Preventing Depressive Relapse and Recurrence in Higher-Risk Cognitive Therapy Responders
A Randomized Trial of Continuation Phase Cognitive Therapy, Fluoxetine, or Matched Pill Placebo

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IMPORTANCE Strategies to improve the course of recurrent major depressive disorder have great public health relevance. To reduce the risk of relapse/recurrence after acute phase cognitive therapy (CT), a continuation phase model of therapy may improve outcomes.

OBJECTIVES To test the efficacy of continuation phase CT (C-CT) and fluoxetine for relapse prevention in a pill placebo (PBO)-controlled randomized trial and compare the durability of prophylaxis after discontinuation of treatments.

DESIGN A sequential, 3-stage design with an acute phase (all patients received 12 weeks of CT); 8-month experimental phase (responders at higher risk were randomized to C-CT, fluoxetine, or PBO); and 24 months of longitudinal, posttreatment follow-up.

SETTING Two university-based specialty clinics.

PATIENTS A total of 523 adults with recurrent major depressive disorder began acute phase CT, of which 241 higher-risk responders were randomized and 181 subsequently entered the follow-up.

INTERVENTIONS Cognitive therapy responders at higher risk for relapse were randomized to receive 8 months of C-CT (n = 86), fluoxetine (n = 86), or PBO (n = 69).

MAIN OUTCOMES AND MEASURES Survival analyses of relapse/recurrence rates, as determined by blinded evaluators using DSM-IV criteria and the Longitudinal Interval Follow-up Evaluation.

RESULTS As predicted, the C-CT or fluoxetine groups were significantly less likely to relapse than the PBO group across 8 months. Relapse/recurrence rates for C-CT and fluoxetine were nearly identical during the 8 months of treatment, although C-CT patients were more likely to accept randomization, stayed in treatment longer, and attended more sessions than those in the fluoxetine and PBO groups. Contrary to prediction, relapse/recurrence rates following the discontinuation of C-CT and fluoxetine did not differ.

CONCLUSIONS AND RELEVANCE Relapse risk was reduced by both C-CT and fluoxetine in an enriched randomization sampling only CT responders. The preventive effects of C-CT were not significantly more durable than those of fluoxetine after treatment was stopped, suggesting that some higher-risk patients may require alternate longer-term interventions.

TRIAL REGISTRATION clinicaltrials.gov Identifiers: NCT00118404, NCT00183664, and NCT00218764

Published online September 4, 2013.
Major depressive disorder (MDD) is a recurrent, disabling, and potentially lethal illness, with high rates of residual symptoms and persistent psychosocial impairment, even among a large percentage of those who respond to treatment. Antidepressants have long been a cornerstone of treatment of recurrent depression, and continuation phase pharmacotherapy has become the standard of care to offset a high risk of relapse\(^{5,6}\); indefinite or even life-long courses of maintenance pharmacotherapy are recommended for prophylaxis against highly recurrent episodes.\(^{5,7}\) However, despite the established efficacy of longer-term pharmacotherapy, treatment utilization data indicate that many patients receive only a few months of treatment with antidepressants.\(^{8,9}\) Thus, identification of alternate therapies that reduce the risks of relapse and recurrence has great public health significance and is the focus of intensive study.\(^{10-15}\)

Time-limited psychotherapies, such as cognitive therapy (CT),\(^{16,17}\) have emerged over the past 30 years as viable alternatives to antidepressant medications and, in controlled trials, CT has been found to have comparable efficacy to pharmacotherapy across 12 to 16 weeks of treatment.\(^{6,17-19}\) Moreover, the relapse risk after completing a 12- to 16-week course of CT is lower than after stopping a similar course of pharmacotherapy, which suggests that the benefits of acute phase CT may be more durable than those of pharmacotherapy after treatment is stopped.\(^{11,13,20}\) Nevertheless, the hypothesis that CT will significantly increase the likelihood of sustained recovery and/or reduce the risk of recurrent depression over a number of years needs more systematic evaluation.\(^{11,18}\) Indeed, in 2 of the longest follow-up studies of CT responders, relapse/recurrence rates of 60%\(^{21}\) and 74%\(^{22}\) were observed across 24 months.

One factor that may moderate the durability of CT response in depression is the quality of the response to acute phase therapy. Specifically, in independent studies conducted in Pittsburgh, Pennsylvania, and Dallas, Texas, CT-treated patients who had not fully remitted by about the seventh week of therapy were found to have 3 to 4 times the risk of relapse/recurrence than those with more rapid and complete remissions.\(^{23}\) Thus, identification of alternate therapies that reduce the risks of relapse and recurrence has great public health significance and is the focus of intensive study.

To address the problem of relapse and recurrence following acute phase therapy, Jarrett and colleagues\(^{24-25}\) (also R.B.J., unpublished treatment manual. Cognitive therapy for recurrent unipolar major depressive disorder: the continuation/maintenance phase, 1989) developed and refined a model of continuation phase CT (C-CT). In the first controlled trial of this intervention, Jarrett et al\(^{23}\) found that C-CT effectively reduced the risk of relapse/recurrence across 8 months of therapy compared with an assessment-only control. Moreover, the protective effect of C-CT across 24 months (including 16 months posttreatment) was strongest among patients with early-onset depression and those who had slow or incomplete remissions.

The current study was undertaken to test prospectively the relative merits of C-CT among patients with recurrent MDD who, despite responding to a 12-week course of acute phase CT, were classified to be at an increased risk of relapse/recurrence. Relative efficacy was assessed by randomizing patients to C-CT or clinical management and either pill placebo (PBO) or fluoxetine. Outcomes were assessed across 8 months of double-blind therapy and, after discontinuation of treatments, across 24 months of follow-up. Predictions were that (1) both C-CT and fluoxetine would significantly reduce the rate of relapse across 8 months compared with PBO and (2) across 20 months, C-CT would have significantly less relapse/recurrence than fluoxetine. Thus, we predicted that whereas both active therapies could suppress the risk of relapse, C-CT would have a more durable benefit after treatment was stopped than fluoxetine.

### Methods

A detailed description of methods is available,\(^{26}\) as are acute phase and additional reports.\(^{27-36}\) The methods are briefly summarized here.

#### Patients

The study procedures and protocol were approved annually by the institutional review boards at the University of Texas Southwestern Medical Center and University of Pittsburgh Medical Center. Patients provided written Health Insurance Portability and Accountability Act authorization and informed consent for evaluation and treatment.

Outpatients were recruited from both clinical referrals and advertisements between March 30, 2000, and July 9, 2008, and were eligible if they presented with a principal diagnosis of recurrent MDD, as diagnosed by the Structured Clinical Interview for the DSM-IV,\(^{37}\) either remitted between depressive episodes or had antecedent dysthymic disorder, and scored 14 or more on the 17-item Hamilton Rating Scale for Depression (HRSD-17)\(^{38}\) at both an initial diagnostic evaluation and a second, confirmatory interview (see footnote A in the eAppendix in Supplement). Exclusion criteria included unstable medical illnesses and other principal psychiatric conditions that warranted separate treatment (eg, substance dependence or obsessive compulsive disorder; see article by Jarrett and Thase\(^{36}\)). Of the 1359 outpatients who began a 2-step clinical evaluation, 523 provided informed consent, were fully eligible for study participation, and began acute phase CT.

#### Study Procedures

Psychotropic medications and other psychosocial interventions were prescribed during the study.

**Acute Phase Cognitive Therapy**

Experienced therapists delivered acute phase CT as described by Beck et al\(^{16}\). The 12-week protocol consisted of 16...
to 20 individual sessions, each lasting 50 to 60 minutes; up to 2 additional weeks were permitted to accommodate scheduling needs. Sessions were twice a week for 4 weeks. Thereafter, patients who had obtained 40% or greater reduction in the HRSD-17 began weekly sessions, whereas the remainder continued twice-weekly sessions for 4 more weeks before beginning weekly sessions.

The 16 therapists had completed at least 1 year of supervised CT training and demonstrated competence as documented by Cognitive Therapy Scale (CTS) scores of 40 or greater. Throughout the study, therapists received ongoing supervision or consultation; CTS ratings were made from randomly selected videotaped sessions.

During the course of acute phase therapy, patients also attended 2 psychoeducational sessions on relapse/recurrence risks and study requirements. 26

**Acute Phase Treatment Response and Stratification**

Therapists completed the HRSD-17 weekly; an evaluator without knowledge of cell assignment completed final blinded clinician ratings at the end of CT or exit. Based on the independent evaluator ratings, response was defined as: (1) no DSM-IV major depressive episode and (2) a 17-item HRSD score of 12 or less. The rationale for this liberal threshold was to include patients who had benefited from treatment but who were at increased relapse risk. Responders were prospectively stratified according to a classification of relapse/recurrence risk derived from earlier research. 22 Higher-risk patients had at least 1 HRSD-17 score of 7 or higher during the final 7 acute phase assessments including the blinded evaluation; these patients were eligible for the randomized continuation phase protocol. Lower-risk patients, defined by HRSD-17 scores of 6 or less during the final 7 assessments, received no further protocol treatment and entered the follow-up phase.

Inter-rater reliability for diagnoses of major depressive episodes was moderate. Based on a sample of 41 patients rated by 3 to 21 clinicians each, the median kappa of all pairwise comparisons was 0.48. However, uncorrected percentage agreement among rater was 91%.

**Randomization to 8-Month Experimental Phase Treatments**

The study statistician used a computer program to randomize patients within strata (site, number of depressive episodes, and presence/absence of dysthymia); assignments were implemented by the study coordinators and research pharmacists (see footnotes B and C in the eAppendix in Supplement). Only dispensing pharmacists knew assignment to fluoxetine or PBO and could break the blind during a clinical emergency. The integrity of the randomization was confirmed by the study statistician.

During the first 6 years of the study, the primary goal was to test the efficacy of C-CT and fluoxetine vs PBO across the 8-month experimental phase, which necessitated allocating 180 patients evenly to the 3 arms. Thereafter, the primary goal was to compare the durability of C-CT and fluoxetine across 20 months postrandomization (ie, 1 year after continuation treatments were discontinued). To maximize the number of patients assigned to the 2 active arms, the proportion allocated to the PBO was reduced to less than 10%. This change in the randomization proportions, which was approved by the funding organization and the study’s data monitoring and safety board, was not revealed to patients, therapists, or research staff.

**8-Month Continuation Phase Cognitive Therapy**

Continuation phase C-CT 25,41 (also R.B.J., unpublished treatment manual. Cognitive therapy for recurrent unipolar major depressive disorder: the continuation/maintenance phase, 1989) aimed to prevent relapse and promote remission and recovery. Patients practiced applying compensatory skills in response to emotional distress and residual and emerging depressive symptoms. Therapists focused on generalizing the skills across problems, situations, and time. Preemptive coping strategies were practiced in relation to previously identified cognitive and behavioral vulnerabilities. The first 4 (60 minutes) sessions occurred biweekly and the last 6 occurred monthly.

**8-Month Clinical Management Plus Fluoxetine/Pill Placebo**

Fluoxetine was chosen because of its established efficacy 42,43 and a low incidence of discontinuation-emergent symptoms. 44 Experienced pharmacotherapists provided clinical management according to the methods of Fawcett et al. 45 Visits occurred at the same frequency as C-CT. The initial session lasted up to 45 minutes; thereafter, sessions lasted up to 30 minutes. Pharmacotherapists evaluated symptoms and negative side effects and could provide support but were not permitted to use the specific methods of C-CT. Negative side effects were rated using a 3-point scale (0 = absent, 1 = mild, 2 = severe).

Research pharmacies at each site packaged and dispensed active fluoxetine or identical PBO capsules in 10- or 20-mg units. Adherence was estimated by pill counts at each visit.

Study medications were titrated upwards using a fixed-flexible protocol: 10 mg/d for 2 weeks, 20 mg/d for 2 weeks, and 40 mg/d thereafter. The dose could be decreased to a minimum of 10 mg/d to lessen negative side effects. Patients who could not tolerate any dose could be followed up for clinical management alone. From week 8 onward, the modal doses of fluoxetine and PBO were 40 mg/d. At the end of the experimental phase, study medication was stopped, without a downward taper schedule.

**Outcome Assessments**

At the end of months 4 and 8 of the experimental phase, an independent evaluator assessed DSM-IV criteria for MDD using the Structured Clinical Interview and Psychiatric Status Ratings (PSR) 46 from the Longitudinal Interval Follow-up Evaluation (LIFE). Interim or emergency evaluations were also performed if a relapse/recurrence was suspected. Assessments were conducted without knowledge of treatment assignment. Infrequently, telephone assessments were performed when patients were not available for in-clinic assessments.

During the longitudinal follow-up, all protocol treatments were discontinued and independent evaluators used the
same methods to evaluate patients every 4 months (ie, 12, 16, 20, 24, 28, and 32 months after randomization). Patients were encouraged to contact study staff if they were experiencing depressive symptoms or worsening in some other way so that an interim blinded evaluation could be completed. The last patient completed the follow-up phase in May 2011.

Across study phases, patients who experienced a relapse/recurrence were immediately referred for nonresearch treatment.

Primary Outcomes: Relapse/Recurrence

Relapse, which designates an exacerbation of the presenting episode after a response but before recovery, was defined by DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks).

Stable remission was synonymous with lower risk and included (1) the last 7 consecutive HRSD-17 scores of less than 7 during the acute phase or (2) return to usual self, according to the LIFE (ie, 6 PSR scores of 2 or less over 6 weeks after randomization).

Recovery, the end of an episode, was defined as a remission lasting 8 or more consecutive months.

Recurrence, a new episode, was defined as meeting DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks) after recovery. Time to relapse/recurrence was computed in weeks, where a week was 7 days and a year was 52 weeks, resulting in a month being 4.33 weeks. Thus, the continuation phase was 8 months or 35 weeks long, followed by 2 years or 104 weeks of follow-up.

Statistical Analyses

The sample size was based on a predicted 30% difference in relapse/recurrence rates between C-CT and fluoxetine (ie, 30% vs 60%) across both the experimental phase and the first 12 months of follow-up. With these assumptions, 180 randomized patients (60 per cell) were required to detect a statistically significant difference using a log-rank test with 1-sided a = 0.05 and 80% power. The study did not have adequate power to detect smaller, but potentially clinically meaningful, differences between the C-CT and fluoxetine groups across the full 32-month study. Patient entry ended when the sample size was sufficient to test the primary hypothesis regarding relapse/recurrence across 20 months.

All analyses used the intention-to-treat sample, with cumulative relapse/recurrence as the primary outcomes for the survival analysis. Patients who dropped out prior to experiencing an event were censored at their last available evaluation. Survival curves were estimated using the Kaplan-Meier product limit method and the relapse/recurrence rates were compared using a log-rank test. Cox proportional hazard regression analysis was used to assess the effect of covariates on the relapse/recurrence rates. The covariates were the site, number of prior depressive episodes, early or late study cohort, length of current episode, and interactions between treatment groups and site, as well as treatment groups and study cohort. The presence/absence of dysthymia was omitted as a covariate because of its low rate. All comparisons were 1-sided with a type I error rate of α = 0.05.

No planned, unmasked interim analyses of the primary hypothesis were done.

Results

Sample Description

Figure 1 displays the sample composition. A total of 523 outpatients entered acute phase CT and 241 higher-risk responders were randomized to C-CT, fluoxetine, or PBO; 50 lower-risk responders were eligible for longitudinal follow-up. The randomized patients were primarily female, white, and in their early 40s. Additional demographic and clinical characteristics are reported in the eTable (Supplement). Race/ethnicity was self-reported by patients to complete the target sample requirements of the sponsor and to comment on generalizability.

Patient Disposition

Acute Phase Cognitive Therapy

Of the 523 patients who began CT, 113 (21.6%) dropped out. Of the 410 completers, 193 had at least 40% reduction in HRSD-17 score by session 9 and attended at least 14 of 16 planned sessions. Among the remainder, 217 completed at least 18 of 20 planned sessions. A total of 395 (96.3%) of the completers attended the blinded evaluation, of which 292 (71.2%) met criteria for response. Of these, 242 (59%) were classified as higher risk and 241 were randomized; 4 patients withdrew consent to be randomized and 3 patients were randomized in error. See footnotes B and C in the eAppendix in Supplement for further details.

Experimental Phase

Randomized assignments were as follows: C-CT, n = 86; clinical management plus fluoxetine, n = 86; and clinical management plus PBO, n = 69. Sixty patients (25%) withdrew: 16 (19%) in C-CT; 24 (28%) in fluoxetine, and 20 (29%) in PBO (χ² = 2.9, P = .24). Attrition during the experimental phase was greater at the Pittsburgh site (22.1%) than at the Dallas site (18.9%) (χ² = 5.5, P = .02). Although attrition did not differ by treatment, significantly more patients in the medication clinic (combined fluoxetine and PBO, n = 13) dropped out before the first continuation phase session compared with those in the C-CT group (n = 1). Patients who dropped out of the experimental phase were significantly more likely to be single, younger, have antecedent dysthymia, and a shorter illness duration. Pre-treatment demographic, clinical, interpersonal, and cognitive characteristics of the drop-outs did not differ across cells.

Follow-up

Of the 181 who entered follow-up (70 in C-CT, 62 in fluoxetine, and 49 in PBO), 145 (80.1%) completed at least 12 months (56 in C-CT, 52 in fluoxetine, and 37 in PBO) and 124 (n = 68.5%) completed 24 months (47 in C-CT, 44 in fluoxetine, and 33 in PBO). The percentage of patients who completed longitudinal follow-up did not differ significantly as a function of continuation phase treatments or between sites.

Adherence to Study Procedures

Sessions Completed

Of the 241 randomized patients, 147 (61.0%) completed all 10 sessions (60 in C-CT, 48 in fluoxetine, and 39 in PBO). Patients in the C-CT arm attended significantly more sessions than...
those in the pharmacotherapy arms (mean [SD], C-CT: 8.9 [2.4] sessions; PBO: 7.1 [3.9] sessions; fluoxetine: 7.5 [3.6] sessions; $F_{2,238} = 6.41, P < .01$). There also was a significant difference in the mean length of the continuation phase ($F_{2, 238} = 6.74, P < .01$), with C-CT patients staying significantly longer compared with those in the pharmacotherapy arms.

**Medication Dosage**

Of the 151 patients with available dosage data, 110 (72.8%) achieved the target medication dosage (ie, either 40 mg/d of fluoxetine or PBO equivalent).

**Use of Concomitant Nonprotocol Therapies**

During the experimental phase, 13 randomized patients reported using nonstudy medications that might have had psychoactive effects (C-CT, n = 7; fluoxetine, n = 2; PBO, n = 5). In most cases (n = 8), the medication was an over-the-counter sleeping pill; 1 patient in the C-CT arm deviated from the protocol by taking an antidepressant prescribed by a primary care physician. Two patients (1 each in the fluoxetine and PBO arms) deviated from the protocol by attending self-help support groups. No relationships were evident between usage and treatment cell (according to $\chi^2$ tests) or between usage and relapse/recurrence (according to Cox regression).

**Therapist Competence**

Randomly selected sessions were rated using the CTS ($n = 368$; [334 acute phase and 34 continuation phase]); only 27 (7.3%) scores fell below 40. Analyses of variance showed that mean (SD) CTS ratings did not differ by study phase, site, or entry cohort.

**Risks of Treatment**

**Severe Adverse Events**

Two patients were hospitalized during acute phase CT for worsening depression and/or suicidal ideation; they were withdrawn from the study and treated as appropriate. During the continuation phase, 1 patient randomized to PBO was hospitalized for suicidal ideation and was withdrawn from the study. Three patients (1 from each cell) were hospitalized during the follow-up due to worsening depression and/or suicidal ideation.

**Negative Side Effects Analysis**

The only negative side effect that was significantly greater in fluoxetine than PBO was tremors (19.8% vs 5.8%; $\chi^2 = 6.4$, $P = .01$).

**Comparisons of Relapse/Recurrence Rates**

The relapse rate for PBO during the experimental phase was estimated using Kaplan-Meier as 32.7% (17 of 69), which was significantly higher than the 18.3% estimated relapse rate in the 2 active treatment arms (Figure 2; 26 of 172; log-rank $\chi^2 = 5.06$, $P = .01$). The relapse rates in the fluoxetine and C-CT arms were nearly identical over 8 months (fluoxetine: 18.0% [12 of 66 relapsed] and C-CT: 18.3% [14 of 78 relapsed]; log-rank $\chi^2 = 0.038$;
and both fluoxetine (log-rank $\chi^2 = 3.92, P = .02$) and C-CT (log-rank $\chi^2 = 3.39, P = .03$) reduced relapse significantly more than PBO. As none of the covariates tested in Cox regression models (including the one significant difference across cells in length of episode) were significantly associated with relapse risk, the log-rank tests were interpreted.

Kaplan-Meier estimates of relapse/recurrence rates across the follow-up are summarized in the Table. At follow-up month 12, the relapse/recurrence rates for C-CT (35%; 24 of 86) and fluoxetine (35%; 22 of 86) did not differ significantly (log-rank $\chi^2 = 0.04, P = .42$). Across the subsequent follow-up, log-rank tests with pairwise comparisons showed no differences among treatments at 24 or 32 months postrandomization.

### Table. Relapse and/or Recurrence Rates in the 3 Treatment Arms Over 8, 20, and 32 Months Postrandomization

<table>
<thead>
<tr>
<th>Time Since Randomization</th>
<th>Rate of Relapse/Recurrence, %</th>
<th>Log-Rank</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>Fluoxetine</td>
<td>C-CT</td>
<td>Fluoxetine or C-CT</td>
</tr>
<tr>
<td>8 mo</td>
<td>32.7</td>
<td>18.0</td>
<td>18.3</td>
<td>18.3</td>
</tr>
<tr>
<td>Fluoxetine vs C-CT</td>
<td>0.038</td>
<td>.42</td>
<td></td>
<td>1.079 (0.50-2.34)</td>
</tr>
<tr>
<td>PBO vs fluoxetine</td>
<td>3.916</td>
<td>.02</td>
<td></td>
<td>0.481 (0.23-1.01)</td>
</tr>
<tr>
<td>PBO vs C-CT</td>
<td>3.391</td>
<td>.03</td>
<td></td>
<td>0.519 (0.26-1.06)</td>
</tr>
<tr>
<td>PBO vs fluoxetine or C-CT</td>
<td>5.057</td>
<td>.01</td>
<td></td>
<td>0.501 (0.27-0.93)</td>
</tr>
<tr>
<td>20 mo</td>
<td>42.7</td>
<td>35.1</td>
<td>35.0</td>
<td>35.1</td>
</tr>
<tr>
<td>Fluoxetine vs C-CT</td>
<td>0.002</td>
<td>.48</td>
<td></td>
<td>0.988 (0.55-1.76)</td>
</tr>
<tr>
<td>PBO vs fluoxetine</td>
<td>1.190</td>
<td>.14</td>
<td></td>
<td>0.717 (0.39-1.31)</td>
</tr>
<tr>
<td>PBO vs C-CT</td>
<td>1.262</td>
<td>.13</td>
<td></td>
<td>0.715 (0.40-1.29)</td>
</tr>
<tr>
<td>PBO vs fluoxetine or C-CT</td>
<td>1.595</td>
<td>.10</td>
<td></td>
<td>0.717 (0.43-1.20)</td>
</tr>
<tr>
<td>32 mo</td>
<td>56.3</td>
<td>41.1</td>
<td>45.2</td>
<td>43.2</td>
</tr>
<tr>
<td>Fluoxetine vs C-CT</td>
<td>0.070</td>
<td>.40</td>
<td></td>
<td>1.075 (0.63-1.84)</td>
</tr>
<tr>
<td>PBO vs fluoxetine</td>
<td>2.407</td>
<td>.61</td>
<td></td>
<td>0.649 (0.37-1.13)</td>
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<tr>
<td>PBO vs C-CT</td>
<td>1.731</td>
<td>.09</td>
<td></td>
<td>0.701 (0.41-1.19)</td>
</tr>
<tr>
<td>PBO vs fluoxetine or C-CT</td>
<td>2.705</td>
<td>.05</td>
<td></td>
<td>0.676 (0.42-1.08)</td>
</tr>
</tbody>
</table>

Abbreviations: C-CT, continuous phase cognitive therapy; PBO, placebo.

* Hazard ratios for the category listed second.

$P = .42$ and both fluoxetine (log-rank $\chi^2 = 3.92, P = .02$) and C-CT (log-rank $\chi^2 = 3.39, P = .03$) reduced relapse significantly more than PBO. As none of the covariates tested in Cox regression models (including the one significant difference across cells in length of episode) were significantly associated with relapse risk, the log-rank tests were interpreted.

Kaplan-Meier estimates of relapse/recurrence rates across the follow-up are summarized in the Table. At follow-up month 12, the relapse/recurrence rates for C-CT (35%; 24 of 86) and fluoxetine (35%; 22 of 86) did not differ significantly (log-rank $\chi^2 = 0.002, P = .48$). Across the full 32-month protocol, the relapse/recurrence rates were again comparable (fluoxetine: 41.1% and C-CT: 45.2%). Across these same intervals, the relapse and recurrence rates for the PBO group were 42.7% and 56.3%, respectively. None of the pairwise comparisons were significantly different. The Cox proportional hazard regression models including covariates yielded similar results.

As between-group differences in outcomes during the experimental phase may have influenced effects during the sub-
sequent follow-up, a frailty analysis was conducted as an additional post hoc test. Results of this independent analysis, completed by J. Vittengl, PhD, confirmed those of the survival analyses.

Discussion

The primary goals of this study were (1) to determine the efficacy of 8 months of C-CT and fluoxetine compared with PBO in patients with recurrent MDD predicted to be at higher risk for relapse/recurrence despite responding to CT and (2) to compare the durability of outcomes of C-CT and fluoxetine after the therapies were stopped. The assessment of risk was based on unstable or partial remission using a prospectively applied algorithm based on earlier research. A prospective comparison of the higher- and lower-risk strata confirmed the validity of this classification; details are the subject of a separate analysis.

As predicted, the patients who received either active therapy had a significantly lower risk of relapse/recurrence (about 18%) than did those who received PBO (about 33%) over 8 months. Contrary to prediction, we found no evidence to support the hypothesis that C-CT conveys more enduring prophylaxis in acute phase CT responders than fluoxetine after continuation phase treatments are stopped.

This research has several implications. First, patients who respond to CT but who remain at high risk because of slow, unstable, or partial remissions not only benefit from C-CT, but also respond to CT but who remain at high risk because of slow, unstable, or partial remissions not only benefit from C-CT, but also respond to C-CT. This finding replicates the earlier randomized clinical trial of Jarrett et al and extends the research by using a more rigorous control condition (ie, clinical management and PBO rather than assessment only). In addition, the current findings show that C-CT’s preventive effects can be generalized to a site that was not involved in its development.

Second, the findings indicate that continuation phase fluoxetine alone also can be used to reduce the risk of relapse after an initial course of CT. To our knowledge, this is the first time that an antidepressant medication has been shown to significantly reduce the risk of relapse/recurrence for patients who first received psychotherapy. We noted that the converse (ie, the use of CT and related therapies in sequence to reduce the risk of relapse/recurrence after antidepressant therapy) has been demonstrated by other groups.

Third, although fluoxetine was effective, patients in the pharmacotherapy arms were more likely to drop out during the first month of the experimental phase, and they attended fewer treatment sessions than did those in the C-CT arm. Therefore, we suspect that, in practice, offering a continuation phase of CT will be preferred by most patients who received psychotherapy alone as the initial intervention. Nevertheless, these results suggest that antidepressant medication can provide a preventive effect for acute phase CT responders when C-CT is either not feasible or not preferred.

Fourth, and contrary to prediction, we found no evidence that C-CT conveyed more durable prophylaxis in acute phase CT responders after treatment was stopped than fluoxetine. Moreover, although our study did not have adequate statistical power to reliably detect modest differences between the active treatments, the groups had comparable survival rates across the full 32-month study. Therefore, it is possible that such higher-risk patients may require more than 8 months of continuation phase treatment (eg, ongoing maintenance phase therapy) or some alternate intervention to reduce the risk of recurrent depression. The timing, amount, and duration of such treatment with the aims of promoting recovery and reducing recurrence of MDD will require additional study among higher-risk CT responders.

Fifth, the null comparisons with the PBO-treated group after the end of the experimental phase cannot be interpreted with confidence because of the different time courses of relapse (ie, those assigned to PBO were most likely to relapse during the experimental phase) and because the study was not designed or powered to make such sequential comparisons.

Finally, the cumulative relapse/recurrence rates for the sample show that even patients judged to be at high risk for relapse/recurrence after CT have a relatively low risk of relapse/recurrence after continuation phase therapies were stopped as compared with both (1) the natural history of recurrent depression or (2) the documented course of patients switched to PBO after responding to acute phase pharmacotherapy. Specifically, whereas recurrence rates as high as 80% might be expected among patients with either highly recurrent MDD or incomplete remission despite adequate pharmacotherapy across 1 to 2 years, only 56% of our at-higher-risk sample treated with PBO during the continuation phase had experienced a relapse/recurrence 32 months after completion of acute phase therapy. In summary, these results are consistent with the hypothesis that acute phase CT does convey some degree of enduring prophylaxis and emphasized in the lower-than-expected relapse/recurrence rates in PBO.

This study has a number of strengths. To our knowledge, it is the largest, well-characterized sample of CT responders ever followed longitudinally. It is also the largest study of recurrence prevention strategies after acute phase CT ever undertaken. The study medication consisted of an identical-appearing pill PBO matched to fluoxetine. The therapists were quite proficient; their competence was monitored and documented longitudinally. The longitudinal evaluation of relapse and recurrence was conducted across 32 months post-randomization by evaluators without knowledge of treatment assignment and was longitudinal over 32 months post-randomization. Patient drop-out rates across all 3 phases of study participation were typical and acceptable. Site and cohort effects over 11 years of data collection were either absent or relatively minor. Effects of tested covariates were null.

The generalizability of the findings is limited by the inclusion/exclusion criteria, particularly the fact that our study involved unmedicated adults with recurrent MDD who responded to a 12-week course of CT but showed a slow or unstable remission. We also noted that our definition of lower risk was very rigorous, as only 17% of CT responders met this definition for stable remission. Attrition across a 3-stage longitudinal study, which for some patients amounted to almost 3 years of research participation, also can limit interpreta-
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In conclusion, CT responders at higher risk of relapse/recurrence due to slow or incomplete remission can be safely and effectively treated with either continuation phase CT or switching modalities to fluoxetine. Although the 2 treatments were comparably effective, continuing CT was the more acceptable strategy, which is perhaps not surprising since they had benefitted from acute phase therapy and were able to continue working with the same clinician. After active therapies were discontinued, the preventative effects of both treatments dissipated, suggesting that some higher-risk patients may benefit from additional continuation/maintenance therapies. The parameters of such continuation/maintenance therapy warrant further study.

ARTICLE INFORMATION

Submitted for Publication: July 31, 2012; final revision received January 18, 2013; accepted February 14, 2013.


Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jarrett, Thase.

Acquisition of data: Jarrett, Gershfenfeld, Friedman, Thase.

Analysis and interpretation of data: All authors.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Minhajuddin

Obtained funding: Jarrett, Thase.

Administrative, technical, or material support: All authors.

Study supervision: Jarrett, Gershfenfeld, Friedman, Thase.

Conflict of Interest Disclosures: Dr Jarrett's medical center collects the payments from the cognitive therapy she personally provides to patients. Dr Jarrett is a paid consultant to the National Institute of Mental Health. Drs Minhajuddin and Gershfenfeld report no related financial interests. Dr Friedman has received grant support from the National Institute of Mental Health and Agency for Healthcare Research and Quality. He has served as an expert forensic psychiatrist for Thompson Rhodes & Cowie PC and Berger and Zavesky Co LPP. He receives royalties from Springer. He has been a member of speaker bureaus or advisory boards for AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, Weth-Ayerst, and Pamlab. He has received grant or research support from Aspect Medical Systems, Indevus, AstraZeneca, Bristol-Myers Squibb, Pfizer, Sanoi-Aventis, Wyeth-Ayerst, Cyberonics, Novartis, Northstar, and Medtronic. During the past 5 years, Dr Thase has consulted with, served on advisory boards for, or received honoraria for talks from Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Co, Forest Laboratories, GlaxoSmithKline, Jansen Pharmaceutical, Lundbeck, MedAvante Inc, Merck, Neurotechnics Inc, Novartis, Otsuka, Pamlab, Pfizer Pharmaceuticals, Pharmeneuroboost, Shire US Inc, Sunovion, Takeda, Teva, and Transcept Pharmaceuticals. And he has received grant support from Alkermes, AstraZeneca, Eli Lilly and Co, Forest Laboratories, GlaxoSmithKline, Neosync, Otsuka, Pharmeneuroboost, and Roche, in addition to funding from the National Institute of Mental Health and the Agency for Healthcare Research and Quality. He has equity holdings for MedAvante Inc and has received royalties from American Psychiatric Publications, the Apipx, Guilford Publications, Herald House, and W. W. Norton & Co Inc. Two books currently promoted by the Apipx specifically pertain to cognitive therapy. Dr Thase also discloses that his spouse is an employee of Peloton Advantage, which does business with several pharmaceutical companies that market medications used to treat depression. No other disclosures were reported.

Funding/Support: This study was supported by grants K24 MH001571, R01 MH058337, and R01 MH069619 (Dr Jarrett) and by R01 MH058356 and R01 MH09618 (Dr Thase) from the National Institute of Mental Health. We acknowledge the unrestricted support of Eli Lilly and Co, which provided fluoxetine and matched pill placebo for the first 6 years of the study. Thereafter, study materials were purchased and prepared to appear identical for both sites by the pharmacy at The University of Texas Southwestern Medical Center.

Role of the Sponsor: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health. The National Institute of Mental Health had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are grateful to our patients, research teams, and colleagues at The University of Texas Southwestern Medical Center, the University of Pittsburgh, and the University of Pennsylvania who made this trial possible and were named earlier.26 We also appreciate the collaboration of Jeffrey Vittengl, PhD (Truman State University), who helped to evaluate the quality of the National Institute of Mental Health or the National Institutes of Health. The National Institute of Mental Health had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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