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Mindfulness-Based Cognitive Therapy to Prevent Relapse in Recurrent Depression

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For people at risk of depressive relapse, mindfulness-based cognitive therapy (MBCT) has an additive benefit to usual care (H. F. Coelho, P. H. Canter, & E. Ernst, 2007). This study asked if, among patients with recurrent depression who are treated with antidepressant medication (ADM), MBCT is comparable to treatment with maintenance ADM (m-ADM) in (a) depressive relapse prevention, (b) key secondary outcomes, and (c) cost effectiveness. The study design was a parallel 2-group randomized controlled trial comparing those on m-ADM ($N = 62$) with those receiving MBCT plus support to taper/discontinue antidepressants ($N = 61$). Relapse/recurrence rates over 15-month follow-ups in MBCT were 47%, compared with 60% in the m-ADM group (hazard ratio = 0.63; 95% confidence interval: 0.39 to 1.04). MBCT was more effective than m-ADM in reducing residual depressive symptoms and psychiatric comorbidity and in improving quality of life in the physical and psychological domains. There was no difference in average annual cost between the 2 groups. Rates of ADM usage in the MBCT group was significantly reduced, and 46 patients (75%) completely discontinued their ADM. For patients treated with ADM, MBCT may provide an alternative approach for relapse prevention.

Keywords: mindfulness-based cognitive therapy, randomized controlled trial, depression, antidepressants, health economics

Depression is a major public health problem, in part because like other chronic conditions it tends to run a relapsing course (Judd, 1997b; Keller et al., 1984). Without treatment, people suffering recurrent depression experience relapse at rates as high as 80% (Frank et al., 1990; Kupfer et al., 1992; Prien & Kupfer, 1986). Currently the majority of those with depression are treated in

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primary care (Katon & Schulberg, 1992), and maintenance antidepressant medication (m-ADM) is the mainstay approach (Geddes et al., 2003; National Institute for Clinical Excellence [NICE], 2004). To stay well, people with a history of recurrent depression are recommended to continue antidepressant medication (ADM) for at least 2 years. However, many experience unpleasant side effects, rates of adherence tend to be low, and many express a preference for psychosocial interventions (Cooper et al., 2007; NICE, 2004; Olfson, Marcus, Tedeschi, & Wan, 2006; van Schaik et al., 2004). User group and professional consensus recommends as priorities for future research (a) the development of psychosocial interventions to prevent depressive relapse and (b) the use of nontraditional delivery systems, such as group interventions, to significantly expand the accessibility of cost-effective therapies (Hirschfield et al., 1997; Hollon et al., 2002).

In response to this challenge, mindfulness-based cognitive therapy (MBCT) was developed with a specific focus on preventing relapse/recurrence of depression (Segal, Williams, & Teasdale, 2002). MBCT is a relatively brief, 8-week group program. With 8–15 patients per group, MBCT has the potential to help a large number of people in primary care settings at relatively low cost compared with individual therapies. In two randomized controlled trials, MBCT plus usual care halved the rates of relapse compared with usual care over a 60-week follow-up period among people who had experienced three or more previous episodes of major depression: Approximately two thirds of the sample relapsed in the usual care arm versus approximately one third relapsed in the MBCT plus usual care arm (Ma & Teasdale, 2004; Teasdale et al., 2000). It is noteworthy that an exclusion criterion for these trials was current ADM treatment, even though this is the most common treatment approach for recurrent depression. Moreover, there are currently no trials comparing MBCT with an active treatment (Coelho et al., 2007).

The rationale for this trial was as follows. First, given that m-ADM over at least 2 years is recommended to prevent relapse/recurrence (Geddes et al., 2003; NICE, 2004) and many patients express a preference for an alternative approach, it is important to establish whether MBCT enables patients to taper/discontinue ADM. Second, the majority of depression presents in primary care, and the generalizability of MBCT to real-world primary care settings has not been established. Third, the two trials to date were conducted by members of the group that developed MBCT, and there is a need for independent replication. Fourth, in health and mental health trials there is a growing acknowledgement of the need for a more sophisticated and patient-centered approach to outcome assessment that extends beyond the assessment of depressive relapse/recurrence to include measures of the nature of depressive relapses/recurrences, comorbidity, and quality of life (e.g., Zimmerman et al., 2006). Finally, MBCT has not yet been compared with another active treatment.

The primary aim of this trial was to examine whether MBCT provides an alternative approach to m-ADM in preventing depressive relapse/recurrence. We compared the sustained recovery of people taking m-ADM with that of people who participated in an MBCT program and were supported in tapering and discontinuing their m-ADM. Our secondary study aim was to compare MBCT and m-ADM in terms of residual depressive symptoms, comorbid psychiatric diagnoses, quality of life, and cost effectiveness. Finally, we sought to establish if MBCT enabled patients to taper/discontinue their ADM.

Method

Design

Study participants had a history of three or more previous episodes of depression, had been treated with a therapeutic dose of ADM over the last 6 months, and were currently either in full or partial remission from the most recent episode. They were randomly allocated to participate in either a traditional m-ADM treatment or an 8-week MBCT class that included support to taper/discontinue their m-ADM. Block randomization (block size = 4) to the two groups was performed by an independent statistician using computer-generated quasi-random numbers. Randomization was stratified according to patients' symptomatic status at intake assessment by using the Hamilton Rating Scale for Depression (HRSD; J. B. Williams, 1988; asymptomatic = HRSD $<$ 8; partially symptomatic = HRSD $\geq$ 8). The study was approved by the UK National Health Service North and East Devon Research Ethics Committee.

Time from randomization to depressive relapse/recurrence was the primary outcome measure, with patients followed up at 3-month intervals for 15 months. Secondary outcome measures were severity/duration of relapses/recurrences, severity of residual depressive symptoms, number of comorbid psychiatric diagnoses, quality of life, and service use.

Participants

The study was conducted in primary care settings across a range of urban and rural locations in Devon, England. Recruitment was designed to screen as wide a population as possible in primary care (White, Holden, Byng, Mullan, & Kuyken, 2007). First, we searched computerized practice databases to identify patients who had been prescribed ADM for the previous 6 months. Medical records were then consulted to establish as far as possible whether patients met study inclusion and exclusion criteria. Primary care physicians then screened the list of selected patients and wrote letters to potential participants describing the study, enclosing the study information sheet, and stating that unless they decided to opt out they would be contacted by a member of the study team. Unless potential participants opted out, a research officer made contact by telephone to discuss the study, and with potential participants' further verbal consent they were screened for eligibility. If eligible and willing, patients attended a meeting for the study intake assessment, where they were invited to sign a formal consent form.

One hundred twenty-three people met the study's criteria and agreed to participate. Inclusion criteria were as follows: three or more previous episodes of depression meeting criteria for depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV;* American Psychiatric Association, 1994); 18 years of age or older; and on a therapeutic dose of m-ADM in line with the British National Formulary (British Medical Association & Royal Pharmaceutical Society of Great Britain [BMA–RPSGB], 2006) for at least the previous 6 months and is in either full or partial remission from the most recent

episode of depression. Exclusion criteria were as follows: comorbid diagnoses of current substance dependence; organic brain damage; current/past psychosis; bipolar disorder; persistent antisocial behavior; persistent self-injury requiring clinical management/therapy; unable to engage with MBCT for physical, practical, or other reasons (e.g., very disabling physical problem, unable to comprehend materials); and formal concurrent psychotherapy.

Interventions

MBCT and antidepressant tapering/discontinuation. MBCT is a manualized, group-based skills training program designed to enable patients to learn skills that prevent the recurrence of depression (Segal, Williams, & Teasdale, 2002). It is derived from mindfulness-based stress reduction, a program with proven efficacy in ameliorating distress in people suffering chronic disease (Baer, 2003; Kabat-Zinn, 1990), and cognitive–behavioral therapy for acute depression (Beck, Rush, Shaw, & Emery, 1979), which has demonstrated efficacy in preventing depressive relapse/recurrence (Hollon et al., 2005). MBCT is intended to enable people to learn to become more aware of the bodily sensations, thoughts, and feelings associated with depressive relapse and to relate constructively to these experiences. It is based on theoretical and empirical work demonstrating that depressive relapse is associated with the reinstatement of automatic modes of thinking, feeling, and behaving that are counterproductive because they contribute to and maintain depressive relapse and recurrence (e.g., self-critical thinking and avoidance; Lau, Segal, & Williams, 2004). Participants learn to recognize these "automatic pilot" modes, step out of these modes, and respond in healthier ways by intentionally moving into a mode in which they decenter from negative thoughts/feelings (e.g., by learning that "thoughts are not facts"), accept difficulties with a stance of self-compassion, and use bodily awareness to ground and transform their experience. In the latter stages of the course, patients develop an "action plan" that sets out strategies for responding when they become aware of early warning signs of relapse/recurrence (see J. M. G. Williams, Teasdale, Segal, & Kabat-Zinn, 2007).

The MBCT relapse prevention intervention was delivered in primary care settings with MBCT groups of 9–15 patients following the treatment protocol (Segal, Williams, & Teasdale, 2002): 2-hr sessions over 8 consecutive weeks, followed by four follow-up sessions in the following year. Session content included guided mindfulness practices (i.e., body scan, sitting meditation, yoga); inquiry into patients' experience of these practices; review of weekly homework (i.e., 40 min of mindfulness practice per day and generalization of session learning); and teaching/discussion of cognitive–behavioral skills. In line with the two previous MBCT trials, *an adequate dose of MBCT* was defined as participation in at least four of the eight MBCT group sessions.

All trial groups were videotaped with digital cameras for therapist supervision, checks on therapist competence, and checks on treatment adherence. The five trial groups were instructed by either a clinical psychologist or an occupational therapist (three and two groups, respectively). Both therapists had undergone a training program taught and supervised by one of the developers of MBCT (John D. Teasdale), had experience of running at least two supervised pilot groups, and had an ongoing personal mindfulness practice. An independent check on therapist competency was established before therapists progressed to running trial groups: An experienced MBCT therapist independent of the trial rated at least two videotapes of MBCT therapy sessions and made an overall judgment as to whether the therapists were competent.

Patients in the MBCT arm were supported in tapering and discontinuing their ADM by their primary care physician. Patients and physicians were initially prompted to begin discussing a tapering/discontinuation regime after 4–5 weeks of the MBCT groups. At the end of the MBCT groups, they were reminded to ensure a tapering/discontinuation regime was in place. We reasoned that because our sample reported three or more previous episodes of depression and had received at least 6 months of m-ADM, their tapering/discontinuation scheme would need to be conducted with great care. Tapering/discontinuation regimes were determined by physicians and patients, although the research team asked that patients consider tapering/discontinuing their medication as soon following MBCT as they deemed appropriate and within 6 months of the MBCT group ending. This allowed (a) tapering to be conducted at a pace determined by physicians and patients and (b) a substantial window to the study's end when patients had discontinued m-ADM to monitor the primary and secondary outcomes. The study team provided guideline information to physicians and patients about typical tapering/discontinuation regimes and possible withdrawal effects. If at any time the study team became aware of difficulties with medication tapering/discontinuation, the MBCT therapist first contacted the patient to understand the difficulty and then wherever appropriate encouraged the patient together with their physician to review the tapering/discontinuation regime.

Maintenance antidepressant treatment. The m-ADM relapse prevention intervention comprised maintenance of the ADM treatment that was an inclusion criterion for the study. Patients were monitored and treated by their physicians in primary care settings. During the maintenance phase, physicians were asked to manage m-ADM in line with standard clinical practice and the British National Formulary. Primary care physicians were asked to meet with patients regularly to review their medication treatment. Changes in medication sometimes occurred during the maintenance treatment stage, but physicians and patients were asked to ensure the dose remained within therapeutic limits.

Medication adherence. Medication adherence was monitored through patients' self-report at follow-ups every 3 months, practice databases, and the Morisky Medication Adherence Scale (MMAS; Morisky, Green, & Levine, 1986). Scores of 0–1 on the MMAS are considered to indicate high levels of adherence; scores of 2 or more in our study were taken to signal a possible adherence problem requiring action. If problems were identified at any assessment point, these were resolved through dialogue between a member of the research team not blind to treatment condition, the prescribing physician, and the patient, but we ensured that the research officer conducting follow-ups remained blind to treatment condition. Normally this addressed any problems with the m-ADM. However, if there were ongoing problems with adherence, these were addressed on a case-by-case basis with the goal of encouraging patients to continue taking a therapeutic dose of m-ADM for the duration of the follow-up period. *Protocol adherence* was defined as continuing to take m-ADM at a therapeutic maintenance dose for the duration of the trial.

Outcome Measures

Patients were assessed by research staff blind to treatment allocation at intake and then again every 3 months up to 15 months postrandomization.

Primary outcome measure: relapse/recurrence. The primary outcome measure was time to relapse/recurrence of depression, using the depression module of the Structured Clinical Interview for *DSM–IV* (SCID; First, Spitzer, Gibbon, & Williams, 1995) to assess retrospectively the 3-month period between assessments. *Relapse/recurrence* was defined as an episode meeting *DSM–IV* criteria for major depressive disorder. An experienced clinical psychologist with formal training in the use of the SCID trained the two research staff. To examine interrater reliability, we followed the method described in the first MBCT randomized control trial (RCT; Teasdale et al., 2000), which has the added benefit of guaranteeing all assessments were blind to treatment condition. For every first actual, borderline, or probable relapse/recurrence, an independent, blind, and experienced rater second-rated an audio recording of the SCID interview. The kappa coefficient for agreement between the study interviewer and blind rater was 0.84, suggesting excellent agreement. Where there were disagreements between the first and independent rater, consensus was reached through discussion. If a relapse/recurrence was considered marginal, a conservative position of no relapse was recorded. Once a judgment about relapse was made, the onset of relapse was dated from randomization to the point at which criteria were met.

Secondary outcome measures. To broaden the measurement of outcomes (Zimmerman et al., 2006), we included several secondary outcome measures. For any relapses/recurrences, the severity of the relapse/recurrence was assessed using the *DSM–IV* specifiers: "mild," "moderate," "severe without psychotic features," and "severe with psychotic features" (scale range 1–4; American Psychiatric Association, 1994). Through the follow-ups, we assessed the duration of any relapse/recurrence (i.e., period of time in months that a person met SCID criteria) and the associated distress, which was rated by patients on a 1–100-point scale ranging from 0 (*the least distressing episode of depression I have ever experienced*) to 100 (*the most distressing episode of depression I have ever experienced*).

Residual depressive symptoms cause impairment and predict future relapse/recurrence (Judd et al., 1999). To assess residual symptoms, we used the observer-rated interviewer-administered, 17-item version of the HRSD (J. B. Williams, 1988) and the 21-item self-report Beck Depression Inventory (2nd ed.; BDI–II; Beck, Steer, & Brown, 1996). Psychiatric comorbidity was assessed at study intake, and all comorbid diagnoses identified at intake were reassessed at the study's end using the relevant SCID modules (First et al., 1995).

To assess quality of life, we used the 26-item, self-report, short version of the World Health Organization Quality of Life instrument (WHOQOL-BREF), which assesses subjective quality of life in four domains: physical (e.g., "How satisfied are you with your sleep?"), psychological (e.g., "How much do you enjoy life?"), social (e.g., "How satisfied are you with your personal relationships?"), and environment (e.g., "How satisfied are you with your access to health services?"[1]; Harper & Power, 1998; World Health Organization, 2004). Data are reported on only the first three domains.

Service Use, Productivity Losses, and Cost

The economic evaluation took a broad perspective, including all hospital (inpatient, outpatient, emergency department) and community health and social services (e.g., primary care, social work, complementary therapies), plus productivity losses resulting from time off work due to illness. Economic data were collected in interview at baseline and then in 3-month intervals up to 15 months postrandomization using the Adult Service Use Schedule (AD-SUS), an instrument designed on the basis of previous studies of adult mental health populations (Bower et al., 2000; Byford et al., 2003). The AD-SUS asks recipients for the number and length of contacts with various services and professionals relevant to the disease of interest over the previous 3 months. To ensure that the AD-SUS covered all services relevant to the current population, we checked the schedule against information from a recent systematic review of economic evaluations in depression (Barrett, Byford, & Knapp, 2005). Studies were reviewed for service use categories included, and any items missing from the AD-SUS were added. Complementary therapies were the main addition. Data on MBCT contacts was collected from therapist records to avoid having patients reveal their treatment group to the research assessors.

All unit costs were for the financial year 2005–2006, the most recent financial year over which the trial data were collected. MBCT group sessions, each lasting 2 hr, were costed on the basis of the salary of the trial therapists plus overhead expenses (administrative, managerial, and capital). Calculation of the indirect time, including preparation and supervision, was based on information provided by the trial therapists on the ratio of direct face-to-face contact to all other MBCT activities. National United Kingdom unit costs were applied to medication, hospital contacts, and community health and social services (BMA–RPSGB, 2006; Curtis & Netten, 2006; Department of Health, 2006). Productivity losses were calculated using the human capital approach, which involves multiplying the individual's salary (mean salary of study participants $28,248 per annum) by reported days off work due to illness (Koopmanschap & Rutten, 1996). All costs were converted to international dollars using a purchasing power parity exchange rate of 0.6 as recommended by the World Bank (2006 World Development Indicators available at http://www.worldbank.org/).

Data Analysis

This is the first trial to directly compare MBCT with an active therapy arm, and consequently an estimate of the relative treatment effect of MBCT versus m-ADM was not available. A formal sample size calculation at the outset was therefore deemed inappropriate. Instead, an estimation approach was taken and the between-group difference in the primary outcome was reported as a mean and 95% confidence interval. Reanalysis of the two previous MBCT trials (Ma & Teasdale, 2004; Teasdale et al., 2000) found an intraclass correlation coefficient for relapse of less than zero in the treatment groups (J. M. G. Williams, personal commu-

[1] From *The World Health Organization Quality of Life (WHOQOL)-BREF,* 2004, Geneva, Switzerland: World Health Organization. Copyright 2004 by the World Health Organization. Reprinted with permission.

nication), suggesting adjustments for clustering were not necessary. Nonetheless, we examined heterogeneity across groups.

Time to relapse/recurrence of depression (primary outcome) for the two treatment groups was compared using Cox regression proportional hazard survival analysis, with treatment condition (MBCT or m-ADM) as the independent variable and allowing for the stratification variable (i.e., asymptomatic vs. partially symptomatic). Individuals who experienced no relapse/recurrence were considered as censored. The analysis was performed according to the principle of intention to treat (ITT; i.e., all patients according to and included in random allocation). A secondary, "per protocol treatment" (PPT) analysis, comprising all patients who stayed within key treatment parameters as set out in the protocol, was undertaken: For the MBCT group, patients attended at least four of eight MBCT sessions, in line with both previous MBCT trials; for the m-ADM patients, they continued to take ADM at a therapeutic maintenance dose for the duration of the trial.

Mixed-models between-groups (ITT and stratification) and repeated measures (3, 6, 9, 12, and 15 months follow-ups) analysis of covariance (baseline) was used to compare the groups with respect to changes in secondary outcomes.

It was intended that all statistical models be run with and without adjustment for baseline characteristics where the covariate selection depended on the baseline comparison of groups. As no differences in baseline covariates between groups were seen, analyses were performed without adjustment for these variables. We compared cases with and without missing data on demographic, psychiatric, and outcome variables, and there were no differences between these cases at $p < .05$. For the primary survival outcome analyses, drop out/missing data were handled by censoring. For the small subset of cases with missing data on secondary outcomes, we used last variable carried forward to impute missing data. Sensitivity analyses were undertaken to explore the impact of imputation of data losses on secondary outcome analyses. The analyses on secondary outcomes were unaffected by data imputation.

Differences in mean costs between MBCT and m-ADM groups were analyzed using standard parametric *t* tests, with the validity of results confirmed using bias-corrected, nonparametric bootstrapping (repeat resampling; Efron & Tibshirani, 1993). Despite the skewed nature of cost data, this approach is recommended to enable inferences to be made about the arithmetic mean (Thompson & Barber, 2000), a more meaningful summary statistic for costs than is the median or geometric mean. Cost effectiveness was explored through the calculation of *incremental cost-effectiveness ratios* (ICER), defined as the difference in mean costs divided by the difference in mean effects (Vanhout, Al, Gordon, & Ruten, 1994). Incremental cost per relapse prevented and per depression-free day is reported.

Nonparametric bootstrapping from the costs and effectiveness data was used to generate a joint distribution of incremental mean costs and effects for the two treatments. This was used to calculate the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision maker might be willing to pay for a unit improvement in outcome. Cost-effectiveness acceptability curves are presented by plotting these probabilities for a range of possible values of the ceiling ratio (Fenwick, Claxton, & Sculpher, 2001). These curves are a recommended decision-making approach to dealing with the uncertainty that exists around the estimates of expected costs and expected effects associated with the interventions under investigation (Claxton, 1999). All economic analyses were adjusted for baseline costs and the stratification variable. All analyses were undertaken using SPSS v15 and Stata v. 8.

Results

Patient Flow

Figure 1 shows the patient flow from screening to follow-up. The three main reasons potentially eligible patients did not participate were (a) they declined to participate (533; 36.3%); (b) the staff team was unable to make contact (451; 30.7%); and (c) they did not meet the study criteria (362; 24.6%). The three main reasons patients proved not to be eligible were (a) they had stopped taking antidepressants (56; 15.5%), (b) they reported fewer than three episodes of major depressive disorder (53; 15.5%), (c) they were on a subtherapeutic dose of antidepressants and/or were intending to reduce their antidepressant dose (52; 14.2%). The three main reasons they declined were (a) the time commitment was too much (103; 19.3%); (b) they wanted to stay on antidepressants (50; 9.4%), and (c) they did not like the group aspect of the therapy (28; 5.3%). In summary, the sample can be characterized as a group of people with recurrent depression, treated pharmacologically in primary care, who following a referral from their primary care physician were interested in a psychological group-based approach that included tapering/discontinuing their m-ADM.

One hundred twenty-three patients who could be located, agreed to participate, and met the inclusion criteria were randomized to either MBCT ($N = 61$) or m-ADM ($N = 62$) treatment. Two patients in the MBCT arm and 6 in the m-ADM arm were lost to follow-up. Of these, 5 were lost to follow-up shortly after intake, and the remaining 3 after a depressive relapse occurred. In the m-ADM arm, 10 (16%) patients were outside protocol because they decided to discontinue their medication. In the MBCT arm, 9 (15%) patients fell outside protocol because they attended fewer than four MBCT sessions (5 patients attended no sessions).

Patient Characteristics

Table 1 shows patient characteristics of the ITT sample. There were no differences between the MBCT and m-ADM groups on any of the patient characteristics ($p > .10$).

Patients who were per protocol were compared with those who were not. In the m-ADM group, patients choosing to discontinue ADM were comparable to those continuing their ADM on all patient characteristics at intake (all ps $> .10$) and on the primary outcome (relapse/recurrence rates in both groups was identical at 60%) and the secondary outcome variables (all ps $> .10$). In the MBCT group, the patients who were within protocol were not significantly different from those outside protocol on any patient characteristics at intake ($p > .05$) except number of previous suicide attempts (within protocol: 0.50, $SD = 1.21$; outside protocol: 1.78, $SD = 1.56$; Mann–Whitney U = 101, $p < .01$, $N = 61$). The within- and outside-protocol MBCT groups were comparable on the primary outcome (within protocol: 46% relapsed; outside protocol: 54% relapsed) and the secondary outcome vari-

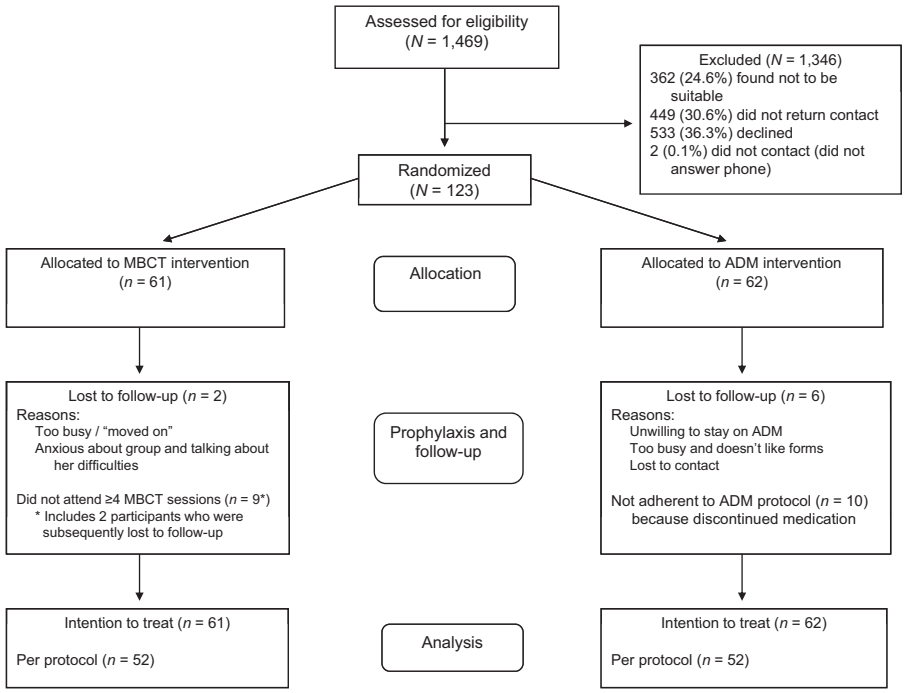

Figure 1. CONSORT flow diagram. MBCT = mindfulness-based cognitive therapy; ADM = antidepressant medication.

ables (all *ps* > .05). No adverse events were recorded through the oversight of the Trial Steering Committee.

Preliminary Analysis

At intake the type of ADM was as follows: selective re-uptake inhibitor 71 (58%), tricyclic 27 (22%), or combination 25 (20%); this was not significantly different across the two groups ($p > .10$). Adherence to the MBCT protocol was assessed by an experienced and independent MBCT therapist with the Mindfulness-Based Cognitive Therapy Adherence Scale (Segal, Teasdale, Williams, & Gemar, 2002). She watched videotapes of all 40 MBCT sessions. The total adherence scale scores in the trial ($M = 29.1$; $SD = 4.69$) were at least comparable to those reported in the psychometric evaluation of this scale (Segal, Teasdale, et al., 2002) and indicate acceptable adherence to protocol. This rater also confirmed that the MBCT was delivered competently across therapists and groups. To assess possible differences owing to MBCT group or MBCT therapist, we compared relapse/recurrence rates across these variables. The relapse/recurrence rates did not differ statistically between the five MBCT groups (46%, 49%, 68%, 44%, and 53%, respectively), $\chi^2(4, N = 61) = 0.87$, $p = .93$, or across the two therapists (Therapist 1: 49%, Therapist 2: 46%), $\chi^2(1, N = 61) = 0.06$, $p = .814$. Given the homogeneity in relapse/recurrence rates across groups and therapists, adjustment for the group-administered nature of MBCT (Baldwin, Murray, & Shadish, 2005) was deemed unnecessary in this case.

At each follow-up point in the m-ADM arm, ADM was checked to ensure that type and dose were within parameters set out in the British National Formulary (BMA–RPSGB, 2006) and that patient adherence was acceptable. The average score on the MMAS (Morisky et al., 1986) was 0.63 ($SD = 0.62$), suggesting consistently high levels of adherence throughout the follow-up period. Our trial sought to ask if MBCT enabled patients to taper/discontinue their ADM. Over the course of the follow-up period (ca. 450 days), the mean number of days on ADM treatment was significantly different between the m-ADM ($M = 411.4$, $SD = 91.77$) and MBCT ($M = 266.46$, $SD = 167.74$) groups, $t(101) = 5.40$, $p < .0001$, $d = 1.07$. At the end of the 6-month window allowed for tapering/discontinuation, 46 (75%) of the patients in the MBCT arm of the trial discontinued their medication. In the further 6 months of the follow-up period (the post–tapering/discontinuation window), the rates of ADM usage between the two groups continued to be highly significantly different, $t(105) = 4.85$, $p < .0001$, $d = 0.93$.

Outcome Analysis: Relapse/Recurrence to Major Depression

Figure 2 shows survival (i.e., non–relapse/recurrence) curves over the 15-month study period for the intention to treat MBCT and m-ADM groups. Cox regression showed borderline evidence of a reduction in the hazard of relapse/recurrence with MBCT compared with m-ADM in both ITT analysis, Wald (1, $N = 123$) = 1.82, $p = .07$, hazard ratio = 0.63 (95% CI: 0.39 to 1.04), and PPT analysis, Wald (1, $N = 101$) = –1.95, $p = .05$, hazard ratio = 0.59 (95% CI: 0.34 to 1.00). In the ITT sample over the total 15-month follow-up period, 47% (29/61) of the MBCT patients relapsed, compared with 60% (37/62) of the m-ADM patients, log-rank $\chi^2(1) = 1.54$, $p = .21$. In the PPT sample, 46% (24/52) of the MBCT patients had a relapse/recurrence, compared

Table 1
Characteristics of MBCT and m-ADM Intention to Treat Samples

Variable	MBCT (n = 61)	m-ADM (n = 62)
Demographic characteristics		
Women: *n* (%)	47 (77)	47 (76)
White: *n* (%)[a]	60 (98)	62 (100)
Age (in years)		
M (*SD*)	48.95 (10.55)	49.37 (11.84)
Range	26–66	21–72
Marital status: *n* (%)		
Single	4 (7)	9 (15)
Married or cohabiting	42 (69)	40 (65)
Separated, divorced, or widowed	15 (25)	13 (21)
Level of education: *n* (%)		
No educational qualification	9 (15)	17 (27)
Some school qualification	16 (26)	16 (26)
High school and/or vocational qualification	24 (39)	15 (24)
University degree/professional qualification	12 (20)	14 (23)
Religion: *n* (%)		
None	12 (20)	16 (26)
Christian	46 (75)	45 (73)
Other[b]	3 (5)	1 (2)
Social class: *n* (%)[c]		
Class 1	22 (36)	23 (37)
Class 2	15 (25)	12 (19)
Class 3	7 (12)	7 (11)
Class 4	6 (10)	2 (3)
Class 5	11 (18)	17 (27)
Psychiatric characteristics		
Depression		
HRSD score: *M* (*SD*)	5.62 (4.3)	5.76 (4.69)
BDI-II score: *M* (*SD*)	18.51 (10.91)	20.15 (12.86)
Depression diagnosis at intake: *n* (%)		
In full remission	42 (69)	41 (66)
In partial remission	19 (31)	21 (34)
Previous episodes: *M* (*SD*)	6.43 (3.04)	6.35 (2.91)
Median	6	6
With ≥ 10 episodes: *n* (%)	23 (38)	19 (31)
No. of comorbid *DSM–IV* Axis I psychiatric diagnoses: *M* (*SD*)	.83 (.96)	1.04 (1.11)
Age (in years) at first depression onset: *M* (*SD*)	26.34 (11.7)	26.11 (12.65)
Time (in months) since last depressive episode: *M* (*SD*)	24.20 (27.74)	18.68 (23.89)
Severity of last depressive episode (no. of *DSM–IV* symptoms recorded): *M* (*SD*)	7.27 (1.3)	7.04 (1.35)
Attempted suicide: *n* (%)	20 (33)	22 (35)
No. of previous attempts: *M* (*SD*)	0.69 (1.37)	0.66 (1.05)
Range	0–7	0–4
Previous psychiatric treatment: *n* (%)	17 (28)	13 (21)
Quality of life[d]: *M* (*SD*)		
Physical	22.64 (5.59)	23.0 (5.18)
Psychological	17.8 (3.82)	18.03 (3.63)
Social	9.52 (2.32)	9.27 (2.65)

Note. MBCT = mindfulness-based cognitive therapy; m-ADM = maintenance antidepressant medication; HRSD = Hamilton Rating Scale for Depression; BDI-II = Beck Depression Inventory II; *DSM–IV = Diagnostic and Statistical Manual of Mental Disorders* (4th ed.).
[a] The non-White participant was British Asian. [b] There was 1 Muslim in the m-ADM group and 1 Bahai, 1 Buddhist, and 1 Spiritualist in the MBCT group. [c] Social class was according to UK National Office of National Statistics, and the range was from professional and managerial occupations (Class 1) to semiroutine and routine occupations (Class 5). Data were missing for 1 case in the m-ADM arm of the trial. [d] Data determined on the basis of the World Health Organization Quality of Life assessment (brief version).

with 60% (31/52) of the m-ADM patients, log-rank $\chi^2(1) = 3.32$, $p = .07$.

Two exploratory subgroup analyses were set out in the analysis plan. First, although we restricted our sample to people with three or more episodes, we wanted to establish that there were no interaction effects for those with more prior episodes, Wald (1, $N = 123$) = –1.29, $p = .20$, hazard ratio = 0.9 (95% CI: 0.76 to 1.06). Second, as this was the first trial to include patients in full *and partial* remission from recurrent depression, we looked at effects of severity of depression (i.e., asymptomatic vs. partially

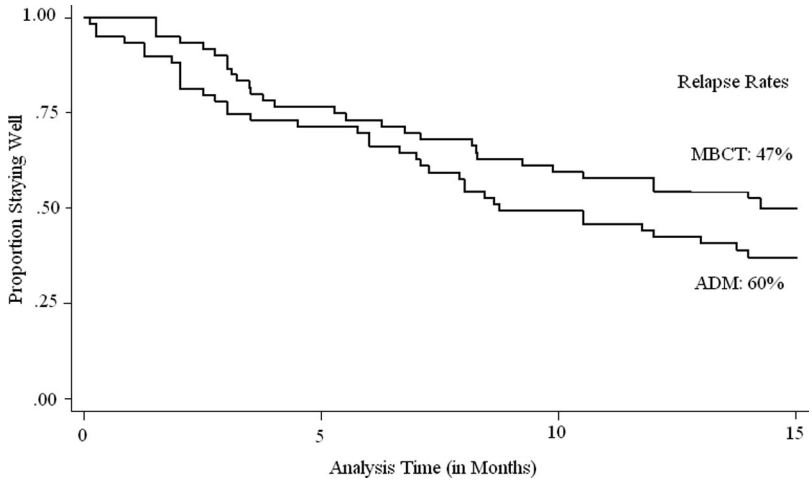

Figure 2. Survival (non–relapse/recurrence) curves comparing relapse/recurrence with major depression for mindfulness-based cognitive therapy (MBCT) and antidepressant medication (ADM) groups over a 15-month follow-up period.

symptomatic). There was no evidence of an interaction with treatment condition for severity of depression, Wald (1, $N = 123$) = –1.50, $p = .13$, hazard ratio = 0.47 (95% CI: 0.17 to 1.26); patients with and without residual symptoms did not respond significantly differently to the two interventions.

To assess the possibility that differential discontinuation of m-ADM affected the primary outcome findings, we undertook two further sets of post hoc analyses on the primary outcome. First, we compared participants in the MBCT arm who did and did not taper/discontinue m-ADM on all demographic and psychiatric characteristics (see Table 1). Only age of onset and severity of last depressive episode were significantly different ($p < .05$), and crucially this was in the direction that patients with earlier age of onset and greater severity of last episode were more likely to taper ADM. Second, we reran the survival analysis including only (a) those patients who received MBCT and tapered/discontinued m-ADM and (b) ADM patients who received an adequate dose of m-ADM throughout the follow-up period. Cox regression showed no difference between MBCT and m-ADM, Wald (1, $N = 89$) = –1.27, $p = .21$, hazard ratio = 0.77 (95% CI: 0.49 to 1.16).

Outcome Analyses: Secondary Outcomes

Each of the secondary outcomes was assessed in turn, covarying the stratification variable in all instances. The first secondary outcome concerned the total number and qualitative nature of depressive relapses/recurrences (duration, severity, and subjective distress) across the MBCT and m-ADM arms. For the ITT analyses, the two groups were not statistically different on any index of relapse/recurrence: mean total number of relapses/recurrences: m-ADM 1.57 (95% CI: 1.32 to 1.81), MBCT 1.45 (95% CI: 1.21 to 1.69), $F(1, 66) < 1$, $d = 0.26$; duration of relapses/recurrences (in months): m-ADM 3.0 (95% CI: 2.1 to 3.9), MBCT 3.36 (95% CI: 2.2 to 4.5), $F(1, 66) < 1$, $d = 0.08$; severity of relapses/recurrences (*DSM–IV* severity specifier, 0–4): m-ADM 1.72 (95% CI: 1.48 to 1.95), MBCT 1.79 (95% CI: 1.56 to 2.02), $F(1, 66) < 1$, $d = 0.13$; and subjective distress: m-ADM 62.56 (95% CI: 56.16 to 68.96), MBCT 59.65 (95% CI: 51.82 to 67.18), $F(1, 66) < 1$, $d = 0.24$. After rerunning these analyses for the PPT sample, we found that the pattern of findings was unchanged, all Fs $(1, 52) < 1$.

Table 2 reports the means and inferential tests for the secondary outcomes concerning residual depressive symptoms and quality of life. The MBCT group reported significantly fewer residual depressive symptoms across the five follow-ups compared with the m-ADM group in both the ITT and PPT analyses. MBCT reported better quality of life than did m-ADM in the physical and psychological domains in both the ITT and PPT analyses.

The fourth secondary outcome was psychiatric comorbidity. The number of comorbid diagnoses at study end was significantly less in the MBCT than m-ADM group for the ITT analysis (Mann–Whitney U = 1,332, $p < .05$, $d = 0.43$) and PPT analysis (Mann–Whitney U = 580, $p < .05$, $d = 0.51$), $N = 114$ (ADM: $M = 0.7$, $SD = 1.01$; and MBCT: $M = 0.34$, $SD = 0.64$).

Service Use, Productivity Losses, and Costs

There was little difference in the use of health and social services between the two groups. Table 3 displays the total costs per participant for the two groups. The most frequently accessed services included UK National Health Service hospital outpatient appointments ($M = 2.2$ in the MBCT group vs. 3.2 in the m-ADM group), primary care physician contacts ($M = 9$ in the MBCT group vs. 8 in the m-ADM group), and primary care nurse contacts ($M = 3$ in the MBCT group vs. 2 in the m-ADM group).

The total cost for an initial one-to-one session ($99) followed by eight MBCT sessions and four follow-up sessions ($16.50 per participant per session) was estimated to be $297 per participant. In practice, some MBCT participants also received additional one-to-one sessions, as well as support by telephone or e-mail, giving a mean cost of $340 per participant (see Table 3). The cost of antidepressant prescriptions was significantly lower in the MBCT group than in the m-ADM group over the 15-month follow-up period ($M = $172 vs. $275, respectively). There were

Table 2
Posttreatment and 15 Months Follow-up for MBCT and m-ADM Groups for Secondary Outcomes

Secondary outcomes	1 month posttreatment		15 months follow-up		Inferential between-groups test (see data analysis)
	MBCT	m-ADM	MBCT	m-ADM	
			Residual depressive symptoms		
HRSD[a]					
M	5.83	7.75	7.05	8.69	
95% CI	4.49 to 7.3	5.86 to 9.34	5.53 to 8.74	6.64 to 10.5	
ITT					$F(1, 116) = 5.8$, $p = .02$, $\eta_p^2 = .06$
PPT					$F(1, 98) = 4.63$, $p = .03$, $\eta_p^2 = .04$
BDI-II[b]					
M	13.12	17.47	12.61	17.02	
95% CI	10.27 to 15.97	14.31 to 20.62	9.96 to 15.26	13.16 to 20.87	
ITT					$F(1, 114) = 2.52$, $p = .12$, $\eta_p^2 = .04$
PPT					$F(1, 97) = 4.0$, $p = .04$, $\eta_p^2 = .04$
			Quality of life[c]		
Physical					
M	24.08	22.86	23.97	22.93	
95% CI	22.62 to 25.53	21.34 to 24.39	22.63 to 25.30	21.18 to 24.69	
ITT					$F(1, 114) = 4.03$, $p = .04$, $\eta_p^2 = .05$
PPT					$F(1, 98) = 4.48$, $p = .04$, $\eta_p^2 = .05$
Psychological					
M	18.88	17.47	18.61	17.36	
95% CI	17.88 to 19.89	16.24 to 18.70	17.65 to 19.57	15.93 to 18.78	
ITT					$F(1, 114) = 6.23$, $p = .01$, $\eta_p^2 = .06$
PPT					$F(1, 98) = 6.37$, $p = .01$, $\eta_p^2 = .06$
Social					
M	10.09	9.07	10.10	9.66	
95% CI	9.55 to 10.64	8.37 to 9.77	9.53 to 10.68	8.88 to 10.44	
ITT					$F(1, 112) = 1.87$, $p = .18$, $\eta_p^2 = .02$
PPT					$F(1, 98) = 0.3$, $p = .59$, $\eta_p^2 = .003$

Note. $n = 61$ for MBCT; $n = 62$ for m-ADM. MBCT = mindfulness-based cognitive therapy; m-ADM = maintenance antidepressant medication; HRSD = Hamilton Rating Scale for Depression; CI = confidence interval; ITT = intention to treat; PPT = per protocol treatment; η_p^2 = the proportion of effect and error variance that is attributed to the effect for the between-groups comparison; BDI-II = Beck Depression Inventory II.
[a] Complete data set for $N = 118$ (i.e., 59 in each group). [b] Complete data set for $N = 117$ (i.e., 59 in MBCT group and 58 in m-ADM group). [c] Data determined on the basis of the World Health Organization Quality of Life assessment (brief version; World Health Organization, 2004). Complete data set for $N = 119$ (i.e., 60 in MBCT group and 59 in m-ADM group).

no significant differences between the two groups in any other cost category. In total, the per-person cost for the MBCT group was $457 more than that for the m-ADM group, but this difference was not significant. Exploration of costs over time reveals that MBCT is consistently more expensive than m-ADM over the first 12 months but that costs converge and MBCT becomes cheaper over the final 3-month period (12 to 15 months).

Including all health and social services costs and productivity losses, the incremental cost-effectiveness ratio was $962 per relapse/recurrence prevented and $50 per depression-free day.

Table 3
Total Cost Breakdown (in Dollars) per Participant

Variable	MBCT *M* (*SD*)	m-ADM *M* (*SD*)	Mean difference of MBCT vs. m-ADM (95% CI)	p[a]
MBCT	340 (58)	0 (0)	340 (325 to 355)	
Antidepressants	172 (212)	275 (279)	–103 (–191 to –14)	
Hospital services	720 (1,245)	733 (1,983)	–13 (–607 to 578)	
Community health and social services	844 (1,091)	569 (580)	275 (–36 to 586)	
Productivity losses	1,297 (2,707)	1,338 (4,343)	–42 (–1,337 to 1,252)	
Total cost over follow-up	3,370 (4,002)	2,915 (4,838)	457 (–1,130 to 2,043)	.865
Total cost per year	2,767 (313)	2,340 (3,822)	427 (–852 to 1,705)	.788

Note. MBCT = mindfulness-based cognitive therapy; m-ADM = maintenance antidepressant medication; CI = confidence interval.
[a] Adjusted for stratification variable and baseline costs.

For health care costs only, these ratios were $439 and $23, respectively.

The cost-effectiveness acceptability curve shown in Figure 3 demonstrates that if society's willingness to pay for preventing an additional relapse/recurrence is zero (society is unwilling to spend any additional amount to prevent relapse/recurrence), then the probability of MBCT being the more cost-effective option is 42%, while the probability of the m-ADM being the more cost-effective option is 58%. However, the probability of MBCT being the more cost effective of the two options increases as willingness to pay increases, suggesting that MBCT has a higher probability of being more cost-effective than has m-ADM for willingness-to-pay levels of approximately $1,000 and above.

Discussion

In people with recurrent depression, MBCT produces comparable outcomes to those for people using m-ADM in terms of relapse/cost effectiveness and superior outcomes concerning residual depressive symptoms, psychiatric comorbidity, and the physical and psychological domains of quality of life. The reductions in ADM usage in the MBCT group were substantial, and 75% of patients in the MBCT arm completely discontinued their ADM. MBCT provides a promising alternative approach to m-ADM, with over 50% of people participating in MBCT staying well through the follow-up period, compared with 40% in the m-ADM group.

Rates of adherence to MBCT were comparable to those in previous trials (85%) and suggest the acceptability of this approach. However, in the recruitment to the study, the time commitment and group aspect were noted as reasons to decline participation. Moreover, 25% of the MBCT patients did not discontinue their m-ADM, and those who experienced relapses/recurrences were more likely to resume ADM. There is increasing acknowledgement that depression is a recurrent disorder (Judd, 1997a), and management in primary care needs to develop prophylactic approaches and routinely monitor for relapses. The fact that MBCT did more to reduce residual symptoms than m-ADM did is significant, as residual symptoms tend to predict relapse/recurrence (Judd, 1997a) and interventions that target residual symptoms tend to produce better outcomes over long-term follow-ups (Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; Paykel et al., 1999). MBCT's positive impact on comorbidity is likely to have longer term benefits as patients have to contend with fewer psychiatric symptoms. Similarly, patient quality of life is an essential aspect of outcome assessment (Kuyken et al., 1995), and the fact that MBCT produced additional gains in the physical and psychological domains of life suggests that it may produce incremental benefits in quality of life for some patients when compared with m-ADM.

Cost-effectiveness analysis suggests that the additional cost of MBCT may be justified in terms of improvements in the proportion of patients who relapse—but only if willingness to pay for such improvements is $1,000 or above. In terms of depression-free days, the incremental cost effectiveness of MBCT is comparable to that of similar studies, with a ratio of $50 per depression-free day for total costs and $23 for health service costs. Recent estimates for collaborative care programs include $33 in terms of total outpatient costs (Liu et al., 2003) and $21 in terms of total inpatient and outpatient costs (Simon et al., 2001). Estimates of $14–$24 have been reported for a depression relapse prevention program (Simon et al., 2002). Exploration of costs over time suggests that differences in cost converge and MBCT becomes cheaper than m-ADM over the final 3-month period of the study. If this trend were to continue, the relative cost effectiveness of MBCT may increase over time. Future studies should consider longer follow-up periods in order to test this hypothesis.

This study does not speak to the mechanism whereby MBCT is efficacious. It is possible that MBCT cultivates greater awareness that empowers people to step out of automatic modes of reacting and respond more skillfully at times of potential relapse (Segal, Williams, & Teasdale, 2002). However, it is also possible that the

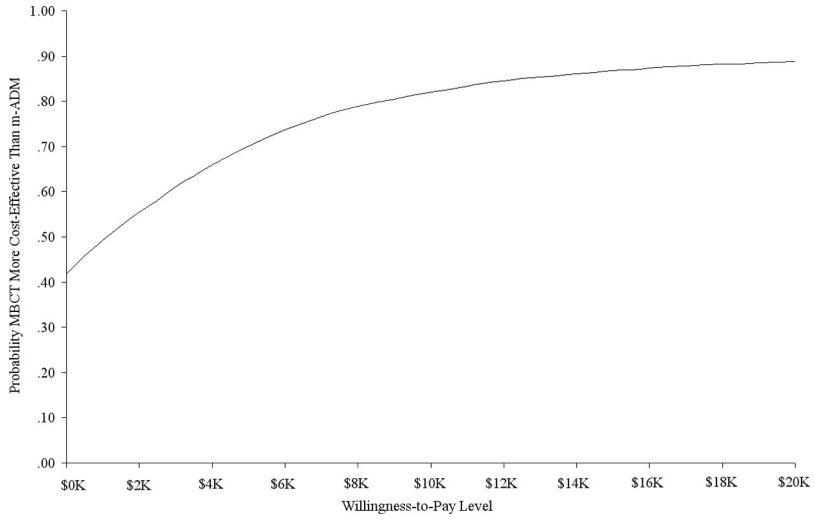

Figure 3. Probability that mindfulness-based cognitive therapy (MBCT) would be more cost effective than maintenance antidepressant medication (m-ADM) over the 15-month follow-up period for a range of levels of willingness to pay for a unit reduction in the proportion of patients who relapse. K = thousand.

behavioral (action at times of potential relapse) and cognitive (noting and responding to negative thinking) components of MBCT are the active ingredients. This would be consistent with recent evidence showing that cognitive and behavioral approaches that target these mechanisms produce prophylactic effects comparable to those for m-ADM (Bockting et al., 2005; Hollon et al., 2005). It is also possible that nonspecific effects of attention and group support are responsible for MBCT's efficacy. Research explicitly focused on studying mechanisms of change is needed to examine these outstanding questions (Coelho et al., 2007; Laurenceau, Hayes, & Feldman, 2007). Observed differences between MBCT and m-ADM in rates of comorbidity, residual depressive symptoms, and quality of life provide promising clues to potential mechanisms of action.

This study has several limitations. First, knowing that rates of adherence to m-ADM tend to be poor (Cooper et al., 2007), in our protocol we sought to maximize adherence in the m-ADM group to ensure that MBCT was indeed being compared with an active treatment. As such, our m-ADM group should be characterized as an enhanced care group in that the study team actively encouraged high levels of adherence at each follow-up. The findings suggest that the enhanced care package was successful in ensuring high rates of adherence to m-ADM. As such, the m-ADM management in this trial was better than would be experienced in routine primary care settings (cf. Katon et al., 2001). However, our checks on MBCT therapists' competence and adherence suggest that this arm is probably also of a higher quality than would be expected in routine health care settings. Second, our recruitment approach was to screen all patients on ADM in primary care and then through several steps establish if these individuals met the study's inclusion criteria and were willing to participate (White et al., 2007). This enabled us to recruit our sample relatively rapidly but meant that a large number of people proved not to be eligible or declined. However, we argue that the sample represents people identified in primary care as suffering depression and who at their physician's invitation were interested in pursuing a psychological approach to relapse prevention. Nonetheless, the next phase of effectiveness treatment outcome research should examine the question of MBCT's generalizability for different subpopulations and different settings (e.g., referral source, primary vs. secondary care, patients with multiple comorbidities). The time commitment of participation (in MBCT and the associated research) and the group aspect of MBCT were given as reasons for declining, so research into MBCT's accessibility is required. Third, different relapse prevention interventions with different populations produce different absolute rates of depressive relapse (Geddes et al., 2003; Hollon et al., 2002). The rates of relapse across both arms of the trial were relatively high, most likely reflecting (a) our selection of a group at particularly high risk (3+ episodes) and (b) self-selection among patients recognizing their risk and wanting help. We would predict that relapse rates in this highly vulnerable group might be reduced further through augmentation of ADM with MBCT, which would be an obvious focus for a future trial. Fourth, this study does not speak to the mechanisms through which MBCT operates. Fifth, the economic evaluation excluded patient and family expenses and the cost of informal care. For assessment of the true societal costs of depression, future studies should consider including these costs. Finally, the fact that a subset of MBCT participants chose not to discontinue their m-ADM suggests that a future additive design (MBCT plus m-ADM) may produce better outcomes, at least among those patients not yet ready to discontinue m-ADM. Alternatively, a future design may need to provide greater or more specialist support in tapering/discontinuing m-ADM.

MBCT has only recently been developed, and this is the first evaluation of its efficacy against another active treatment and the first evaluation of MBCT's cost effectiveness. This study differs most significantly from previous trials (Ma & Teasdale, 2004; Teasdale et al., 2000) in that it recruited only people being treated with the currently most commonly used prophylactic approach (m-ADM) and supported people participating in MBCT to taper/discontinue their medication. Future trials will be able to base themselves on extant effect sizes and examine outstanding questions such as external validity in increasingly real-world settings, the costs of training MBCT therapists, the efficacy of augmenting m-ADM treatment with MBCT, and comparisons with other psychosocial approaches to relapse prevention, such as behavioral activation and cognitive therapy (Dimidjian et al., 2006; Hollon et al., 2005).

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The Publications and Communications Board of the American Psychological Association announces the appointment of 4 new editors for 6-year terms beginning in 2010. As of January 1, 2009, manuscripts should be directed as follows:

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