation group ($P < .05$). At the end of the follow-up phase (2 years), 55 subjects (92%) in the control group fulfilled criteria for recurrence vs 40 subjects (67%) in the psychoeducation group. This difference was statistically significant ($P < .001$). If mild episodes were excluded (hypomania), the recurrence rates would be 87% and 63%, respectively ($P < .004$). **Table 3** presents the number of patients who had each type of recurrence. The total number of episodes and the number of depressive episodes were significantly lower in psychoeducated patients at any time point.

TIME TO RECURRENCE

Survival analyses of patients remaining in remission for each condition are shown in **Figures 1, 2, 3, and 4**. The event curves for the control and treatment groups were significantly different for time to any recurrence ($\log \text{rank}_1 = 13.45$, $P < .001$); time to manic, mixed or depressive episode ($\log \text{rank}_1 = 9.3$, $P < .004$); time to depressive recurrence ($\log \text{rank}_1 = 15.47$, $P < .001$); time to mixed recurrence ($\log \text{rank}_1 = 7.95$, $P < .05$); and time to manic or hypomanic recurrence ($\log \text{rank}_1 = 7.79$, $P < .006$).

HOSPITALIZATIONS

During the treatment phase, 8 (13.3%) of 60 patients in the control group were hospitalized owing to recurrence compared with 9 (16.1%) in the control group ($P = .67$). At the end of the follow-up period, 21 patients

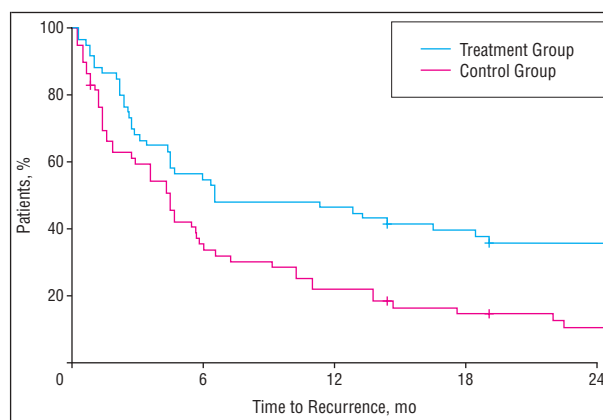


Figure 1. Survival curves for recurrence with mania, depression, or mixed episode ($\log \text{rank}_1 = 9.3$, $P < .003$).

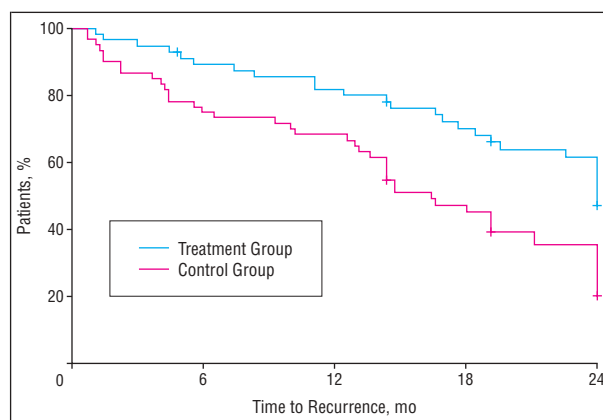


Figure 2. Survival curves for recurrence with manic or hypomanic episode ($\log \text{rank}_1 = 7.79$, $P < .006$).

(35%) in the control group had been hospitalized vs 14 (25%) in the treatment group ($P = .24$).

During the treatment phase and the first 6 months of follow-up, there was no difference between groups regarding the mean number of hospitalizations per patient, but thereafter, the cumulative mean number of hospitalizations per patient was significantly lower for psychoeducated patients. At the 12-month follow-up, psychoeducated patients had 0.23 admissions vs 0.63 in the control group (Mann-Whitney $U = -2.24$, $P < .05$); at the 18-month follow-up, 0.24 vs 0.86, respectively ($U = -2.69$, $P < .01$), and at 24 months, 0.30 vs 0.78 ($U = -2.14$, $P < .05$). The mean number of days of hospitalization per patient

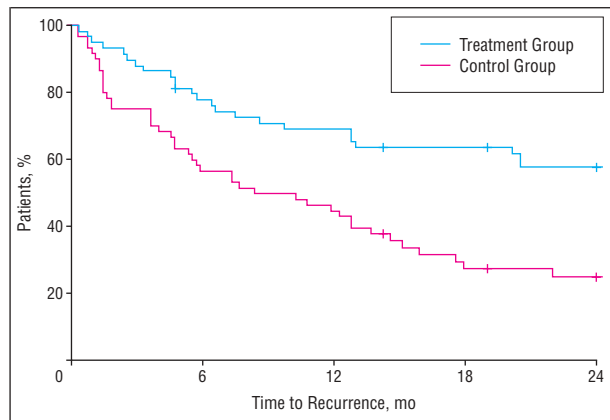


Figure 3. Survival curves for recurrence with depression (log rank₁=15.47, *P*<.001).

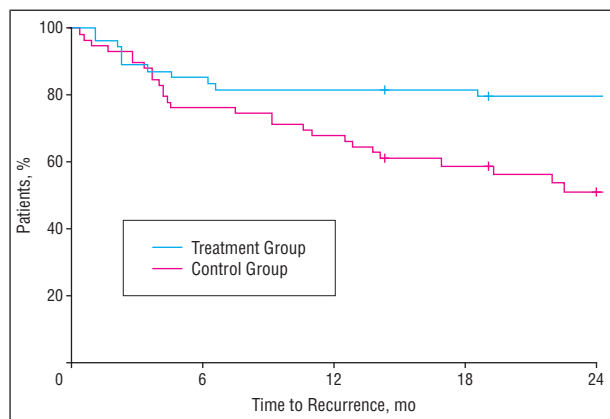


Figure 4. Survival curves for recurrence with mixed episode (log rank₁=7.95, *P*<.05).

was also clearly lower for the psychoeducated patients; 4.75 days vs 14.83 in the control group ($U=-2.23$, $P<.05$). There was no difference regarding time to hospitalization between the 2 groups (log rank₁=1.34, $P=.24$).

TREATMENT VARIABLES

We did not find any baseline difference regarding plasma concentrations of mood stabilizers between the 2 groups: both groups, control and experimental, had similar serum levels of lithium (mean \pm SD, 0.71 ± 0.20 vs 0.74 ± 0.19 mEq/L; $t=-0.86$), valproate (72.66 ± 11.67 vs 76.0 ± 8.4 μ g/mL; $t=-0.52$), and carbamazepine (7.76 ± 1.38 vs 7.1 ± 1.81 μ g/mL; $t=1.21$).

At the 2-year follow-up, a difference was found between the 2 groups regarding lithium levels (0.68 ± 0.20 vs 0.76 ± 0.16 mEq/L; $t=-2.13$, $P=.03$), but there was no difference regarding levels of valproate (81.75 ± 7.79 vs 80.70 ± 9.2 μ g/mL; $t=0.26$) or carbamazepine (8.3 ± 1.52 vs 8.1 ± 1.39 μ g/mL; $t=0.38$). There were no differences regarding pharmacologic treatment between the 2 groups during the 2-year follow-up.

COMMENT

To our knowledge, this is the first blinded controlled study on group psychoeducation for bipolar disorder. To date,

there has only been 1 published randomized study on individual psychoeducation,⁴ but group intervention has not been tested. Most of the literature on psychological interventions is merely descriptive, and the few studies that include a control group usually compare intervention vs waiting list controls.⁵⁻⁷ This design does not control the effect of the time spent with the therapist or meeting other patients, which may be therapeutic in itself for some patients, as shown by the increasing popularity of self-help groups for bipolar patients.¹⁷

An important issue for the study was the strict criteria for euthymia: all patients had to have been euthymic since 6 months prior to inclusion. None of the published studies have used such narrow criteria and, thus, some recurrences reported in those studies may be nothing but a full-blown presentation of a previous subsyndromal ongoing episode. Another main strength of the study is the prior prospective follow-up of at least 2 years; in most of the published articles, the prior course of the patients is based on retrospective data that are not as reliable.

Because 2 similarly skilled therapists direct all of the groups in both treatment conditions, we avoided biases due to the training differences among therapists. This may have been a limitation, however, because it remains unclear to what extent this therapy could be administered by less experienced professionals.

As seen in our results, group psychoeducation is a useful as an adjunctive treatment with maintenance pharmacotherapy to prevent recurrences in bipolar affective disorder. Our intervention appears to be efficacious in preventing episodes of elation, mixed episodes, and depression. As presented in Table 3, psychoeducation is useful for preventing hypomania but does not reach statistical significance—although there is a trend to significance—in mania. This may have to do with the presence of sudden manic switches that cannot be behaviorally prevented. For mania and hypomania as a whole, psychoeducation shows its efficacy. This result is at odds with previous studies that have shown the efficacy of (individual) psychotherapy in reducing manic recurrences but not depression.⁴ The study of Lam and Wong,¹⁸ which shows a greater difficulty in detecting depressive prodromes than in detecting early manic signs among bipolar patients, may support the results of Perry and colleagues.

However, it seems that our patients may tend to overestimate or, at least, be especially sensitive to detecting early manic and hypomanic signs. At the end of follow-up, psychoeducation patients had a lower number of all types of recurrences but mania. These can be caused by the methods of the study, which include checking symptoms every 2 weeks during the follow-up for both study groups. When a new episode was detected, the study psychiatrist started the corresponding treatment, aborting several instances of hypomania and, in most cases, precluding the onset of mania. This may have reduced the number of manic recurrences among the control group.

The effectiveness of psychoeducation appears to be patent very early, as shown by the lower number of recurrences during treatment, but its effect lasts for a long time. Our proposed program is one of the longest interventions in the existing literature on psychoeducation,

and this may enhance generalization and perdurable behavioral changes during long-term treatment.

Although the number of patients who needed hospitalization was practically equal in both groups, the number of hospitalizations per patient and the number of days of hospitalization were significantly lower for psychoeducated patients. Therefore, psychoeducation may not be enough to help some patients avoid hospitalization but may facilitate early detection of an episode and thereby decrease the severity of the episode. The efficacy of group psychoeducation goes beyond the mere supportive role of the group, a variable that could seriously interfere with the final results, and that was controlled by the control group procedures. This comparative result points out the importance of structured psychological interventions for bipolar disorders.

The results of this study highlight the need for the progressive incorporation of psychoeducative interventions in treatment guidelines for bipolar disorders. Through the enhancement of compliance and illness awareness, psychoeducation may bridge the gap that exists between the efficacy results of pharmacologic treatment obtained in clinical trials and the "real world" effectiveness, which is usually lower. Compared with control patients, psychoeducated patients had higher lithium levels at the 2-year follow-up, which may suggest an effect of psychoeducation on pharmacotherapy adherence.

The continuing follow-up visits may have been "psychoeducative" for some of the patients in the control group, since an important part of the interview was aimed at identifying recurrences. This could have given the patient an idea of the key issues that were being addressed to identify a recurrence, as the same questions were asked at each visit. This source of variability is almost impossible to control with any study design: any assessment of mental health may in some way be an intervention. However, this assessment was equal for both treatment arms. Despite this problem, our intervention still showed efficacy when compared with control patients.

The Bipolar Disorders Program of Barcelona is a reference center for bipolar affective disorders for a big population, and mostly complex patients are accepted. This may bias the sample and it may be a limitation of this study. The control group relapse rates were strikingly higher than those expected, looking at the existing literature. Similar studies with "soft" samples are needed. However, the intrinsic difficulty of our patients' illnesses may make the efficacy of the intervention especially valuable.

Another limitation of this study is the lack of separate comparisons for each block of the intervention (early detection of prodromal symptoms, enhancement of treatment compliance, and inducing lifestyle regularity). Thus, we cannot conclude whether there is only one useful part or determine the major or minor efficacy of each block. As cognitive therapy has been reported to be efficacious as an add-on treatment of bipolar depression,¹⁹ it remains unclear whether prevention of depressive episodes comes from a real psychoeducative action on habits and adherence or from a cognitive effect of psychoeducation itself. This issue deserves further attention.

How does psychoeducation work? What is the nature of its efficacy? The mechanism of action of psychoeducation remains unknown. We may hypothesize that teaching lifestyle regularity would play a main role in the prevention of depression, while the early detection of prodromal symptoms would be crucial to prevent mania, as reported by previous studies.⁴ Promotion of treatment adherence would partially explain the large outcome differences found in our study. Future studies on this issue should aim at determining the specific content of the psychoeducative program that elicits a more favorable response and they should clarify whether there is a biological implication in this psychological intervention.

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