



Published in final edited form as:

Arch Gen Psychiatry. 2010 December ; 67(12): 1256–1264. doi:10.1001/archgenpsychiatry.2010.168.

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

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Abstract

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 remitted depressed patients receiving MBCT against maintenance antidepressant pharmacotherapy, the current standard of care

Design—Patients who met remission criteria following 8 months of algorithm informed antidepressant treatment were randomized to either: Maintenance Antidepressant Medication (M-ADM), MBCT or placebo (PLA) and were followed for 18 months.

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

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

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Interventions—Remitted patients either discontinued their antidepressants and attended eight weekly group sessions of MBCT, continued on their therapeutic dose of antidepressant medication or discontinued active medication onto 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 SCID.

Results—Intention to treat analyses revealed a significant interaction between the quality of acute phase remission and subsequent prevention of relapse in randomized patients ($p = .03$). Among unstable remitters (defined as 1 or more HRSD >7 during remission) patients in both MBCT and M-ADM showed a 73% decrease in hazard compared to PLA ($p = .03$), whereas for stable remitters (all HRSD ≤ 7 during remission) there were no group differences in survival. Findings remained significant after accounting for the effects of past depressive episodes on relapse.

Conclusion—For depressed patients who are unwilling or unable to tolerate long term maintenance antidepressant treatment, MBCT offers equivalent protection from relapse.

Relapse and recurrence following recovery from Major Depressive Disorder (MDD) are common and debilitating outcomes that carry enormous personal, familial and societal costs¹. Maintenance antidepressant monotherapy (M-ADM), the current standard for depressive relapse prophylaxis² is effective as long as it is continued, yet in practice, this plan is compromised by rates of patient noncompliance 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 post-remission care⁵. Such models involve treating patients to remission pharmacologically and then providing psychotherapy aimed at preventing relapse by teaching affect regulation and self-management skills to be used during recovery. Implicit here is the view that the mechanisms underlying the onset of a depressive episode differ from those responsible for its return⁶ 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^{7,8} reported lower relapse rates at 4 year follow up and fewer multiple relapses for remitted patients who discontinued medication and received CBT, compared to clinical management. Frank et al.,⁹ found that time to recurrence was greater for patients who discontinued antidepressants at remission and received Interpersonal Therapy (IPT) or IPT and pill placebo (PLA) versus PLA 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 behaviours 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 RCTs with outcomes suggesting a 50% reduction in relapse for patients receiving MBCT compared to treatment as usual^{10,11} or no difference in survival compared to maintenance pharmacotherapy¹².

These data, while encouraging, do not address the frequently encountered clinical scenario where a remitted patient wishes, whether for reasons of preference¹³, side effect burden¹⁴ or suitability¹⁵, (e.g. pregnancy) to discontinue antidepressant treatment but requires additional prophylactic care. Although previous studies have enrolled patients who were already in

remission, no study has explicitly treated patients to remission pharmacologically with the aim of testing MBCT's prevention effects directly following discontinuation, against active treatment or a placebo (PLA) 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 (versus PLA and clinical management) for prevention of relapse 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 PLA 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 respective institutional review boards at the Centre for Addiction and Mental Health (CAMH), Toronto and St. Joseph's Healthcare, Hamilton. All participants provided written consent prior to any research activity. Subjects were recruited through clinical referrals, physician outreach and from media announcements that described the Mood Disorders Clinics at CAMH and St. Joseph's. There were two study phases. During the acute phase, all patients received open label, 2 step antidepressant pharmacotherapy in accord with the Texas Medication Algorithm Project guidelines¹⁶. Patients who met the criteria for remission were treated for five additional months and then randomly assigned to one of the three study arms.

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

Inclusion criteria were: (1) diagnosis of Major Depressive Disorder (MDD) according to DSM-IV criteria, (2) a score of ≥ 16 on the Hamilton Depression Rating Scale (HRSD-17), (3) ≥ 2 previous episodes of MDD [to ensure that those randomized would have a minimum of 3 past episodes], (4) between 18 and 65 years of age and (5) English speaking and the ability to provide informed consent. Exclusion criteria were: (1) a current diagnosis of Bipolar Disorder, Substance Abuse Disorder, Schizophrenia or Borderline Personality Disorder, (2) a trial of ECT within the past six months (3) depression secondary to a concurrent medical disorder, (4) current or planned pregnancy within the 6 months of acute phase treatment, (5) current practice of meditation more than once per week or yoga more than twice per week.

A total of 478 patients were evaluated for the study, 112 of whom either did not meet diagnostic criteria for MDD or did not achieve HDRS scores of 16 or higher at both the screen and baseline study visits. Another 150 patients met the following exclusion criteria: (1) history of bipolar disorder (n=14); (2) substance abuse or dependence judged to require treatment (n=33); (3) current or past psychosis (n=3); (4) another *DSM-IV* Axis I disorder judged to require treatment in preference to the depression (n=36); (5) *DSM-IV* Axis II disorders deemed to be poorly suited to the treatments under investigation (n=23); (6) suicide risk requiring immediate hospitalization (n=1); or (7) other exclusion criteria (n=40). This left a final sample of 216 patients eligible for acute treatment and of these 22 were ruled out for medical reasons and 34 declined consent, leaving a final sample of 160 patients that entered the open label study (see 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 Project¹⁶ designed to maximize the likelihood of treatment response. Patients in Step 1 started treatment with citalopram at a target dose of 20mg that was increased in 10mg steps if needed to a maximum of 60 mg, until either response was achieved or dose-limiting side effects emerged. In patients who could not tolerate citalopram, a trial of sertraline starting at 50mg/day with 50mg increments per week was initiated with a target dose of at least 100 mg and a maximum of 200mg/day. Patients with documented SSRI failure in this episode over at least an eight week trial were switched to a novel antidepressant, either venlafaxine or mirtazapine based on symptom profile and patient preference. Patients in Step 2 were started after no more than 24 hours washout following the taper of Step 1 medication. Venlafaxine was started at 37.5mg per day for one week, increased to 75mg the next week, 150mg (the minimum target dose) the following week and then in 75mg increments until the patient showed a full response (HRSD-17 < 8) or was unable to tolerate side effects (to a maximum of 375mg). For patients who could not tolerate venlafaxine, mirtazapine was started at 15mg per day for one week and increased in 15mg increments per week to a minimum target dose of 30mg and a maximum of 45mg based on response and tolerability. Patients meeting criteria²⁰ for treatment response (50% reduction in HRSD) and clinical remission (HRSD ≤ 7 for 8 weeks) were treated for five additional months to ensure full remission. 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 compliance 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 two week period were considered to be non-compliant.

Clinical Remission during the Acute Phase—Prior work has demonstrated that the quality of acute phase remission strongly influences the risk of subsequent relapse^{20,21}. To examine this relationship across our two study phases, we classified all remitters as having had either an unstable or stable remission, based on the presence or absence of 'symptom flurries'²⁰ 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 across this interval, while unstable remitters achieved the same HRSD threshold but had occasional elevated scores across this interval. These patients were considered in remission if 1) their score subsequent to an elevation was ≤ 7 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; see Table 2).

Double/Single Blind Maintenance Phase—Following a minimum of seven months clinical remission (8 weeks to meet criteria and 5 months of additional treatment) patients entered the maintenance phase, where they were randomly assigned to one of the three study arms: maintenance antidepressant medication, medication taper plus MBCT, medication taper plus PLA. Block randomization, utilizing a block size of 4 was performed at CAMH by an independent statistician (TB) using computer generated quasi-random numbers. Details of group assignment were contained in sealed envelopes which 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 at the maximum tolerated and effective dose as outlined above. With respect to M-ADM and PLA+CLIN, 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 PLA+CLIN and MBCT conditions were tapered gradually, over 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 (e.g. zopiclone and benzodiazepines). Study psychiatrists met with patients biweekly for the first four weeks of both acute and maintenance treatment phases, then monthly for the next three months and bimonthly thereafter. Meeting frequency with study psychiatrists was identical in all three conditions.

MBCT was delivered according to the protocol described in 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, patients had the option of attending a monthly one hour mindfulness meditation class that was offered throughout the maintenance phase. MBCT 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 state²⁵ (e.g. 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 non-judgmental awareness of bodily sensations, thoughts and feelings, 2) accepting difficulties with a stance of self-compassion and 3) in later sessions, developing an 'action plan' comprised 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 eight weeks, monthly for the next three 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 greater on the HRSD-17 at a scheduled physician visit were re-interviewed 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 symptomatology met criteria for MDD. In addition, 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. In those cases when a patient 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 based on the Longitudinal Interval Follow Up Evaluation²⁸. A patient was judged to have an episode of major depression if they had a score of ≥ 5 for 2 consecutive weeks at any time during the maintenance phase. 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 K^{29} coefficient of 0.82 (n=22). Diagnoses were also confirmed by an experienced research psychiatrist.

Data Analysis

Tests of potential differences across study groups on demographic and clinical history variables were performed using ANOVA for continuous measures and Pearson Chi Square for categorical variables. Where applicable, post-hoc testing for continuous variables was performed with Tukey's HSD. To examine whether receiving preferred maintenance treatment was associated with relapse, we assessed treatment preference via the Treatment Preference Index Form (TXPR)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 using the Cox proportional hazards regression model³⁰. Patients unavailable for follow-up and those who accessed non-study depression treatment without a documented relapse were treated as censored observations. Survival rates for the three conditions were compared with the log-rank test.

RESULTS

Patient Flow and Dropout

One hundred and 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 M-ADM, 5 from MBCT and 6 from PLA. Attrition was evenly distributed across the 18 month follow up interval, with 50% of drop outs occurring by the 9th month. Some patients missed 1 or more physician visits but did complete the LIFE interviews at subsequent meetings. We, therefore, have complete information on 66 (75%) of the 84 remitted patients.

Demographic and Clinical Characteristics

Patients in the overall sample had a mean age at study entry of 44 years (11.49) and 58% of the sample was female, with 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 in pre to post treatment scores on the HRSD ($P < .001$) and the Quick Inventory of Depressive Symptoms³¹ (QIDS) ($P < .001$). Non-randomized patients had higher QIDS scores ($P < .05$) 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 while 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 ($P < .05$), took longer to reach remission ($P < .05$) and spent more days in remission than stable remitters ($P < .05$), 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 three prevention arms, with the only exception being a greater percentage of Axis II comorbidity in MBCT ($P < .05$).

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 using Chi Square, on 70 of the 84 randomized patients who completed the TXPR. Of these, 23 (32.9%) stated a preference for medication during the maintenance phase, 35 (50%) stated a preference to receive MBCT, 1 (1.4%) stated a preference for PLA and 11 (15.7%) stated no preference. Chi square analyses revealed no significant difference in relapse rate between matched (12/19 or 63% relapse) and mismatched patients (20/40 or 50% relapse) suggesting no effect of preference matching on the key outcome measure.

The three MBCT therapists were two PhD level psychologists and one Master's level social worker, each of whom had attended a 7 day residential training workshop with Dr. Segal and taught the MBCT program in their respective clinical workplaces. All MBCT group sessions were videotaped and therapist performance was monitored using the Mindfulness-Based Cognitive Therapy Adherence Scale³² (MBCT-AS) 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, 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 out of the 8 weekly MBCT sessions. An independent rater viewed all MBCT sessions and rated them for treatment adherence. His score of 1.8 indicated that adherence was very good across all groups.

Study psychiatrists were trained by Dr. Young in accordance with the manual used in the Treatment of Depression Collaborative Research Project³³. Pharmacotherapy sessions were 20 minutes in duration 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 CBT techniques were prohibited. Monthly and informal consultation continued throughout the study to address any issues that arose as a result of pharmacological 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 the interaction of treatment group by quality of remission. The overall model was significant ($X^2 = 13.70$, $df=6$, $P=.03$) and there was a significant interaction between the quality of acute phase remission (stable or unstable) and treatment group ($X^2 = 7.27$, $df=2$, $P=.03$) but no main effects for treatment group ($X^2 = 0.84$, $df=2$, $P=.66$ - relapse rates: MBCT 38%, M-ADM 46%, PLA 60%) or quality of acute phase remission ($X^2 = 2.40$, $df=1$, $P=0.12$ - relapse rates: unstable remitters 42% and stable remitters 56%). As shown in Figure 2, for unstable remitters, MBCT reduced the risk for subsequent relapse relative to PLA ($X^2 = 6.01$, $df=1$, $P=.01$) as did M-ADM ($X^2 = 4.55$, $df=1$, $P=.03$). MBCT and M-ADM did not differ from each other in their protective effects ($X^2 = 1.07$, $df=1$, $P=.93$). Adjusted relapse rates for each condition were 27% for M-ADM, 28% for MBCT and 71% for PLA. Hazard ratios were calculated between PLA and each of the active treatments. Exposure to MBCT was associated with a hazard ratio for subsequent relapse of .26 (95% CI 0.09–0.79) relative to PLA which means that MBCT reduced risk by 74%. Maintenance antidepressant pharmacotherapy was associated with a hazard ratio of .24 (95% CI 0.07–0.89) indicating a 76% reduction in risk relative to PLA. The hazard associated with the comparison of MBCT to 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). MBCT did not differ from PLA ($X^2 = .73$, $df=1$, $P=.39$) and neither did M-ADM ($X^2 = .47$, $df=1$, $P=.49$) in reducing risk for subsequent relapse. In patients showing a stable remission, MBCT and M-ADM did not differ in their effects ($X^2 = .08$, $df=1$, $P=.77$). Adjusted relapse rates for each condition were 59% for M-ADM, 62% for MBCT and 50% for PLA.

Examining the combined outcomes of patients receiving any active treatment compared to PLA, we found that the overall model was significant ($X^2 = 13.70$, $df=4$, $P=.009$) and that the interaction between the quality of acute phase remission and the type of prevention treatment patients received was also significant ($X^2 = 7.23$, $df=1$, $P=.007$). For patients with

an unstable remission during the acute phase, active treatment during the maintenance phase reduced the risk for subsequent relapse relative to PLA ($X^2 = 8.26$, $df=1$, $P=.004$). Adjusted relapse rates for each condition were 28% for active treatment and 71% for PLA. Prior exposure to active treatment was associated with a hazard ratio of .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 symptoms⁸. Surprisingly, for stable remitters, there was no difference in relapse rates between active treatment or PLA ($X^2 = .74$, $df=1$, $P=.39$). Adjusted relapse rates for each condition were 60.5% for active treatment and 50% for PLA.

As has been reported previously³⁴, 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 ($X^2 = 5.55$, $df=1$ $P=.02$) or combined ($X^2 = 5.51$, $df=1$ $P=.02$). Each additional episode of depression was associated with a 16% increase in hazard (HR = 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 above.

COMMENT

Naturalistic studies of depressed outpatients suggest that many will stop medication prematurely on their own despite recommendations for continuation⁴. 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 were discontinued from antidepressant medication after achieving full remission and compared their long term outcomes to those who stayed on 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 symptoms flurries^{20,21}, discontinuing ADM and receiving MBCT or continuing with M-ADM significantly lowered relapse risk compared to discontinuation to PLA. 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 impact on survival between the treatments we studied. While the 50% relapse rate in PLA is in line with other studies in which antidepressants were discontinued following continuation treatment (e.g. Keller et al,⁴⁰: 47.3%, Montgomery et al.,⁴¹: 55%), the protective effects of active treatment were smaller. What explains this discrepancy? First, since sample characteristics are known to vary across studies it makes it difficult to compare absolute relapse rates from other trials. Second, stable and unstable remitters did not differ on a number of demographic or clinical history variables known to impact relapse risk. One possibility is that stable remitters may have had lower motivation to comply with treatment in the maintenance phase where, having shown a robust clinical response, they faced a two out of three chance of discontinuation. Secondary analyses of treatment mediators may help to clarify these group differences.

In spite of 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 uncouple their habitual responses to dysphoria-triggering cues^{26,42} 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 in reduced suppression of right viscerosomatic networks such as the insula and right lateral prefrontal cortex²⁷. Reduced suppression in the insula and subgenual ACC have also been observed in depressed patients treated with cognitive therapy⁴³ and may point to a common locus of effect. The affect regulation afforded by these growing capacities, may make it easier for patients to adopt lifestyle and behavioural 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, due to low power, an important effect may be missed. One way to address this involves calculating E^{44} , the expected number of relapse events required to replicate the reported hazard ratios for the comparisons between M-ADM and MBCT. The analysis revealed that in both stable and unstable groups, detecting hazard ratios different from one would require extremely large samples ($N > 1000$). This suggests that the lack of significance between M-ADM and MBCTs is less likely attributable to under sampling, 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. Only slightly more than half of the patients initially enrolled were eligible for randomization into the maintenance phase, most due to nonresponse but also because once having achieved remission they declined to move into the maintenance phase. This raises the question of how closely the randomized sample represents the initial group. Although we relied on randomization to equate the treatment groups on baseline characteristics, differential retention cannot be fully ruled out for clinical features we did not consider.

It is well established that patients with recurrent depression require care past the point of episode remission. For those, unwilling or unable to tolerate maintenance antidepressant treatment our data suggest that MBCT offers equal protection from relapse over 18 months and highlights the importance of maintaining at least one active long term treatment in unstable remitters.

Acknowledgments

We thank the following colleagues for contributing to this research. Richard Bloch MA, Shelly Ferris, MA, Kate Szacun-Shimizu, MA and Karyn Hood, MA served as study coordinators. Susan Woods, MA and Theresa Casteels, PhD and Peter Bieling, PhD served as MBCT study therapists. Robert Levitan MD, Trevor Young MD, Glenda MacQueen MD, Lawrence Martin MD, Robert Cooke MD and Jennifer Brasch MD served as study psychiatrists. Lori Hoar, MA, Joanne Nault, MA, Rebecca Pedersen MA and Zoe Laksman, MA served as project interviewers, Bao Chau Du and Heidy Morales provided research support. Tom Buis, MA, and Mr Andrew Pedersen provided programming and data analytic support. David Streiner PhD provided statistical and study design consultation.

This study was funded by Grant #066992 (R01: Dr. Segal) from the National Institute of Mental Health, Bethesda, MD and was presented at the Association for Behavioural and Cognitive Therapies, New York, November 2009.

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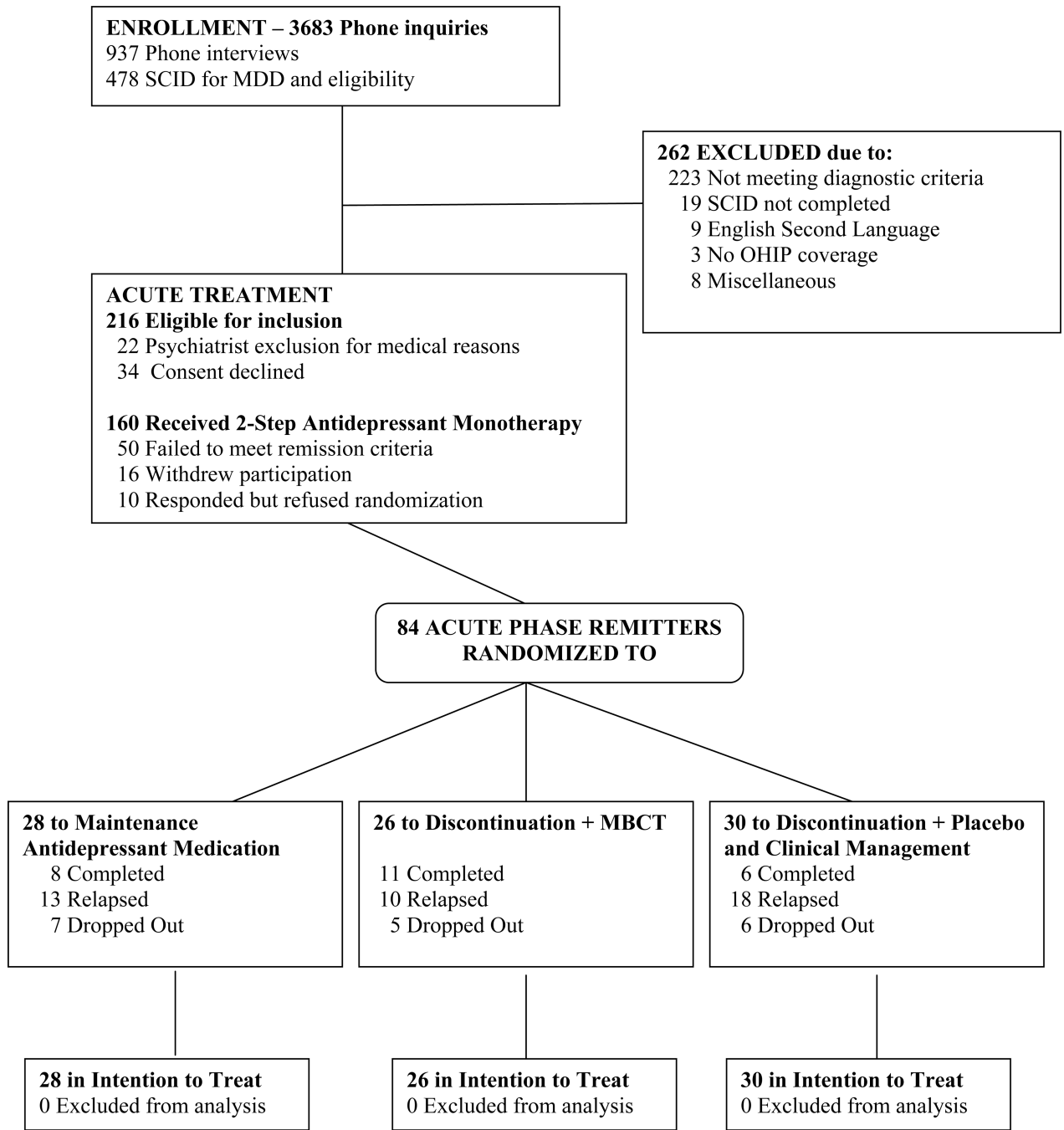
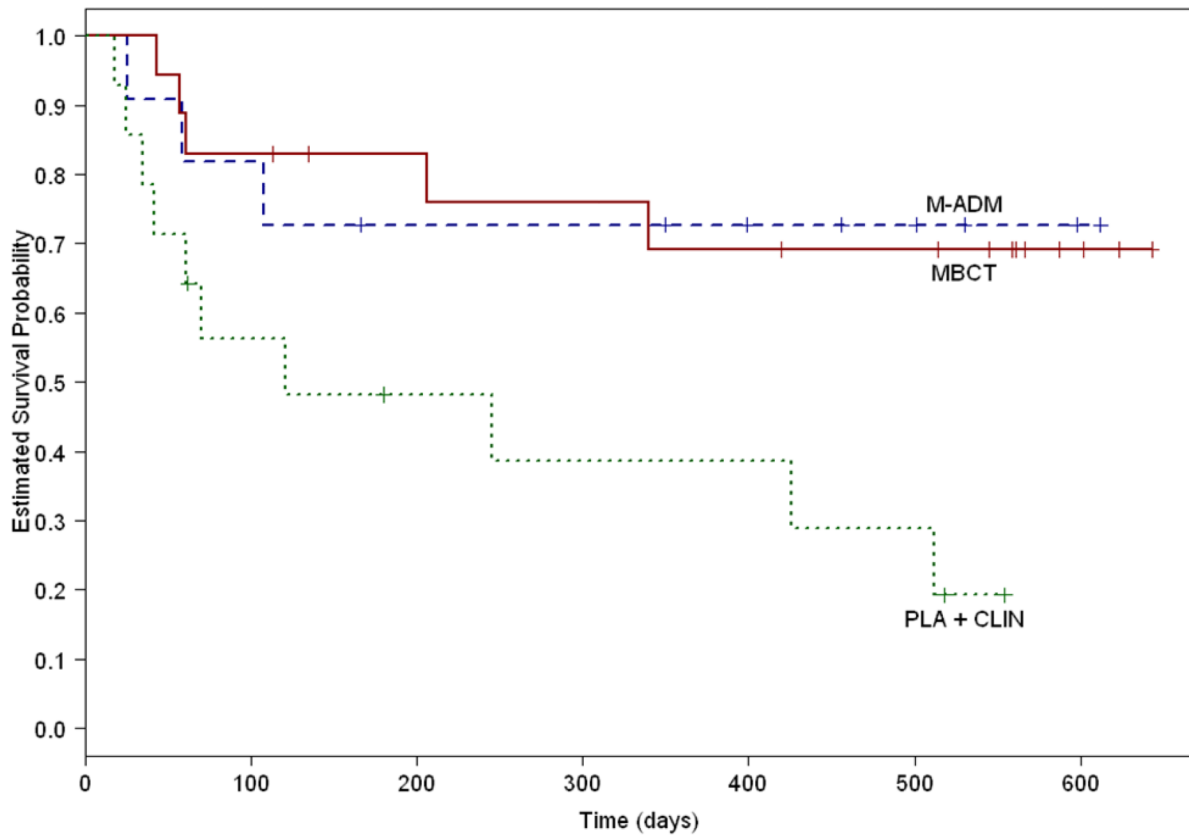
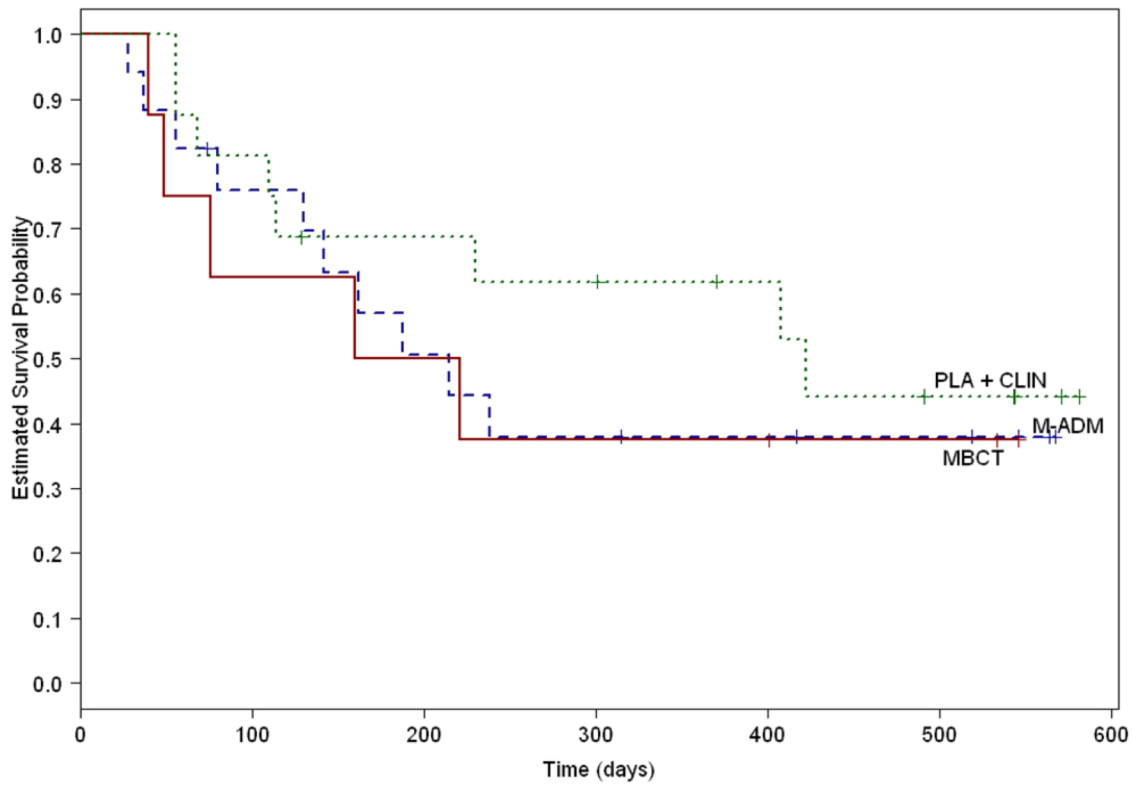


Figure 1.
Study Flow of Patients from Screening to Analysis



11	9	7	7	6	4	1	M-ADM
18	14	11	11	10	9	2	MBCT
14	7	5	4	4	2	0	PLA + CLIN

Figure 2. Cumulative proportion of **unstable remitters** who survived without relapse during maintenance/follow up. M-ADM indicates maintenance antidepressant pharmacotherapy, MBCT indicates taper + Mindfulness Based Cognitive Therapy and PLA+CLIN indicates taper + pill placebo and clinical management.



17	12	8	6	5	4	0	M-ADM
8	4	3	2	2	2	0	MBCT
16	12	10	8	6	4	0	PLA + CLIN

Figure 3. Cumulative proportion of **stable remitters** who survived without relapse during maintenance/follow up. M-ADM indicates maintenance antidepressant pharmacotherapy, MBCT indicates taper + Mindfulness Based Cognitive Therapy and PLA+CLIN indicates taper + pill placebo and clinical management.

Table 1

Baseline Characteristics

Variable	Whole Sample (n=160)	Randomized (n=84)	Non-Randomized (n=76)
HRSD score at entry, <i>mean</i> ± <i>SD</i>	19.4 ± 3.5	19.1 ± 3.1	19.7 ± 3.9
HRSD score at randomization		2.8 ± 2.8	
QIDS at entry	14.5 ± 3.9	14 ± 4.0	15.3 ± 3.8*
QIDS at randomization		3.11 ± 2.13	
Female, %	58	63	53
White, %	80	79	82
Age, yrs	44 ± 11	44 ± 11	45 ± 12
Married/cohabitating, %	40	38	42
Employed, %	67	72	61
Age of onset first	31 ± 12.3	31 ± 11.6	31 ± 13.3
No. of prior episodes	4.3 ± 3.5	4.7 ± 2.3	3.9 ± 4.6
Duration current episode in weeks	100 ± 128.8	83 ± 101.6	119 ± 151
Days in acute phase	188.0 ± 85.9	233.3 ± 63.8	138 ± 79.2**
Days to reach remission	N/A	79.9 ± 56.8	
Days in remission	N/A	153.4 ± 37.3	N/A
Hx prior Antidepressant, %	54	55	52
Hx psychiatric hospitalization, %	8	7	9
Any Axis I comorbidity, %	38	33	42
Hx substance abuse/depend. %	9	6	12
Any Axis II comorbidity, %	39	37	41

Comparisons between randomized and non randomized patients:

* p < .05,

** p < .001

Table 2

Baseline Characteristics of Clinical Remitters

Variable	Stable Remission (n=41)	Unstable Remission (n=43)
HRSD score at entry, <i>mean ± SD</i>	18.7 ± 3.2	19.5 ± 2.9
HRSD score at randomization	2.12 ± 2.3	3.42 ± 3.0*
QIDS at entry	13.6 ± 4.4	14.4 ± 3.7
QIDS at randomization	2.8 ± 2.2	3.4 ± 2.0
Female, %	59	67
White, %	84	73
Age, yrs	44 ± 11.6	44 ± 10.4
Married/cohabitating, %	33	44
Employed, %	65	79
Age of first onset	33 ± 11.4	29 ± 11.6
No. of prior episodes	4.9 ± 2.6	4.6 ± 2
Duration current episode in weeks	63.3 ± 84.2	100.3 ± 113.3
Days in acute phase	217.1 ± 56.9	248.8 ± 66.9*
Days to reach remission	72.7 ± 51.76	86.8 ± 61.1
Days in remission	144.4 ± 32.7	162 ± 39.7*
Hx of prior antidepressant %	45	65
Hx of psychiatric hospitalization, %	10	5
Any Axis I comorbidity, %	39	28
Hx substance abuse/dependence, %	10	2
Any Axis II comorbidity, %	37	37

* p < .05

Table 3

Baseline Characteristics of Treatment Groups

Variable	M-ADM (n=28)	MBCT (n=26)	PLA+Clin (n=30)
HRSD score at entry, <i>mean ± SD</i>	19.2 ± 3	18.9 ± 3.5	19.2 ± 2.8
HRSD score at randomization	2 ± 2.3	3 ± 2.8	3.3 ± 3
QIDS at entry	14.3 ± 4.6	13.6 ± 3.7	14.1 ± 3.9
QIDS at randomization	3 ± 1.7	3.4 ± 2.4	2.9 ± 2.3
Unstable remission in acute phase	N = 11	N = 18	N = 14
Stable remission in acute phase	N = 17	N = 8	N = 16
Female, %	71.4	50.0	66.7
White, %	85.7	73.1	76.7
Age, yrs	45.8 ± 11.4	44.8 ± 9.4	41.9 ± 11.6
Married/cohabitating, %	36	39	40
Employed, %	79	77	62
Age of first onset	34.6 ± 12.7	28.78 ± 10	29.9 ± 11.3
No. of prior episodes	4.9 ± 2.6	4.5 ± 2.2	4.8 ± 2.1
Duration of current episode in weeks	80.7 ± 111.6	102.6 ± 92.2	67.8 ± 101.1
Days in acute phase	231.4 ± 59.7	228 ± 52.6	239.7 ± 34.2
Days to reach remission	80.1 ± 60	68.1 ± 51.9	90 ± 57.8
Days in remission	151.3 ± 31.7	160 ± 34.2	149.7 ± 44.5
Hx of prior antidepressant, %	61	54	52
Hx psychiatric hospitalization, %	7	4	10
Any Axis I comorbidity, %	39	35	27
Hx substance abuse/dependence, %	4	4	10
Any Axis II comorbidity, %	18	58	37*

* p < .05