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ORIGINAL ARTICLE

The Role of Cognitive-Behavioral Therapy and Fluoxetine in Prevention of Recurrence of Major Depressive Disorder

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Abstract This study evaluated the role of cognitive-behavioral therapy (CBT) and fluoxetine in preventing recurrence of a depressive episode during maintenance phase treatment for patients with remitted major depressive disorder (MDD). Patients (n = 52) completed open acute fluoxetine treatment and sustained remission during a 28-week randomized continuation treatment (CBT + fluoxetine vs. fluoxetine only). They were assigned to one of four maintenance treatments: CBT + fluoxetine, CBT + placebo, fluoxetine only, and placebo only. There were no statistically significant differences in MDD recurrence between maintenance treatments, but continued antidepressant treatment (with or without CBT) provided an 18–21% lower MDD recurrence rate than placebo. These findings are consistent with those of recent antidepressant studies of chronic and recurrent MDD populations. Although sample sizes were small, CBT did not significantly lower rates of MDD recurrence.

Keywords CBT · Fluoxetine · Recurrence · Relapse · Major Depressive Disorder · Treatment · Prevention

Major depressive disorder (MDD) is a highly recurrent, often chronic illness (Fava and Kaji 1994). Even following successful acute phase treatment, patients remain at risk for relapse of the index depressive episode or the emergence of a new episode (recurrence). Patients not

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achieving full remission following the acute treatment phase (i.e., partial response with remaining residual symptoms) are at greater risk for both relapse and recurrence (Judd et al. 1997). As a result, emphasis has been placed on evaluating treatments according to their ability to produce acute phase remission and prevent relapse and recurrence.

Evidence indicates that continuation and maintenance of antidepressant treatment lowers rates of relapse and recurrence relative to placebo (Fava and Kaji 1994). In addition, both interpersonal psychotherapy and variants of cognitive-behavioral therapy (CBT) have shown efficacy in preventing relapse and recurrence relative to control treatments (Fava et al. 1998; Frank et al. 1990; Reynolds et al. 1999; Teasdale et al. 2000). Specifically, variants of CBT modified to specifically address residual symptoms in patients who have recovered from depression appear to be most efficacious in preventing relapse and recurrence (Segal et al 2002).

In spite of recent clinical advances, the precise role of antidepressants and CBT in preventing depressive recurrence during the maintenance phase of treatment remains unclear. Past research suggests that medication maintenance prevents recurrence (Fava and Kaji 1994; Keller et al. 1998), and the addition of CBT methods to medication maintenance confers a long-term treatment advantage (Paykel et al. 1999; Teasdale et al. 2000). This study sought to investigate the efficacy of different forms of maintenance treatment. To accomplish this goal, the present study compared rates of MDD recurrence and symptom change during maintenance phase treatment for remitted MDD patients who were randomized to one of four treatment groups: (a) antidepressant (fluoxetine) treatment only, (b) CBT plus antidepressant treatment, (c) CBT plus placebo, and (d) placebo only. Patients had previously achieved sustained remission through open acute and randomized continuation treatment, the results of which are described elsewhere (Perlis et al. 2002). Based upon previous research suggesting beneficial effects of maintenance treatment, we hypothesized that patients receiving active treatment (antidepressant and/or CBT) would show lower rates of MDD recurrence compared to those receiving placebo. Furthermore, in light of research suggesting superiority of combined maintenance treatments, we hypothesized that those receiving a combination treatment (CBT + medication) would have a superior outcome relative to those receiving monotherapy (CBT or medication alone).

Method

Participants were recruited through the Depression Clinical and Research Program (DCRP) of the Massachusetts General Hospital between 1992 and 1998. All participants signed written consent approved by the Massachusetts General Hospital's Institutional Review Board. Patients were randomized to one of four 80-week maintenance treatment groups: CBT + placebo, CBT + medication (40 mg fluoxetine), medication (40 mg fluoxetine) only, and placebo only. Participants entered the maintenance phase of treatment after completing the acute and continuation phases of treatment (Table 1).

The *acute phase* was an open, eight-week, fixed dose of fluoxetine at 20 mg/day (n = 391 patients; 55% female; mean age 39.8 ± 10.6; Fava et al. 2002). Sixty patients dropped out during the acute phase of treatment (391 – 60 = 331). Of the remaining 331 patients, 101 (52 men and 49 women; mean age, 41.6 ± 10.6 years) met criteria for partial response (n = 49) or nonresponse (n = 52). These patients were randomized, as part of a separate study, to four weeks of double-blind treatment with high-dose fluoxetine (40–60 mg/day), fluoxetine plus lithium (300–600 mg/day), or fluoxetine plus desipramine (25–50 mg/day). Eighty-two

Table 1 Demographic and clinical features by maintenance treatment group

Characteristic	CBT + placebo (n = 11)	CBT + medication (fluoxetine) (n = 11)	Medication (fluoxetine) (n = 14)	Placebo (n = 16)
Age (years)	42.9 (±9.3)	45.1 (±8.1)	43.5 (±8.8)	43.2 (±9.8)
Current episode duration (years)	1.9 (±3.0)	2.1 (±2.5)	1.7 (±1.7)	6.6 (±9.0)
# of prior episodes	8.6 (±15.1)	2.3 (±1.5)	4.2 (±5.6)	4.2 (±5.6)
Age of onset (years)	22.4 (±8.3)	32.6 (±8.9)	32.6 (±13.4)	27.3 (±17.6)
HAMD-17 acute baseline	17.4 (±2.4)	19.7 (±4.2)	17.7 (±2.3)	18.5 (±3.1)
HAMD-17 continuation baseline	3.5 (±1.9)	4.4 (±2.9)	4.3 (±2.1)	4.2 (±2.6)
HAMD-17 maintenance baseline	2.8 (±2.5)	5.4 (±4.5)	5.5 (±2.1)	4.3 (±3.7)
Female (%)	70	67	47	53
4+ years of post-secondary education (%)	50	22	27	40
Employed (%)	30	33	20	7
Married (%)	70	67	40	60

Note. HAMD-17 = 17-item Hamilton Rating Scale for Depression

patients (33 men and 49 women; mean age 40.4 ± 9.1 years) met criteria for response and were offered open-label treatment within the DCRP program. Of the 148 patients who met criteria for full remission, 16 refused randomization to the continuation study described in this report. The remaining remitters (n = 132; 54.5% female; mean age 39.9 ± 10.3) to this acute phase treatment [remission = 17-item Hamilton Rating Scale for Depression (HAMD-17; Hamilton 1960)] ≤7 for three consecutive weeks) were randomized to two, 28-week *continuation phase* treatment groups: (1) increase in fluoxetine to fixed dose 40 mg/day (n = 66) or, (2) the same increased fixed dose plus 12 weekly sessions and then seven biweekly CBT sessions (n = 66) (Perlis et al. 2002).

There were no significant differences between the two continuation treatment groups in rates of relapse, discontinuation, change in well-being, or residual symptoms and symptom questionnaire scores. Rates of relapse were 6% (4/66) for the CBT + medication group and 8% (5/66) for the medication only group (Perlis et al. 2002). Of the 132 patients randomized to the continuation study groups, 47 discontinued the study (9 due to relapse), 30 exited the study to receive open-label treatment of worsened depressive symptoms, and 55 met criteria for and were randomized to *maintenance phase* treatments.

Acute Phase Inclusion/Exclusion Criteria

Participants were drug-free outpatients who met criteria for MDD, as diagnosed with the Structured Clinical Interview for DSM-III-R—Patient Edition (Spitzer et al. 1989), had an initial 17-item Hamilton Rating Scale for Depression (HAM-D-17; Hamilton 1960) score >16, and were 18 to 65 years of age. Patients were also required to meet at least one of the following criteria: history of three or more major depressive episodes, with the prior episode no more than 2.5 years before the onset of the current episode; diagnosis of current episode as chronic (onset of continuous depressive symptoms ≥36 months prior to study); history of poor interepisode recovery; or both MDD and dysthymia.

Exclusion criteria included pregnant women and women of child-bearing potential who were not using a medically accepted means of contraception, women of child-bearing potential

taking a birth control pill, or women who were currently lactating. Also excluded were patients with a serious risk of suicide, seizure disorder history, major unstable medical illness, history of multiple adverse drug reactions or allergy to the study drugs, antisocial personality disorder, or a DSM-III-R comorbid diagnosis of axis I pathology other than anxiety disorders. Furthermore, patients currently using nonstudy related psychotropic drugs or exhibiting evidence of hypothyroidism were excluded. Patients were excluded if their depression failed to respond in the past to a trial of (1) a higher dose of fluoxetine (60–80 mg/day), (2) the combination of fluoxetine and desipramine, or (3) the combination of fluoxetine and lithium. Finally, patients were excluded if they failed to respond during the course of their current major depressive episode to at least one adequate antidepressant trial, defined as six weeks or more of treatment with either >150 mg of imipramine (or its tricyclic equivalent) or >60 mg of phenelzine (or its monoamine oxidase inhibitor equivalent).

Maintenance Phase Protocol

Fifty-five patients (54% women; mean age: 43.6 years) met criteria for remission at the end of the continuation treatment phase and were randomized to one of four maintenance treatments: CBT plus placebo (n = 12), CBT plus medication (n = 11), medication only (n = 15), and placebo only (n = 17). Three patients (one in the CBT + placebo group, one in the medication only group, and one in the placebo group) discontinued the study before beginning maintenance phase treatment, resulting in the following group sizes for analyses: CBT plus placebo (n = 11), CBT plus medication (n = 11), medication only (n = 14), and placebo only (n = 16). All three patients who discontinued were lost to follow up. With such low frequency, no differences in discontinuation were detected across the four groups. Patients were randomized to one of the four maintenance treatment groups on the basis of their continuation treatment assignment. Patients who received CBT during continuation treatment were eligible for randomization to either the CBT plus placebo or CBT plus medication maintenance arms. Patients who did not receive CBT during continuation treatment were eligible for randomization to either the medication only or placebo only maintenance arms.

Patients were seen for 20 monthly study visits by psychiatrists or psychologists. During each visit, patients were administered the 31-item version of the HAM-D (allowing the scoring of the HAMD-17; Hamilton 1960), and the Clinical Global Impressions—Severity (CGI-S) and Improvement (CGI-I) Scales (Guy 1976). To assess symptom change and therapeutic improvement, patients completed the 92-item Symptom Questionnaire (SQ; Kellner 1987), the Beck Hopelessness Scale (BHS; Beck et al. 1974), the Beck Depression Inventory (BDI; Beck et al. 1961), the Patient Global Impression of Improvement (PGI-I; Guy 1976), and the Beck Anxiety Inventory (BAI; Beck et al. 1988) at the conclusion of each study visit.

Cognitive therapy was conducted by highly trained doctoral-level psychologists according to a treatment manual adapted from Beck et al. (1979) and Mercier and Leahy (1992). CBT was modified to address residual symptoms specifically and to enhance patient coping skills. The therapy used for this study was designed specifically to target symptoms and issues common to remitted depressed patients, who are at high risk for relapse and recurrence. Three content domains are emphasized when working with remitted depressed patients. The first is *recovery*, which involves working to resolve any residual symptoms that are present after clinical remission. Such residual symptoms are common and include: irritability, neurovegetative disturbances, and hopelessness. The second content area is *re-entry*, which entails working to increase a patient's functioning in key life roles such as student, family member, spouse, and employee. An acute depressive episode typically results in lowered levels of functioning in one or more of these areas, thus the gap between current and optimal

psychosocial functioning may be significant. One common target of this content area is avoidant behavior, which is often activated by a patient to maintain tentative short-term stability but in turn prevents return to premorbid levels of functioning. The third content area, *risk*, involves focusing on maladaptive cognitive and behavioral patterns that contribute to heightened relapse rates. Such patterns include lack of assertiveness and self-care, as well as perfectionism and unrealistic self-expectations. The structure of therapy for the maintenance phase of this protocol (an 80-week period) consisted of seven biweekly, 50-min sessions followed by 16 monthly, 50-min sessions. Each session followed a conventional cognitive therapy format, which includes: symptom check, agenda setting, homework review, cognitive and behavioral exercises for specific problem areas, and assignment of new homework. For details on what specific techniques are matched to certain problem areas, a full treatment manual is available upon request (Pava et al. 1996). Psychopharmacologists followed a standard protocol for medication management visits (Fawcett et al. 1987) and were instructed not to engage in cognitive or behavioral interventions (Pava et al. 1994).

Data Analysis

The primary study endpoint was depressive recurrence, defined as either meeting criteria for a new episode of MDD at any maintenance visit or scoring 15 or higher on the HAM-D-17 over two consecutive visits. Recurrence was confirmed by a follow-up visit one week later with another clinician blind to treatment status. The chi-square method was used to compare MDD recurrence rates across the four treatment groups. The Kaplan–Meier survival analysis was also utilized for time-to-recurrence or study discontinuation, with observations censored after 80 weeks, following completion of this phase of the study. The Mantel–Cox (log-rank) test was used to compare survival curves between study conditions. Paired *t*-tests were used to compare within-group changes on secondary measures (from baseline to week 80 or study discontinuation), and factorial ANOVAs were used to compare groups. Effect sizes of within-group changes were calculated using the method suggested by Cohen (1992). Factorial ANOVAs were used to compare mean outcome measure values across treatment groups for the entire maintenance phase. All values for a given outcome measure for each patient were totaled and divided by the number of observed data points for that patient. All analyses were conducted on the intent-to-treat sample, with last observation carried forward. All tests were two-tailed, with the threshold for statistical significance set at $p < 0.05$.

Results

The primary outcome of this study was rate of recurrence, which was not significantly different across the four treatment groups: CBT + placebo = 5/11 (45%); CBT + medication = 4/11 (36%); medication only = 4/14 (29%); placebo = 8/16 (50%; $X^2 = 1.91$, $p = 0.19$). The overall MDD recurrence rate for medication (with or without CBT) was not significantly lower (8/25, 32%) than the recurrence rate for placebo (50%). Kaplan–Meier survival curves were constructed with results censored at end of maintenance phase or at study discontinuation for reason other than recurrence, and there were no significant differences between groups (log-rank $X^2 = 2.37$, $df = 3$, $p > 0.40$). We also examined rates of recurrence between the two patient groups defined as continuation treatment assignments (medication only and CBT + medication). Rates of recurrence, using this methodology, were: medication only = 9/22 (41%) and CBT + medication = 12/30 (40%). Kaplan–Meier survival curves were

Table 2 Mean change and effect size (Cohen's *d*) of change during maintenance treatment

Measure	CBT + placebo (n = 11)	CBT + medication (n = 11)	Medication (n = 14)	Placebo (n = 16)
BAI	0.66 (±2.04)	–0.34 (±0.65)	0.40 (±0.64)	–0.31 (±0.15)
	d = 0.35	d = –0.12	d = –0.11	d = –0.06
BDI	2.38 (±4.64)	0.43 (±0.82)	1.50 (±1.33)	–0.47 (±0.48)
	d = 0.59	d = 0.08	d = 0.30	d = 0.05
HAMD-17	2.50(±1.36)	1.71 (±1.25)	1.44 (±0.89)	0.29 (±0.16)
	d = 0.83	d = 0.39	d = 0.50	d = 0.08
CGI-I	0.20 (±0.47)	0.33 (±0.44)	0.18 (±0.27)	0.32 (±0.29)
	d = 0.40	d = 0.47	d = 0.23	d = 0.60
PGI-I	0.33 (±0.22)	0.29 (±0.26)	0.08 (±0.31)	0.33 (±0.12)
	d = 0.59	d = 0.39	d = 0.11	d = 0.41
CGI-S	0.43 (±0.24)	0.35 (±0.15)	0.11 (±0.09)	0.50 (±0.32)
	d = 0.74	d = 0.48	d = 0.17	d = 0.76
SQ Depression	2.67 (±1.32)	0.14 (±0.10)	0.15 (±0.08)	0.56 (±0.28)
	d = 1.01	d = 0.03	d = 0.03	d = 0.08
SQ Anxiety	2.05 (±1.32)	0.79 (±0.47)	0.02 (±0.07)	1.53 (±1.10)
	d = 0.87	d = 0.18	d = 0.01	d = 0.32
SQ Hostility	1.69 (±1.18)	0.34 (±0.59)	0.77 (±0.62)	0.51 (±0.77)
	d = 0.45	d = 0.11	d = 0.17	d = 0.09
SQ Somatic	1.19 (±1.01)	0.61 (±0.45)	0.28 (±0.54)	–0.01 (±0.32)
	d = 0.41	d = 0.13	d = 0.09	d = 0.01
BHS	1.07 (±1.02)	0.48 (±0.20)	–0.17 (±0.23)	–0.83 (±1.06)
	d = 0.36	d = 0.22	d = 0.04	d = 0.13

Note. BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HAMD-17 = 17-item Hamilton Rating Scale for Depression; CGI-I = Clinical Global Impressions, Improvement; PGI-I = Patient Global Impressions, Improvement; CGI-S = Clinical Global Impressions, Severity; SQ = Symptom Questionnaire; BHS = Beck Hopelessness Scale

constructed for these results censored at end of maintenance phase or at study discontinuation for reason other than recurrence, and there were no significant differences between groups (log-rank $\chi^2 = 0.14$, $df = 1$, $p = 0.71$). For those who received CBT (with or without medication), the mean number of psychotherapy sessions completed was 21.1 ($SD = 2.5$) of 23 for the CBT + medication group and 21.6 ($SD = 1.9$) for the CBT + placebo group.

As seen in Table 2, there were no significant differences in change scores between groups on the BAI, BDI, HAMD-17, CGI-I, PGI-I, CGI-S, and SQ (depression, anxiety, hostility, somatic), and BHS. The 52 patients randomized to maintenance treatment did not differ significantly from the remainder of the sample ($n = 339$; all comparisons $p > 0.05$) on any of the demographic characteristics.

Discussion

As with a number of studies on the long-term effects of therapies for depression (e.g., Frank et al. 1990; Paykel et al. 1999), the sample size in this investigation of maintenance treatments is small. Conclusions about the lack of statistically significant differences between groups

therefore must be tentative. Nonetheless, a discussion of the findings can stimulate future research on prevention efforts in the treatment of depression, which is increasingly being characterized as a recurrent and chronic disorder (McCullough et al. 2003). An unexpected finding was that CBT did not provide further protection from recurrence when added to pharmacotherapy. This finding is inconsistent with some recent studies in which CBT conferred an advantage in long-term treatment outcome when compared with antidepressant treatments alone or with no treatment control conditions (Jarrett et al. 2001; Teasdale et al. 2000). For example, in a recent study by Teasdale and colleagues (Teasdale et al. 2000), 145 patients who had remitted or recovered by the end of acute phase pharmacologic treatment were randomized to receive medication management only or medication management plus Mindfulness-Based Cognitive Therapy (MBCT). MBCT is a group intervention designed to train recovered recurrently depressed patients to disengage from depressogenic thinking that may mediate relapse/recurrence. Relapse/recurrence to major depression was assessed over a 60-week study period. Patients treated with MBCT experienced 30% fewer relapses/recurrences compared to the usual care group. The Teasdale et al. (2000) study included a larger sample than the present study, a group rather than individual psychotherapy, and a different cognitively-based therapy that included meditation. However, there was no placebo control group, and medication was provided naturalistically, with no dosing restrictions or limitations on type of antidepressant used.

Jarrett and colleagues (2001) studied 84 treatment responsive patients with recurrent MDD who were randomized to either eight months (10 sessions) of cognitive (CT) or a control condition (evaluation without CT). Over an eight-month period, only 10% of patients receiving CT relapsed, whereas 31% of those in the control condition relapsed. This study differs from ours in that patients did not receive antidepressant treatment during any phase of treatment. In addition, the psychotherapy utilized was CT, not CBT, and involved far fewer sessions. However, the Jarrett et al. (2001) study does suggest a prophylactic effect of CT when compared with no treatment.

Two other recently published studies provide important additional data regarding the long-term impact of psychotherapeutic treatments for depression. Gelenberg et al. (2003) examined recurrence rates in two maintenance treatment arms—nefazodone treatment ($n = 76$) and placebo only ($n = 74$). All patients randomized to these two arms had achieved and sustained clinical response during the acute and continuation treatment phases with either nefazodone alone or in combination with psychotherapy specifically designed for chronically depressed patients (CBASP). Findings of this maintenance study, while supporting the importance of long-term antidepressant maintenance treatment to prevent recurrence, did not reveal any added protective effect of psychotherapy. In a companion study, some patients from the same cohort who received maintenance psychotherapy sessions (up to 13 monthly sessions) had lower recurrence rates (10.7%; $n = 42$) than patients receiving clinical management (CM) only (32.0%; $n = 40$) (Klein et al. 2004). This latter investigation is most similar to ours in that psychotherapy was provided throughout all phases of treatment.

Recent studies have also evaluated the ability of CT or CBT to resolve residual depressive symptoms and lower rates of relapse and recurrence. For example, Paykel et al. (1999) randomized 158 patients who responded to acute phase pharmacotherapy but still reported residual symptoms to either 16 CBT sessions plus medication or to usual CM (medication only). After this continuation treatment, patients were followed for one year. The cumulative relapse rate was 47% for the CM group and 29% for the CBT group. Patients were allowed to have up to a 30% increase in antidepressant dosing during continuation treatment. Our study differs in that dosing of fluoxetine was doubled after acute phase treatment, and only those

who remitted in our continuation and maintenance study arms were included, thus excluding patients with significant residual symptoms.

G.A. Fava and colleagues have also conducted a series of investigations (1998b,c) to evaluate CBT in resolving residual symptoms and reducing relapse/recurrence rates. In brief, 43 patients were followed for a six-year period following acute phase antidepressant response and randomization to either CBT or usual CM. CBT consisted of 10 biweekly sessions and was modified to specifically address residual symptoms and relapse prevention. All patients in the CM group had antidepressants tapered and ultimately discontinued during continuation treatment. Relapse/recurrence rates for the CM and CBT groups were 35% vs. 15% at two year, 70% vs. 35% at four year, and 75% vs. 50% at six-year follow-up points.

G.A. Fava and colleagues then devised a modified form of cognitive therapy known as Well Being Therapy (WBT; Fava et al. 1998b). The rationale for WBT is that continuation psychotherapy should not only target depressive cognitions and behaviors, but also ways to enhance well-being and modify problematic lifestyles. In a study that evaluated WBT vs. CM during the continuation phase of treatment (Fava et al. 1998c), patients' antidepressant medications were tapered after about three months into the continuation phase. Results indicate that over a period of two years, 80% of patients in the CM group experienced a depressive relapse, as compared with 25% in the WBT group. Although it is unclear how WBT might have its prophylactic effects, this finding has led to increased interest in the use of this specialized form of psychotherapy to prevent depressive relapse and recurrences. The major difference between Fava et al.'s work and ours is that patients in their protocols tapered and ultimately discontinued antidepressant medications, whereas patients in our protocol remained on an increased dosage throughout the continuation phase of treatment. In addition, the initial focus of our post-acute treatment was on resolving residual depressive symptoms.

Other studies are consistent with our findings of no significant prophylactic effect of CT (Blackburn and Moore 1997; Frank et al. 1990; Shea et al. 1992). In analyses of follow-up data from the NIMH collaborative study, Shea and colleagues (1992) found that neither IPT nor CT provided additional benefit in terms of prevention of relapse and recurrence, when compared with medication only and placebo conditions. Blackburn and Moore (1997) randomized 75 outpatients with recurrent major depression to three groups: 16 weeks of acute treatment and two years' maintenance treatment with antidepressants and maintenance antidepressants; cognitive therapy and maintenance cognitive therapy; and antidepressants and maintenance cognitive therapy. In the acute phase of treatment, all patients improved significantly, and there were no significant differences among treatments or in the pattern of improvement over time. In the maintenance stage, CT therapy had a similar prophylactic effect to maintenance medication, and there were no differences in symptom improvement or relapse/recurrence between the three treatment groups. Some patients in this protocol received acute phase CT, whereas patients in our protocol received only medication during acute phase treatment.

Although the findings were not statistically significant, on some secondary measures we did see a trend toward separation of groups. For instance, the CBT + placebo and CBT + medication groups demonstrated lower mean scores on the BAI, BDI, and SQ anxiety subscale when compared with the medication only group. With a larger sample, it is possible that such differences would have reached statistical significance. We speculate that these results may represent a tendency for CBT to provide a greater prophylactic effect than medications alone, as previous research mentioned above suggests.

As suggested by Segal et al. (2002), sequenced or crossover treatment in which the delivery of antidepressant medication is followed by structured psychotherapy appears to provide superior prophylaxis than either treatment alone or concurrently combined. However, studies

to date are few and generally include small sample sizes. Much work remains to further elucidate optimal forms of psychotherapy and how to integrate such psychosocial treatments with antidepressant medications.

Aside from insufficient power, another limitation of the study is that we did not include independent ratings of treatment quality and fidelity. As a result, it is possible that the quality of CBT and/or adherence to the treatment manual differed between therapists. However, the therapists who provided treatment in this study are formally trained and certified to provide CBT treatment for depression, which makes it more likely that psychotherapy was uniform. A second limitation is that patients randomized to maintenance treatment entered via two different continuation phase pathways (CBT and medication or medication only) and thus may represent groups with different degrees of relapse risk before receiving maintenance treatment. In addition, given that patients were experiencing minimal depressive symptoms upon entry to the maintenance phase (HAMD-17 mean score range = 2.8–5.5 across treatment groups), it is conceivable that there were limited targets for CBT interventions (e.g., residual depressive symptoms). In this way, it is possible that there was less room for CBT to provide a prophylactic effect. Modified forms of CBT, such as Well Being Therapy (Fava et al. 1998a) or MBCT (Teasdale et al. 2000) may be a better match for remitted patients. Future investigations may benefit from a more streamlined design, where patients who respond or remit to acute phase treatment are randomized to maintenance treatment arms immediately, rather than adding an intervening continuation phase. In addition, keeping continuation and maintenance phase antidepressant doses at the same level as in the acute phase would help to clarify the specific relapse prevention effects of CBT. Such a design would also mitigate antidepressant side effects that can contribute to dropout or be confused for re-emergence of symptoms.

Even with these limitations, data from this study provide an important contribution to a relatively understudied area in the long-term treatment of depression and confirm the importance of the design and execution of larger size, well-controlled, randomized trials to investigate the role of CBT-based psychotherapies and antidepressant medication in the prevention of depressive relapse and recurrence.

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