

# Prevention of Recurrent Depression With Cognitive Behavioral Therapy: Preliminary Findings

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ABSTRACT

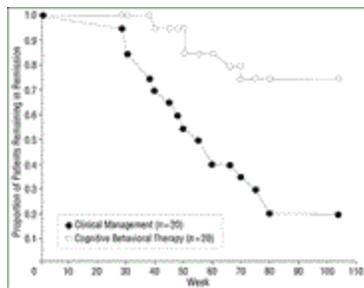
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**Background** Cognitive behavioral treatment (CBT) of residual symptoms after successful pharmacotherapy yielded a substantially lower relapse rate than did clinical management in patients with primary major depressive disorders. The aim of this study was to test the effectiveness of this approach in patients with recurrent depression ( $\geq 3$  episodes of depression).

**Methods** Forty patients with recurrent major depression who had been successfully treated with antidepressant drugs were randomly assigned to either CBT of residual symptoms (supplemented by lifestyle modification and well-being therapy) or clinical management. In both groups, during the 20-week experiment, antidepressant drug administration was tapered and discontinued. Residual symptoms were measured with a modified version of the Paykel Clinical Interview for Depression. Two-year follow-up was undertaken, during which no antidepressant drugs were used unless a relapse ensued.

**Results** The CBT group had a significantly lower level of residual symptoms after discontinuation of drug therapy compared with the clinical management group. At 2-year follow-up, CBT also resulted in a lower relapse rate (25%) than did clinical management (80%). This difference attained statistical significance by survival analysis.

**Conclusions** These results challenge the assumption that long-term drug treatment is the only tool to prevent relapse in patients with recurrent depression. Although maintenance pharmacotherapy seems to be necessary in some patients, CBT offers a viable alternative for other patients. Amelioration of residual symptoms may reduce the risk of relapse in depressed patients by affecting the progression of residual symptoms to prodromes of relapse.



## Figures in this Article

THE CHRONIC and recurrent nature of major depressive disorders is getting increasing attention.<sup>1 - 2</sup> The development of improved maintenance treatment strategies for depressed patients with a history of recurrent episodes has thus become a crucial clinical and research issue.<sup>3 - 4</sup> Substantial evidence supports the efficacy of long-term antidepressant medication use in patients with recurrent depression.<sup>3 - 4</sup> In particular, Frank et al<sup>5</sup> conducted a randomized 3-year maintenance trial in 128 patients with recurrent depression who had responded to combined short-term and continuation treatment with imipramine hydrochloride and interpersonal psychotherapy. A 5-cell design was used to determine whether imipramine therapy, placebo, and interpersonal psychotherapy could play a significant role in the prevention of recurrence. Use of imipramine hydrochloride, at an average dosage of 200 mg/d, provided the strongest prophylactic effect, whereas monthly interpersonal psychotherapy displayed a modest protective effect, although the latter was superior to placebo<sup>5</sup> and was more pronounced when the psychotherapy was of higher quality.<sup>6 - 7</sup> Extension of treatment with imipramine or placebo provided additional evidence for the prophylactic effect of drug treatment.<sup>8</sup> The clinical consequence of this important investigation is that patients with recurrent depression merit continued antidepressant drug prophylaxis for at least 5 years, although psychological therapies also were useful.<sup>6 - 7</sup>

Indeed, in a recent study,<sup>9</sup> 75 patients with recurrent depression were allocated to 3 groups: short-term and maintenance (2 years) treatment with antidepressant drugs, cognitive behavioral treatment (CBT) in the short-term and maintenance phases, and antidepressant use in the short-term phase and CBT for maintenance. Cognitive therapy displayed a similar prophylactic effect to maintenance medication.<sup>9</sup>

The criterion for recurrent depression (at least 1 previous episode of depression) was different, however, from that endorsed by Frank et al<sup>5</sup> ( $\geq 3$  episodes of unipolar depression, with the immediately preceding episode being no more than 2

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years before the onset of the present episode). It is difficult to know, thus, whether the cognitive approach would be effective also in a patient population characterized by a more severe course of illness.<sup>5</sup>

In earlier studies,<sup>10 - 11</sup> an alternative treatment strategy for decreasing the relapse rate of major depression was developed. This strategy is based on the fact that the presence of residual symptoms after completion of drug or psychotherapeutic treatment has been correlated with poor long-term outcome<sup>1</sup> and that some residual symptoms of major depression may progress to prodromal symptoms of relapse.<sup>12</sup> In those studies,<sup>10 - 11</sup> 40 patients with primary major depressive disorder who had been successfully treated with antidepressant drugs were randomly assigned to either CBT of residual symptoms or standard clinical management (CM).<sup>10</sup> In both types of treatment, antidepressant drugs were gradually tapered and discontinued. The CBT group had a significantly lower level of residual symptoms after discontinuation of drug therapy than the CM group. Cognitive behavioral treatment also resulted in a significantly lower rate of relapse (35%) at 4-year follow-up than did CM (70%).<sup>11</sup>

The purpose of this study was to apply this therapeutic approach to a sample of depressed patients, whose clinical features matched those in the study by Frank et al<sup>5</sup> on recurrent depression, and to compare the effectiveness of this approach with that of standard CM without the use of CBT. In both types of treatment, antidepressant drug use was gradually tapered and discontinued. In view of the considerable clinical challenge, CBT of residual symptoms was supplemented by relapse preventive strategies.

## PATIENTS AND METHODS

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### PATIENTS

Forty-five consecutive outpatients satisfying the criteria described below who had been referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine, Bologna, Italy, were enrolled in the study. The patients' diagnoses were established by the consensus of a psychiatrist (G.A.F.) and a clinical psychologist (C.R.) independently using the Schedule for Affective Disorders and Schizophrenia.<sup>13</sup> Patients had to meet the following criteria: (1) a current diagnosis of major depressive disorder according to the Research Diagnostic Criteria for a Selected Group of Functional Disorders<sup>14</sup>; (2) 3 or more episodes of depression, with the immediately preceding episode being no more than 2

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years before the onset of the present episode<sup>5</sup>; (3) a minimum 10-week remission according to Research Diagnostic Criteria ( $\leq 2$  symptoms present to no more than a mild degree with absence of functional impairment) between the index episode and the immediately preceding episode<sup>5</sup>; (4) a minimum global severity score of 7 for the current episode of depression<sup>15</sup>; (5) no history of manic, hypomanic, or cyclothymic features; (6) no history of active drug or alcohol abuse or dependence or of personality disorder according to DSM-IV criteria<sup>16</sup>; (7) no history of antecedent dysthymia; (8) no active medical illness; and (9) successful response to antidepressant drugs administered by 2

psychiatrists (S.G. and S.C.) according to a standardized protocol.<sup>17</sup> The latter protocol involved the use of tricyclic antidepressant drugs, with gradual increases in dosages. Patients who could not tolerate tricyclic antidepressant drugs were switched to selective serotonin reuptake inhibitors (Table 1).

Table 1. Sociodemographic and Clinical Characteristics of Patients Assigned to Cognitive Behavioral Treatment (CBT) of Residual Symptoms or Clinical Management (CM)\*

Characteristic	CBT Group (n=25)	CM Group (n=20)
Age at entry (M)	45.1 (12.3)	46.7 (10.7)
Sex, male/female	16/9	14/6
Marital status, married/unmarried	16/9	14/6
Single (last, middle, upper/middle)	16/9	14/6
Location of origin, km	88.17 (5)	89.9 (4.6)
No. of previous depressive episodes	2.9 (2.5)	3.2 (2.6)
Comorbidity		
Generalized anxiety disorder	0	4
Agoraphobia	0	0
Social phobia	0	7
Treatment of acute depression		
Amitriptyline hydrochloride, 100-200 mg/d	7	7
Imipramine hydrochloride, 100-200 mg/d	7	6
Desipramine hydrochloride, 100-200 mg/d	0	0
Nortriptyline, 25-40 mg/d	0	0
Sertraline hydrochloride, 100 mg/d	1	0
Residual symptoms		
Clonidine, 20 mg/d	0	1
Clonazepam, 1 mg/d	0	1
Fluphenazine, 20 mg/d	0	1
Fluoxetine hydrochloride, 75 mg/d	0	1
Sertraline, 50 mg/d	0	0
Venlafaxine, 3 mg/d	0	0
Number of treatments, n	19.4 (3.8)	15.8 (3.7)

\*Data are given as mean (SD) and number of patients.  
 †According to the classification of complications by Gattafioro and Ruggi.<sup>18</sup>

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After drug treatment, all patients were assessed by the same psychologist (C.R.) who had evaluated them on intake but who did not take part in the treatment. Only patients rated as "better" or "much better" according to a global scale of improvement<sup>15</sup> and as being in full remission<sup>19</sup> were included in the study. Patients also had to show no evidence of depressed mood after treatment according to a modified version of the Paykel Clinical Interview for Depression (CID).<sup>20</sup> Patients fit the criteria for stage 3 (the residual phase) of unipolar depression according to a staging system developed previously.<sup>21</sup> Written informed consent was secured from all patients.

All patients were treated for 3 to 5 months with full doses of antidepressant drugs (Table 1), after which the modified version of the CID was administered by the clinical psychologist. This interview covered 19 symptom areas, as described in detail elsewhere.<sup>10</sup> Each item is rated on a 1- to 7-point scale, with 1 indicating absence of symptoms and 7, very incapacitating symptoms. The scale includes a wider range of symptoms (such as irritability and phobic anxiety) compared with other scales and is particularly suitable for assessing subclinical symptoms of affective disorders,<sup>22 - 27</sup> also in view of its capacity to measure small increments or small changes near the normal end of the spectrum.<sup>10, 22</sup> Furthermore, it has been fully and independently validated for Italian populations.<sup>24 - 26, 28 - 31</sup>

## TREATMENT

After assessment with the CID, the 45 patients were randomly assigned to 1 of 2 treatment groups: (1) pharmacotherapy and CBT or (2) pharmacotherapy and CM. In both groups, treatment consisted of ten 30-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week, and then the drugs were withdrawn completely (in the last 2 sessions, all patients were drug free). Discontinuation of antidepressant drug

use was not feasible for 5 patients (3 in the CBT group and 2 in the CM group), and they were excluded from the study at that point. The same psychiatrist (G.A.F.) performed all treatments in both groups.

Cognitive behavioral treatment consisted of the following 3 main ingredients: (1) CBT of residual symptoms of major depression.<sup>10,32</sup> Cognitive therapy was conducted as described by Beck et al.<sup>33-34</sup> The psychiatrist (G.A.F.), an experienced therapist, used strategies and techniques designed to help depressed patients correct their distorted views and maladaptive beliefs, particularly regarding symptoms concerned with anxiety and irritability, which constitute the bulk of residual symptoms in patients with depression.<sup>10</sup> Whenever appropriate, as in the case of residual symptoms related to anxiety, exposure strategies were planned with the patient,<sup>35</sup> eg, in the case of exposure to phobic external cues in agoraphobia or social phobia.<sup>25</sup> (2) Lifestyle modification. Patients were instructed that depression is merely the consequence of a maladaptive lifestyle, which does not take life stress, interpersonal friction, excessive work, and inadequate rest into proper account. Antidepressant drugs restore normal mood, but relapse may ensue if inappropriate lifestyle behaviors are continued after drug withdrawal. Patients were encouraged to modify their schedules, arrangements, etc, accordingly. The strategies used technically derived from lifestyle modification approaches that were effective in clinical cardiological studies.<sup>36</sup> (3) Well-being therapy. In the last 2 or 3 sessions, a psychotherapeutic strategy for enhancing well-being<sup>37</sup> was used. The technique is aimed at changing beliefs and attitudes detrimental to well-being, stimulating awareness of personal growth and recovery from affective illness, and reinforcing behavior promoting well-being.<sup>37</sup> It is based on Ryff and Singer's<sup>38</sup> conceptual model of well-being as the result of self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth.

Clinical management consisted of monitoring medication tapering, reviewing the patient's clinical status, and providing the patient with support and advice if necessary. In CM, specific interventions such as exposure strategies, diary work, and cognitive restructuring were proscribed. The patient was encouraged to share the main events that took place in the previous 2 weeks. Treatment integrity was checked by submitting 8 randomly selected taped sessions (4 involving CBT and 4 involving CM) to 2 independent assessors, who correctly identified all sessions.

The 40 patients were reassessed with the CID, after treatment and while drug free, by the same clinical psychologist (C.R.) who had performed the previous evaluations and who was unaware of treatment assignment. The patients were then assessed 3, 6, 9, 12, 15, 18, 21, and 24 months after treatment. They were instructed to call immediately if any new symptoms appeared and were guaranteed a renewed course of antidepressant drug therapy only in the event of relapse. Follow-up evaluation consisted of a brief update of clinical and medical status, including any treatment contacts or use of medications. Relapse was defined as the occurrence of a Research Diagnostic Criteria–defined episode of major depression. During follow-up (unless a relapse occurred), no patient received additional antidepressant drug treatment or psychotherapeutic intervention.

## STATISTICAL METHODS

The 2-tailed t test and the  $\chi^2$  test were used to compare the 2 groups and to evaluate changes in residual symptoms within each of the treatment groups. Analysis of covariance was used for comparing the means of the residual symptoms scores, with adjustment for any difference in the first assessment. Survival analysis<sup>39</sup> was used for time until relapse into major depression. Six factors were investigated as possible predictors of outcome: assignment to CBT or CM, age, sex, duration of the depressive episode, number of previous depressive episodes, and number of residual symptoms regardless of—and before—treatment assignment. The Kaplan-Meier method was used for estimating survival curves. Because relapse was the event of interest, survival refers to relapse-free status. Each factor was dichotomized with a cutoff point around the median for measurement-type factors. The log-rank test and the Cox proportional hazards regression model were used to compare any 2 survival distributions for each of the 6 factors considered. For all tests performed, the significance level was .05, 2-tailed. Results are expressed as mean (SD).

## RESULTS

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Forty patients (20 in each group) completed the 20-week experiment. There were no significant differences between the groups in any of the variables listed in Table 1 or in severity of residual symptoms as measured by the CID (Table 2). Comorbidity was considered only if it persisted after treatment of acute depression and satisfied Research Diagnostic Criteria.<sup>14</sup> A few patients were taking benzodiazepines at low doses and continued to do so throughout the study.

Table Graphic Jump LocationTable 2. Scores at the Clinical Interview for Depression (CID) Before and After Cognitive Behavioral Treatment (CBT) of Residual Symptoms or Clinical Management (CM)

Table 2. Scores at the Clinical Interview for Depression (CID) Before and After Cognitive Behavioral Treatment (CBT) of Residual Symptoms or Clinical Management (CM)

Group	Week (SD) CID Score		F <sub>1,37</sub>
	Pretreatment	Posttreatment	
CBT	30.6 (5.3)	24.0 (3.8)	10.00*
CM	29.7 (29.0)	28.1 (4.1)	0.41

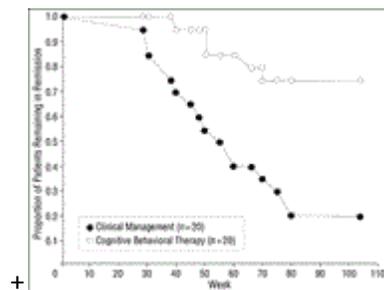
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Cognitive behavioral treatment induced significant improvement in residual symptoms, whereas there were no significant changes in the CM group. When the residual symptoms at the second assessment (after CBT or CM) of the groups were compared, with their initial measurements as covariates, a significant effect of CBT was found ( $F_{1,37}=31.54$ ,  $P<.001$ ).

During the 2-year follow-up, 5 patients (25%) in the CBT group and 16 patients (80%) in the CM group relapsed. The mean survival times were 91.8 (22.4) weeks for the CBT group and 62.2 (26.6) weeks for the CM group ( $t_{38}=3.81$ ,  $P<.001$ ). Of the 6 variables selected for survival analysis, only treatment assignment (Figure 1) attained statistical significance (log-rank test,  $\chi^2_{21}=11.98$ ;  $P<.001$ ). Using the Cox proportional hazards regression model, CBT was highly significant in delaying recurrence ( $P=.003$ ).

Proportions of depressed patients remaining in remission 2 years after cognitive behavioral therapy or clinical management.



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## COMMENT

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This study has obvious limitations because of its preliminary nature. First, it involved a small number of patients in the evaluation of long-term effects. Second, it had a seminaturalistic design because patients were initially treated with different types of antidepressant drugs, and there was no placebo-controlled withdrawal of medication. Finally, treatment was provided by only 1 psychiatrist with extensive experience in affective disorders and CBT. The results might have been different with multiple, less experienced therapists. Nonetheless, the study provides new, important clinical insights regarding the treatment of recurrent, unipolar, major depressive disorder.

Short-term CBT after successful antidepressant drug therapy had a substantial effect on relapse rate after discontinuation of antidepressant drugs. Patients who received CBT reported a substantially lower relapse rate (25%) during the 2-year follow-up than those assigned to CM (80%). This difference was significant in terms of comparison of mean survival time and survival analysis. The high relapse rate in the CM group is in line with the findings by Frank et al.<sup>5</sup> However, the patients assigned to CM in the study by Frank et al had a much shorter survival time than those in this investigation. This may be due to the very slow taper of antidepressant drugs that was endorsed by this study because this may affect outcome in mood disorders.<sup>40</sup> For 5 patients not included in the study, discontinuation of antidepressant drug therapy was not feasible, suggesting that the long-term outlook of recurrent depression is grim if patients are left without appropriate pharmacological support or have not received psychotherapy.

The results of this investigation lend support to the findings on the importance of psychotherapy in recurrent depression by Frank et al,<sup>5-6</sup> Spanier et al,<sup>7</sup> and Blackburn and Moore.<sup>9</sup> Results of the latter study,<sup>9</sup> which had less stringent criteria for recurrent major depression, suggest the possibility that both short-term and maintenance treatment with cognitive therapy may yield better results than pharmacotherapy followed by psychotherapy. This possibility, which is intriguing also in light of sensitization hypotheses related to antidepressant use,<sup>40-42</sup> should be explored with future investigations.

Cognitive behavioral treatment was effective in decreasing residual symptoms of depression, replicating previous results.<sup>1</sup> By deferring the psychotherapeutic intervention until after pharmacotherapy, we were able to provide a less intensive course of therapy (10 sessions) than is customary (eg, 16-20 sessions) because psychotherapy could be concentrated only on the symptoms that did not abate after pharmacotherapy. The fact that most of the residual symptoms of depression are also prodromal,<sup>10</sup> and that prodromal symptoms of relapse tend to mirror those of the initial episode,<sup>43</sup> explains the protective effect of this targeted treatment. Cognitive behavioral treatment may act on those residual symptoms of major depression that progress to become prodromal symptoms of relapse.<sup>12</sup> This may particularly apply to anxiety and irritability, which are prominent in the prodromal phase of depression,<sup>43 - 44</sup> may be covered by mood disturbances but are still present in the acute phase,<sup>45</sup> and are again a prominent feature of its residual phase.<sup>1</sup> Substantial comorbidity concerned with anxiety disorders was found in both groups. Compared with results of the previous investigation,<sup>10</sup> CBT was not targeted to decreasing residual symptoms only. Two additional ingredients were added in view of the clinical challenge represented by a patient population with recurrent depression. One was defined as lifestyle modification. Clinical experience has suggested that recovered depressed patients are often unaware of the long-term consequences of a maladaptive lifestyle, which does not take long-term, minor life stress; interpersonal friction; excessive work (particularly in male professionals 40-50 years old); and inadequate rest into proper account. Although lifestyle modification often has been incorporated in relapse preventive strategies in depression,<sup>46</sup> it has been specifically addressed mainly in the clinical cardiological arena (eg, modification of type A behavior after myocardial infarction).<sup>36</sup> We postulated that the presence of subsyndromal psychiatric symptoms<sup>47</sup> and long-term stress exposure may cause an allostatic load, ie, fluctuating and heightened neural or endocrine responses resulting from environmental challenge.<sup>48</sup> Furthermore, interventions that bring the person out of negative functioning (eg, exposure treatment in panic disorder with agoraphobia<sup>25</sup>) are one form of success, but facilitating progression toward restoration of the positive is another.<sup>38</sup> Ryff and Singer<sup>38</sup> suggested that the absence of well-being creates conditions of vulnerability to possible future adversities. A specific psychotherapeutic strategy that enhances well-being<sup>37</sup> was the third main ingredient of the CBT approach. It is not possible to know from our study whether these 2 additional ingredients (lifestyle modification with the ensuing sense of control and well-being therapy) yielded specific contributions to the clinical results obtained in our investigation. In an independent, preliminary, small-scale study,<sup>37</sup> a significant advantage of well-being therapy over standard CBT strategies in decreasing residual symptoms was observed. Further research should elucidate these points.

The results of studies by Frank et al,<sup>5 - 6</sup> Spanier et al,<sup>7</sup> and Kupfer et al<sup>8</sup> alerted the clinician to the need for providing maintenance therapies to patients with recurrent depression. Long-term, high-dose antidepressant drugs seemed to be the treatment of choice. This preliminary investigation, using a similar patient population, would challenge such a stance and confirm the unfavorable long-term outcome of patients not receiving pharmacotherapy or psychotherapy. Long-term maintenance drug treatment<sup>3 - 4</sup> or psychotherapy<sup>4</sup>,<sup>49</sup> may be necessary in several patients. However, our approach (CBT after pharmacotherapy) does not fall within the realm of maintenance strategies. It is a 2-stage, sequential, intensive approach that is based on the fact that treatment of depression by pharmacological means is likely to leave a substantial amount of residual symptoms in most patients.<sup>1</sup>

Whether they reach the threshold of comorbidity, these residual symptoms hinder lasting recovery. The findings of this preliminary investigation await further large-scale, independent replications. If the effectiveness of this approach is established, the result might have important implications for the clinician and for current conceptualizations of affective disorders.<sup>50</sup>

#### AUTHOR INFORMATION

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