Preventing Recurrent Depression Using Cognitive Therapy With and Without a Continuation Phase

A Randomized Clinical Trial

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Background: Cognitive therapy (CT) may reduce depressive relapse and recurrence when patients learn and use the associated skills. Reported relapse and recurrence rates after CT discontinuation vary widely. The factors that determine when CT is preventive remain unidentified. We developed continuation-phase CT (C-CT) to teach responders skills to prevent relapse. This is the first randomized trial comparing CT with and without a continuation phase in responders to CT who were vulnerable, given their history of recurrent unipolar depression.

Methods: Patients aged 18 to 65 years (n=156) with recurrent DSM-IV major depressive disorder (MDD) entered 20 sessions of acute-phase CT (A-CT). Unmedicated responders (ie, no MDD and 17-item Hamilton Rating Scale for Depression score ≤9; n=84) were randomized to either 8 months (10 sessions) of C-CT or control (evaluation without CT). Follow-up lasted an additional 16 months. A clinician blind to assignment evaluated relapse and recurrence (ie, DSM-IV MDD).

Results: Over an 8-month period, C-CT significantly reduced relapse estimates more than control (10% vs 31%). Over 24 months, including the CT-free follow-up, age of onset and quality of remission during the late phase of A-CT each interacted with condition assignment to influence durability of effects. In patients with early-onset MDD, C-CT significantly reduced relapse and recurrence estimates (16% vs 67% in control). When patients had unstable remission during late A-CT, C-CT significantly reduced relapse and recurrence estimates to 37% (vs 62% in control).

Conclusions: Findings suggest that 8 months of C-CT significantly reduces relapse and recurrence in the highest-risk patients with recurrent MDD. Risk factors influenced the necessity for C-CT.

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PATIENTS AND METHODS

PATIENTS

The recruitment and protocol were approved by the institutional review board. Patients (n=3500; recruited through media, announcements, and referrals) were triaged by telephone. If potentially eligible, patients were scheduled for evaluation (n>1200).

Outpatients (n=608) presented for evaluation at the Department of Psychiatry at The University of Texas Southwestern Medical Center at Dallas with the complaint of depression. Inclusion criteria involved the following: (1) DSM-IV\textsuperscript{16} nonpsychotic unipolar MDD; (2) recurrent MDD with clear interepisode recovery (ie, 2 or more episodes of MDD separated by at least 2 months of a return to more-or-less normal functioning); (3) 17-item Hamilton Rating Scale for Depression\textsuperscript{17} (HRSD-17) score of 16 or higher at initial diagnostic evaluation and at a follow-up; and (4) written informed consent.

Trained evaluators, using the Structured Clinical Interview for DSM-III-R (SCID outpatient version)\textsuperscript{18} and strictly applying DSM-III-R\textsuperscript{19} and DSM-IV criteria for MDD and other disorders, referred 361 patients (59%) for nonprotocol treatment. Exclusion criteria were (1) did not meet criteria for MDD (n=91); (2) MDD not recurrent (n=116); (3) HRSD-17 score less than 16 (n=66); (4) contraindicated medical condition or medication (n=28); (5) exclusionary comorbid psychiatric disorder (MDD with psychotic features, n=2; current alcohol or other drug abuse, n=9; primary sleep, eating, or sexual disorders, n=1 each; and borderline personality disorder, n=7); (5) imminent suicide risk at triage (n=2); or (6) inability to comply with the protocol (n=24). Thirteen patients were lost to follow-up after the initial clinic contact and were mailed referrals.

The remaining 247 patients completed the SCID and supplemental questions to allow evaluation of DSM-IV diagnoses, entry criteria, and the characteristics described in the Table. A faculty-level diagnostician reassessed eligibility criteria at a follow-up interview. Fifty patients were excluded because they (1) did not meet criteria for MDD (n=13); (2) had nonrecurrent MDD (n=12); (3) had a concurrent medical disorder or received treatment that might cause depressive symptoms (n=11); or (4) had comorbid exclusionary psychiatric disorders (MDD with psychotic features, n=7; delusional disorder, n=1; current alcohol or other drug abuse, n=6). An additional 36 patients were excluded because they (1) had an HRSD-17 score less than 16 at follow-up (n=16); (2) had primary panic disorder with agoraphobia (n=1); (3) had primary bulimia nervosa (n=1); (4) had borderline personality disorder (n=6); (5) could not complete questionnaires or comply with the protocol (n=10); or (6) preferred alternative treatment (n=2).

A total of 161 patients were eligible for the study and 3 refused consent; thus, 158 patients consented to enter A-CT.

STUDY PROCEDURES

Pharmacotherapy was not a study procedure. From entry through follow-up, patients agreed to postpone or report the use of psychotropic medication, nonprotocol psychotherapy, or other psychiatric or psychosocial treatment.

Acute-Phase Cognitive Therapy

Acute-phase cognitive therapy was conducted as described by Beck et al\textsuperscript{2} within a 12- to 14-week protocol (twenty 50- to 60-minute individual sessions held twice weekly for the first 8 weeks and once weekly for the last 4 weeks). The therapists completed clinician rating scales. Strategies were focused on symptom reduction but could include relapse prevention.

Five experienced therapists provided CT. Each had completed 1 or more years of CT training, achieving and maintaining Cognitive Therapy Scale\textsuperscript{24} (CTS) scores of 40 or more before treating any study patient.

An off-site consultant (see the acknowledgments at the end of the article) used the CTS to evaluate competence and provide feedback. Therapists received weekly group supervision.

Randomization to the Experimental Phase

Only responders (no MDD and HRSD-17 score of 9 or less by a blind evaluator) who completed 20 sessions of A-CT and consented to randomization to either C-CT or evaluation only (control) entered the 8-month experimental phase. Responders were randomized using PROC PLAN in SAS statistical software, version 6.04 (SAS Institute Inc, Cary, NC) by strata that included the following: (1) number of episodes (ie, 2 vs \(\geq 3\)); (2) HRSD-17 score less than 6 and 6 to 9 based on the blind evaluator’s score collected within 7 days of session 20; and (3) double depression (presence or absence of DSM-IV dysthymia before onset of the presenting episode). Research personnel and patients concealed assignment from blind evaluators.

In both conditions, patients agreed to remain unmedicated and were scheduled for 10 sessions that occurred biweekly for the first 2 months and monthly for the remaining 6 months. The clinician collected self-report questionnaires, assessed diagnostic status according to DSM-IV MDD, recorded any medication use, and completed rating scales. Regardless of diagnostic status, all patients proceeded with C-CT or evaluation until consent was withdrawn or through month 8. All patients were instructed to telephone the evaluator if they became symptomatic between visits. When patients experienced

continuation-phase treatment\textsuperscript{3,10,11} or different from the continuation and maintenance phases,\textsuperscript{1,9,11-14} we have focused on evaluating relapse and recurrence rates in patients who respond to 3 to 4 months of CT. We reported high rates of relapse and recurrence over a 2-year follow-up.\textsuperscript{9} After discontinuing CT, relapse and recurrence rates were 43% over 8 months, 50% over 1 year, and 74% over 2 years. These data motivated us to develop and test continuation-phase CT (C-CT)\textsuperscript{3} in a second cohort of patients who responded to A-CT. The cohort receiving C-CT had reduced relapse rates of 20% after 8 months of A-CT, 27% after 1 year, and 36% after 2 years.\textsuperscript{5} Since the patients were not randomized, the results were inconclusive, which prompted us to design the current trial.

To our knowledge, this is the first randomized clinical trial to compare CT with and without a

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relapse or recurrence, they were referred for additional treatment (eg, pharmacotherapy).

Continuation-Phase Cognitive Therapy

The same therapist provided A-CT and 10 sessions of C-CT as described by Jarrett (unpublished manual available on request) and elaborated by Jarrett and Kraft. Patients were taught to use emotional distress or symptoms to trigger coping skills learned in A-CT. The purpose of C-CT is to prevent relapse and recurrence, review strategies associated with effective symptom reduction, maintain skills acquired during A-CT, and develop coping strategies in preparation for identified or anticipated vulnerabilities. Whereas A-CT emphasized reducing symptoms and acquiring skills, C-CT emphasized preventing relapse and recurrence, reducing residual symptoms, and generalizing skills.

Most sessions lasted 60 minutes, although 90 minutes was allowable. Patients received no monetary incentives.

Evaluation Only (Control)

An evaluator who had not provided A-CT conducted 10 assessment visits scheduled at the same frequency as C-CT for 8 months. Prescribed control procedures prohibited the use of CT or other psychosocial interventions before relapse. When patients described psychosocial problems, the evaluator did not intervene. Self-reports and clinician ratings were collected. Sessions lasted approximately 20 to 30 minutes, and patients were paid $25 for each visit.

Longitudinal Follow-up Phase

All consenting patients attended follow-up assessments for 16 months or until they withdrew consent. When clinic assessments were not feasible, evaluations were conducted by telephone. An evaluator followed up the patient monthly for the first 4 months and bimonthly for the remaining 12 months. Procedures were identical to the control cell.

OUTCOME MEASURES

The primary dependent variables were the proportion of DSM-IV diagnoses of MDD (ie, relapse or recurrence) as specified by an evaluator who was blind to cell assignment and used the Longitudinal Interval Follow-up Evaluation (LIFE). Blind evaluations were conducted at (1) the end of A-CT; (2) any time the patient, therapist, or follow-up evaluators suspected relapse or recurrence; (3) early exit; (4) months 4 and 8 of the experimental phase; and (5) months 12 and 24 of follow-up. Assessment for months 13 to 20 was conducted by unblinded evaluators because of the high cost of blind evaluations. If relapse or recurrence was suspected, a blind evaluation occurred.

The following definitions were used to conceptualize and define change points in the course of unipolar MDD. Response, the extent of patient response to A-CT, was defined by the blind evaluator within 7 days after session 20 as (1) absence of DSM-IV MDD and (2) an HRSD-17 score of 9 or less. Remission, when the patient is no longer fully symptomatic, was defined by a diagnostician (ie, therapist, blind evaluator, or other clinic evaluator) specifying for 6 consecutive weeks that (1) DSM-IV criteria for MDD were not met and (2) HRSD-17 score was 6 or less (during the acute phase) or the LIFE Psychiatric Rating Scale (PSR) rating was 1 or 2 (during experimental and follow-up phases). Recovery, the end of an episode, was defined as any project diagnostician declaring for 8 consecutive months that (1) DSM-IV criteria for MDD were not met and (2) HRSD-17 score was 6 or less (during the acute phase) and/or the LIFE PSR rating was 1 or 2 (during experimental and follow-up phases). Relapse, a continuation of the presenting episode, was defined by the blind evaluator as symptoms meeting DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 weeks) before the criteria for recovery were met. Recurrence, the emergence of a new episode distinct from the presenting episode, was defined by the blind evaluator as meeting DSM-IV criteria for MDD after the criteria for recovery were met.

STATISTICAL ANALYSES

The hypothesized relapse rates over the 8-month experiment were 47% for control and 19% for C-CT based on early analyses of previous samples. A minimum sample size of 72 was necessary to detect a significant difference. Recurrence estimates were reported as secondary measures during the 24-month follow-up.

All analyses were of an intention-to-treat strategy (N = 84; n for C-CT = 41; n for controls = 43). The end point in all the survival analyses was either relapse or recurrence. Patients who dropped out or survived were censored. Survival curves and relapse and recurrence rates were estimated using Kaplan-Meier product-limit methods. The survival rates for the 2 cells were compared using the log-rank test. The Cox proportional hazard regression was used to evaluate the influence of each candidate covariate (age of onset, age, sex, number of episodes, length of current episode, comorbid lifetime diagnoses, and definite Research Diagnostic Criteria endogenous diagnosis) as described by Collett. Covariates were compared with the null model to determine their influence on relapse over 8 months or on relapse and recurrence over 24 months without regard to condition assignment.

Categorical variables were reported as percent frequency (eg, number and percentage) and continuous variables as mean and SE. Significance was defined as P ≤ .05; Fisher exact tests (FETs) were 2-tailed.

RESULTS

SAMPLE CHARACTERISTICS

Figure 1 enumerates the sample composition. Eligible outpatients (n = 156) with recurrent MDD and clear interepisode recovery entered A-CT. Eligible responders (n = 84) consented to randomization. The demographic

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PATIENT DISPOSITION

Of the 156 patients who entered A-CT, 130 (83%) completed 20 sessions (2 patients became psychotic or homicidal and were withdrawn; 24 dropped out). Of these 130 patients, 128 (98%) consented to the first blind evaluation. Of these 128, 87 (68%) were judged to have responded to A-CT. Eighty-four (97%) of those eligible consented to randomization (1 patient refused to discontinue treatment with the A-CT therapist, 1 sought alternative treatment, and 1 had scheduling conflicts).

Seventy-six (90%) of the 84 randomized patients completed 10 sessions of the 8-month experiment or had a relapse or recurrence. When dropouts (n=8) were compared with completers (ie, had 10 sessions or had a relapse or a recurrence; n=76), 2 significant differences emerged. Dropouts had fewer previous episodes of depression (|t|15.5=4.03, P=.04). There was no significant difference in the number of patients who completed C-CT (95%; 39 of 41) compared with controls (86%; 37 of 43; FET, P=.28). One patient dropped out of C-CT because of a scheduling conflict and 1 failed to attend the first session. The 6 patients who dropped out of the control cell reported that the study was taking too much time.

Sixty responders survived the experiment and entered follow-up. Of these, 92% (n=55) completed 16 months of follow-up or experienced a relapse or recurrence. The percentage of patients completing follow-up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Randomized (N = 84)</th>
<th>Control (n = 43)</th>
<th>C-CT (n = 41)</th>
<th>Statistics†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%) female</td>
<td>61 (72.6)</td>
<td>31 (72.1)</td>
<td>30 (73.2)</td>
<td>P=.99</td>
</tr>
<tr>
<td>Race, No. (%) white</td>
<td>76 (90.5)</td>
<td>40 (93.0)</td>
<td>36 (87.8)</td>
<td>P=.48</td>
</tr>
<tr>
<td>Age, mean ± SE, y</td>
<td>42.74 ± 1.14</td>
<td>42.05 ± 1.59</td>
<td>43.46 ± 1.64</td>
<td>t60 = 0.62, P=.54</td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>13 (15.5)</td>
<td>4 (9.3)</td>
<td>9 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>48 (57.1)</td>
<td>29 (67.4)</td>
<td>19 (46.3)</td>
<td>P=.12</td>
</tr>
<tr>
<td>Divorced, separated, or widowed</td>
<td>23 (27.4)</td>
<td>10 (23.2)</td>
<td>13 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Education, mean ± SE, y</td>
<td>15.40 ± 0.30</td>
<td>15.16 ± 0.44</td>
<td>15.66 ± 0.41</td>
<td>t82 = 0.83, P=.41</td>
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<tr>
<td>Employment outside home, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least part-time</td>
<td>60 (71.4)</td>
<td>32 (74.4)</td>
<td>28 (68.3)</td>
<td>P=.63</td>
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<tr>
<td>Not employed</td>
<td>24 (28.6)</td>
<td>11 (25.6)</td>
<td>13 (31.7)</td>
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</tr>
<tr>
<td>Primary role function, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>60 (71.4)</td>
<td>33 (76.7)</td>
<td>27 (65.9)</td>
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<tr>
<td>Homemaker</td>
<td>5 (6.0)</td>
<td>2 (4.7)</td>
<td>3 (7.3)</td>
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<tr>
<td>Student</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1 (2.4)</td>
<td>P=.58</td>
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<tr>
<td>Retired</td>
<td>1 (1.2)</td>
<td>1 (2.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>17 (20.2)</td>
<td>7 (16.3)</td>
<td>10 (24.4)</td>
<td></td>
</tr>
<tr>
<td>HRSD-17 score, mean ± SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At presentation</td>
<td>20.12 ± 0.34</td>
<td>20.28 ± 0.46</td>
<td>19.95 ± 0.51</td>
<td>t60 = 0.48, P=.63</td>
</tr>
<tr>
<td>At final pretreatment follow-up</td>
<td>19.39 ± 0.34</td>
<td>19.84 ± 0.47</td>
<td>18.93 ± 0.48</td>
<td>t60 = 1.36, P=.18</td>
</tr>
<tr>
<td>Age at onset, mean ± SE, y</td>
<td>20.54 ± 1.00</td>
<td>20.14 ± 1.56</td>
<td>20.95 ± 1.25</td>
<td>t82 = 0.40, P=.69</td>
</tr>
<tr>
<td>Length of current episode, mean ± SE, y</td>
<td>2.71 ± 0.37</td>
<td>3.16 ± 0.60</td>
<td>2.24 ± 0.41</td>
<td>t133.5 = 1.27, P=.21</td>
</tr>
<tr>
<td>Length of illness, mean ± SE, y</td>
<td>21.81 ± 1.08</td>
<td>21.53 ± 1.67</td>
<td>22.10 ± 1.36</td>
<td>t82 = 0.60, P=.80</td>
</tr>
<tr>
<td>No. of episodes, mean ± SE</td>
<td>3.35 ± 0.13</td>
<td>3.35 ± 0.19</td>
<td>3.34 ± 0.17</td>
<td>t60 = 0.03, P=.98</td>
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<tr>
<td>Comorbid DSM-IV diagnoses, No. (%)‡</td>
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<td></td>
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<td></td>
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<tr>
<td>Current</td>
<td>34 (40.5)</td>
<td>16 (37.2)</td>
<td>18 (43.9)</td>
<td>P=.66</td>
</tr>
<tr>
<td>Lifetime</td>
<td>60 (71.4)</td>
<td>26 (60.5)</td>
<td>34 (82.9)</td>
<td>P=.03</td>
</tr>
<tr>
<td>Current double depression, No. (%)§</td>
<td>4 (4.8)</td>
<td>2 (4.7)</td>
<td>2 (4.9)</td>
<td>P&gt;.99</td>
</tr>
<tr>
<td>Depressive subtype, No. (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDC primary depression</td>
<td>54 (64.3)</td>
<td>26 (60.5)</td>
<td>28 (68.3)</td>
<td>P=.50</td>
</tr>
<tr>
<td>RDC endogenous, definite</td>
<td>21 (25.0)</td>
<td>11 (25.6)</td>
<td>10 (24.4)</td>
<td>P&gt;.99</td>
</tr>
<tr>
<td>DSM-IV melancholia</td>
<td>17 (20.2)</td>
<td>8 (18.6)</td>
<td>9 (22.0)</td>
<td>P=.79</td>
</tr>
<tr>
<td>DSM-III melancholia</td>
<td>1 (1.2)</td>
<td>1 (2.3)</td>
<td>0</td>
<td>P=.99</td>
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<tr>
<td>Family history, No. (%)‡</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Familial depressive disease</td>
<td>22 (26.2)</td>
<td>10 (23.3)</td>
<td>12 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Depressive spectrum disease</td>
<td>36 (42.9)</td>
<td>20 (46.5)</td>
<td>16 (39.0)</td>
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<tr>
<td>Sporadic depressive disease</td>
<td>15 (17.9)</td>
<td>8 (18.6)</td>
<td>7 (17.1)</td>
<td>P=.94</td>
</tr>
<tr>
<td>Bipolar family</td>
<td>9 (10.7)</td>
<td>4 (9.3)</td>
<td>5 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.4)</td>
<td>1 (2.3)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

* These 84 patients responded to acute-phase cognitive therapy and were randomized to the experimental phase. C-CT indicates acute-phase cognitive therapy plus continuing-phase cognitive therapy; HRSD-17, 17-item Hamilton Rating Scale for Depression‡; and RDC, Research Diagnostic Criteria.†

†P values correspond to 2-tailed Fisher exact test except for entries with t test values.

‡Current comorbidity is defined as at least 2 current DSM-IV Axis 1 disorders. Lifetime comorbidity reflects at least 2 DSM-IV Axis 1 disorders occurring during the lifetime. All patients with current comorbidity are included in the lifetime comorbidity percentages.

§Double depression is defined as the presence of dysthymia before the onset of the current episode.

| See Winokur22 and Winokur et al.23 |
in the 2 cells did not differ significantly (C-CT = 86%, 30 of 35; control = 100%, 25 of 25; FET, P = .08).

**PATIENT COMPLIANCE**

When relapse status was disregarded, the Wilcoxon rank test showed that neither the number of sessions (z = 1.8, P = .07) nor the number of months (z = 0.43, P = .67) differed in the 2 conditions. The 41 responders randomized to C-CT completed an average of 9.49 ± 0.30 (mean ± SE; mode = 10) sessions during an average of 7.26 ± 0.25 months (mode = 7.66). The 43 responders randomized to the control cell completed an average of 9.05 ± 0.29 sessions (mode = 10) during an average of 7.03 ± 0.26 months (mode = 7.59).

At randomization, all patients planned to defer psychiatric treatment until they experienced a relapse or recurrence or the study ended. Only 10 patients reported seeking psychiatric “treatment” lasting 2 or more weeks before relapse or recurrence. During the experimental phase, 2 patients reported “treatment”: 1 C-CT patient took methylphenidate hydrochloride (Ritalin) for 8 weeks and 1 control patient had 4 sessions of “peer support” for grief. None reported depressive symptoms (ie, PSR score ≥ 4) 4 weeks before or during the interval in which they received treatment.

During the follow-up phase and before relapse or recurrence, 8 patients (4 in C-CT and 4 in control) reported “treatment” for 2 or more weeks. One patient from C-CT who reported depressive symptoms also received 4 sessions of psychotherapy. The following treatment occurred during intervals in which the patients did not report depressive symptoms (ie, PSR score ≥ 4): 1 C-CT patient sought marital therapy with the cognitive therapist during longitudinal follow-up (36 sessions); 1 C-CT patient attended 2 sessions in a “women’s employment support group”; 2 patients (1 C-CT and 1 control) received 2 to 3 psychotherapy or family therapy sessions; 1 control patient had 19 sessions of marital therapy; 1 control patient took 5 conflict resolution classes with his partner; and 1 control patient reported taking melatonin for 3 weeks.

**THERAPIST COMPETENCE**

Of 210 total CTS ratings during A-CT, only 18 scores (8.6%) fell below 40. The mean A-CT CTS score was 47.10 ± 0.35 (mode = 52) with all therapists achieving mean scores of more than 46. The ANOVA produced nonsignificant effects across years (F4 = 1.21, P = .32) or across years (F3 = 2.56, P = .07).

The primary aim of the trial was to test the hypothesis that C-CT reduced relapse more than control (ie, assessment only) during the 8 months in which C-CT was provided. Patients who did not relapse or drop out during the 8 months were censored after 8 months. A log-rank test showed that during the 8 months of C-CT, it reduced the proportion of relapse significantly more than the control (relapse estimate: 10.3% vs 30.9%; χ21 = 5.26, P = .02; Figure 2).

**SECONDARY ANALYSES**

Both age of onset and patient age were identified as potential covariates (P = .10) by influencing relapse over 8 months (age, χ21 = 3.17, P = .09; age of onset, χ21 = 9.32, P = .002) and relapse or recurrence over 24 months (age, χ21 = 6.43, P = .01; age of onset, χ21 = 4.40, P = .04). The correlation between age and age of onset for the randomized sample (n = 84) was 0.5 (P < .001). Age of onset was used as the covariate because previous studies show that it predicted relapse and recurrence.31,32 A comparison of
Akaike Information Criteria\textsuperscript{30} verified that age of onset by itself was as good a predictor as both age and the 2 variables combined.

Since age of onset was identified as a covariate, the sample was divided into 2 strata (onset $\leq$ 18 years vs onset $> 18$ years) using an approximate median split. A log-rank test revealed significant interaction between condition (continuation-phase cognitive therapy [C-CT] or control [CT-free evaluation]) and age of onset (early, 18 years vs onset $> 18$ years) ($\chi^2 = 10.09, P = .002$).

For 24 months after randomization, a log-rank test revealed a significant interaction between age of onset and condition ($\chi^2 = 4.22, P = .039$; Figure 3). Post hoc results for 8 months' experimental phase replicated the following pattern found throughout 24 months.

For 24 months after randomization, a log-rank test revealed a significant interaction between age of onset and condition ($\chi^2 = 10.09, P = .002$; Figure 3). Control patients with an earlier age of onset were significantly more likely to experience a relapse than were those with later onset (67% vs 36%; $\chi^2 = 4.34, P = .049$). Patients with an earlier onset were significantly less likely to experience a relapse or recurrence if they received C-CT than if they did not (16% vs 67%; $\chi^2 = 6.78, P = .009$). There was no difference in the relapse and recurrence estimates for patients with early and late onset who were treated with C-CT (16% vs 50%; $\chi^2 = 2.71, P = .10$). Similarly, there was no significant difference in the relapse and recurrence estimates for patients with later-onset MDD who did and did not receive C-CT (50% vs 36%; $\chi^2 = 0.549, P = .47$).

Since previous studies\textsuperscript{4,7,13,14,33-35} showed that quality of acute-phase remission predicted relapse or recurrence, we hypothesized that C-CT might reduce relapse or recurrence when remission was unstable in late-phase A-CT. Based on the work of Thase and associates,\textsuperscript{7} we formed 2 strata to determine whether the pattern of remission interacted with condition to influence the cumulative survival rates. Fifty-two (62%) of 84 patients showed "unstable" remission (1 or more HRSD-17 scores were $\geq 7$ during the 6 final A-CT sessions and first blind evaluation spread over an average of 6.70±0.13 weeks). Thirty-two (38%) of 84 patients showed "stable" remission (all 7 HRSD-17 scores were $< 7$ over an average of 6.34±0.15 weeks).

An overall log-rank test comparing the survival curves throughout 8 months for condition and stability of remission showed that the interaction between condition and stability was significant ($\chi^2 = 14.96, P = .002$; Figure 4).
stable pattern of remission (62% vs 30%; $\chi^2 = 4.70, P = .03$). All other comparisons were nonsignificant.

**COMMENT**

To our knowledge, this is the first randomized clinical trial that compares CT with and without a continuation phase in CT responders who remain at high risk for relapse and recurrence because of a history of recurrent depression. Eight months of C-CT focusing on residual symptoms, relapse prevention, and consolidation of skills reduced estimated relapse rates significantly more than the control. The 24-month analyses revealed that in patients at higher risk for relapse and recurrence (ie, those with early onset of their first depression or unstable remission late in the acute phase), C-CT reduced rates even after therapy was discontinued. This finding suggests that in vulnerable patients, the effects of C-CT may endure after discontinuation, distinguishing the effects of CT from those of pharmacotherapy. Furthermore, the estimates of relapse and recurrence during 2 years in the higher-risk patients treated with C-CT are comparable to rates observed during continuation and maintenance pharmacotherapy. When the higher-risk patients received C-CT, their estimated relapse or recurrence did not differ from those at lower risk who had only A-CT. Specifying these interactions between C-CT and unstable remission or age of onset in robust prediction of relapse or recurrence adds to similar, emerging literature.

The major limitation of this study is that the sample size decreases over time. The findings require replication. Changing any combination of the parameters defining the sample or treatment may affect generalizability. This study design differs from studies with (1) CT in all 3 phases, (2) pharmacotherapy in all 3 phases, (3) acute-phase pharmacotherapy followed by continuation- and maintenance-phase CT (combination therapy), or (4) CT focused exclusively on residual symptoms.

When combined with the literature, results suggest that CT used as a continuation- and maintenance-phase treatment deserves more evaluation and appears to offer patients safe, tolerable, and effective prevention for an extended period. To date, after response to the acute phase has been documented, C-CT and its variants have protected responders to A-CT, acute-phase pharmacotherapy, and acute-phase pharmacotherapy plus CT. The appropriate number of CT sessions, as well as the months needed to prevent relapse and recurrence, likely depends on age of onset and the extent of remission that a patient achieves during A-CT. Current results suggest that A-CT alone (a total of 20 sessions) can reduce depressive relapse when stable remission has been achieved or in patients with a later age of onset. On the other hand, A-CT plus C-CT (30 sessions total, including a focus on prevention) can reduce relapse and recurrence in patients with an earlier age of onset or unstable remission. Clinicians and third-party payers can easily use extent of acute-phase remission to identify patients who no longer meet DSM-IV criteria for MDD, yet continue to require additional CT because the risk of relapse or recurrence is high.

The finding that people who develop depression early in life are vulnerable to depressive relapse and recurrence after successful treatment highlights the importance of evaluating early intervention and preventive strategies for children and adolescents. Psychosocial treatments offer promise for this population.

To reduce residual symptoms and relapse and recurrence, C-CT should be standard practice, not only in psychopharmacology, but also in cognitive therapy when acute-phase remission is unstable. Additional controlled studies are necessary to evaluate the relative efficacy and effectiveness of 6 months of C-CT vs continuation-phase pharmacotherapy in patients at highest risk for depressive relapse and recurrence. Future treatments that reduce residual symptoms, relapse, and recurrence further will increase the relevance of the findings for affected patients.

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