ORIGINAL ARTICLE

Antidepressant Monotherapy vs Sequential Pharmacotherapy and Mindfulness-Based Cognitive Therapy, or Placebo, for Relapse Prophylaxis in Recurrent Depression

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Context: Mindfulness-based cognitive therapy (MBCT) is a group-based psychosocial intervention designed to enhance self-management of prodromal symptoms associated with depressive relapse.

Objective: To compare rates of relapse in depressed patients in remission receiving MBCT against maintenance antidepressant pharmacotherapy, the current standard of care.

Design: Patients who met remission criteria after 8 months of algorithm-informed antidepressant treatment were randomized to receive maintenance antidepressant medication, MBCT, or placebo and were followed up for 18 months.

Setting: Outpatient clinics at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada, and St Joseph's Healthcare, Hamilton, Ontario.

Participants: One hundred sixty patients aged 18 to 65 years meeting *DSM-IV* criteria for major depressive disorder with a minimum of 2 past episodes. Of these, 84 achieved remission (52.5%) and were assigned to 1 of the 3 study conditions.

Interventions: Patients in remission discontinued their antidepressants and attended 8 weekly group sessions of MBCT, continued taking their therapeutic dose of antidepressant medication, or discontinued active medication and were switched to placebo.

Main Outcome Measure: Relapse was defined as a return, for at least 2 weeks, of symptoms sufficient to meet the criteria for major depression on module A of the Structured Clinical Interview for *DSM-IV*.

Results: Intention-to-treat analyses showed a significant interaction between the quality of acute-phase remission and subsequent prevention of relapse in randomized patients ($P=.03$). Among unstable remitters (1 or more Hamilton Rating Scale for Depression score >7 during remission), patients in both MBCT and maintenance treatment showed a 73% decrease in hazard compared with placebo ($P=.03$), whereas for stable remitters (all Hamilton Rating Scale for Depression scores ≤ 7 during remission) there were no group differences in survival.

Conclusions: For depressed patients achieving stable or unstable clinical remission, MBCT offers protection against relapse/recurrence on a par with that of maintenance antidepressant pharmacotherapy. Our data also highlight the importance of maintaining at least 1 long-term active treatment in unstable remitters.

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RELAPSE AND RECURRENCE after recovery from major depressive disorder (MDD) are common and debilitating outcomes that carry enormous personal, familial, and societal costs.[1] Maintenance antidepressant monotherapy (M-ADM), the current standard for depressive relapse prophylaxis,[2] is effective as long as it is continued, but in practice this plan is compromised by rates of patient nonadherence that can reach 40%.[3,4] Alternatives to long-term antidepressant monotherapy, especially those that address mood outcomes in a broader context of well-being, may appeal to patients wary of continued intervention.

One such approach involves the use of sequenced, phase-specific depression treatments within an envelope spanning both acute-phase and postremission care.[5] Such models involve treating patients to remission pharmacologically and then providing psychotherapy aimed at preventing relapse or recurrence by teaching affect regulation and self-management skills to be

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used during recovery. Implicit in this approach is the view that the mechanisms underlying the onset of a depressive episode differ from those responsible for its return[6] and that unique interventions are required to address each. Prevention outcomes from the sequential treatment of mood disorders are largely supportive of the approach. Fava et al[7,8] reported lower relapse rates at 4-year follow-up and fewer multiple relapses for patients in remission who discontinued medication and received cognitive behavioral therapy compared with clinical management. Bockting et al[9] found that brief cognitive behavioral therapy, when added to usual care and initiated after episode remission, provided a significant protective effect during a 5-year period compared with usual care alone.

Similar findings have been obtained with mindfulness-based cognitive therapy (MBCT), a group intervention designed to train recovered, recurrently depressed patients to disengage from dysphoria-activated depressogenic thinking that increases risk for relapse/recurrence. In addition, MBCT's emphasis on the daily practice of health-enhancing behaviors such as meditation or yoga is a positive incentive for the type of long-term engagement required by any maintenance therapy. To date, this intervention, designed to be suitable for patients achieving remission via antidepressant treatment, has been evaluated in 3 randomized controlled trials, with outcomes suggesting a 50% reduction in relapse for patients receiving MBCT compared with treatment as usual[10,11] or no difference in survival compared with maintenance pharmacotherapy.[12]

These data, while encouraging, do not address the frequently encountered clinical scenario in which a patient in remission wishes, for reasons of preference,[13] adverse effect burden,[14] or suitability (eg, pregnancy),[15] to discontinue antidepressant treatment but requires additional prophylactic care. Although previous studies have enrolled patients who were already in remission, no study, to our knowledge, has explicitly treated patients to remission pharmacologically with the aim of testing MBCT's prevention effects directly after discontinuation against active treatment or a placebo control. Addressing this question would help determine MBCT's generalizability to real-world clinical settings and evaluate, more broadly, the sequential staging through which both treatments are delivered.

The present study was designed to test the relative efficacy of MBCT and M-ADM (vs placebo plus clinical management) for prevention of relapse or recurrence in patients with recurrent depression who have achieved remission through antidepressant pharmacotherapy. We predicted that both MBCT and M-ADM would offer effective protection when compared against placebo and that the level of protection achieved by MBCT would not differ from that provided by M-ADM.

METHODS

The study protocol was approved by institutional review boards at the Centre for Addiction and Mental Health (CAMH), Toronto, and St Joseph's Healthcare, Hamilton. Participants provided written consent before engaging in any research activity. Subjects were recruited through clinical referrals, physician outreach, and media announcements describing the Mood Disorders Clinics at CAMH and St Joseph's. There were 2 study phases. During the acute phase, all patients received open-label, 2-step antidepressant pharmacotherapy according to the Texas Medication Algorithm Project guidelines.[16] Patients who met the criteria for remission were treated for 5 additional months and then randomly assigned to 1 of the 3 study arms.

Diagnostic eligibility for the study was determined by means of the Structured Clinical Interview for *DSM-IV* diagnosis (Axis I and II) (SCID).[17,18] In addition, the first 17 items of the Hamilton Rating Scale for Depression (HRSD)[19] were used to determine whether the severity of depressive symptoms warranted inclusion in the trial.

Inclusion criteria were as follows: (1) diagnosis of MDD according to *DSM-IV* criteria, (2) a score of 16 or higher on the HRSD, (3) 2 or more previous episodes of MDD (to ensure that those randomized would have a minimum of 3 past episodes), (4) age between 18 and 65 years, and (5) English speaking and the ability to provide informed consent. Exclusion criteria were as follows: (1) a current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline or antisocial personality disorder; (2) a trial of electroconvulsive therapy within the past 6 months; (3) depression secondary to a concurrent medical disorder; (4) current or planned pregnancy within the 6 months of acute-phase treatment; and (5) current practice of meditation more than once per week or yoga more than twice per week.

A total of 478 patients were considered for the study and 262 were excluded. Diagnostic exclusions included 112 patients not meeting criteria for MDD or not scoring 16 or higher at both the screen and baseline study visits, 14 patients with a history of bipolar disorder, 33 patients with substance abuse or dependence judged to require treatment, 3 patients with current or past psychosis, 37 patients with another *DSM-IV* Axis I disorder judged to require treatment in preference to the depression, 23 patients with a *DSM-IV* Axis II disorder deemed to be poorly suited to the treatments under investigation, 1 patient with suicide risk requiring immediate hospitalization, and 39 patients excluded for miscellaneous reasons. This left a final sample of 216 patients eligible for acute treatment; of these, 22 were ruled out for medical reasons and 34 declined consent, leaving a final sample of 160 patients who entered the open-label study (**Figure 1**).

STUDY PHASES

Open Label, Acute Phase

All patients were treated with a 2-step, standardized monotherapy algorithm informed by the Texas Medication Algorithm Project[16] designed to maximize the likelihood of treatment response. Patients in step 1 started treatment with citalopram hydrobromide at a target dose of 20 mg that was increased in 10-mg steps if needed to a maximum of 60 mg until either response was achieved or dose-limiting adverse effects emerged. In patients who could not tolerate citalopram, sertraline hydrochloride at 50 mg/d with 50-mg increments per week was initiated with a target dose of at least 100 mg and a maximum of 200 mg/d. Patients with documented failure of selective serotonin reuptake inhibitors in this episode during at least an 8-week trial were switched to a novel antidepressant, either venlafaxine hydrochloride or mirtazapine, on the basis of symptom profile and patient preference.

Patients started step 2 after no more than 24 hours of washout following the taper of step 1 medication. Venlafaxine hydrochloride was started at 37.5 mg per day for 1 week, in-

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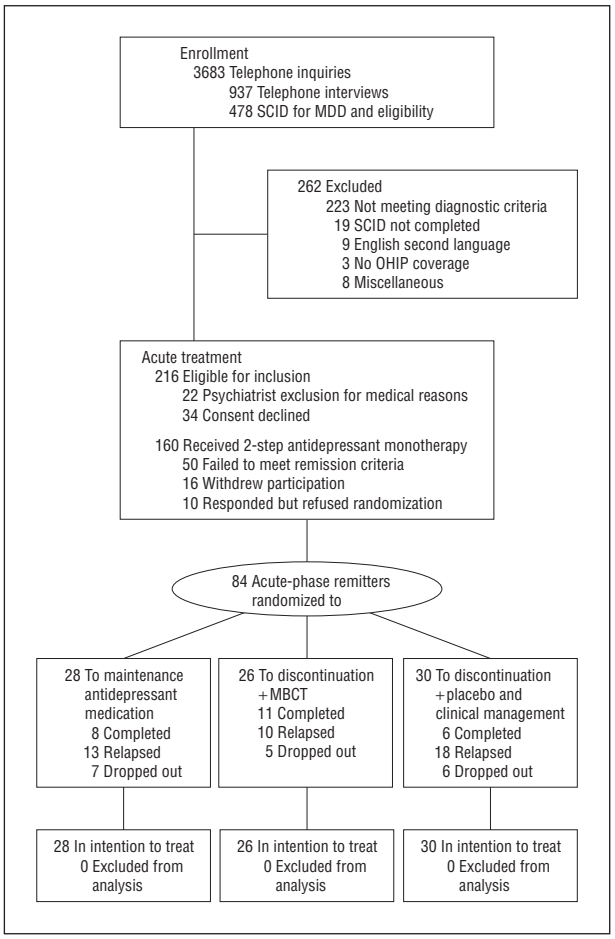

Figure 1. Study flow of patients from screening to analysis. MBCT indicates mindfulness-based cognitive therapy; MDD, major depressive disorder; OHIP, Ontario Health Insurance Plan; and SCID, Structured Clinical Interview for *DSM-IV*.

creased to 75 mg the next week and 150 mg (the minimum target dose) the following week, and then increased in 75-mg increments until the patient showed a full response (HRSD score, <8) or was unable to tolerate adverse effects (maximum of 375 mg). For patients who could not tolerate venlafaxine, mirtazapine was started at 15 mg per day for 1 week and increased in 15-mg increments per week to a minimum target dose of 30 mg and a maximum of 45 mg on the basis of response and tolerability. Patients meeting criteria[20] for treatment response (50% reduction in HRSD score) and clinical remission (HRSD score, ≤7 for 8 weeks) were treated for 5 additional months to ensure full remission. Among patients who achieved clinical remission, 14 of 84 (17%) required a second treatment step. Patients who did not respond to or tolerate the treatment options allowed in the protocol were withdrawn from the study and offered treatment based on clinical profile and preference in the respective Mood Disorders Clinic.

Medication was prepared by the pharmacy at CAMH according to CAMH formulary standards and dispensed in blister packs containing patients' daily dosage for the time between visits. Patients met with their study psychiatrist biweekly for the first 8 weeks and monthly thereafter. Study psychiatrists inquired about adherence during the interval between visits, and patients were asked to return unused pills. Raters noted the number of unused pills on a medication dosage record form. Patients who had not taken at least 75% of the prescribed dose in any 2-week period were considered to be nonadherent.

Clinical Remission During the Acute Phase

Previous work has demonstrated that the quality of acute-phase remission strongly influences the risk of subsequent relapse.[20] To examine this relationship across our 2 study phases, we classified all remitters as having had either an unstable or a stable remission according to the presence or absence of "symptom flurries"[21] during the approximately 5 months between initial remission and randomization. Patients who had a stable remission were those who maintained an HRSD score of 7 or less across this interval, whereas unstable remitters achieved the same HRSD threshold but had occasional elevated scores across this interval. These patients were considered to be in remission if (1) their score subsequent to an elevation was 7 or less and (2) the range of elevated scores fell between 8 and 14. This classification divided the entire sample in half (49% stable remitters and 51% unstable remitters).

Double-blind/Single-blind Maintenance Phase

After a minimum of 7 months' clinical remission (8 weeks to meet criteria and 5 months of additional treatment), patients entered the maintenance phase, in which they were randomly assigned to 1 of the 3 study arms: M-ADM, medication taper plus MBCT, or medication taper plus placebo with clinical management. Block randomization, with a block size of 4, was performed at CAMH by an independent statistician using computer-generated quasi-random numbers. Details of group assignment were contained in sealed envelopes that were opened by the statistician and communicated to the coordinator once a patient was deemed suitable for study entry. Patients in the M-ADM condition remained on the same drug regimen at the maximum tolerated and effective dose as outlined earlier. With respect to M-ADM and placebo, study psychiatrists were blind to treatment assignment, whereas once patients in MBCT completed their taper they no longer took any pills. Patients in both the placebo and MBCT conditions had their medication tapered gradually, during a 4-week period, via placebo substitution and reduced pill count, respectively, at the recommended rate for their specific medication to minimize the risk of discontinuation syndrome.[22,23] Prescription of additional medication for sleep complaints or anxiety symptoms was also permitted during this period (eg, zopiclone and benzodiazepines). Study psychiatrists met with patients biweekly for the first 4 weeks of both acute and maintenance treatment phases, then monthly for the next 3 months and bimonthly thereafter. Meeting frequency with study psychiatrists was identical in all 3 conditions.

The MBCT was delivered according to the protocol described by Segal et al.[24] Patients attended 8 weekly group meetings of 2 hours' duration and a retreat day held between sessions 6 and 7. In addition, an optional, monthly, 1-hour mindfulness meditation class was offered throughout the maintenance phase. Mindfulness-based cognitive therapy is based on empirical work showing that relapse is associated with the reinstatement of automatic modes of thinking and feeling that are characteristic of the depressed state[25] (eg, rumination and avoidance). By deliberately monitoring and observing their thinking patterns when they feel sad, patients develop skills in metacognition or decentering that serve to render this type of automatic processing more accessible to effortful reflection.[26,27] This is accomplished through daily homework exercises featuring (1) guided (taped) awareness exercises directed at increasing moment-by-moment nonjudgmental awareness of bodily sensations, thoughts, and feelings; (2) accepting difficulties with a stance of self-compassion; and (3) developing an

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Table 1. Baseline Characteristics

Variable	Whole Sample (N=160)	Randomized (n=84)	Nonrandomized (n=76)
HRSD score at entry, mean (SD)	19.4 (3.5)	19.1 (3.1)	19.7 (3.9)
HRSD score at randomization, mean (SD)	NA	2.8 (2.8)	NA
QIDS score at entry, mean (SD)	14.5 (3.9)	14.0 (4.0)	15.3 (3.8)[a]
QIDS score at randomization, mean (SD)	NA	3.11 (2.13)	NA
Female, No. (%)	93 (58)	53 (63)	40 (53)
White, No. (%)	128 (80)	66 (79)	62 (82)
Age, mean (SD), y	44 (11)	44 (11)	45 (12)
Married/cohabitating, No. (%)	64 (40)	32 (38)	32 (42)
Employed, No. (%)	107 (67)	60 (72)	46 (61)
Age at first onset, mean (SD), y	31 (12.3)	31 (11.6)	31 (13.3)
No. of previous episodes, mean (SD)	4.3 (3.5)	4.7 (2.3)	3.9 (4.6)
Duration of current episode, mean (SD), wk	100 (128.8)	83 (101.6)	119 (151.0)
Days in acute phase, mean (SD)	188.0 (85.9)	233.3 (63.8)	138 (79.2)[b]
Days to reach remission, mean (SD)	NA	79.9 (56.8)	NA
Days in remission, mean (SD)	NA	153.4 (37.3)	NA
History of previous antidepressant use, No. (%)	86 (54)	46 (55)	40 (52)
History of psychiatric hospitalization, No. (%)	13 (8)	6 (7)	7 (9)
Any Axis I comorbidity, No. (%)	60 (38)	28 (33)	32 (42)
History of substance abuse/dependence, No. (%)	14 (9)	5 (6)	9 (12)
Any Axis II comorbidity, No. (%)	62 (39)	31 (37)	31 (41)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; NA, not applicable; QIDS, Quick Inventory of Depressive Symptomatology.
[a] $P=.02$, randomized vs nonrandomized patients.
[b] $P<.001$, randomized vs nonrandomized patients.

"action plan" composed of strategies for responding to early warning signs of relapse/recurrence. A key theme stressed throughout the program is the transfer of these awareness skills into patients' everyday lives.

OUTCOME MEASURES

Patients were assessed by clinical evaluators blind to treatment allocation at randomization, biweekly for the first 8 weeks, monthly for the next 3 months, and bimonthly for the remainder of the 18-month maintenance phase.

The primary outcome measure was time to relapse/recurrence of *DSM-IV* major depressive episode, using the depression module of the SCID. Patients who scored 16 or higher on the 17-item HRSD at a scheduled physician visit were reinterviewed in a week's time, and, if their scores were in the same range, they were then assessed with the SCID to determine whether their level of symptoms met criteria for MDD. The Quick Inventory of Depressive Symptomatology[28] was also administered. Patients were encouraged to call the clinic if they were concerned that depressive symptoms were reemerging, in which case an ad hoc assessment was scheduled as soon as possible. If patients did not attend a scheduled visit or failed to notify study staff when they began to experience new symptoms, they could be judged to have relapsed on the basis of the Longitudinal Interval Follow-up Evaluation.[29] Patients were judged to have an episode of major depression if they had a score of 16 or higher for 2 consecutive weeks at any time during the maintenance phase and they met criteria on the SCID depression module for that specific interval. All interviews were audiotaped. Interviewers' ratings of a subset of taped assessments using the 17-item HRSD yielded an intraclass correlation coefficient of 0.94 (n=18), and the reliability of the major depressive episode diagnosis based on the SCID, in a subset of taped interviews, yielded a κ coefficient[30] of 0.82 (n=22). Diagnoses were also confirmed by an experienced research psychiatrist (R.D.L.).

DATA ANALYSIS

Tests of potential differences across study groups on demographic and clinical history variables were performed by means of analysis of variance for continuous measures and Pearson χ^2 for categorical variables. Where applicable, post hoc testing for continuous variables was performed with the Tukey honestly significant difference test. To examine whether receiving preferred maintenance treatment was associated with relapse, we assessed treatment preference via the Treatment Preference Index Form.[10] Survival curves and relapse rates testing the main effect of intervention and potential effects of quality of acute-phase remission and number of past episodes were estimated by means of the Cox proportional hazards regression model.[31] Patients unavailable for follow-up and those who accessed nonstudy depression treatment without a documented relapse or recurrence were treated as censored observations. Survival rates for the 3 conditions were compared with the log-rank test.

RESULTS

PATIENT FLOW AND DROPOUT

One hundred sixty patients enrolled in the open-label, acute treatment phase. Of these, 50 failed to reach remission, 16 withdrew participation, and 10 responded but declined consent for moving to the next study phase. During the maintenance phase, 18 patients dropped out of the protocol: 7 from the M-ADM group, 5 from the MBCT group, and 6 from the placebo group. Attrition was evenly distributed across the 18-month follow-up interval, with 50% of dropouts occurring by the ninth month. Some patients missed 1 or more physician visits but did complete the Longitudinal Interval Follow-up

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Table 2. Baseline Characteristics of Clinical Remitters

Variable	Remission	
	Stable (n=41)	Unstable (n=43)
HRSD score at entry, mean (SD)	18.7 (3.2)	19.5 (2.9)
HRSD score at randomization, mean (SD)	2.12 (2.3)	3.42 (3.0)[a]
QIDS score at entry, mean (SD)	13.6 (4.4)	14.4 (3.7)
QIDS score at randomization, mean (SD)	2.8 (2.2)	3.4 (2.0)
Female, No. (%)	24 (59)	29 (67)
White, No. (%)	30 (73)	36 (84)
Age, mean (SD), y	44 (11.6)	44 (10.4)
Married/cohabitating, No. (%)	18 (44)	14 (33)
Employed, No. (%)	26 (65)	34 (79)
Age at first onset, mean (SD), y	33 (11.4)	29 (11.6)
No. of previous episodes, mean (SD)	4.9 (2.6)	4.6 (2.0)
Duration of current episode, mean (SD), wk	63.3 (84.2)	100.3 (113.3)
Days in acute phase, mean (SD)	217.1 (56.9)	248.8 (66.9)[a]
Days to reach remission, mean (SD)	72.7 (51.8)	86.8 (61.1)
Days in remission, mean (SD)	144.4 (32.7)	162.0 (39.7)[a]
History of previous antidepressant use, No. (%)	18 (45)	28 (65)
History of psychiatric hospitalization, No. (%)	4 (10)	2 (5)
Any Axis I comorbidity, No. (%)	16 (39)	12 (28)
History of substance abuse/dependence, No. (%)	4 (10)	1 (2)
Any Axis II comorbidity, No. (%)	15 (37)	16 (37)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; QIDS, Quick Inventory of Depressive Symptomatology.
[a] $P < .05$.

Evaluation interviews at subsequent meetings. Therefore, complete information was available on 64 (76%) of the 84 patients who entered remission.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Patients in the overall sample had a mean (SD) age at study entry of 44 (11) years, and 93 (58%) of the sample was female, with 32 (20%) self-identified as a member of an ethnic/racial minority group. Differences on baseline demographic and clinical history variables between clinical remitters and patients who were not randomized are shown in **Table 1**. As expected, randomized patients showed significant decreases from pretreatment to posttreatment scores on the HRSD ($P < .001$) and the Quick Inventory of Depressive Symptomatology ($P < .001$). Nonrandomized patients had higher Quick Inventory of Depressive Symptomatology scores ($P = .046$) and spent fewer days in the acute phase ($P < .001$) than remitters. During open-label, acute-phase treatment, 43 patients (51%) were classified as unstable remitters, whereas 41 (49%) met criteria for stable remission, essentially dividing the remitter sample in half. As shown in **Table 2**, unstable remitters had higher HRSD scores ($P = .03$), spent more days in the acute phase ($P = .02$), and spent more days in remission than stable remitters ($P = .03$), but interestingly, there was no difference in the time taken by each group to reach remission. **Table 3** shows that there were no differences in baseline characteristics between the 3 prevention arms, with the only exception being a greater percentage of Axis II comorbidity in the MBCT arm ($P = .02$, MBCT vs M-ADM and placebo).

PRELIMINARY ANALYSES

Patients were asked at study entry to indicate which condition they would prefer being assigned to in the maintenance phase. An analysis was performed by χ^2 on responses from 70 of the 84 randomized patients who completed the Treatment Preference Index Form. Of these, 23 (33%) stated a preference for medication during the maintenance phase, 35 (50%) stated a preference to receive MBCT, 1 (1%) stated a preference for placebo, and 11 (16%) stated no preference. Analyses by χ^2 showed no significant difference in relapse rate between matched (12 of 19, or 63% relapse) and mismatched (20 of 40, or 50% relapse) patients, suggesting no effect of preference matching on the key outcome measure.

Of the 3 MBCT therapists, 2 were PhD-level psychologists (including P.B.) and 1 a master's-level social worker, each of whom had attended a 7-day residential training workshop with one of us (Z.V.S.) and taught the MBCT program in their respective clinical workplaces. All MBCT group sessions were videotaped, and therapist performance was monitored by means of the Mindfulness-Based Cognitive Therapy Adherence Scale,[32] a 17-item scale describing specific mindfulness exercises and cognitive therapy content. Scores range from 0 to 2 for each item describing one of the therapeutic tasks included in the protocol (0, no evidence for item; 1, slight evidence; and 2, definite evidence). A rating of 0 on any item indicates unsatisfactory performance and calls for specific supervisory intervention. Across all groups, study patients attended an average of 6 of the 8 weekly MBCT sessions. An independent rater viewed all MBCT sessions and rated them for treatment adherence. His score

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Table 3. Baseline Characteristics of Treatment Groups

Variable	M-ADM (n=28)	MBCT (n=26)	Pla + Clin (n=30)
HRSD score at entry, mean (SD)	19.2 (3.0)	18.9 (3.5)	19.2 (2.8)
HRSD score at randomization, mean (SD)	2.0 (2.3)	3.0 (2.8)	3.3 (3.0)
QIDS score at entry, mean (SD)	14.3 (4.6)	13.6 (3.7)	14.1 (3.9)
QIDS score at randomization, mean (SD)	3.0 (1.7)	3.4 (2.4)	2.9 (2.3)
Unstable remission in acute phase, No.	11	18	14
Stable remission in acute phase, No.	17	8	16
Female, No. (%)	20 (71)	13 (50)	20 (67)
White, No. (%)	24 (86)	19 (73)	23 (77)
Age, mean (SD), y	45.8 (11.4)	44.8 (9.4)	41.9 (11.6)
Married/cohabitating, No. (%)	10 (36)	10 (39)	12 (40)
Employed, No. (%)	22 (79)	20 (77)	18 (62)
Age at first onset, mean (SD), y	34.6 (12.7)	28.78 (10.0)	29.9 (11.3)
No. of previous episodes, mean (SD)	4.9 (2.6)	4.5 (2.2)	4.8 (2.1)
Duration of current episode, mean (SD), wk	80.7 (111.6)	102.6 (92.2)	67.8 (101.1)
Days in acute phase, mean (SD)	231.4 (59.7)	228.0 (52.6)	239.7 (34.2)
Days to reach remission, mean (SD)	80.1 (60.0)	68.1 (51.9)	90.0 (57.8)
Days in remission, mean (SD)	151.3 (31.7)	160.0 (34.2)	149.7 (44.5)
History of previous antidepressant use, No. (%)	17 (61)	14 (54)	15 (52)
History of psychiatric hospitalization, No. (%)	2 (7)	1 (4)	3 (10)
Any Axis I comorbidity, No. (%)	11 (39)	9 (35)	8 (27)
History of substance abuse/dependence, No. (%)	1 (4)	1 (4)	3 (10)
Any Axis II comorbidity, No. (%)	5 (18)	15 (58)	11 (37)[a]

Abbreviations: HRSD, Hamilton Rating Scale for Depression; M-ADM, maintenance antidepressant monotherapy; MBCT, mindfulness-based cognitive therapy; Pla + Clin, placebo plus clinical management; QIDS, Quick Inventory of Depressive Symptomatology.
[a] $P = .02$.

of 1.8 indicated that adherence was very good across all groups.

Study psychiatrists were trained by one of us (T.Y.) in accordance with the manual used in the Treatment of Depression Collaborative Research Program.[33] Pharmacotherapy sessions were 20 minutes long and emphasized both medication management (education, dosage adjustment, dosage scheduling, and side effects) and clinical management (discussion of functionality, support, and limited advice). Psychotherapeutic strategies, especially cognitive behavioral therapy techniques, were prohibited. Monthly and informal consultation continued throughout the study to address any issues that arose as a result of pharmacologic treatment.

RELAPSE

In the intention-to-treat sample, the model we used to test the association between predictors of interest and the hazard of relapse included separate terms for the number of past depressive episodes, treatment group, quality of remission, and interaction of treatment group × quality of remission. The overall model was significant ($\chi^2_6 = 13.70$, $P = .03$), and there was a significant interaction between the quality of acute-phase remission (stable or unstable) and treatment group ($\chi^2_2 = 7.27$, $P = .03$) but no main effects for treatment group ($\chi^2_2 = 0.84$, $P = .66$; relapse rates: MBCT, 38%; M-ADM, 46%; placebo, 60%) or quality of acute-phase remission ($\chi^2_1 = 2.40$, $P = .12$; relapse rates: unstable remitters, 42%; stable remitters, 56%). As shown in **Figure 2**, for unstable remitters, MBCT reduced the risk for subsequent relapse relative to placebo ($\chi^2_1 = 6.01$, $P = .01$), as did M-ADM ($\chi^2_1 = 4.55$, $P = .03$).

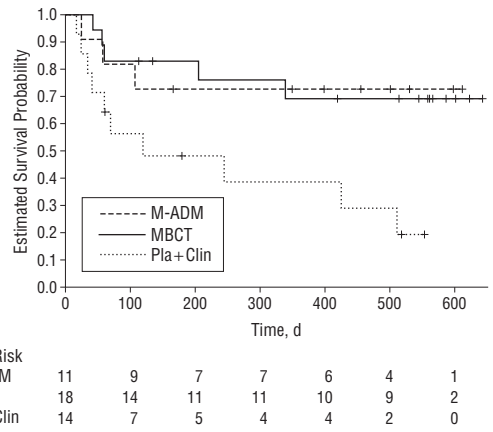

Figure 2. Cumulative proportion of unstable remitters who survived without relapse during maintenance/follow-up. M-ADM indicates maintenance antidepressant monotherapy; MBCT, mindfulness-based cognitive therapy; and Pla + Clin, placebo plus clinical management.

The protective effects of MBCT and M-ADM did not differ ($\chi^2_1 = 1.07$, $P = .93$). Relapse rates were 27% for M-ADM, 28% for MBCT, and 71% for placebo. Hazard ratios were calculated between placebo and each of the active treatments. Exposure to MBCT was associated with a hazard ratio for subsequent relapse of 0.26 (95% confidence interval [CI], 0.09-0.79) relative to placebo, which means that MBCT reduced risk by 74%. Maintenance antidepressant pharmacotherapy was associated with a hazard ratio of 0.24 (95% CI, 0.07-0.89), indicating a 76% reduction in risk relative to placebo. The haz-

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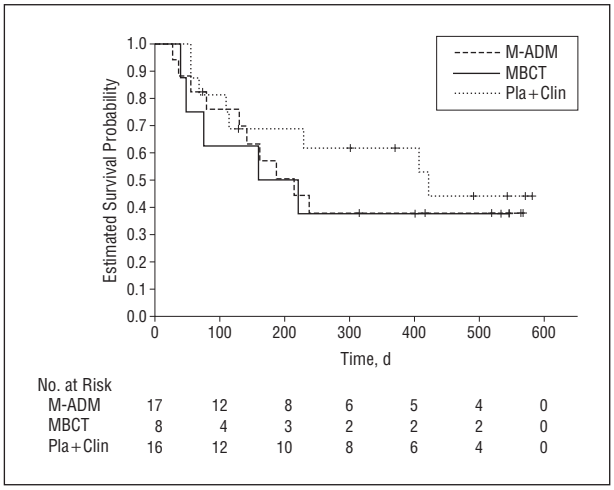

Figure 3. Cumulative proportion of stable remitters who survived without relapse during maintenance/follow-up. M-ADM indicates maintenance antidepressant monotherapy; MBCT, mindfulness-based cognitive therapy; and Pla + Clin, placebo plus clinical management.

ard associated with the comparison of MBCT with M-ADM was 1.07 (95% CI, 0.25-4.49), indicating no change in risk status.

For stable remitters, there was no difference between the treatments in relapse rates (**Figure 3**). In reducing risk for subsequent relapse, MBCT did not differ from placebo (χ^2_1=0.73, P=.39) and neither did M-ADM (χ^2_1=0.47, P=.49). In patients showing a stable remission, MBCT and M-ADM did not differ in their effects (χ^2_1=0.08, P=.77). Relapse rates were 59% for M-ADM, 62% for MBCT, and 50% for placebo.

Examining the combined outcomes of patients receiving any active treatment compared with placebo, we found that the overall model was significant (χ^2_4=13.70, P=.009) and that the interaction between the quality of acute-phase remission and the type of prevention treatment patients received was also significant (χ^2_1=7.23, P=.007). For patients with an unstable remission during the acute phase, active treatment during the maintenance phase reduced the risk for subsequent relapse relative to placebo (χ^2_1=8.26, P=.004). Relapse rates were 28% for active treatment and 71% for placebo. Previous exposure to active treatment was associated with a hazard ratio of 0.25 (95% CI, 0.10-0.65). In sum, these data suggest that providing a long-term active treatment to unstable remitters allowed them to maintain their treatment gains over time, a finding previously reported in studies of patients with residual symptoms.[8] Surprisingly, for stable remitters, there was no difference in relapse rates between active treatment and placebo (χ^2_1=0.74, P=.39). Relapse rates were 60.5% for active treatment and 50% for placebo.

As has been reported previously,[34] the number of past depressive episodes at study entry was a significant predictor of relapse during the maintenance phase in analyses with either MBCT and M-ADM examined singly (χ^2_1=5.55, P=.02) or combined (χ^2_1=5.51, P=.02). Each additional episode of depression was associated with a 16% increase in hazard (hazard ratio, 1.15; 95% CI, 1.02-1.30). Inclusion of past depressive episodes in the larger statistical model did not alter the pattern of results reported herein.

COMMENT

Naturalistic studies of depressed outpatients suggest that many will stop medication prematurely on their own despite recommendations for continuation.[4] Another group of patients may be unsuitable for long-term antidepressant treatment because of emergent clinical issues, such as pregnancy or drug interactions.[5,15,35] We studied a preventive MBCT intervention in recurrently depressed patients who discontinued antidepressant medication after achieving full remission and compared their long-term outcomes with the outcomes of those who continued taking medication or received placebo. Our findings indicated that the quality of remission achieved during the acute-phase interacted with the type of prevention treatment patients received to determine relapse outcomes during the subsequent maintenance phase. For patients whose acute phase remission was marked by periodic symptom flurries,[20,21] discontinuing M-ADM and receiving MBCT or continuing with M-ADM significantly lowered relapse/recurrence risk compared with discontinuation to placebo. These results are in accord with previous reports that the temporal features of remission or the presence of residual symptoms are correlated with poorer acute- and maintenance-phase outcomes[36,37] and that reduction of this risk with targeted treatment is beneficial.[34,38,39] Of note, in this group of patients in need of continued intervention, MBCT and M-ADM were equally effective.

Surprisingly, for patients whose acute-phase remission was stable, there was no differential effect on survival between the treatments we studied. Although the 50% relapse/recurrence rate in the placebo group is in line with other studies in which antidepressants were discontinued after continuation treatment (eg, Keller et al,[40] 47.3%; Montgomery et al,[41] 55%), the protective effects of active treatment were smaller. There is no obvious mechanism to account for this finding. We found no differences on a post hoc analysis of demographic and clinical characteristics of stable and unstable remitters, and other studies reporting results for patients randomized after a sustained period of remission are lacking. One speculation is that, in the acute phase of treatment, at least some individuals who achieved a rapid and sustained response were in fact responding to the supportive, nonspecific aspects of treatment rather than the pharmacologic properties of the medication.[42] If they were responsive only to the supportive aspects of the protocol, one might expect such individuals to show no difference in relapse rates by treatment condition in the 18-month follow-up phase, as was in fact the case. Ultimately, because our study was not designed to capture such effects, future work is needed to test this and other hypotheses related to the quality of acute-phase remission and prevention effects more directly.

Despite its growing evidence base, exactly how MBCT exerts its preventive effect is not fully understood. Because the daily practice of mindfulness invariably cues exposure to negative emotions, patients learn how to un-

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couple their habitual responses to dysphoria-triggering cues[26,43] in favor of responses informed by a metacognitive relationship to the very same mental contents. Data on the neural changes associated with mindfulness training support this view. Mindfulness practitioners demonstrated less neural reactivity to sadness provocation relative to a group of novices, as seen via both reduced activation of posterior cortical midline structures and reduced suppression of right viscerosomatic networks, such as the insula and right lateral prefrontal cortex.[27] Reduced suppression in the insula and subgenual anterior cingulate cortex have also been observed in depressed patients treated with cognitive therapy[44] and may point to a common locus of effect.[45] The affect regulation afforded by these growing capacities may make it easier for patients to adopt lifestyle and behavioral strategies that support recovery, a sine qua non of any effective maintenance treatment.

This study had a number of limitations. Reporting a lack of difference between M-ADM and MBCT in both stable and unstable remitters raises the risk of type II error, in which, because of low power, an important effect may be missed. One way to address this involves calculating E,[46] the expected number of relapse events required to replicate the reported hazard ratios for the comparisons between M-ADM and MBCT. The analysis showed that in both stable and unstable groups, detecting hazard ratios different from 1.0 would require extremely large samples (>1000). This suggests that the lack of significance between M-ADM and MBCT is less likely attributable to undersampling and more likely due to a very small measured effect.

As with any long-term treatment study, there is a possibility for bias through differential retention of patients, duration of follow-up,[47] and the focus on relapse, rather than other measures of depression burden, as our main index.[48] Only slightly more than half of the patients initially enrolled were eligible for randomization into the maintenance phase, mostly because of nonresponse but also because, once having achieved remission, some declined to move into the maintenance phase. In addition, our exclusion of patients with depression secondary to a medical illness may have narrowed the patient pool we studied and reduced the generalizability of our findings.

Our data highlight the importance of maintaining at least one active long-term treatment in recurrently depressed patients whose remission is unstable. For those unwilling or unable to tolerate maintenance antidepressant treatment, MBCT offers equal protection from relapse during an 18-month period.

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