

# Preventing Relapse/Recurrence in Recurrent Depression With Cognitive Therapy: A Randomized Controlled Trial

Claudi L. H. Bockting and Aart H. Schene  
University of Amsterdam

Philip Spinhoven  
Leiden University

Maarten W. J. Koeter, Luuk F. Wouters,  
Jochanan Huyser, and Jan H. Kamphuis  
University of Amsterdam

The DELTA Study Group

This article reports on the outcome of a randomized controlled trial of cognitive group therapy (CT) to prevent relapse/recurrence in a group of high-risk patients diagnosed with recurrent depression. Recurrently depressed patients ( $N = 187$ ) currently in remission following various types of treatment were randomized to treatment as usual, including continuation of pharmacotherapy, or to treatment as usual augmented with brief CT. Relapse/recurrence to major depression was assessed over 2 years. Augmenting treatment as usual with CT resulted in a significant protective effect, which intensified with the number of previous depressive episodes experienced. For patients with 5 or more previous episodes (41% of the sample), CT reduced relapse/recurrence from 72% to 46%. Our findings extend the accumulating evidence that cognitive interventions following remission can be useful in preventing relapse/recurrence in patients with recurrent depression.

**Keywords:** cognitive–behavior therapy, depression, prevention, relapse/recurrence, randomized controlled trial, antidepressant medication

The immense contribution of major depressive disorder to the total burden of disease is largely due to its highly recurrent nature (Murray & Lopez, 1997). In the absence of prophylactic treatment, the rate of recurrence rises to about 80% (Frank et al., 1990).

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Claudi L. H. Bockting, Aart H. Schene, Maarten W. J. Koeter, Luuk F. Wouters, and Jochanan Huyser, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; Philip Spinhoven, Department of Psychology and Department of Psychiatry, Leiden University, Leiden, the Netherlands; Jan H. Kamphuis, Faculty of Social and Behavioral Sciences, Department of Clinical Psychology, University of Amsterdam.

The following colleagues contributed to the DELTA (Depression Evaluation Longitudinal Therapy Assessment) Study: Hanneke Assies, Claudi L. H. Bockting, Jochanan Huyser, Maarten W. J. Koeter, Anja Lok, Guido Nabarro, Aart H. Schene, Philip Spinhoven, Ieke Visser, Elly Wekking, and Luuk F. Wouters.

This study was supported by grants from the Health Research Development Counsel, Department of Prevention Program, and the National Foundation for Mental Health.

We are most grateful to the participants of our study. In addition, we express our appreciation to the participating psychiatric sites for their recruitment efforts and to the following therapists for conducting the cognitive therapy: Willemijn Scholten, Swanny Wierenga, Mieke van der Rijken, Ruud Kol, Birgitta Schalken, Els Loeb, Vera van der Kraan, and Annemarie Fouwels. We also thank our interviewers and independent raters and specifically Irene Visch for assistance with data management and support. Finally, we thank Zindel Segal for reviewing this article.

Correspondence concerning this article should be addressed to Claudi L. H. Bockting, Academic Medical Center of the University of Amsterdam, Psychiatric Center, P2-221 Tafelbergweg 25 1105 BC Amsterdam, the Netherlands. E-mail: c.l.bockting@amc.uva.nl

Recidivism in (partly) treated populations varies as a function of setting. Reported rates are 50% over 20 years for the general population (Eaton et al., 1997), 40% over 10 years for patients in primary care (van Weel-Baumgarten, van den Bosch, Hekster, van den Hoogen, & Zitman, 2000), 40% in just 5 years for psychiatric outpatients (Van Londen, Molenaar, Goekekoop, Zwinderman, & Rooijmans, 1998), and 30% in 1 year for inpatients (Piccinelli & Wilkinson, 1994). Moreover, about 10% to 20% have a chronic depressive course (Angst, 1997). The number of previous episodes of depression was found to be one of the strongest predictors of relapse/recurrence in several studies (Kessing, Hansen, Andersen, & Angst, 2004).

Currently, maintenance antidepressant medication is the most commonly used preventive strategy (Geddes et al., 2003). However, this strategy has its limitations. Not all patients are willing to take this medication indefinitely, and it may be contraindicated because of somatic illness or side effects. Noncompliance with medication is yet another problem. The estimated prevalence of partial or total nonadherence to prescribed dosages is 15%–25% (Johnston, 1981; Klerman, 1990). Finally, the patient's protection from relapse/recurrence ceases on discontinuation of the antidepressant medication (Viguera, Baldessarini, & Friedberg, 1998).

Not only maintenance antidepressant medication but also cognitive therapy (CT) during the acute phase of depression appears to be effective in reducing subsequent relapse/recurrence rates. CT teaches patients to change depressogenic thoughts and assumptions and thereby presumably protects against relapse/recurrence. Studies that compared relapse/recurrence rates for patients who remitted on CT with patients who remitted on antidepressant medication and were withdrawn from medication found lower

relapse/recurrence rates following CT than following withdrawal from medication (Blackburn, Eunson, & Bishop, 1986; Evans et al., 1992; Shea et al., 1992; Simons, Murphy, Levine, & Wetzel, 1986). However, estimates of relapse/recurrence rates following CT during the acute phase of the depressive episode vary substantially, ranging from 74% down to 21% (over 2 years). Moreover, CT is not available to all patients during the acute phase of depression (Evans et al., 1992; Jarrett et al., 1998).

There is further encouraging evidence that psychological interventions are helpful in preventing relapse/recurrence (Blackburn & Moore, 1997; Fava, Grandi, Zielezny, Rafanelli, & Canestrari, 1996; Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998; Jarrett et al., 2001; Paykel et al., 1999; Teasdale et al., 2000). Jarrett et al. reported that continuation CT for patients remitted on CT significantly reduced relapse/recurrence in a patient group with a higher risk for MDD compared with no continuation therapy at all. Fava et al. (1996, 1998) and Teasdale et al. (2000) studied the combination of antidepressant medication for acute depression and psychological interventions following remission in recurrent depression. In both studies, psychological interventions significantly reduced relapse/recurrence in patients with at least three previous episodes while they were remitted on antidepressant medication. Moreover, Teasdale et al. (2000) noted a positive linear relationship between risk of relapse/recurrence and the number of previous episodes (three episodes or more) in a treatment as usual group, which was not observed in the intervention group. Ma and Teasdale (2004) replicated Teasdale et al.'s (2000) study, obtaining comparable findings. Of note, these studies excluded patients who were not off medication at entry and did not apply solely cognitive interventions. Fava et al. (1996, 1998) applied psychological interventions with some cognitive elements, whereas Teasdale et al. (2000) used cognitive interventions combined with mindfulness meditation.

In this study, we added eight sessions of group CT to treatment as usual (which included no treatment at all) of remitted patients with recurrent depression. To date, no randomized controlled trial had been conducted that (a) included patients with recurrent depression remitted on either medication and/or psychological therapy or no treatment at all; (b) placed no restrictions on the patient's medication status on entry to the study; (c) followed a preventive program consisting of exclusively cognitive interventions. Our primary hypothesis was that in remitted patients with recurrent depression, augmenting treatment as usual with CT would reduce and/or postpone relapse/recurrence. In view of Teasdale et al.'s (2000) findings, we expected this effect to be moderated by the number of previously experienced depressed episodes. As secondary hypotheses, we expected that augmenting treatment as usual with CT would also reduce the severity of a depressive episode, and the number of times a patient would have a relapse/recurrence. Finally, an exploratory aim of the study was to analyze differences in demographic, clinical and psychological characteristics between patients below or above the reversal point for number of previous depressive episodes needed for potential benefit from CT.

## Method

### Participants

To be eligible, patients had to meet the following criteria: (a) experienced at least two major depressive episodes in the previous 5 years, as

defined according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*; American Psychiatric Association, 1994) and assessed with the Structured Clinical Interview for *DSM-IV* (SCID; First, Gibbon, Spitzer, & Williams, 1996) administered by trained interviewers; (b) were currently in remission, according to *DSM-IV* criteria, for longer than 10 weeks and no longer than 2 years (i.e., a high-risk group of relapse/recurrence); and (c) obtained a current score of <10 on the Hamilton Rating Scale for Depression (M. Hamilton, 1960).

Exclusion criteria were current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent ECT, recent cognitive treatment or receiving CT at the start of the study, or current psychotherapy with a frequency of more than two times a month.

Participants were recruited from February 2000 through September 2000 at psychiatric centers (31% of the participants) and through media announcements (69% of the participants) in the Netherlands. After complete description of the study to the participants, written informed consent was obtained prior to randomization. The protocol was approved by the relevant institutional ethics review committees.

### Procedure

Patients were screened on inclusion and exclusion criteria with the telephone version of the SCID. The kappa for interrater agreement between the interviewers (psychologist/research assistants) regarding inclusion or exclusion criteria, as based on audiotaped interviews, was .77 (good/excellent agreement).

Patients meeting the inclusion criteria were randomly allocated to (a) treatment as usual or (b) treatment as usual plus a group CT. Randomization was performed using random permuted blocks and was stratified by study location and type of aftercare (family physician, psychiatric center, or no aftercare). Consecutively numbered, sealed envelopes contained computer-generated cards with concealed assignment codes. This procedure was organized and administered by an independent research associate.

### Treatment

**Cognitive therapy.** The CT in the experimental condition involved eight weekly 2-hr sessions. As in other prevention studies (Ma & Teasdale, 2004; Teasdale et al., 2000), a group format was chosen, for cost-effectiveness reasons but also because we were dealing with a patient group without current psychopathology. More specifically, we used a closed format with a mean membership of 8 (7 to 12 members). Each CT session followed a fixed structure, with agenda setting, review of homework, explanation of rationale of each session, and assignment of homework. Nine specifically trained psychologists (one of them was the principal investigator) delivered the prevention module; all were fully trained cognitive behavior therapists (minimum of 5 years of training). Before conducting the experimental groups, each therapist received 16 hr of additional specific training. A treatment manual (available on request from Claudi L. H. Bockting) was used and regular supervision was provided. All intervention group sessions were audiotaped to enable treatment integrity to be evaluated, using a checklist of all particular interventions. Any adherence or competence issues were resolved with the therapist prior to the subsequent session (in fact only one instance: an overlooked homework assignment).

The CT was focused mainly on identification and change of dysfunctional attitudes. Unlike CT for acutely depressed patients (Beck, 1987; Beck, Rush, Shaw, & Emery, 1979), the present module was not primarily directed toward modifying negative thoughts. Instead, it started with the identification of negative thoughts (Session 1) and dysfunctional attitudes, aided by a self-report questionnaire with examples of attitudes and techniques such as vertical arrow technique (Sessions 1–3) and then proceeded to focus on changing of these attitudes using different cognitive techniques, such as Socratic questioning and identification of positive attitudes (Sessions 3–7). Moreover, patients were encouraged to practice with alternative

attitudes (Sessions 6–8). In contrast with the preventive program of Teasdale et al. (2000), involving additional meditation interventions, solely cognitive interventions were used in the present study, concentrated on change of content. Several studies have found that in comparison with normal controls, acutely depressed patients have a tendency to retrieve more overgeneral autobiographical memories on a cue-word task (i.e., more generic memories of past events rather than specific memories referring to a particular event happening on a particular time and place; Goddard, Dritschel & Burton, 1996; Williams & Scott, 1988). This inability to retrieve specific memories from the past is associated with impaired problem-solving skills (i.e., Pollock & Williams, 2001), long-term course of depressive disorders (Peeters, Wessel, Merkellbach, & Boon-Vermeeren, 2002), and difficulties in recovering from depression (i.e., Brittlebank, Scott, Williams, & Ferrier, 1993). Unlike with traditional acute CT, patients were asked to keep a diary of positive experiences in order to enhance specific memories of positive experiences, instead of retaining overgeneral memories (Sessions 4–6). Further, specific relapse/recurrence prevention strategies were formulated in the last three sessions.

*Treatment as usual.* The treatment as usual involved "naturalistic" care, that is, standard treatment (including no treatment), as typically provided by the referring agencies. There was no restriction on the use of pharmacotherapy during the period from entry through follow-up. Patients agreed to report the use of medication and psychotherapy or counseling over the follow-up period.

### Study Measures

*Relapse/recurrence.* To assess relapse/recurrence, we used the Structured Clinical Interview for *DSM-IV* (SCID-I; First, Gibbon, Spitzer, & Williams, 1996). At baseline and at three follow-up assessments (3, 12, and 24 months), current and past depressive episodes were checked. To maintain the assessors' unawareness of treatment condition, we instructed participants not to reveal this information to the interviewers (psychologist/research assistants). All interviews were audiotaped. Two independent, experienced psychiatrists who were blind to treatment condition evaluated all 108 occasions in which participants met *DSM-IV* criteria for major depression. In cases of disagreement, the ratings of the psychiatrists were used for further analyses. The kappa for interrater agreement between the interviewers and the psychiatrist on categorization of a relapse/recurrence or no relapse/recurrence was .96, indicating high agreement. The severity of a relapse during follow-up period was assessed by the SCID (low, <6 symptoms; moderate, 6–7 symptoms; severe, 8–9 symptoms).

*Severity of depressive residual symptoms.* The 17-item Hamilton Rating Scale for Depression (HRSD; M. Hamilton, 1960) was used to assess patients' baseline levels of depressive symptomatology. The HRSD, administered by psychologist/research assistants who were blind to treatment condition, is a widely used semistructured clinical interview that covers a range of affective, behavioral, and biological symptoms and has acceptable psychometric properties (Rabkin & Klein, 1987). Scores can range from 0 to 52. Our four interviewers (psychologist/research assistants) provided a second rating of 17 interviews. The intraclass correlation (ICC) was .94, indicating high agreement.

*Dysfunctional attitudes.* Dysfunctional attitudes were assessed with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS-A; Douma, 1991; Weissman, 1979). The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck (1987) to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point scale ranging from totally agree to totally disagree. Scores range from 40 to 280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS was used, which has been shown to have good psychometric properties (Dozois, Covin, & Brinker, 2003).

*Stress: Daily hassles.* To measure daily hassles, we used the 114-item Everyday Problem Checklist (EPCL; Vingerhoets & van Tilburg, 1994). The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities. The EPCL assesses both the frequency and the level of subjective experi-

ence of the daily hassles and has good psychometric properties (Vingerhoets & van Tilburg, 1994).

*Stress: Life events.* The amount of negative life events experienced was measured with a 15-item checklist that covered different developmental periods, that is, childhood (0–15 years), adulthood (16 years through the start of the study), and recent (the 2-year period of the study). The checklist is based on the Negative Life Events Questionnaire (Kraaij & de Wilde, 2001). Events can involve the participant or significant others. A total score for each period is calculated by adding all negative life events experienced within that period. In previous studies (Garnefski, Kraaij, & Spinhoven, 2001; Kraaij & de Wilde, 2001) the predictive validity of the questionnaire proved to be good, as the number of negative life events predicted severity of depressive symptoms.

*Medication and other psychological treatment.* Every 3 months, information on antidepressant medication (type and dosage) and other psychological treatment (number of counseling or psychotherapy sessions) over the previous months was monitored with the Trimbos/Institute for Medical Technology Assessment (IMTA) Self-Report Questionnaire for Costs Associated With Psychiatric Illness (TICP; Hakkaart-van Roijen, van Straten, Donker, & Tiemens, 2002). After 2 years the interviewer collected information (one question) on the continuous use of medication over the follow-up period.

### Statistical Analysis

The present study had a power of .90 to detect a between-groups difference of 25% in relapse risk with a .05-level two-sided log-rank test for equality of survival curves (assessing the intention-to-treat group with at least 84 participants in each group and estimated relapse rates of .60 in the treatment as usual and .35 in the CT group, respectively).

To detect time to first relapse/recurrence, survival analyses were conducted in two steps. First, a proportional hazard approach to survival analysis (Cox regression) was used with relapse/recurrence as the dependent variable and treatment condition as independent variable. The analysis was performed with an intention-to-treat and a completers-analyses approach (including only patients who attended at least five CT sessions). In the second step, we fitted a proportional hazard model with relapse/recurrence as the dependent variable and treatment group, number of previous episodes, and the interaction of treatment condition with number of previous episodes, as independent variables. This model was used to estimate survival in the treatment as usual plus CT condition, stratified on the number of previous episodes. The estimated hazard ratios were defined relative to the baseline treatment as usual group with two previous major depressive episodes.

The endpoint for all survival analyses was relapse/recurrence. Patients who dropped out or had experienced no relapse/recurrence during the study period were considered censored. We used preliminary Cox regression analyses, including the stratification variables (i.e., site and type of treatment) to assess the individual confounding or modifying effect of each of these stratification variables on the treatment effect parameter. No effect of site or type of treatment on the effect of treatment condition on relapse/recurrence was observed. Consequently, further analyses were performed without these stratifying variables.

### Results

Patient flow through the trial is displayed in Figure 1. A total of 321 potential participants were contacted. Exclusions were because of (a) current depression/HRSD 9 ( $n = 48$ ), (b) fewer than two depressive episodes/last episode more than 2 years ago ( $n = 35$ ), (c) current or past psychoses ( $n = 15$ ), (d) substance abuse ( $n = 1$ ), (e) bipolar disorder ( $n = 13$ ), (f) predominant anxiety disorder ( $n = 1$ ), (g) current and frequent psychotherapy ( $n = 12$ ), and (h) other ( $n = 9$ ), for example, unwillingness to participate in a group or doubts about the time involved. All remaining 187

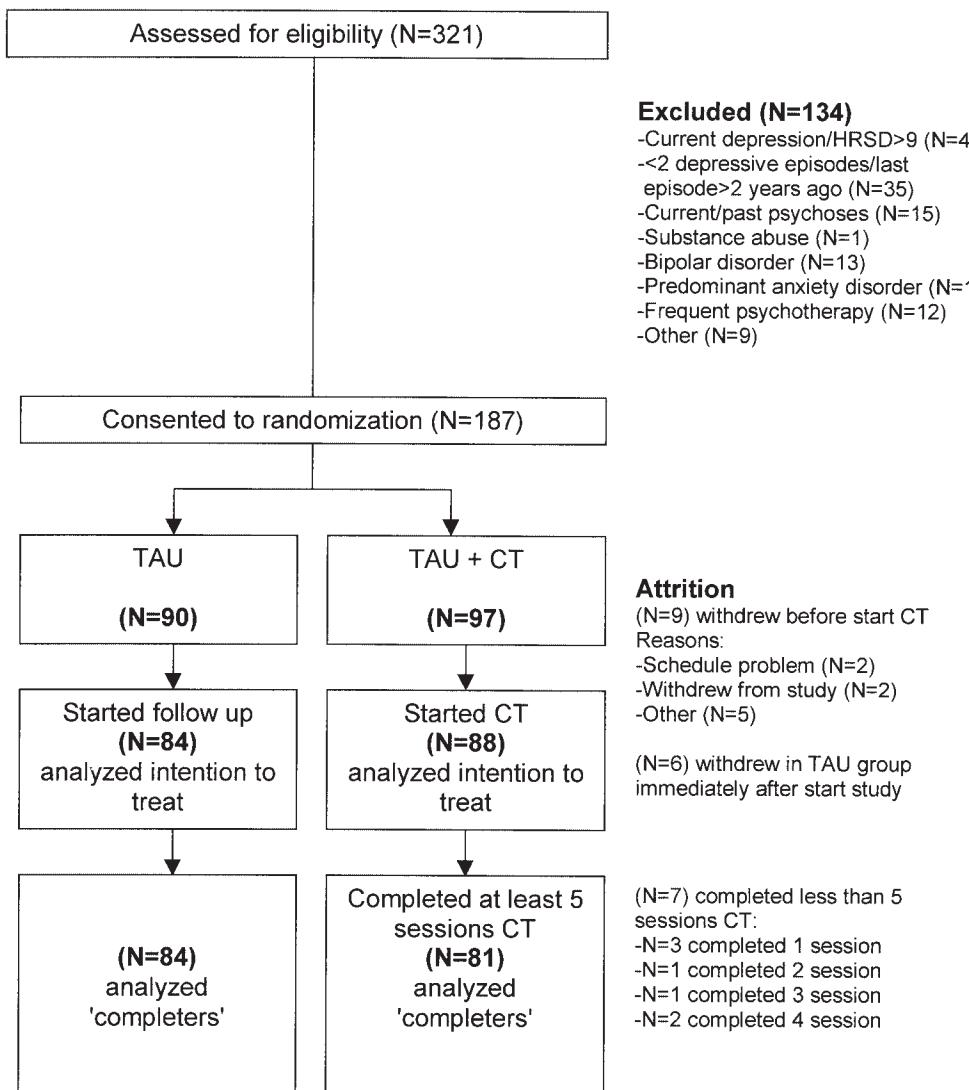


Figure 1. Flow diagram for patients through follow-up, including attrition. TAU = treatment as usual; CT = cognitive group therapy; HRSD = Hamilton Rating Scale for Depression.

patients fulfilled the inclusion criteria, and consented to randomization. For the intention-to-treat analyses we excluded 15 patients (dropouts), 9 from the CT group because they did not attend any sessions and 6 from the treatment as usual group because they dropped out from the study immediately. Dropouts ( $n = 15$ ) were slightly younger than the intention-to-treat group ( $N = 172$ ),  $t(170) = -2.25$ ,  $p = .03$  (dropout:  $M = 38.9$ ,  $SD = 10.6$ ; intention-to-treat group:  $M = 44.8$ ,  $SD = 9.5$ ) but equivalent on all other characteristics. For the completers-analyses, we excluded an extra 7 patients of the CT group because they attended fewer than five sessions. When these patients were compared with patients who attended at least five sessions ( $n = 81$ ), two significant differences emerged. Noncompleters were younger,  $t(170) = -2.85$ ,  $p = .01$  (<5 sessions:  $M = 36.9$ ,  $SD = 8.7$ ;  $\geq 5$  sessions:  $M = 46.6$ ,  $SD = 8.7$ ) and had a lower score on the Dysfunctional Attitude Scale,  $t(170) = -2.01$ ,  $p = .05$  (<5 sessions:  $M = 97$ ,  $SD = 21.2$ ;  $\geq 5$  sessions:  $M = 121.4$ ,  $SD = 29.1$ ).

### Patient Characteristics

Demographic and clinical characteristics of the intention-to-treat group are summarized in Table 1. Both groups were comparable on each of the variables (all  $p > .10$ ), except for number of previous episodes,  $\chi^2(1, N = 172) = 4.43$ ,  $p = .04$  (77/88 in the CT group had more than two previous episodes vs. 63/84 in the treatment as usual group); the subjective experience of daily hassles,  $t(170) = 2.27$ ,  $p = .03$  (for CT,  $M = 3.5$ ,  $SD = 1.0$ ; for treatment as usual,  $M = 3.8$ ,  $SD = 0.8$ ); and experience of negative life events before the 16th year,  $\chi^2(1, N = 172) = 6.74$ ,  $p < .01$  (84/88 in the CT group experienced negative life events vs. 70/84 in the treatment as usual group). To examine whether initial differences in these variables confounded or modified the effect of treatment condition, we first fitted a Cox regression model with treatment condition (C), potential confounder (PC), and the C  $\times$  PC interaction. When the interaction term was not

Table 1  
*Demographic and Clinical Characteristics*

Characteristic	Cognitive group therapy (n = 88)	Treatment as usual (n = 84)
Sex, female (%)	73	74
White <sup>a</sup> (%)	98	99
Age (years; $M \pm SD$ )	$45.9 \pm 9.1$	$43.4 \pm 9.8$
Years of education ( $M \pm SD$ )	$14.1 \pm 2.5$	$14.4 \pm 2.6$
Marital status (%)		
Single	19	29
Married/cohabiting	59	57
Divorced/widowed	22	12
Type of current treatment (%)		
Family physician	32	25
Psychiatric help	29	33
No treatment	39	42
Antidepressant medication (%)	52	50
HRSD-17 score ( $M \pm SD$ )	$3.8 \pm 2.8$	$3.7 \pm 2.9$
Previous episodes		
$\geq 2$ previous episodes (%)	88	75
Median previous episodes $\pm$ IQR	$4 \pm 3.8$	$3 \pm 3.8$
Age of first onset (year, $M \pm SD$ )	$28.7 \pm 12.6$	$28.1 \pm 12.5$
Social class <sup>b</sup> (%)		
Class 1	61	56
Class 2	30	29
Class 3	9	15

Note. HRSD-17 = 17-item Hamilton Rating Scale for Depression; IQR = interquartile range.

<sup>a</sup> Remainder of the sample was Asian and mixed (Asian/Black). <sup>b</sup> Example professions for Class 1, Class 2, and Class 3, respectively, are cleaner, nurse, and general manager.

significant, the treatment effect parameter in a model, with treatment condition as sole dependent variable, was compared with the value in a model with both treatment condition and potential confounder. In both the intention-to-treat analyses and the compliers analyses, this procedure was followed for each individual potential confounder, with no confounding effect; however, a modifying effect did appear to be present for the number of previous depressive episodes. Consequently, the number of previous episodes and the interaction of previous episodes with treatment condition were included as covariates in all of the analyses.

#### *Efficacy of Cognitive Therapy*

Cox regression intention-to-treat analyses, with previous episodes as covariate, revealed a significant interaction effect between previous episodes and treatment condition, *Wald statistic* (1,  $N = 172$ ) = 6.52,  $p = .01$ , hazard ratio = .57, 95% confidence interval (CI) = 0.37 to 0.88; for treatment condition effect, *Wald statistic* (1,  $N = 172$ ) = 1.20,  $p = .27$ , hazard ratio = 1.45, 95% CI = 0.75 to 2.81; for number of previous episodes effect, *Wald statistic* (1,  $N = 172$ ) = 11.09,  $p < .01$ , hazard ratio = 1.62, 95% CI = 1.22 to 2.16. Difference in outcome was dependent on the number of previous depressive episodes. Results are similar for the compliers group.

To compare survival in the two groups for the number of previous episodes, we used the fitted proportional hazard model to estimate survival in both groups stratified on number of previous episodes. The hazard ratios were defined relative to the baseline group (treatment as usual) with two previous episodes. An increase-

ing hazard ratio for the treatment as usual group indicates that the risk of relapse/recurrence increases with the number of previous episodes. Figure 2 shows that for patients in the treatment as usual group, their hazard increased (their survival prospect decreased) with the number of previous episodes (intention to treat). For patients in the CT group, the effect of the number of previous episodes is negated, and even slightly reversed, albeit not significantly. With an increasing number of previous episodes, the CT seemed to have an increasing protective effect.

According to this model, the reversal in condition effect was at three previous episodes. However, differences near this reversal point were small. They became statistically significant at five or more previous episodes. Dichotomization of the number of previous episodes in fewer than five versus five or more previous episodes revealed a significant interaction effect between treatment condition and previous episodes, *Wald statistic* (1,  $N = 172$ ) = 5.07,  $p = .02$ , hazard ratio = .40, 95% CI = 0.18 to 0.88; for treatment condition effect, *Wald statistic* (1,  $N = 172$ ) = 1.90,  $p = .66$ , hazard ratio = 1.12, 95% CI = .67 to 1.85; for fewer than five vs. five or more previous episodes effect, *Wald statistic* (1,  $N = 172$ ) = 3.12,  $p = .08$ , hazard ratio = 1.64, 95% CI = .95 to 2.84. Figure 3 shows the survival curves comparing relapse/recurrence in the CT group and the treatment as usual group for patients with fewer than five previous episodes ( $n = 101$ ; 63% for CT vs. 59% for treatment as usual) versus five or more previous episodes ( $n = 71$ ; 46% for CT vs. 72% for treatment as usual). This figure shows only small differences between treatment as usual and CT for the group of patients with fewer than five episodes ( $p = .71$ ). For patients with five or more previous episodes, CT significantly reduced relapse/recurrence ( $p = .01$ ).

Over the total study period of 24 months, the cumulative rate for relapse/recurrence for the 71 patients with five or more previous episodes rose for the treatment as usual group up to 72% (95% CI = 56% to 86%,  $n = 34$ ) compared with 46% for CT participants (95% CI = 30% to 62%,  $n = 37$ ), a 26% reduction in risk of relapse/recurrence in the CT group. The 26% difference in relapse/recurrence rates was achieved in the first 3 months and remained stable over the follow-up period. In 101 patients with fewer than five previous episodes, these figures were 59% (95% CI = 45% to 72%,  $n = 50$ ) for the treatment as usual group compared with 63% (95% CI = 49% to 75%,  $n = 50$ ) for CT participants.

#### *Secondary Outcome: Number of Times Relapse/Recurrence Occurred and Severity*

Secondary analyses were used to explore the effect of treatment on depression severity and number of times patients experienced a relapse/recurrence during the 2 years of follow-up. We used the general linear model univariate analysis of variance (ANOVA) approach, with depression severity as the dependent variable, and treatment condition, number of previous episodes (<5 vs.  $\geq 5$ ), and the interaction of treatment condition by number of previous episodes as the independent variables.

To compare the severity of relapse/recurrences, we computed the mean severity over all relapses (low, moderate, or severe relapse). The interaction of treatment condition and previous episodes was significant,  $F(1, 168) = 3.79$ ,  $MSE = 1.37$ ,  $p = .05$ . For

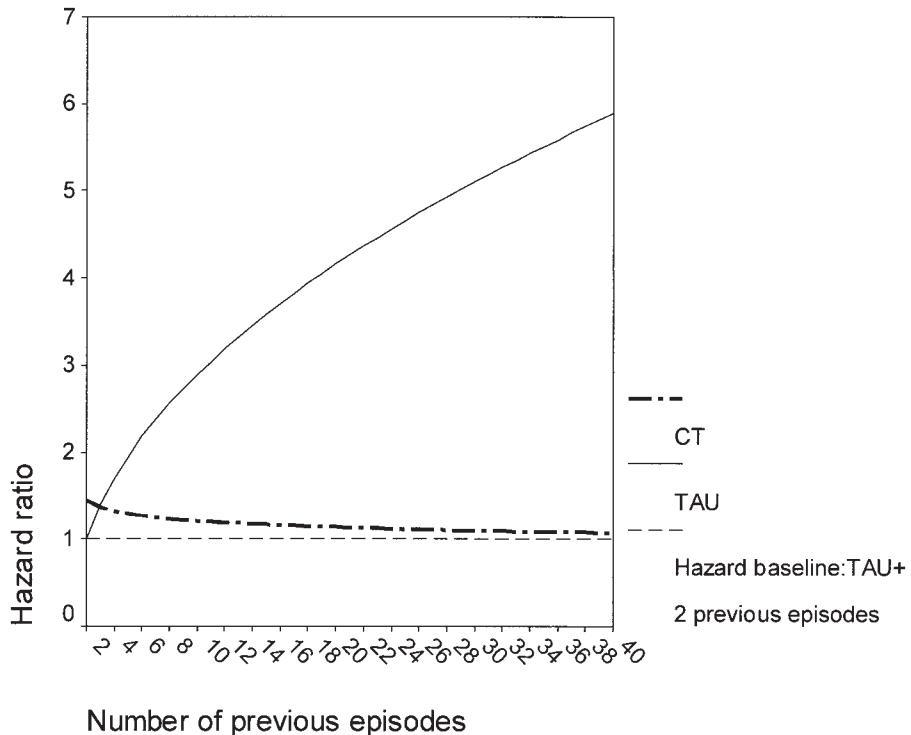


Figure 2. Hazard ratios of cognitive group therapy (CT) and treatment as usual (TAU);  $N = 172$ , intention to treat.

patients with five or more previous episodes, the mean severity of relapse/recurrence tended to be lower in the CT group than in the treatment as usual group ( $\geq 5$  previous episodes: for treatment as usual,  $M = 1.60$ ,  $SD = 1.10$ ; for CT,  $M = 0.95$ ,  $SD = 1.10$ ;  $< 5$  previous episodes: for treatment as usual,  $M = 1.34$ ,  $SD = 1.30$ ; for CT,  $M = 1.39$ ,  $SD = 1.15$ ). To compare the number of times a patient relapsed, we converted differences in follow-up time to number of relapses per 2 years at risk. The ANOVAs revealed a significant interaction between treatment condition and previous episodes,  $F(1, 166) = 3.94$ ,  $MSE = 1.04$ ,  $p = .05$ . The mean number of relapses/recurrences was less in the CT group than in the treatment as usual group in patients with five or more previous episodes ( $\geq 5$  previous episodes: for treatment as usual,  $M = 1.35$ ,  $SD = 1.10$ ; for CT,  $M = 0.78$ ,  $SD = 0.98$ ;  $< 5$  previous episodes: for treatment as usual,  $M = 0.94$ ,  $SD = 1.08$ ; for CT,  $M = 1.00$ ,  $SD = 0.95$ ).

#### Use of Medication and Other Treatment

To examine whether the reduction in relapse/recurrence in the experimental group was secondary to use of antidepressant medication or other psychological treatment, we compared the proportions of patients with fewer than five previous episodes and patients with five or more episodes in both conditions who had used such medication and other psychological treatment at any time over the follow-up. Table 2 summarizes the treatment of the last depressive episode before joining the study and treatment for depression over 2 years for the four groups. No significant differences were found between the four groups on all times in proportion of antidepressant medication use and other psychological

treatment: treatment of last depression,  $\chi^2(12, N = 164) = 10.21$ ,  $p = .60$ ; treatment during follow-up,  $\chi^2(12, N = 164) = 8.58$ ,  $p = .74$ . Selective serotonin reuptake inhibitors (SSRIs) were the most commonly prescribed antidepressants. Comparison of the dosage in milligrams of fluoxetine daily dose equivalents, at any time over the follow-up period, by ANOVA revealed no significant differences between the four groups (smallest  $p = .34$ ;  $\geq 5$  previous episodes: for CT,  $M = 12.1$ ,  $SD = 11.5$ ; for treatment as usual,  $M = 10.0$ ,  $SD = 11.1$ ;  $< 5$  previous episodes: for CT,  $M = 10.5$ ,  $SD = 10.5$ ; for treatment as usual,  $M = 12.0$ ,  $SD = 13.5$ ). In addition, we examined in both groups (fewer than 5 episodes and 5 or more episodes) whether the effect of treatment condition on relapse/recurrence was moderated by type of psychological aftercare (including no treatment at all) or by antidepressant medication during the follow-up period. Cox regression analyses were performed that included type of aftercare and its interaction with treatment condition. These analyses revealed no effect on relapse/recurrence of type of aftercare and its interaction with treatment condition; type of aftercare by treatment condition interaction:  $< 5$  previous episodes, *Wald statistic* (1,  $N = 97$  [4 missing]) = 0.92,  $p = .34$ ; hazard ratio = 0.57, 95% CI = 0.18 to 1.80;  $\geq 5$  previous episodes, *Wald statistic* (1,  $N = 67$  [4 missing]) = 0.62,  $p = .43$ , hazard ratio = 1.70, 95% CI = 0.46 to 6.31.

The effect of antidepressant medication was incorporated in the Cox regression model in two ways: (a) adequacy of medication at two assessments (6 months) before relapse/recurrence ( $< 20$ -mg fluoxetine equivalent vs.  $\geq 20$ -mg equivalent fluoxetine) and (b) mean equivalent dosage usage during follow-up and its interactions with treatment condition. These analyses

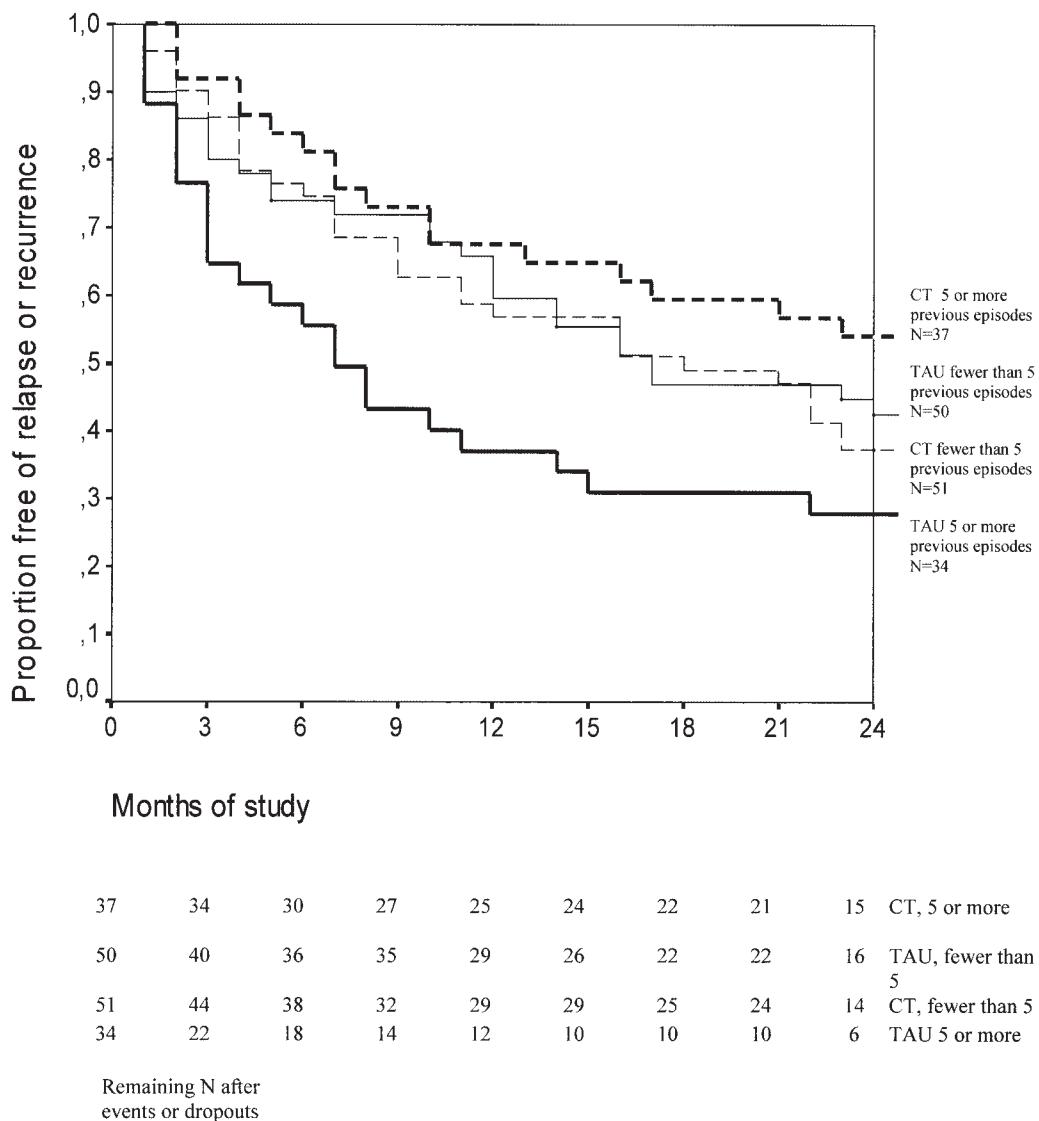


Figure 3. Relapse in patients with fewer than 5 previous episodes and patients with 5 or more previous episodes treated with cognitive group therapy (CT) or receiving treatment as usual (TAU).

showed no effect on relapse/recurrence for adequacy of medication before relapse/recurrence or for its interaction with treatment condition: for patients with  $<5$  previous episodes, *Wald statistic* (1,  $N = 93$  [8 missing]) = 1.16,  $p = .28$ , hazard ratio = .55, 95% CI = 0.18 to 1.64; for patients with  $\geq 5$  previous episodes, *Wald statistic* (1,  $N = 69$  [2 missing]) = 0.50,  $p = .48$ , hazard ratio = 1.61, 95% CI = 0.43 to 5.94. No effect on relapse/recurrence of mean equivalent dosage usage during follow-up or for its interaction with treatment condition was found: for patients with fewer than five previous episodes, *Wald statistic* (1,  $N = 96$  [5 missing]) = 1.44,  $p = .23$ , hazard ratio = 0.98, 95% CI = 0.94 to 1.02; for patients with  $\geq 5$  previous episodes, *Wald statistic* (1,  $N = 69$  [2 missing]) = 1.21,  $p = .27$ , hazard ratio = 1.03, 95% CI = 0.98 to 1.09. That is, the effect of CT seemed not to be moderated by type of aftercare or use of antidepressant medication.

#### Comparison of Patients With Fewer Than Five Previous Episodes Versus Patients With Five or More Previous Episodes

Exploratory analyses were performed to identify differences, at a .05 level, between patients with fewer than five previous episodes and patients with five or more episodes per condition on demographic, clinical, and psychological baseline characteristics. There were no statistically significant differences in these variables between the CT and treatment as usual conditions, either for patients with fewer than five previous episodes or for patients with five or more episodes.

Comparison of patients with fewer than five previous episodes with patients with five or more episodes revealed significant differences in age of onset, number of years since first depression, duration of remission and number of patients with a family mem-

Table 2

Treatment of Last Episode and Treatment for Depression From Other Sources Received by Patients in Treatment as Usual and Cognitive Group Therapy Over a 2-Year Period

Variable	Cognitive group therapy (n = 88)		Treatment as usual (n = 76) <sup>a</sup>	
	≥5 previous episodes (n = 37)	<5 previous episodes (n = 51)	≥5 previous episodes (n = 34)	<5 previous episodes (n = 50)
Treatment of last episode before study entry (%)				
Antidepressant medication total	70.3	78.5	66.6	76.0
No treatment	13.5	3.9	13.3	10.9
Antidepressant medication only	13.5	11.8	20.0	13.0
Psychotherapy/counseling only	10.8	17.6	6.7	10.9
Combination psychotherapy/counseling plus antidepressant medication	56.8	66.7	53.3	63.0
Other	5.4	0.0	6.7	2.2
Treatment during follow-up (%)				
Antidepressant medication total	64.8	68.6	73.4	64.1
No treatment	21.6	21.6	20.0	26.1
Antidepressant medication only	24.3	19.6	36.7	17.4
Psychotherapy/counseling only	10.8	9.8	6.7	13.0
Combination psychotherapy/counseling plus antidepressant medication	40.5	49.0	36.7	39.1
Other	1.1	2.7	0.0	4.3

<sup>a</sup> 8 patients in the treatment as usual condition dropped out; treatment of last episode and during follow-up is unknown.

ber with a psychiatric illness. As shown in Table 3, patients with five or more previous episodes experienced their first depressive episode at a younger age,  $t(170) = 6.83, p < .01$  ( $M = 21.5, SD = 11.8$  vs.  $M = 33.3, SD = 10.7$ ; the biserial correlation of age of onset with number of previous episodes, i.e.,  $\geq 5$  vs.  $<5$  previous episodes, was .59); experienced their first depression longer ago, unequal-variances  $t(120.70) = -9.68, p = .01$  ( $M = 24.6, SD = 11.2$  vs.  $M = 10.3, SD = 8.21$ ); fewer of the participants were more than 6 months in remission since their last episode,  $\chi^2(1, N = 172) = 6.13, p = .01$  (42% [30/71] were more than 6 months in remission vs. 61% [62/101]); and more of them had family members with a psychiatric illness,  $\chi^2(1, N = 157$  [15 missing]) =

6.36,  $p = .01$  (84% [53/63] among patients with  $\geq 5$  previous episodes vs. 66% [62/94] in the other group had a family member with a psychiatric illness).

To examine whether the significant effect of treatment condition by previous episodes interaction for relapse/recurrence was moderated by age of onset, we performed Cox regression analyses that included age of onset. These analyses were compared with the null model to determine their influence on relapse/recurrence over 24 months. No effect on relapse/recurrence was found for age of onset on the interaction of treatment with previous episodes, *Wald statistic* ( $1, N = 172$ ) = 6.96,  $p < .01$ , hazard ratio = .55, 95% CI = .35 to .86.

Table 3

Demographic, Clinical, and Psychological Characteristics: Patients With Fewer than Five Previous Episodes and Patients With Five or More Episodes

Variable	Patients with 5 or more previous episodes (n = 71)		Patients with fewer than 5 previous episodes (n = 101)		Statistical significance (p)
	CT (n = 37)	TAU (n = 34)	CT (n = 51)	TAU (n = 50)	
Age (years, $M \pm SD$ )	47.2 ± 8.9	44.9 ± 9.8	44.9 ± 9.2	42.4 ± 9.8	ns
Age of onset (years, $M \pm SD$ )	21.5 ± 11.1	22.1 ± 12.1	34.4 ± 10.6	32.3 ± 10.8	<.01 <sup>a</sup>
Years since first depression ( $M \pm SD$ )	26.2 ± 10.3	22.8 ± 12.1	10.5 ± 7.4	10.1 ± 9.1	<.01 <sup>a</sup>
More than 6 months in remission (%)	38 (14/37)	47 (16/34)	63 (32/51)	60 (30/50)	<.01 <sup>a</sup>
Antidepressant medication, last episode (%)	70 (26/37)	77 (26/34)	78 (40/51)	78 (39/50)	ns
Familial psychiatric disease <sup>b</sup> (%)	83 (30/36)	85 (23/27)	64 (32/50)	68 (30/44)	<.10 <sup>a</sup>
DAS-A score ( $M \pm SD$ )	120.20 ± 29.90	136.00 ± 38.20	120.50 ± 29.80	124.50 ± 35.30	ns
HRSD-17 score ( $M \pm SD$ )	3.77 ± 2.82	4.00 ± 3.08	4.00 ± 2.95	3.48 ± 2.78	ns
Number of life events <sup>c</sup> ( $M \pm SD$ )	6.81 ± 4.54	6.71 ± 5.57	7.41 ± 6.32	7.96 ± 7.58	ns
Number of daily hassles ( $M \pm SD$ )	3.10 ± 0.72	3.45 ± 0.70	3.24 ± 0.75	3.33 ± 0.63	ns

Note. CT = cognitive group therapy; TAU = treatment as usual; DAS-A = Dysfunctional Attitude Scale; HRSD-17 = Hamilton Rating Scale for Depression.

<sup>a</sup> Significant difference between patients  $\geq 5$  versus  $<5$  episodes. <sup>b</sup> Familial psychiatric disease of 15 patients is unknown. <sup>c</sup> Number of life events of 1 person is missing.

## Discussion

We studied a preventive program with exclusively cognitive interventions in patients with recurrent depression remitted on medication and/or psychological therapy or who received no treatment at all. Our findings show that augmenting treatment as usual, including no treatment, with CT resulted in a significant protective effect, which intensified with the number of previous depressive episodes experienced by the patient (a well-known predictor of relapse/recurrence).

The beneficial effect observed in the CT group could not be attributed to other psychological treatments or use of antidepressant medication. Although we cannot rule out that CT may have had a positive effect on compliance and/or the responsiveness to antidepressant medication or other psychological treatment, it seems more likely that medication and auxiliary psychological treatment contributed equally to the prevention of relapse/recurrence in both groups. More specifically, the present findings show that cognitive treatment significantly reduced relapse/recurrence for high-risk patients who experienced approximately five or more previous episodes (i.e., 41% of the sample) and were in remission following various treatments. Of the patients with five or more previous episodes over the preceding 2 years, 72% versus 46% respectively relapsed in the treatment as usual and CT groups. This implies that 3.8 patients must be treated with CT to prevent one patient from having a relapse/recurrence. Moreover, in the last group of patients, CT also reduced the number of times a patient had a relapse/recurrence and the severity of the depression. CT had no significant protective effect for those patients with two previous episodes over the preceding 2 years. However, this apparent indication of the number of episodes experienced for CT to be beneficial, should be interpreted with caution because of the modest sample size.

These findings replicate and extend the findings of Teasdale et al. (2000) and Ma and Teasdale (2004), in which a positive linear relationship was found between risk of relapse/recurrence and number of previous episodes in the treatment as usual group but not in the intervention group. We observed a similar association, albeit that the estimated number of previous depressive episodes needed to benefit from the cognitive intervention was higher in our study (i.e., five rather than three episodes). How is the differential effect to be explained? Segal, Teasdale, and colleagues (Segal, Williams, Teasdale, & Gemar, 1996; Segal, Williams, & Teasdale, 2002; Teasdale, Segal, & Williams, 1995) have proposed two explanations. First, they hypothesized that depressive thinking results from repeated associations between the depressed state and negative thinking patterns. The strengthening of these associations with repeated episodes is assumed to contribute to increased risk of relapse/recurrence following each subsequent episode. This observed greater risk of relapse/recurrence for three or more previous episodes is thought to be attributable to autonomous relapse/recurrence processes involving reactivation of depressogenic thinking patterns by dysphoria. With repeated experiences of episodes of major depression, less environmental stress is required to provoke relapse/recurrence (Post, 1992). The prophylactic effect of the authors' interventions was hypothesized to arise from disruption of those processes at times of potential relapse/recurrence by reduction of the extent to which patterns of depressive thinking reactivated by sad moods could feed factors responsible for relapse/recurrence (Segal et al., 2002; Teasdale et al., 2000). The

second explanation offered by Segal and colleagues for the differential preventive effect of the cognitive intervention is that there might be different types of depression. Some depressions may be closely associated with reaction to life events, possibly reflecting the group of patients with fewer previous episodes in our study. The other type of depression may be brought about by rumination, reflecting the group of patients with a high number of episodes. Ma and Teasdale (2004) found in their study that mindfulness-based CT is effective in reducing autonomous, presumably internally provoked, relapse/recurrence but quite ineffective in reducing relapse/recurrence associated with severe life events.

Consistent with the findings of Teasdale et al. (2000) and Ma and Teasdale (2004), we found that, besides a longer history of illness and a shorter duration of remission of the last episode, the age of onset in the group of patients with five or more previous episodes was significantly lower (11–12 years), also suggesting distinct subpopulations. The fact that this group consisted of relatively more patients with a family member with a psychiatric illness, might indicate (more) endogenicity. It may be that the group of patients characterized by a lower age of onset and more previous episodes suffers from a more biological subtype of depression, with a weaker link between stress and relapse/recurrence. Although we did not find any difference between the two groups on daily hassles and life events, we cannot rule out differences in relation to relapse/recurrence, as we did not have the exact timing of life events to verify that stress occurred prior to depressive relapse/recurrence. Moreover we did not find any difference between the two groups on reported adverse childhood experience, contrary to the findings of Ma and Teasdale.

Alternatively, we suggest that CT may protect against relapse/recurrence in patients with more episodes by reducing residual symptoms. Residual symptoms in remitted patients are a known predictor of relapse/recurrence (e.g., Fava, 1999; Thase et al., 1992). Despite the fact that scores on the HRSD were less than 10 at entry to the study, which is similar to observed levels of remitted patients at entry to the studies of Teasdale et al. (2000) and Ma and Teasdale (2004), it is possible that our CT intervention inadvertently reduced the level of residual depressive symptoms, whereas this risk factor for relapse/recurrence was not affected by treatment as usual in the high-risk control group. This line of reasoning may imply that the acute treatment was insufficient in the high-risk control group.

We are not aware of any other study that included patients with recurrent depression remitted on medication and/or psychological therapy or with no treatment at all, without restrictions on medication status at entry to the study and using a preventive program with exclusively cognitive interventions, as delivered by several therapists. As such, this study was designed to maximize external validity, which suggests good generalizability of the findings. In contrast to other studies, treatment of the last episode in this study was not only by medication (Fava et al., 1996, 1998) or exclusively by CT (Jarrett et al., 2001) but also included other psychotherapies, psychiatric help, counseling, or no treatment at all. Moreover, there were no restrictions in using medication at entry to the study. Fava et al. (1996, 1998) and Teasdale et al. (2000) only included patients who managed to stay well while they were off medication at entry to the study. This difference in patient population may explain why the number of previously experienced depressive episodes needed for a protective effect from the cognitive intervention was higher in our study.

Further, this study differs from other studies with respect to the preventive interventions used (Fava et al., 1996, 1998; Ma & Teasdale, 2004; Paykel et al., 1999; Teasdale et al., 2000, 2001). Other CT programs state that extra interventions in addition to cognitive interventions are essential, as for example in Teasdale et al.'s (2000) and Ma and Teasdale's (2004) study of mindfulness-based CT with meditation interventions in which distancing/decentering is thought to be an essential ingredient (Teasdale et al., 2001). However, it is conceivable that cognitive interventions alone, as used in this study, also lead to distancing of thoughts and thereby reduce the extent to which patterns of depressive thinking are reactivated by sad moods. The final common pathway for different forms of preventive therapies may be teaching patients to focus on their subjective experiences and cognitions without trying to judge, avoid, or suppress them. Further process studies are needed to validate the claim that some interventions such as meditation training are more suitable and effective in achieving this goal than other cognitive interventions, which also instruct patients to monitor and investigate their cognitions in a nonjudgmental way.

Despite these generally positive findings, there were several limitations that need to be acknowledged. A limitation of the present design is that there was no control for nonspecific factors, such as extra attention and group participation. Moreover, sample sizes decreased over time. Although the attrition rate did not exceed rates reported in similar studies, these findings require replication. A further limitation concerns our antidepressant medication data. Every 3 months during follow-up, we gathered information on use and dosage reflecting the prior month, which possibly underestimates fluctuations in use. Another issue is that it is unclear whether the beneficial effect was attributable to specific skills in CT or to a total package of the treatment as usual in combination with this CT. Future research is necessary to control for these nonspecific factors.

In sum, our findings extend the evidence that CT after remission, either alone or in combination with antidepressant medication or other psychological interventions, is effective in preventing relapse/recurrence in a high-risk group with a common chronic and disabling disease (Blackburn & Moore, 1997; Fava et al., 1996, 1998; Jarrett et al., 2001; Paykel et al., 1999; Teasdale et al., 2000). We believe that our sample reflects clinical practice, including primary care and specialty care. Adding this brief group CT to regular care or to no care at all, may provide us with an important tool to protect a high-risk group from relapse/recurrence, at relatively low cost and time investment. In accordance with the findings in Teasdale's study, we found that the difference in relapse/recurrence rates was already achieved in the first 3 months. Replication of this early preventive intervention effect and elucidation of the underlying mechanisms in larger patient samples is necessary.

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Received January 30, 2004

Revision received November 1, 2004

Accepted November 17, 2004 ■