ORIGINAL ARTICLE

Prevention of Relapse Following Cognitive Therapy vs Medications in Moderate to Severe Depression

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Background: Antidepressant medication prevents the return of depressive symptoms, but only as long as treatment is continued.

Objectives: To determine whether cognitive therapy (CT) has an enduring effect and to compare this effect against the effect produced by continued antidepressant medication.

Design: Patients who responded to CT in a randomized controlled trial were withdrawn from treatment and compared during a 12-month period with medication responders who had been randomly assigned to either continuation medication or placebo withdrawal. Patients who survived the continuation phase without relapse were withdrawn from all treatment and observed across a subsequent 12-month naturalistic follow-up.

Setting: Outpatient clinics at the University of Pennsylvania and Vanderbilt University.

Patients: A total of 104 patients responded to treatment (57.8% of those initially assigned) and were enrolled in the subsequent continuation phase; patients were initially selected to represent those with moderate to severe depression.

Interventions: Patients withdrawn from CT were allowed no more than 3 booster sessions during continuation; patients assigned to continuation medication were kept at full dosage levels.

Main Outcome Measures: Relapse was defined as a return, for at least 2 weeks, of symptoms sufficient to meet the criteria for major depression or Hamilton Depression Rating Scale scores of 14 or higher during the continuation phase. Recurrence was defined in a comparable fashion during the subsequent naturalistic follow-up.

Results: Patients withdrawn from CT were significantly less likely to relapse during continuation than patients withdrawn from medications (30.8% vs 76.2%; P=.004), and no more likely to relapse than patients who kept taking continuation medication (30.8% vs 47.2%; P=.20). There were also indications that the effect of CT extends to the prevention of recurrence.

Conclusions: Cognitive therapy has an enduring effect that extends beyond the end of treatment. It seems to be as effective as keeping patients on medication.

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ANTIDEPRESSANT MEDICATION (ADM) is effective in the treatment of moderate and severe depression, and it prevents the return of symptoms as long as it is continued. However, evidence is lacking that it does anything to reduce risk once its use is discontinued.[1] There is some evidence that cognitive therapy (CT) has an enduring effect that reduces risk following successful treatment.[2] In a series of studies, patients who responded to CT were about half as likely to relapse following treatment termination as patients who discontinued taking medications after responding to ADM.[3-6] Prior exposure to CT was at least as effective as continuation ADM (cADM) in preventing subsequent relapse in the one study in which they were compared.[6] To our knowledge, the only study that failed to find an enduring effect for prior CT (pCT) was the National Institute of Mental Health Treatment of Depression Collaborative Research Program, and in that trial, such differences as were apparent favored CT.[7]

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Although these findings have been fairly robust, the studies typically have been small (using cell sizes of ≤15) and, in most instances, patients have known that medications were being withdrawn. Moreover, it cannot be assumed that CT's en-

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during effect would be obtained with more severely depressed outpatients. Since the publication of findings from the Treatment of Depression Collaborative Research Program, questions have been raised about the effectiveness of CT with more severely depressed patients.[8] To our knowledge, no other published trial has focused specifically on psychosocial treatment in this subpopulation. The present study asks whether CT has an enduring effect that extends to the prevention of relapse among more severely depressed outpatients, and it allows for a comparison of the magnitude of CT's prevention effect relative to cADM.

METHODS

This study examines the subsequent course following initial treatment for patients randomized to either CT or ADM. A placebo-controlled continuation design was used to compare patients who responded to 16 weeks of CT with patients who responded to 16 weeks of ADM. Subjects were patients with moderate to severe unipolar depression aged 18 to 70 years who were recruited from outpatient psychiatric clinics at 2 sites, the University of Pennsylvania and Vanderbilt University. The full details of the screening process and the patient characteristics are given elsewhere.[9] Institutional review boards at the University of Pennsylvania and Vanderbilt University reviewed and approved the study, including the withdrawal of active medication from patients who responded to treatment. Written informed consent was obtained from all participants, so that all of them knew that treatment might be withdrawn shortly after their initial response. All patients met the criteria for major depressive disorder as ascertained by the Structured Clinical Interview for *DSM-IV-TR* diagnoses.[10] Moreover, they had to have scores of 20 or above for 2 consecutive weeks on the first 17 items of the Hamilton Depression Rating Scale (HDRS).[11] This was the criterion used by Elkin and colleagues to define patients as severely depressed in the National Institute of Mental Health Treatment of Depression Collaborative Research Program.[12] Exclusion criteria were kept to a minimum, but patients were screened out if they had any history of psychosis or bipolar I disorder, had another Axis I disorder that was the predominant aspect of the clinical presentation, or met the criteria for borderline, antisocial, or schizotypal personality disorder, as ascertained by interviews on the Structured Clinical Interview for *DSM-III-R* Personality Disorders.[13] Patients were also screened out if they had a clinically significant medical disorder that precluded treatment with an ADM or required hospitalization for imminent suicidal risk.

Two hundred forty patients met all inclusion and exclusion criteria. They were randomly assigned to 16 weeks of acute treatment with either CT (n=60) or ADM (n=120); the remaining 60 patients received 8 weeks of pill placebo (cP-P) and will not be considered further in this article.

Of the 180 patients who had been assigned to one of the active treatments, 104 (57.8%) met the criteria for response and were enrolled into the 12-month continuation phase of the study. The definition of response accounted for the absolute symptom level at the end of treatment and the stability of that level. Patients who completed 16 weeks of treatment met response criteria if they had the following: (1) a 16-week HDRS score of 12 or less and either a 14-week HDRS score of 14 or less or 10- and 12-week HDRS scores of 12 or less; or (2) weeks 12, 14, and 18 HDRS scores of 12 or less. These criteria prevented a transient exacerbation of depressive symptoms at either week 14 or 16 from precluding recognition of a patient as a responder. Because all patients in the trial began with an HDRS score of 20 or more, a score of 12 reflected a reduction of at least 40%, a substantial reduction in depressive symptoms. In the ADM group, 69 (57.5%) of 120 patients met the response criteria; and in the CT group, 35 (58.3%) of 60 patients met these criteria. These 104 patients constitute the focus of this report.

STUDY PROCEDURES

This study used a placebo-controlled continuation design to compare patients who responded to CT with patients who responded to ADM. The ADM patients who had responded to acute phase treatment were randomly assigned to either cADM (n=34) or withdrawal onto cP-P (n=35). They were monitored closely for the reemergence of depressive symptoms during this time, as were patients who had responded to CT (n=35). All patients were asked not to pursue treatment for depression other than that provided in the research protocol during the yearlong continuation phase. Patients who completed the continuation phase without relapse were withdrawn from all treatment and observed across a subsequent yearlong naturalistic follow-up.

TREATMENT

Clinical Management and Drug Continuation

Patients treated with ADM continued with the same psychiatrist they saw for acute treatment. Sessions were held at least every 2 weeks for the first month of continuation, and at least monthly thereafter. Clinical management sessions typically lasted about 15 to 30 minutes, and were conducted in accordance with the manual used in the Treatment of Depression Collaborative Research Program.[14] Jan Fawcett, MD, the author of that manual, provided training in clinical management before the study began, and consultation on its implementation during the study. Session content focused on symptoms and adverse effects. Limited advice giving was allowed, and support was provided. Techniques and strategies specific to CT were prohibited.

Patients typically had been treated with paroxetine during acute treatment; treatment in those who had experienced less than a full response by 8 weeks was augmented with lithium or desipramine hydrochloride. Patients who were randomly assigned to stay on medications during the continuation phase typically continued on the same medications and dosages to which they responded, although dosage reduction was allowed as a means of dealing with adverse effects. In a few cases, medications were switched or augmented to deal with the reemergence of depressive symptoms.

Patients who were withdrawn onto cP-P continued to meet with their treating psychiatrist on the same schedule as previously described, and continued to receive placebos identical in appearance to the medications to which they had initially responded. Placebos were phased in during a 4- to 6-week period, with the dose of paroxetine typically reduced in 10-mg decrements weekly. Withdrawal onto cP-P was conducted on a blinded basis; patients, psychiatrists, and evaluators were all kept blind as to whether the patient was receiving an active medication or a placebo. Adjustments to medication doses for patients taking placebo were handled in the same manner as for patients taking active medications. Fabricated plasma levels were provided to the treating psychiatrists for those patients augmented with placebo lithium during the continuation phase, to maintain the blinding.

Booster Sessions (CT)

Although responders to CT discontinued treatment at the end of the acute phase, they were allowed up to 3 booster sessions

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during the 12-month continuation phase. These sessions could be scheduled at any time, with the proviso that they be scheduled at least 1 month apart. Patients and therapists were left to decide if and when to have booster sessions. Some dyads scheduled booster sessions at regular intervals (eg, months 1, 3, and 6), whereas others saved their booster sessions to see if they would be needed. Session content was left free to vary within the domain of CT. Some sessions involved crisis intervention, designed to keep emerging difficulties from turning into a relapse, whereas others focused on more generic training in relapse prevention or a simple review of recent events.

OUTCOME MEASURES

The assessment schedule called for patients to be assessed weekly by a blind clinical evaluator for the first 2 weeks, every other week through the end of month 2, and monthly thereafter. Assessments were conducted more frequently at the beginning of the continuation phase to ensure that emerging relapses were not missed among patients in whom treatment was being withdrawn. In addition, patients were encouraged to call the clinic if they were concerned that depressive symptoms were reemerging, in which case an ad hoc examination was scheduled as soon as possible. Moreover, whenever a patient met the severity criterion for relapse, an examination was scheduled for 1 week later, to ascertain whether the temporal criterion was also met.

The primary measure used in the ascertainment of relapse was a 17-item version of the HDRS,[11] modified to include atypical symptoms.[15] (An additional 7 items, including 3 that emphasize cognitive symptoms, were assessed, but not used to ascertain relapse.) A patient met relapse criteria if he or she was given a score of 14 or greater on the HDRS for 2 consecutive weeks. In those instances when patients failed to come in for a scheduled examination, or failed to notify project personnel when they began to become symptomatic between reexaminations, patients could also be judged to have met relapse criteria based on the Longitudinal Interval Follow-up Evaluation,[16] which was conducted at least every 3 months. On the Longitudinal Interval Follow-up Evaluation, patients are rated for level of depression on a 6-point scale for each week during the preceding interval; elevated scores are used to trigger a review of full major depressive disorder criteria. A patient was judged to have relapsed if he or she was diagnosed as having major depressive disorder (a score of ≥ 5 for 2 consecutive weeks) at any time during the continuation period. All examinations were videotaped. Interviewers at both sites (4 at University of Pennsylvania and 3 at Vanderbilt University) rated a subset of these tapes. An intraclass correlation coefficient of 0.96 was obtained for the 17-item total HDRS score (n=24). Assessment of the reliability of the major depressive episode designation yielded a κ coefficient of 0.80 (n=12).[17]

Once it was determined that a patient met the relapse criteria, the onset of the relapse was dated to the point at which those criteria were met, typically 2 weeks after symptom onset. Three weeks of increased symptoms were required to meet the criteria for relapse during the first month of continuation, so as not to misconstrue transient withdrawal symptoms as indicative of a bona fide clinical relapse.

DATA ANALYSIS

To identify potential confounds in the relapse analyses, 5 demographic, 5 history of illness, 4 diagnostic subtype, 13 comorbidity, and 2 personality variables were examined to determine whether any of them differentiated the 3 follow-up conditions and predicted relapse. By using a liberal $P=.10$, 2 indexes, dysthymia and atypical subtype, met these criteria. Therefore, for the main relapse analyses, both were used as covariates. The number of prior episodes (which did predict subsequent relapse) and sex (which did not predict subsequent relapse) were also included as covariates, because both were used as stratification variables during the randomization before continuation. Inclusion of the covariates did little to affect the comparisons involving pCT, but they did sharpen differences comparing cADM with cP-P.

Survival curves and relapse rates were estimated using the Cox proportional hazards regression model.[18] As is typically done, patients unavailable for follow-up were treated as censored observations, as were patients who returned to depression treatment without a documented relapse. Survival rates for the 3 conditions were compared using the log-rank test. The Cox proportional hazards regression model was used to evaluate the influence of potential prognostic indexes, as described by Collett.[19] Statistical significance was set at $P<.05$ (2-tailed), and specific contrasts were conducted among the respective conditions using the Cox proportional hazards regression model for the survival curves and Cochran-Mantel-Haenszel analysis controlling for site for relapse rates. In the presence of small cell sizes, Fisher exact tests replaced the Cochran-Mantel-Haenszel analysis. Similar analyses were applied to data collected during the naturalistic follow-up.

RESULTS

PATIENT FLOW AND DROPOUT

Sixteen patients dropped out of protocol during the continuation phase, 8 from the cP-P group, 5 from the cADM group, and 3 from the pCT group. The bulk of the attrition happened early; 4 patients never returned for any visits, and 8 more dropped out by the end of month 3. The remaining 4 patients dropped out in month 6 or 7. Some patients missed 1 or more of the monthly reexaminations but did complete Longitudinal Interval Follow-up Evaluation interviews at subsequent reexaminations. Thus, we have complete information on 88 (84.6%) of the 104 treatment responders. Two patients were censored because of a premature return to depression treatment: 1 cADM patient insisted on adding psychotherapy because of functional impairment in month 2 and 1 CT patient began taking an ADM in month 10. Neither patient met the criteria for relapse either before or after pursuing additional treatment, although the patient in the cADM group came close on several occasions before and after her return to treatment.

INITIAL CHARACTERISTICS OF TREATMENT GROUPS

As a group, relative to those who did not enroll in the continuation phase of this study, patients who completed and responded to treatment were less likely than dropouts and nonresponders to have comorbid diagnoses of posttraumatic stress disorder or cluster A personality disorders, especially paranoid personality disorder. Treatment responders also were more likely to be employed at the start of the study. Nevertheless, the sample considered herein was still marked by high levels of comorbidity and chronic depression. More than 80% of the sample met the criteria for at least 1 other disor-

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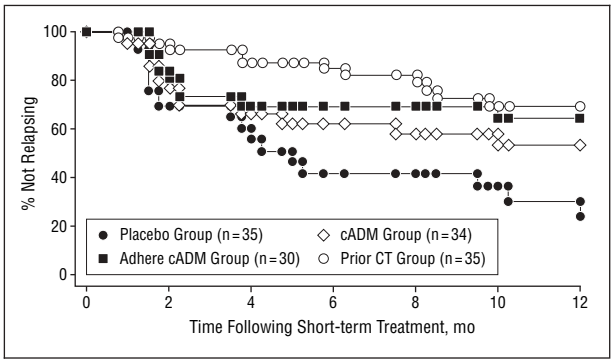

Figure 1. Cumulative proportion of treatment responders who survived without relapse during continuation/follow-up. CT indicates cognitive therapy; cADM, continuation antidepressant medication (paroxetine plus possible augmentation); adhere cADM, adherence to continuation medication (censoring patients who failed to adhere to continuation medication); and placebo, withdrawal onto pill placebo.

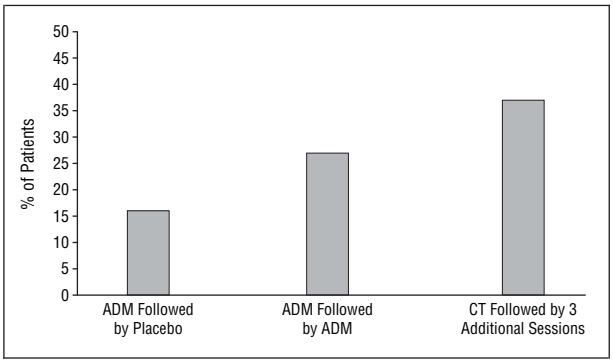

Figure 2. Sustained improvement for all patients initially assigned to treatment. ADM indicates antidepressant medication (paroxetine plus possible augmentation); CT, cognitive therapy.

der (69.2% for another Axis I disorder and 49.0% for an Axis II disorder), and 33.6% met the criteria for double depression.

RELAPSE

A main effect of condition was obtained (χ^2_2=8.68, P=.01). As shown in **Figure 1**, prior exposure to CT reduced the risk for subsequent relapse relative to cP-P (χ^2_1=8.53, P=.004). Relative to cP-P, cADM reduced relapse at the level of a nonsignificant trend (χ^2_1=3.14, P=.08). Prior CT and cADM did not differ significantly (χ^2_1=1.62, P=.20). Adjusted relapse rates for each condition were 30.8% for pCT, 47.2% for cADM, and 76.2% for cP-P. Hazard ratios were calculated between cP-P and each of the respective active treatments. Prior exposure to CT was associated with a hazard ratio of 0.30 relative to cP-P, which means that prior exposure to CT reduced risk by 70%. Continuation ADM was associated with a hazard ratio of 0.50 relative to cP-P, which means that keeping patients on medications essentially cut risk by half. This is comparable to what has been reported elsewhere in the ADM continuation literature.[20]

Four of the patients who relapsed in the cADM condition did so when they were not adhering to their medication regimen (defined as taking <75% of the prescribed medication for at least 1 week during the month before relapse). Therefore, a second set of analyses was conducted in which these observations were censored for nonadherence. In these analyses, cADM significantly outperformed cP-P (χ^2_1=5.44, P=.02). Taking nonadherence into consideration decreased the relapse rate for cADM to 42% and produced a hazard ratio of 0.37 relative to cP-P. This denotes a reduction in risk of 63%, close to that produced by pCT.

SUSTAINED RESPONSE

We also examined the proportion of patients in each condition who showed sustained response, defined as completing and responding to acute treatment and staying free from relapse across the 12-month continuation phase, adjusted for censored observations. As shown in **Figure 2**, only 16.4% of the patients initially assigned to ADM and subsequently withdrawn onto cP-P evidenced a sustained response, compared with 26.9% of the patients originally assigned to ADM who continued to take ADM. Of the 60 patients initially assigned to CT, 37.3% experienced a sustained response. A main effect of condition was obtained for this variable (χ^2_2=7.49, P=.02). Pairwise Cochran-Mantel-Haenszel tests indicated a significant difference between only the pCT condition and the cP-P condition (χ^2_1=7.50, P=.006).

NATURALISTIC FOLLOW-UP

A total of 40 patients who remained active in ongoing assessments completed the 12-month continuation phase without relapse. This included 20 patients in the pCT, 14 in the cADM, and 6 in the cP-P group. These patients were observed for an additional year in a naturalistic follow-up; pCT patients were allowed no further booster sessions, and all pills were withdrawn from the patients in the cADM and cP-P groups in accordance with the same schedule followed at the end of acute treatment. Given that these patients had gone 12 months without relapse following initial remission, they can be considered to have recovered from the index episode. Any subsequent return of symptoms would be considered a recurrence, the onset of a wholly new episode.[21] In other respects, recurrence was defined in the same manner as relapse (≥2 weeks of increased symptoms on the HDRS or Longitudinal Interval Follow-up Evaluation). None of these patients were unavailable for follow-up. As shown in **Figure 3**, survival analyses indicated that CT's enduring effect extended to the prevention of recurrence. In the pCT group, 5 of 20 patients had a recurrence during the naturalistic follow-up, vs 7 of the 14 cADM group patients withdrawn from medication; adjusted recurrence rates were 17.3% for the pCT vs 53.6% for prior cADM following withdrawal from medication (χ^2_1=6.81, P=.009). The hazard ratio for this comparison was 0.15, meaning that prior exposure to CT reduced risk for recurrence by 85%. Although not depicted in the figure, 2 of 6 patients in whom cP-P was withdrawn also experienced a recurrence. Although it would be inappropriate to extend analyses across the full 2-year follow-up in the absence of a maintenance medication condition, 15

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(25.0%) of the 60 patients initially assigned to CT showed a sustained response free of either relapse or recurrence. Given that only 14 patients assigned to continuation medication ended continuation treatment free from relapse (23.3% of a total possible 60), cADM could have done no better than pCT even if patients who survived the continuation phase had been kept on maintenance medication.

COMMENT

The findings of this study suggest that CT has an enduring effect that reduces risk following successful treatment, as indicated by the reduced relapse rates relative to medication withdrawal. Moreover, the magnitude of the CT effect seems to be at least as great as that achieved by keeping patients on continuation medication, which is widely regarded as the most effective means of preventing relapse.[8] Thus, it seems that there are at least 2 ways to protect patients against relapse following successful treatment: to either continue ADM or provide CT during acute treatment. Moreover, there are indications that the enduring effect of CT may extend to the prevention of recurrence.

These findings need to be interpreted cautiously. No one would recommend withdrawing ADM from depressed patients treated solely with medication after only 4 months of treatment. In this study, ADM was withdrawn and patients began to take cP-P solely to determine whether CT had an enduring effect.

To the extent that CT has an enduring effect, it might prove less costly than ADM to provide over time. Assuming costs of at least $100 per hour for 20 to 25 sessions of CT and $75 per hour for briefer pharmacotherapy sessions (and $125 per month for medications), CT costs about twice as much as ADM during a 4-month acute phase, but this gap is closed by the eighth month of continuation medication treatment, and is reversed beyond that point, such that direct treatment costs for ADM exceed those of CT thereafter. We did not make assessments of other direct or indirect costs that would have allowed us to conduct a sophisticated econometric analysis, but others who have compared CT with medications on such indexes have found that medications alone may result in a 33% higher expected cost than individual CT.[22]

It remains unclear just how CT exerts its enduring effect. Patients are trained from the start to "do the therapy for themselves" rather than to be passive recipients of the therapy. From the first session on, patients are encouraged to test the accuracy of their beliefs in homework assignments, and considerable time is devoted in later sessions to anticipating problems that are likely to arise after treatment is completed. Our impression is that patients initially need to apply the skills they learned during treatment in a concerted fashion, but that these compensatory strategies eventually become second nature, coinciding with a parallel change from problematic underlying beliefs to more adaptive ones. Such a change in beliefs would be expected to reduce the likelihood of becoming distressed in situations that formerly were problematic.[23] This process might hold whether the actual mechanism was a change in the content of the beliefs or a change in the way that patients react to their thoughts.[24]

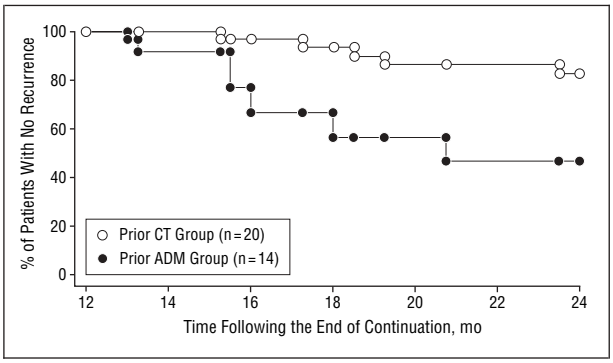

Figure 3. Cumulative proportion of recovered patients who survived without recurrence during naturalistic follow-up. Abbreviations are explained in the legend to Figure 2.

The present findings speak primarily to the prevention of relapse, the return of the treated episode. Although there were indications that CT's enduring effect may extend to the prevention of recurrence, direct comparisons to maintenance medication in larger samples would be required to fully assess its relative value. Moreover, these findings also do not speak to the consequences of combining CT and ADM, although prior studies suggest that CT's enduring effect is robust even when combined with medications. Both of these questions should be examined further.

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