Cognitive-Behavioral Management of Patients With Bipolar Disorder Who Relapsed While on Lithium Prophylaxis

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Background: The application of cognitive-behavioral treatment (CBT) to patients with bipolar disorder who had an affective episode while on lithium prophylaxis has received little research attention. The aim of this preliminary study was to test whether reduction of residual symptomatology by cognitive-behavioral methods could yield long-term beneficial effects in patients with bipolar disorder, as was found to be the case in recurrent unipolar depression.

Method: Fifteen patients with RDC bipolar disorder, type I, who relapsed while on lithium prophylaxis despite initial response and adequate compliance were treated by cognitive-behavioral methods in an open trial. A 2- to 9-year follow-up was performed.

Results: Five of the 15 patients had a new affective episode during follow-up. CBT was associated with a significant reduction of residual symptomatology.

Conclusion: These preliminary results suggest that a trial of CBT may enhance lithium prophylaxis and improve long-term outcome of bipolar disorder.

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The problem of relapse in patients with bipolar disorder who are receiving lithium prophylaxis is attracting increasing attention.[1] Several complex pharmacologic strategies have been developed for improving long-term outcome when affective episodes occur despite lithium treatment.[2] Limited research has been conducted on nonpharmacologic approaches, despite the logical appeal of treating patients who do not respond to lithium with psychotherapy.[3,4] Such appeal is increased by the emerging role of cognitive-behavioral strategies in mood disorders[5] and the recent awareness that these strategies may prevent relapse in depression.[6–9]

Several psychotherapeutic strategies have been employed in bipolar disorder. They encompass preventing lithium noncompliance with cognitive therapy principles,[10] lifestyle modification,[11] teaching patients to identify early symptoms of relapse and obtain treatment,[12] modification of family conflicts,[13] and dealing with interpersonal issues at both the individual[11] and group[14] levels.

Substantial evidence shows that patients with bipolar and unipolar disorders report residual symptoms despite successful treatment.[15] These symptoms have been correlated with poor long-term outcome.[15] This finding has led to the development of a sequential strategy consisting of pharmacotherapy in the acute phase of illness and cognitive-behavioral therapy (CBT) in its residual phase.[16] In unipolar depression, the preventive effect of cognitive-behavioral strategy has been found to be directly related to the abatement of residual symptoms.[16]

The aim of this study was to apply a sequential approach (based on CBT of residual symptoms) to patients with bipolar disorder, type I, who relapsed while on lithium prophylaxis.

METHOD

Fifteen consecutive outpatients satisfying the criteria below who had been referred to the Affective Disorders Program of the University of Bologna were enrolled in the study. The patients' diagnoses were established by the consensus of a psychiatrist and a clinical psychologist

independently using the Schedule for Affective Disorders and Schizophrenia.[17] Subjects had to meet a current diagnosis of bipolar disorder, type I, according to Research Diagnostic Criteria (RDC),[18] which were also used to define affective episodes, and have no history of drug or alcohol abuse or dependence. All patients were treated with lithium as the only mood-stabilizing agent. Blood levels were monitored, compliance was checked, and blood lithium levels were maintained at 0.8 to 1.1 mmol/L. All patients had to display initial successful response to lithium therapy, rated as "better" or "much better" according to a global scale of improvement,[19,20] and be in full remission[21] 3 months after beginning lithium therapy. Despite the fact that all patients were compliant with treatment, they all had a relapse of illness within 30 months from the beginning of therapy. In 10 cases, a major depressive episode occurred, whereas in 5 cases mania ensued. The 15 patients were selected from a total sample of 40 patients with bipolar disorder, type I, who responded to lithium prophylaxis: 22 did not have affective episodes at a follow-up of at least 2 years, whereas 3 patients who had a relapse were found to show poor compliance with lithium and were therefore excluded from this sample.

The mean ± SD age of the 15 patients was 37.6 ± 6.8 years. There were 4 men and 11 women. Six patients were married, and 9 were single. The majority of patients (N = 12) were of middle-to-upper socioeconomic status.[22] Seven had had more than 13 years of education. The mean ± SD duration of illness before lithium treatment was 65 ± 61 months. Comorbidity was present in 4 patients (in 3, social phobia and in 1, obsessive-compulsive disorder). In 2 cases there was a personality disorder (histrionic and dependent). Four patients were taking low-dose benzodiazepines (lorazepam, diazepam, and bromazepam), and 1 took zopiclone on an intermittent basis. Upon occurrence of an affective episode, patients were treated with antidepressant drugs (amitriptyline, clomipramine, or desipramine) or antipsychotic drugs (haloperidol or perphenazine) in addition to lithium. When the episode was judged to be remitted[21] and the patient was rated as "better" or "much better"[19,20] compared with the time of relapse, all patients were assessed by a clinical psychologist (C.R.) who did not take part in the treatment. She administered the Bech et al. version of the Brief Psychiatric Rating Scale (BPRS),[23] encompassing 18 items. Each item is rated on a 0- to 4-point scale, with specific anchor points.[23] Written informed consent was obtained after the procedures had been explained fully to the patients.

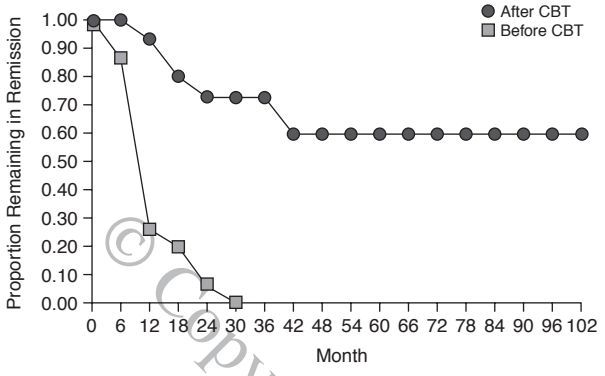
Patients were then assigned to CBT, which consisted of the following 3 main ingredients:

1. CBT of residual symptoms of bipolar disorder.[6,8] Both cognitive restructuring and exposure treatment for symptoms concerned with depression, anxiety, and irritability were used. This was the main focus of treatment.
2. Lifestyle modification.[8] Patients were instructed that bipolar disorder is also the consequence of a maladaptive lifestyle that does not take life stress, interpersonal friction, excessive work, or inadequate rest into proper account. Patients were instructed to modify their schedules, arrangements, and so on, accordingly. The strategies used technically derived from lifestyle modification approaches that were effective in clinical cardiological studies.[24]
3. Psychoeducation.[25] This aspect of treatment was based on a biopsychosocial model of bipolar disorder, with the aim of giving the patient and his or her family a practical approach for understanding and coping with the consequences of illness, with particular emphasis on symptom monitoring and detection of prodromal symptomatology.[12]

In all cases, CBT was started after stabilization but within 3 months from the relapse episode. CBT consisted of ten 30-minute sessions, once every other week. At the beginning of therapy, antidepressant drugs or antipsychotics were slowly tapered and discontinued.[6,8] All psychotherapies were conducted by 2 experienced therapists (G.A.F., G.B.), who also handled the pharmacologic management of patients. This latter was not different (including blood lithium levels) from the pharmacologic management before CBT. No psychotropic drugs aside from lithium were allowed during follow-up unless a relapse ensued. Three patients had previously undergone long-term (longer than 1 year) psychodynamic therapy. The 15 patients were reassessed with the BPRS after CBT by the same clinical psychologist who had performed the previous evaluations. The patients were then assessed every 6 months after treatment. Follow-up evaluations consisted of a brief update of clinical and medical status, including any treatment contacts or use of medications. Patients were instructed to call immediately if any new symptoms appeared and were guaranteed treatment. Relapse was defined as the occurrence of an RDC-defined episode of major depression or mania. All patients had a follow-up of at least 2 years.

Survival analysis[26] was used for time until relapse into major depression or mania. The following 7 risk factors were investigated as possible predictors of outcome: age, sex, BPRS scores before CBT, BPRS scores after CBT, duration of lithium treatment, duration of illness, and comorbidity. The Kaplan-Meier method was used for estimating survival curves. Since relapse was the event of interest, survival refers to relapse-free status. Each risk factor was dichotomized with the cutoff around the median for measurement type factors. The log-rank test was used to compare any 2 survival distributions in each of the

Figure 1. Proportion of Patients With Bipolar Disorder (N = 15) Remaining in Remission[a]



[a]Abbreviation: CBT = cognitive-behavioral treatment.

7 factors considered.[18] In addition, a 2-tailed, paired t test was used to compare variables before and after CBT.

RESULTS

Follow-up evaluations ranged from 24 to 108 months (median = 42 months). Five of the 15 patients had a relapse of bipolar disorder at some time during follow-up (in 4 cases, within 30 months). Figure 1 indicates the cumulative proportion remaining in remission after CBT plotted against time. For the sake of internal comparison, the cumulative proportion remaining in remission before CBT is also displayed. The mean ± SE survival time after CBT was 76 ± 13 months. Even a conservative comparison of the number of months to relapse before CBT and the number of months to relapse or last observation after CBT demonstrated a significantly higher ($t = 3.74$, $df = 14$, $p < .01$) number of months in the latter group (mean ± SD difference = 29.7 ± 30.6 months). None of the 7 risk factors considered attained statistical significance by log-rank test. However, in view of the small sample, for the BPRS score after CBT there was a statistical trend (log-rank test, $\chi^2 = 2.45$, $df = 1$, $p = .117$): the higher the BPRS score, the more likely was relapse to occur. Further, CBT was associated with a significant reduction ($t = 9.50$, $df = 14$, $p < .001$) in BPRS scores: from a mean ± SD of 13.3 ± 3.2 before treatment to 6.1 ± 2.8 after therapy. The 5 patients who relapsed were offered other pharmacologic interventions.

DISCUSSION

This study has obvious limitations because of its preliminary nature. First, it was an open clinical trial. The positive results that were obtained could be largely nonspecific. Second, it had a naturalistic design and involved a small number of patients. Finally, CBT was provided by 2 very experienced psychotherapists. The results might have been different with less experienced therapists. Nonetheless, the study provides important new clinical insights regarding the treatment of bipolar disorder.

CBT was associated with a significant reduction in residual symptomatology, as measured by BPRS scores. While all patients had a relapse within 30 months from starting lithium prophylaxis, a depressive or manic episode occurred in only 4 (27%) of 15 in the same time period after CBT. The results were thus clinically impressive. However, the 2 time periods are not directly comparable because of the unpredictable course of bipolar disorder. Only randomized controlled trials may shed some light on the effectiveness of CBT. As in unipolar depression,[6,8] an important therapeutic ingredient appeared to be abatement of residual symptomatology. Subsyndromal fluctuations have been found, in fact, to increase the risk of relapse in bipolar disorder.[27,28] Even though the main focus of treatment was on residual-symptom reduction, the specific contribution of the 3 therapeutic ingredients that were used cannot be ascertained. This contribution could be unraveled only by studies comparing the 3 CBT ingredients in a controlled way. Further, the role of nonspecific psychotherapeutic ingredients such as attention and increase in sense of control cannot be assessed by this type of study.[29,30] It is also conceivable, even though it is yet to be tested, that improved treatment protocols[31,32] and additional ingredients, such as enhancement of well-being,[33,34] may further improve the outcome.

The results of this preliminary investigation lend support to the literature on the role of CBT in bipolar disorder[3,4] and in management of drug-resistant unipolar depression.[35] If these results are replicated with larger samples and appropriate controls, they may challenge current trends in the treatment of bipolar disorder, which are based on complex pharmacologic augmentation strategies and neglect psychotherapeutic approaches. As in unipolar depression, the time may have come for switching gears: too often clinicians have partial therapeutic targets, neglect residual symptoms, and equate therapeutic response with full remission.[15,16]

The approach that was outlined in this article does not need to be limited to patients who relapse while on lithium prophylaxis. It is a 2-stage, sequential, intensive approach that is based on the fact that pharmacologic treatment of bipolar disorder is likely to leave a substantial amount of residual symptomatology in most of the patients.[15] Whether they reach the threshold of comorbidity, these residual symptoms hinder lasting recovery. They need to be assessed by a careful phenomenological interview, with particular reference to anxiety and irritability, which are an often overlooked component of bipolar illness.[15] The monitoring that is part of CBT offers a unique opportunity to observe (and challenge) what the patient regards as "normal" in his or her lifestyle and the effects

of tapering adjunctive medication when judged to be feasible. It is for this reason that medication is tapered during CBT and not afterward.[6,8,35] A 10-session format (1 session every other week) may be sufficient for addressing key issues concerned with lifestyle modification, psychoeducation, and changing maladaptive views and behavior.

The results should alert the clinician to include cognitive-behavioral treatment in the therapeutic options of bipolar disorder, before venturing into complex pharmacologic strategies. Reduction of residual symptoms and improved functioning may in fact add to pharmacologic tools in preventing relapse.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Valium and others), haloperidol (Haldol and others), lorazepam (Ativan and others), perphenazine (Trilafon and others).

REFERENCES

1. Solomon DA, Keitner GI, Miller IW, et al. Course of illness and maintenance treatments for patients with bipolar disorder. J Clin Psychiatry 1995; 56:5–13
2. Licht RW. Drug treatment of mania: a critical review. Acta Psychiatr Scand 1998;97:387–397
3. Scott J. Psychotherapy for bipolar disorder. Br J Psychiatry 1995;167: 581–588
4. Callahan AM, Bauer MS. Psychosocial interventions for bipolar disorder. Psychiatr Clin North Am 1999;22:675–688
5. Antonuccio DO, Danton WG, De Nelsky GY, et al. Raising questions about antidepressants. Psychother Psychosom 1999;68:3–14
6. Fava GA, Grandi S, Zielezny M, et al. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. Am J Psychiatry 1996;153:945–947
7. Blackburn M, Moore RG. Controlled acute and follow-up trial of cognitive therapy in outpatients with recurrent depression. Br J Psychiatry 1997; 171:328–334
8. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy. Arch Gen Psychiatry 1998;55:816–820
9. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. Arch Gen Psychiatry 1999;56:829–835
10. Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. J Consult Clin Psychol 1984;52: 873–878
11. Frank E, Hlastala S, Ritenour A, et al. Inducing lifestyle regularity in recovering bipolar disorder patients. Biol Psychiatry 1997;41:1165–1173
12. Perry A, Tarrier N, Morriss R, et al. Randomized controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 1999;318:149–153
13. Reinares M, Colom F, Martinez-Arán A, et al. Therapeutic interventions focused on the family of bipolar patients. Psychother Psychosom. In press
14. Weiss RD, Griffin ML, Greenfield SF, et al. Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. J Clin Psychiatry 2000;61:361–367
15. Fava GA. Subclinical symptoms in mood disorders. Psychol Med 1999; 29:47–61
16. Fava GA. Sequential treatment. Psychother Psychosom 1999;68:227–229
17. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837–844
18. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria for a Selected Group of Functional Disorders [Updated]. 3rd ed. New York, NY: Biometric Research, New York State Psychiatric Institute; 1989
19. Kellner R. Improvement criteria in drug trials with neurotic patients. Psychol Med 1972;2:73–80
20. Sonino N, Boscaro M, Fallo F, et al. A clinical index for rating severity in Cushing's syndrome. Psychother Psychosom 2000;69:216–220
21. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry 1991;48:851–855
22. Goldthorpe J, Hope K. The Social Grading of Occupations. Oxford, England: Oxford University Press; 1974
23. Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia, with corresponding DSM-III syndromes. Acta Psychiatr Scand 1986;73(suppl 326):1–37
24. Littman AB. Review of psychosomatic aspects of cardiovascular disease. Psychother Psychosom 1993;60:149–167
25. Jacobson JE. The hypomanic alert. Am J Psychiatry 1965;125:295–299
26. Lee ET. Statistical Methods for Survival Data Analysis. 2nd ed. New York, NY: Wiley; 1992
27. Keller MB, Lavori PW, Kane JM, et al. Subsyndromal symptoms in bipolar disorder. Arch Gen Psychiatry 1992;49:371–376
28. Benazzi F. Prevalence and clinical correlates of residual depressive symptoms in bipolar II disorder. Psychother Psychosom 2001;70:232–238
29. Marks IM. Is a paradigm shift occurring in brief psychological treatments? Psychother Psychosom 1999;68:169–170
30. Fava GA, Sonino N. Psychosomatic medicine. Psychother Psychosom 2000;69:184–191
31. Ramirez-Basco M, Rush AJ. Cognitive Behavioral Therapy for Bipolar Disorder. New York, NY: Guilford Press; 1996
32. Jarrett RB, Kraft D, Schaffer M, et al. Reducing relapse in depressed outpatients with atypical features. Psychother Psychosom 2000;69:232–239
33. Fava GA. Well-being therapy. Psychother Psychosom 1999;68:171–179
34. Ryff CD, Singer BH. Biopsychosocial challenges of the new millennium. Psychother Psychosom 2000;69:170–177
35. Fava GA, Savron G, Grandi S, et al. Cognitive-behavioral management of drug-resistant major depressive disorder. J Clin Psychiatry 1997;58: 278–282