ORIGINAL ARTICLE

Prevention of Relapse in Residual Depression by Cognitive Therapy

A Controlled Trial

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Background: Previous studies indicate that depressed patients with partial remission and residual symptoms following antidepressant treatment are common and have high rates of relapse. There is evidence that cognitive therapy may reduce relapse rates in depression.

Methods: One hundred fifty-eight patients with recent major depression, partially remitted with antidepressant treatment (mean daily doses equivalent to 185 mg of amitriptyline or 33 mg of fluoxetine) but with residual symptoms of 2 to 18 months' duration, were included in a controlled trial. Subjects were randomized to receive clinical management alone or clinical management plus cognitive therapy for 16 sessions during 20 weeks, with 2 subsequent booster sessions. Subjects were assessed regularly throughout the 20 weeks' treatment and for a further year. They received continuation and maintenance antidepressants at the same dose throughout.

Results: Cognitive therapy reduced relapse rates for acute major depression and persistent severe residual symptoms, in both intention to treat and treated per protocol samples. The cumulative relapse rate at 68 weeks was reduced significantly, from 47% in the clinical management control group to 29% with cognitive therapy (hazard ratio 0.54; 95% confidence interval, 0.32-0.93; intention to treat analysis). Cognitive therapy also increased full remission rates at 20 weeks but did not significantly improve symptom ratings.

Conclusion: In this difficult-to-treat group of patients with residual depression who showed only partial response despite antidepressant treatment, cognitive therapy produced worthwhile benefit.

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THERE IS widespread recognition that the long-term outcome in depression is still disappointing. Substantial rates of relapse and recurrence have been reported in many follow-up studies.[1-4] Antidepressant continuation and maintenance reduce the rates of relapse and recurrence compared with placebo, but these remain substantial.

A common problem after acute treatment is partial remission with presence of residual symptoms. High relapse rates have been found in subjects with residual depression.[5-12]

The treatment of such patients presents a challenge. The incomplete remission usually reflects limited response to antidepressants and suggests other treatment possibilities. A promising approach is cognitive therapy (CT). Follow-up studies of acute treatment trials have found lower relapse rates following CT than following medication.[10,11,13] In 2 of 3 recent small-sample controlled trials using CT after complete or partial remission, there was also evidence of relapse reduction.[14-16] However, medication was withdrawn in these trials.

We report a large randomized controlled trial of CT with clinical management vs clinical management alone in 158 subjects with residual depressive symptoms, who continued to receive maintainance treatment with antidepressants throughout the trial.

RESULTS

PATIENT FLOW AND DROPOUT

Eighty-three patients were recruited from Cambridge and 75 from Newcastle, with 78 randomized to clinical management and 80 to CT. Within the clinical management group, 66 subjects (85%) adhered to protocol until the end of the study or relapse; within the CT group, 61 patients (76%) did so (**Figure 1**). The 8.4% difference was not significant (95% confidence interval [CI], –3.9% to 20.7%). Full or fairly complete ratings to relapse or end of study were obtained for all except 6 subjects in the clini-

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SUBJECTS AND METHODS

SUBJECTS

Subjects were patients with unipolar depression aged 21 to 65 years, recruited from psychiatric outpatient clinics, satisfying *DSM-III-R*[17] criteria for major depression within the last 18 months but not in the last 2 months, and who had residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)[18] and 9 on the Beck Depression Inventory (BDI)[19] (modified from criteria of Frank et al[20]). Residual symptoms had lasted 2 to 18 months.

Patients were excluded if there was a history of bipolar disorder, cyclothymia, schizoaffective disorder, definite drug or alcohol dependence, persistent antisocial behavior or repeated self-harm, *DSM-III-R* dysthymia with onset before age 20 years, borderline personality, learning disability (estimated IQ <70), organic brain damage, or any other primary Axis I disorder at the time of the index illness. Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions.

Patients had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. Most of our subjects were receiving much larger doses for longer treatment periods than this (**Table 1**). For a small number of patients who were receiving 2 antidepressants, dose was determined by adding the dose equivalents.

Patients not meeting dose criteria received a preliminary dose increase. Change of medication was permitted before inclusion. A range of antidepressant drugs was allowed, as was lithium augmentation. Small doses of neuroleptics or benzodiazepines were allowed for night sedation only; no other medications were given during the study.

STUDY DESIGN

This was a parallel 2-group trial with 20 weeks of treatment and 1 year of follow-up, carried out in 2 centers, Cambridge and Newcastle, England, and approved by both research ethical committees.

There were 2 phases. The *treatment phase* comprised 20 weeks of randomized treatment, during which all patients received drug continuation and clinical management, and 1 group received additional CT. The subsequent *follow-up phase* comprised 48 weeks, during which antidepressants, clinical management, and rating procedures were continued.

After written informed consent, patients received a full set of baseline ratings and were then randomized. Assignments in consecutively numbered sealed envelopes were prepared by the trial statistician (A.L.J.) and stratified by center, previous major depressive episodes (≥2 vs <2), length of present illness, including both index major depression and residual symptoms (≥1 year vs <1 year), and severity of index major depression (global ratings of mild or moderate vs severe or psychotic).

The preset sample size was 80 subjects per treatment group, which gave 80% power at $P = .05$ to detect by the log rank test (2 tailed) a reduction in relapse rates from 40% in one group to 20% in the other, and an effect size of 0.45 in 2-tailed parametric tests of continuous measures.

TREATMENT

Clinical Management and Drug Continuation (All Patients)

Patients were seen by the study psychiatrist every 4 weeks during the treatment phase and every 8 weeks during the follow-up phase. Psychiatrists (one in Cambridge, 2 successive in Newcastle) had a minimum of 4 years' experience and the MRCPsych qualification. Interviews were modified from Elkin et al.[21] Sessions lasted approximately 30 minutes. Symptoms were rated, limited support provided, and drugs prescribed. Specific CT techniques were excluded. Treatment with the same antidepressant used at inclusion was continued, prescribed by the study psychiatrist. Dose reduction was permitted for troublesome adverse effects, within minimum criteria levels. When symptoms were worsening, dosage increase was permitted to 30% greater than at the point of inclusion and up to a total of 2 consecutive extra sessions once weekly. No formal psychotherapy, CT, or behavior therapy was permitted without withdrawal from the study.

Cognitive Therapy

Patients were seen for 16 sessions of CT during a 20-week period plus 2 booster sessions for all subjects, approximately 6 and 14 weeks later.

Cognitive therapy was modified from Beck et al[22] and included a manual. Therapists (1 per center) were already trained in CT with a recognized diploma from a postqualification training center and at least 4 years' CT experience. There was preliminary training in the study approach with treatment of a small number of patients. During the study there was regular joint therapist supervision (J.S.).

Sessions were audiotaped and rated on the Cognitive Therapy Rating Scale (CTRS)[23] by an independent rater to ensure fidelity and competency. The median score was 54, with no rating below 39, the accepted threshold level, and no significant differences between therapists. Psychia-

cal management group and 10 in the CT group. The most common reasons for nonadherence to the protocol (not shown in the figure) were failure to attend (clinical management group = 4, CT group = 10), withdrawal of consent (clinical management group = 2, CT group = 6), development of additional excluded diagnosis (clinical management group = 3, CT group = 1). One patient receiving clinical management died and 1 moved away.

INITIAL CHARACTERISTICS OF TREATMENT GROUPS

The 2 treatment groups were closely comparable on initial variables, including stratification variables and covariates (Table 1).

Subjects were middle aged (mean age, 43 years) and about 50% were male. Initial severity ratings lay in the

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trists' clinical management sessions were also audiotaped and rated randomly on the CTRS. Ratings were high on nonspecific items such as professionalism and empathy, but low on CT strategies. Median scores were 19, with no tape rated higher than 24.

Each CT session followed a fixed structure, with agenda setting, review of homework, exploration of issues in order of priority, and assignment of new homework. Content varied with symptom severity.

Early sessions involved case formulation and generation of an individualized problem list, which was then worked through systematically, with cognitive and behavioral strategies identified to resolve problems and manage symptoms. Later sessions focused on modification of underlying beliefs and self-management techniques to prevent relapse. Because of long-standing depression, some recent elaborations[24] were permitted, including techniques for engagement in CT and schema-focused approaches to core unconditional beliefs.

The 2 later booster sessions were for review of problem-solving strategies, discussion of difficulties, and reinforcement of self-management techniques.

Assessments

Subjects were assessed every 4 to 20 weeks and every 8 weeks thereafter by the study psychiatrist and at baseline, 8 weeks, 20 weeks, and 68 weeks by a research assistant. Both were blind to treatment group and patients were requested not to reveal significant details.

Baseline assessments included history of present episode, previous history, and recent treatment; Schedule for Affective Disorders and Schizophrenia[25] modified for *DSM-III-R* criteria; and baselines for repeated ratings. Personality was assessed on the self-report Eysenck Personality Inventory[26] and other instruments.

Repeated symptom ratings included the 17-item HDRS,[18] the BDI,[19] and other secondary measures.

Details of all treatment received from psychiatric sources and from general practitioners were recorded at each psychiatrist rating. Also recorded were psychotropic medication, any changes in medication, and reasons for change. Compliance was assessed by inquiry of the patient and recorded on a 5-point scale based on the proportion of the full dose taken.

Definition of Relapse

The most important outcome was relapse, for which 2 separate criteria were defined in advance, to be combined into one. A second psychiatrist also rated the patient using both criteria.

Patients had a major depression relapse if they met *DSM-III-R* criteria for major depressive disorder for a minimum of 1 month (2 weeks longer than *DSM-III-R* criteria require). Further, at 2 successive face-to-face assessments at least 1 week apart, they were required both to meet severity criteria for major depression and score 17 or more on the HDRS.

The second relapse criterion applied only during follow-up, where the major depression criterion might fail to capture slowly worsening residual symptoms. Patients were considered to have a persistent symptom relapse if residual symptoms had persisted between 2 successive ratings 2 months apart, reaching a score on the HDRS of at least 13 on both occasions and a level of distress or dysfunction for which the withholding of additional active treatment was no longer justified. In all such patients, the 30% medication increase should already have been implemented.

Patients were withdrawn from protocol treatment constraints if they reached either relapse criterion, if consent was withdrawn or cooperation refused, if major physical illness or other factors precluded study treatment, if formal psychotherapy or nonprotocol CT was provided, or if medication changed. Following a failure to engage in CT (<4 sessions) or failure to take medication in the first 4 weeks, patients were also withdrawn from protocol constraints. Wherever possible, all withdrawn patients were assessed regularly to the end of the study and included in intention to treat analyses.

Remission

A remission criterion was defined after the study, to comprise symptom levels below 8 on the HDRS and 9 on the BDI at 2 successive ratings 4 weeks apart. This applied only up to 20 weeks to avoid the mixed outcome of remission following relapse, which no subject experienced to this point.

DATA ANALYSIS

Relapse-free curve analyses were by Cox regression, including as covariates the stratification variables used in randomization, and 5 additional variables: HDRS score at inclusion, Eysenck Personality Inventory score, age, sex, and presence of melancholia in index major depressive episode (*DSM-IV* criteria). Analyses were conducted for the 2 relapse criteria combined and for major depression relapse alone and in 2 separate samples: intention to treat, including all subjects randomized in the study (including dropouts), and per protocol, including only subjects satisfying protocol treatment (up to the point in the study where they failed to do so). One subject from the control group with insufficient baseline data was excluded from the analyses. Statistical significance was set at $P<.05$. Remission was analyzed similarly by Cox regressions with BDI score as an additional covariate. Symptom ratings were analyzed by analysis of covariance with the same covariates and initial level.

middle of the residual depression range, with a mean HDRS score of 12 and a BDI score of 22. The majority of episodes had lasted more than 1 year, including the period of residual symptoms, and index major depressions were rated as severe in a little more than 50% of cases. Only one third of subjects were in their first episode.

About 40% of subjects were receiving tricyclic antidepressants (including a small number receiving atypical antidepressants) at inclusion and 60% were receiving selective serotonin reuptake inhibitors, with very few receiving monoamine oxidase inhibitors. About 15% were receiving lithium augmentation. Doses of antidepressants were equivalent to 186 mg of amitriptyline daily for those receiving tricyclics, and 33 mg of fluoxetine daily for those receiving selective serotonin reuptake inhibitors.

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Table 1. Initial Characteristics of Groups*

	Control Group (n = 78)	CT Group (n = 80)
Mean (SD) age, y	43.2 (11.2)	43.5 (9.8)
Female	41 (53)	37 (46)
Mean (SD) HDRS total score	12.2 (2.9)	12.1 (2.7)
Mean (SD) initial BDI total score	22.3 (8.0)	21.9 (7.7)
Mean (SD) EPI-N score	16.7 (4.7)	17.1 (4.0)
Median length of episode, mo (first and third quartile)	13.0 (9, 21)	14.5 (9, 18)
Severity of index episode		
Mild or moderate	35 (45)	39 (49)
Severe	43 (56)	41 (51)
Index episode		
Melancholia (*DSM-IV*)	37 (48)	42 (53)
Dysthymia (*DSM-IV*)	19 (25)	20 (25)
Inpatient during index episode	11 (14)	10 (13)
No. of episodes		
1	27 (35)	29 (36)
2	22 (29)	21 (26)
≥3	28 (36)	30 (38)
Antidepressant at inclusion		
Tricyclic	26 (33)	38 (48)
Selective serotonin reuptake inhibitor	50 (64)	41 (51)
Monoamine oxidase inhibitor	2 (3)	1 (1)
Lithium augmentation at inclusion	9 (12)	15 (19)
Mean (SD) doses at inclusion, mg		
Tricyclic (amitriptyline equivalent)	188 (45)	186 (45)
Selective serotonin reuptake inhibitor (fluoxetine equivalent)	36 (15)	31 (11)

**Data are presented as number (percentage) unless otherwise indicated. CT indicates cognitive therapy, HDRS, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; and EPI-N, Eysenck Personality Inventory, Neuroticism.*

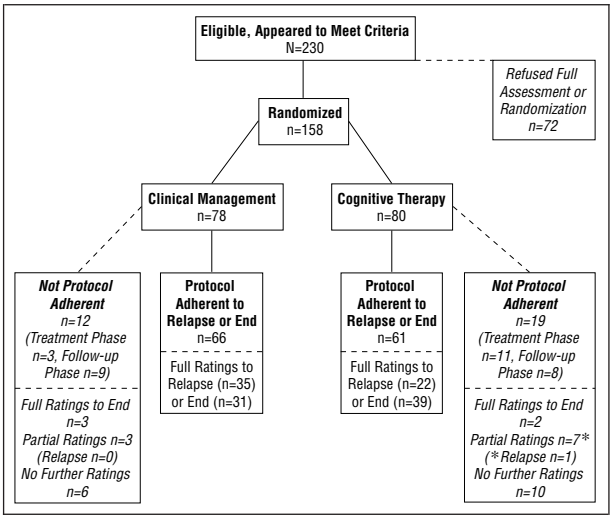

Figure 1. *Study flow and dropout.*

RELAPSE

During the study 35 subjects (45%) in the control group satisfied the criteria for relapse (27 for major depression, 8 for persistent symptoms), compared with 23 (29%) in the CT group (18 for major depression, 5 for persistent symptoms).

The findings, including the magnitude of effects, were very similar for all relapses and for major depression alone, and for the intention to treat and per protocol samples (**Table 2**). Relapse rates showed consistent reduction in the CT group, with the reduction amounting to about 40% of the relapse rate in the control group. The between-group differences were significant for both intention to treat and per protocol analyses of the combined relapse criterion, the key outcome measure. They just failed to reach significance for major depression relapse alone, owing to fewer events.

Actuarial cumulative rates for all relapses for control and CT groups, respectively, in the intention to treat analyses (**Figure 2**) were 18% and 10% at 20 weeks, 40% and 24% at 44 weeks, and 47% and 29% at 68 weeks. The adjusted hazard ratio for relapse was 0.51 (95% CI, 0.32-0.93).

REMISSION AND SYMPTOM RATINGS

Relatively few patients achieved the remission criterion by 20 weeks; 10 (13%) in the control group and 19 (25%) in the CT group. Cox regressions (**Table 3**) showed significant effects ($P<.05$) of CT in both intention to treat and per protocol analyses, with a hazard ratio of 2.42 (95% CI, 1.08-5.45) for intention to treat analyses and 2.38 (95% CI, 1.04-5.44) in the per protocol analyses. Actuarial cumulative remission rates at 20 weeks were 11% in the control group and 24% in the CT group in the intention to treat analysis.

Analyses of covariance for the HDRS and BDI total scores at 20 weeks showed no significant effects of CT, although the BDI scores showed a trend for advantage for CT at $P = .07$. The adjusted 20-week means in the control and CT groups for HDRS scores were 9.40 and 8.58, respectively (mean difference = 0.79; 95% CI, –0.74 to 2.38). For BDI scores, they were 16.06 and 13.46, respectively (mean difference = 2.60; 95% CI, –0.18 to 5.38).

TREATMENT RECEIVED

To check whether treatment received during the study was comparable, the 2 groups were examined with respect to contacts with study psychiatrists and other health professionals and with respect to drug doses and compliance (**Table 4**).

There was only 1 significant difference. The control group received significantly more clinical management sessions than the CT group. The findings confirmed that the benefits of CT were not due to higher medication doses or compliance.

The CT group received a median of 16 CT sessions during the treatment phase, and 57 patients (71%) received the 2 subsequent booster sessions.

COMMENT

Cognitive therapy significantly reduced the relapse rate over 17 months on clinical management from a high level of 47%, which occurred despite continued treatment with antidepressants. The reduction to a 29% rate of relapse by the addition of CT was definitely worthwhile. There was also a significant effect on remission by 20 weeks,

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Table 2. Actuarial Cumulative Relapse Rates*

	20 Weeks		44 Weeks		68 Weeks		Hazard Ratio for Relapse (95% Confidence Interval)†	*P*
	Control Group	CT Group	Control Group	CT Group	Control Group	CT Group		
Intention to treat analysis								
Major depression and persistent symptoms	18	10	40	24	47	29	0.54 (0.32-0.93)	.02
Major depression alone	18	11	31	19	36	22	0.58 (0.37-1.07)	.08
Per protocol analysis								
Major depression and persistent symptoms	19	10	40	24	49	30	0.53 (0.31-0.91)	.02
Major depression alone	19	11	32	19	38	23	0.55 (0.29-1.02)	.06

*Data are presented as the percentage of patients relapsing unless otherwise indicated. CT indicates cognitive therapy.

†Adjusted for variables described in text. For intention to treat analyses of major depression plus persistent symptom relapse the only significant covariate was initial Hamilton Depression Rating Scale total score (regression coefficient 0.12, P = .02), which was also significant in per protocol analyses. For the per protocol analysis of major depression plus persistent symptoms length of depressive episode was also significant (regression coefficient 0.57, P = .05).

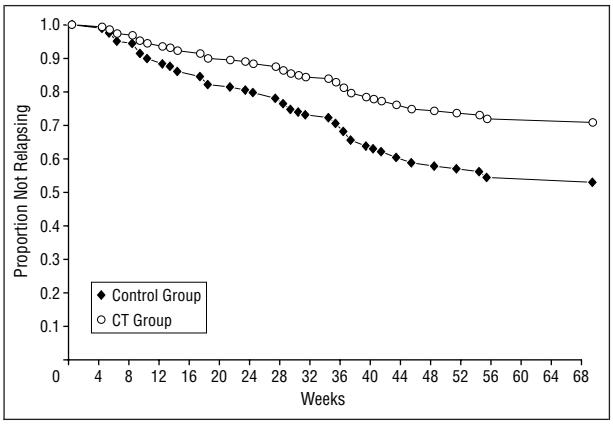

Figure 2. *Relapse-free curves from Cox regression intention to treat analysis of combined major depression and persistent symptom relapse. Number at risk in control and CT groups at 0 weeks was 77 and 80, respectively; at 20 weeks, 57 and 69, respectively; at 44 weeks, 40 and 53, respectively; and at 68 weeks, 37 and 47, respectively. Hazard ratio for relapse was 0.54 (95% confidence interval, 0.32-0.93;* P = .02).

but remission was uncommon in either group and mean symptom levels were not affected.

We tested hypotheses arising from 2 sets of previous findings: consistently higher relapse rates after residual depressive symptoms and suggestive evidence of relapse reduction by CT.

Residual depression is common, and occurred in 32% of patients achieving remission in an earlier Cambridge longitudinal study.[5] In many follow-up studies residual depression is not separately identified, obscuring its frequency. In the influential article by Frank et al,[20] residual depression fell between criteria formulated for remission and those for clinical illness. Most subjects, both in this and in our earlier study, were not dysthymic and residual depression seems to be a different phenomenon, namely, the failure of major depression to respond fully to treatment.[5] The high relapse rates have been reported in naturalistic follow-up studies,[5,6] antidepressant continuation studies,[7-9] and follow-up of CT trials.[10,11]

Treatment of residual depression is difficult. Our earlier follow-up did not point to major underprescribing and in many of these cases several antidepressants have been tried without adequate improvement and with problematic adverse effects and subsequent demoralization. In these circumstances, a psychological therapy could have a major place.[27]

There is also some relevant literature concerning CT. Relapse prevention emerged first from follow-up studies of controlled trials of antidepressants vs CT in acute treatment. Three studies[10,11,13] showed significantly lower relapse rates, with rates of 50% to 80% after antidepressant treatment reduced to 12% to 23% after CT. Nonsignificant similar trends were found in 3 other studies.[28-30]

These acute studies cannot be conclusive. First, a differential sieve may occur in acute treatment.[31] Patients with different prognoses for relapse may respond initially to CT and to antidepressants. Second, antidepressant continuation was not always undertaken or was not always well controlled. In one study,[11] a relapse rate of 52% when treatment with antidepressants was withdrawn was reduced to approximately 20% at 1 year and 32% at 2 years with 1 year's maintenance, compared with 21% after CT.

In a small long-term trial, Blackburn and Moore[14] randomized patients with depression to 3 groups: acute antidepressant treatment and 2 years of maintenance antidepressant treatment, acute CT plus maintenance CT, and acute antidepressant treatment followed by maintenance CT. Relapse rates were comparable but sample sizes were very low.

While our study was under way, Fava et al[32] described a total of 40 subjects with residual symptoms, randomized either to modified CT targeting anxiety and irritability or to clinical management. Cognitive therapy significantly reduced symptoms. A difference in relapse rates (70% vs 35%) became significant by 4 years[33] and persisted at 6 years, but only in number of episodes.[15] In a subsequent study[16] of recurrent depression, a total of 40 patients were randomized either to an approach including CT lifestyle modification and well-being therapy or to a control group. Modified CT reduced episodes from 80% to 20% during 2 years.

The Fava et al studies have some important differences from the present study. There the level of residual symptoms was low and the CT was considerably modified. Importantly, therapy with antidepressant medication was withdrawn. Continuation of medication is more

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Table 3. Actuarial Cumulative Remission Rates*

	12 Weeks		16 Weeks		20 Weeks		Hazard Ratio for Remission (95% Confidence Interval)†	*P*
	Control Group	CT Group	Control Group	CT Group	Control Group	CT Group		
Intention to treat analysis	3	8	5	12	11	24	2.42 (1.08-5.45)	.03
Per protocol analysis	3	6	5	11	12	26	2.38 (1.04-5.44)	.04

*Data are presented as percentage of patients experiencing remission unless otherwise indicated. CT indicates cognitive therapy.
†Adjusted for variables described in text. The only significant covariate was length of depression in per protocol analysis (regression coefficient –0.87, P = .03).

Table 4. Treatment Received During Study (Intention to Treat Sample)

	Control Group (n = 77)	Cognitive Therapy Group (n = 77)	*P* (*t* Test)*
Median (first and third quartile) contacts over whole study with			
General practitioner	6.0 (3.5-10.0)	6.0 (3.0-8.5)	.38†
Other health professionals	0.0 (0.0-6.0)	0.0 (0.0-1.0)	.22†
Extra contacts with study psychiatrist	1.0 (0.0-2.0)	0.0 (0.0-1.0)	.04‡
Mean (SD) time per psychiatric contact, min	29.6 (6.5)	27.9 (6.7)	.11
Mean (SD) daily medication dose, mg			
Tricyclic and atypical antidepressants	181 (40)	190 (50)	.41
Selective serotonin reuptake inhibitors	34 (13)	33 (13)	.73§
No. (%) receiving lithium at any point during study‡	24 (31)	17 (21)	.17
Compliance rating (SD)¶			
Antidepressant	2.1 (0.3)	2.0 (0.4)	.33
Lithium	2.3 (0.6)	2.1 (0.1)	.10

*Degrees of freedom were 151 for psychiatric contact time, 152 for antidepressant compliance, 59 for tricyclic dose, 89 for selective serotonin reuptake inhibitor dose, and 39 for lithium compliance.
†By 2-tailed Mann-Whitney test, with sample sizes as given above.
‡Often after relapse.
§By χ^2 (df = 1).
¶On a scale of 1 to 5, where 1 = more than prescribed dose, 2 = 75% to 100% of prescribed dose, and 5 = less than 25% of prescribed dose.

realistic in patients with residual depression who have a high risk of further episodes.

Our study was large and to our knowledge is the first to conclusively show relapse prevention by CT as having an additive effect with medication. Cognitive therapy started after partial remission, avoiding a differential acute treatment sieve. Relapse criteria were rigorous and required rating by a second psychiatrist. Psychiatrists and interviewers were blinded. Although we distinguished 2 kinds of relapse, most were in fact full major depressions and magnitude of treatment effects was similar for both kinds of relapse.

The effect of CT was mainly to prevent relapse. Although there was a significant effect on remission at 20 weeks, it was comparatively small and not reflected in mean symptom ratings. Interpretation is not easy without other evidence, but it may be that preventive effects of CT on relapse are more powerful than immediate effects on symptoms.

These patients with relatively chronic disease, who were often orientated to biological models, were challenging for the skilled cognitive therapists, who had considerable previous experience. Results may not apply with inexperienced therapists. Both groups received considerable care, reflecting clinical necessity. Cognitive therapy did reduce psychiatric contacts somewhat. Benefits of CT were not due to better drug compliance.

There were some limitations. Like most controlled trials of CT and of psychotherapies, the study did not include a control group equated for therapeutic contact. Therefore we cannot with certainty attribute effects to CT, but it is unlikely that 18 additional nonspecific treatment sessions would have reduced relapses so much. Medication doses were moderately high for outpatients in the United Kingdom. Although higher doses may be used in the United States, our mean tricyclic dose of 186 mg was comparable with the imipramine dose of 200 mg used in the maintenance study by Frank et al.[34] Dose increase was limited to 30% to avoid obscuring of relapse but, in practice, very high doses are often impossible in these subjects because of adverse effects.

Relapse reduction was less than in the studies by Fava et al,[15,16,32,33] probably because of antidepressants. The evidence of an additional effect of CT not achieved by medication alone is particularly useful and could be incorporated in stepped-care guidelines. The magnitude of the benefit from combined treatment over medication alone in this study was moderate, larger than the 15% suggested in follow-up studies of acute treatment.[35]

In acute treatment of milder depression, CT is more expensive than antidepressants and requires patient commitment to 15 to 20 therapeutic sessions. This study shows a clear place for CT added to antidepressants in cases where the additional health gain balances any additional cost.

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