Prevention of relapse/recurrence in major depression by Mindfulness-based Cognitive Therapy

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Prevention of Relapse/Recurrence in Major Depression by Mindfulness-Based Cognitive Therapy

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This study evaluated mindfulness-based cognitive therapy (MBCT), a group intervention designed to train recovered recurrently depressed patients to disengage from dysphoria-activated depressogenic thinking that may mediate relapse/recurrence. Recovered recurrently depressed patients ($n = 145$) were randomized to continue with treatment as usual or, in addition, to receive MBCT. Relapse/recurrence to major depression was assessed over a 60-week study period. For patients with 3 or more previous episodes of depression (77% of the sample), MBCT significantly reduced risk of relapse/recurrence. For patients with only 2 previous episodes, MBCT did not reduce relapse/recurrence. MBCT offers a promising cost-efficient psychological approach to preventing relapse/recurrence in recovered recurrently depressed patients.

Relapse and recurrence following successful treatment of major depressive disorder (MDD) is common and often carries massive social cost (Mintz, Mintz, Arruda, & Hwang, 1992). Reviewing

studies of lifetime course of depression, a recent commentary concluded that "it has been established that unipolar major depressive disorder is a chronic, lifelong illness, the risk for repeated episodes exceeds 80%, patients will experience an average of 4 lifetime major depressive episodes of 20 weeks duration each" (Judd, 1997, p. 990). Such data suggest that the prevention of relapse and recurrence poses a central challenge in the overall management of MDD. Currently, maintenance pharmacotherapy is the best validated and most widely used approach to prophylaxis in depression, the lowest rates of recurrence occurring when patients are continued at the dosage of antidepressant medication used to achieve remission (Kupfer et al., 1992).

Maintenance psychotherapy may also be helpful. The pioneering work of Frank, Kupfer, and colleagues (e.g., Frank et al., 1990; Frank, Kupfer, Wagner, McEachran, & Cornes, 1991; Kupfer et al., 1992) has shown that continuation of a psychological treatment (interpersonal psychotherapy) in maintenance form can also significantly extend survival time following recovery. Cognitive–behavioral therapy (CBT) for depression (Beck, Rush, Shaw, & Emery, 1979), administered during depressive episodes, appears to be effective in reducing subsequent rates of relapse and recurrence. Studies comparing the long-term outcome of patients who recovered following treatment of acute depression by CBT with the outcome of patients who recovered following treatment with antidepressant medication and who were then withdrawn from medication have consistently found less relapse or need for further treatment in the CBT group (Blackburn, Eunson, & Bishop, 1986; Evans et al., 1992; Shea et al., 1992; Simons, Murphy, Levine, & Wetzel, 1986). Such findings suggest that CBT may be a treatment for acute depression that has long-term effects in reducing risk of future relapse and recurrence, presumably through patients acquir-

ing skills, or changes in thinking, that confer some degree of protection against future onsets.

A recent novel approach to the prevention of relapse and recurrence in depression, for which there is encouraging preliminary evidence, is to combine pharmacotherapy for the acute episode with psychological prophylactic interventions administered following recovery. Fava and colleagues (e.g., Fava, Grandi, Zielezny, Canestrari, & Morphy, 1994; Fava, Grandi, Zielezny, Rafanelli, & Canestrari, 1996; Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998) have reported successful use of such an approach, combining treatment of the acute episode by antidepressant medication with provision of CBT, following recovery, while antidepressant medication is gradually withdrawn. For example, Fava et al. (1998) described the results of a trial comparing the long-term outcome of 40 patients with recurrent major depression (three or more episodes) successfully treated with antidepressant medication and then randomized to clinical management or a combination of (a) CBT for residual symptoms, (b) lifestyle modification, and (c) well-being therapy, while antidepressant medication was withdrawn. Over a 2-year follow-up, the CBT group showed significantly less relapse/recurrence (25%) than the clinical management group (80%).

The strategy of combining acute pharmacotherapy with psychological prophylaxis offers the possibility of (a) capitalizing on the cost-efficiency of antidepressant medication to reduce acute symptomatology while (b) avoiding the need for patients to remain indefinitely on maintenance medication to reduce future relapse and recurrence. In this article, we describe a multicenter trial evaluating the effectiveness of this strategy using a novel, theory-driven approach to psychological prophylaxis, mindfulness-based cognitive therapy (MBCT). To increase the potential cost-efficiency of this strategy, MBCT was designed as a group skills-training approach rather than as an individual psychological therapy. In contrast to Fava et al. (1998), we (a) focused on a group intervention rather than an individual intervention, (b) studied more than a single therapist, (c) used a larger sample size, and (d) administered the psychological intervention at least 3 months after, rather than during, withdrawal of antidepressant medication.

The theoretical background to MBCT (referred to previously [Teasdale, Segal, & Williams, 1995] as attentional control [mind-fulness] training) has been described in detail elsewhere (Segal, Williams, Teasdale, & Gemar, 1996; Teasdale et al., 1995). It is assumed that vulnerability to relapse and recurrence of depression arises from repeated associations between depressed mood and patterns of negative, self-devaluative, hopeless thinking during episodes of major depression, leading to changes at both cognitive and neuronal levels. As a result, individuals who have recovered from major depression differ from individuals who have never experienced major depression in the patterns of thinking subsequently activated by dysphoria.

Specifically, it is suggested that, in recovered depressed patients, the thinking activated by dysphoria will show similarities to the thinking patterns previously present in episode. These reactivated patterns of thinking can act to maintain and intensify the dysphoric state through escalating and self-perpetuating cycles of ruminative cognitive–affective processing (Teasdale, 1988, 1997). In this way, in those with a history of major depression, states of mild dysphoria will be more likely to progress to more intense and persistent states, thereby increasing risk of further onsets of episodes of major depression.

Studies that have compared the patterns of thinking activated by mild dysphoria in those with and without a history of major depression support this account (Ingram, Miranda, & Segal, 1998; Segal, Gemar, & Williams, 1999). This analysis provides a parallel explanation, at the cognitive level, to more biological accounts of episode sensitization and kindling in recurrent affective disorder (Post, 1992). Accounts at both biological and cognitive levels are consistent with the finding that, with repeated experiences of episodes of major depression, less environmental stress is required to provoke relapse/recurrence (Post, 1992). That is, the processes mediating relapse/recurrence appear to become progressively more autonomous with increasing experience of episodes of depression.

The above account suggests that risk of relapse and recurrence will be reduced if patients who have recovered from episodes of major depression can learn, first, to be more aware of negative thoughts and feelings at times of potential relapse/recurrence and, second, to respond to those thoughts and feelings in ways that allow them to disengage from ruminative depressive processing (Nolen-Hoeksema, 1991). MBCT was designed to achieve those aims (Teasdale et al., 1995). MBCT is based on an integration of aspects of CBT for depression (Beck et al., 1979) with components of the mindfulness-based stress reduction program (MBSR) developed by Kabat-Zinn and colleagues (e.g., Kabat-Zinn, 1990). There is preliminary evidence for the effectiveness of MBSR in the treatment of generalized anxiety disorder (GAD) and panic (Kabat-Zinn et al., 1992) and chronic pain (Kabat-Zinn, Lipworth, Burney, & Sellers, 1986). Unlike CBT, there is little emphasis in MBCT on changing the content of thoughts; rather, the emphasis is on changing awareness of and relationship to thoughts. Aspects of CBT included in MBCT are primarily those designed to facilitate "decentered" views, such as "Thoughts are not facts" and "I am not my thoughts."

The focus of MBCT is to teach individuals to become more aware of thoughts and feelings and to relate to them in a wider, decentered perspective as "mental events" rather than as aspects of the self or as necessarily accurate reflections of reality. It is assumed that the cultivation of a detached, decentered relationship to depression-related thoughts and feelings is central in providing individuals with skills to prevent the escalation of negative thinking patterns at times of potential relapse/recurrence (Teasdale, 1997; Teasdale et al., 1995). Because, unlike CBT, there is little explicit emphasis in MBCT on changing the content or specific meanings of negative automatic thoughts, in MBCT training can occur in the remitted state, using everyday experience as the object of training.

We report an initial multicenter randomized clinical trial evaluating the efficacy of MBCT in reducing relapse and recurrence in patients with recurrent depressive disorder. Patients entered the trial in remission, following treatment of previous episodes by antidepressant medication. Choice of an appropriate design for the initial evaluation of a novel intervention, such as MBCT, is influenced by a number of factors. At the time this trial was planned, there was no published evidence that any psychological intervention, initially administered in the recovered state could, prospectively, reduce risk of future recurrence in major depression. Given this situation, the first priority for research was to evaluate whether MBCT was of any benefit in reducing relapse/recurrence; if benefits were observed, subsequent research could compare MBCT with other psychological interventions, including controls for

attention-placebo factors, and with alternative approaches to prevention, such as maintenance pharmacotherapy.

We used a design in which patients who continued with treatment as usual (TAU) were compared with patients who, additionally, received training in MBCT. Such a design does not aim to compare MBCT with the best available alternative preventive intervention. Nor does it allow any reduction in rates of relapse and recurrence for patients receiving MBCT to be attributed unambiguously to the specific components of MBCT rather than to nonspecific factors, such as therapeutic attention or group participation. However, this design is the most appropriate to answer the question that was of primary interest in this initial evaluation of MBCT: Does this intervention, when offered in addition to TAU, reduce rates of relapse and recurrence compared to TAU alone?

Method

Design

At three treatment sites, 145 patients, currently in remission or recovery from major depression at the time of the baseline assessment, were randomized to continue with TAU or, additionally, to receive MBCT training. Following an initial treatment phase, patients entered a 1-year follow-up phase; a period of 1 year was selected because it has been a follow-up reported in earlier studies (e.g., Simons et al., 1986) and because it was not considered appropriate to defer the possibility for patients allocated to TAU to participate in the MBCT program for a longer time (all of the patients initially allocated to TAU were offered the possibility of MBCT on completion of the follow-up year). Thus, the total 60-week study period comprised an initial 8-week treatment phase followed by a 52-week follow-up phase.

Randomization involved treatment sites faxing patient initials, date of birth, gender, date of assessment, and details of number and recency of previous episodes of depression to a central independent allocator. Information was sent for groups of eligible patients at a time. The central allocator randomly allocated patients to treatment condition, gave each a study number, and faxed the allocations and study numbers back to treatment sites.

Patients were stratified on two baseline variables—recency of recovery from last episode of depression (within 0–12 months prior to randomization vs. within 13–24 months prior to randomization) and number of previous episodes of MDD (two vs. more than two)—and randomized by strata within each site. Both of these variables have been found to be related to risk of relapse/recurrence in previous studies (e.g., see Evans et al., 1992; Post, 1992). A 1-year cutoff for recency of recovery meant that all those in the less recent stratum were clearly recovered from their last episode and all those who satisfied criteria for remission from episode, but did not yet satisfy criteria for recovery, fell in the more recent stratum (Frank, Prien, et al., 1991). A cutoff between those with only two episodes and those with more than two episodes meant that those in the latter stratum were broadly comparable with patient samples studied in other trials of psychological treatments for recurrent depression (e.g., Fava et al., 1998; Frank et al., 1990).

Sample size was calculated on the basis that a sample of 120 patients (60 per group), would have 80% power to detect at $p < .05$ a reduction in relapse/recurrence rates from 50% in the TAU group to 28% in the MBCT group on a directional hypothesis (Cohen, 1988).

Participants

Patients were recruited from community health care facilities and by media announcements at three different sites: a predominantly rural, Welsh-speaking area of north Wales centered on the small city of Bangor (population 20,000); an area centered on and including the city of Cam-

bridge, England (population 110,000), together with surrounding small towns, villages, and rural area; and the metropolitan area of Toronto, Ontario, Canada (population 3 million). Although Cambridge is a well-known university city, no participants at that site were actually academic staff or students of the University of Cambridge.

Inclusion criteria were (a) 18 to 65 years of age; (b) meeting enhanced *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; *DSM–III–R*; American Psychiatric Association, 1987) criteria for a history of recurrent major depression (these normally require a history of two or more previous episodes of *DSM–III–R* major depression in the absence of a history of mania or hypomania; in addition, we required that at least two episodes of major depression occurred within the past 5 years and that at least one of those episodes was within the past 2 years); (c) a history of treatment by a recognized antidepressant medication, but off antidepressant medication, and in recovery/remission, at the time of baseline assessment and for at least the preceding 12 weeks (it was not possible to determine the adequacy of treatment by antidepressant medication; rather, this criterion was used as an indicator that, in the naturalistic course of service delivery, patients had been judged as appropriate for pharmacotherapy by a treating physician); and (d) at baseline assessment, a 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) score of less than 10. Exclusion criteria were (a) history of schizophrenia or schizoaffective disorder; (b) current substance abuse, eating disorder, or obsessive–compulsive disorder (OCD); (c) organic mental disorder, pervasive developmental delay, or borderline personality disorder (BPD); (d) dysthymia before age 20; (e) more than four sessions of cognitive–behavioral treatment ever; (f) current psychotherapy or counseling more frequently than once per month; and (g) current practice of meditation more than once per week or yoga more than twice per week. Patients with eating disorders were excluded because they frequently experience depression secondary to those disorders and the MBCT program was not designed to deal with the primary eating disorder. Patients with OCD were excluded because the obsessional quality of their thoughts might have rendered the implementation of mindfulness strategies particularly difficult. Patients with dysthymia before the age of 20 were excluded because of the possible characterological nature of their depression. Patients who currently practiced yoga more than twice a week were excluded because yoga overlaps considerably with mindfulness training and is, indeed, a component of the MBCT program.

Informed Consent

Patients meeting the inclusion criteria, and willing to participate in the study after it had been explained to them, gave written informed consent on forms approved by local research ethics committees prior to randomization.

Measures

HRSD. As part of the assessment of inclusion criteria, the baseline assessment interview included the 17-item HRSD (Hamilton, 1960), a widely used interview-based measure of severity of depressive symptomatology that covers a range of affective, behavioral, and biological symptoms. Scores can range from 0 to 52. This measure, administered by doctoral-level psychologists or an experienced psychiatric social worker, was also repeated at each subsequent follow-up assessment. The HRSD has acceptable psychometric properties that have been reviewed elsewhere (see Rabkin & Klein, 1987). A sample of 41 interviews from the follow-up period were second-rated for the HRSD by an independent psychiatric rater to yield an interrater correlation of $r(39) = .963, p < .001$.

Beck Depression Inventory (BDI). The BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), a widely used 21-item self-report measure of severity of depressive symptoms, was completed by patients at the baseline assessment and at each follow-up assessment. The BDI covers affective, cognitive, motivational, behavioral, and biological symptoms of depression and yields scores ranging from 0 to 63. The BDI has acceptable psycho-

metric properties that have been reviewed elsewhere (Rabkin & Klein, 1987).

Relapse/recurrence. The primary-outcome variable was the occurrence of relapse or recurrence meeting *DSM–III–R* criteria for major depressive episode (American Psychiatric Association, 1987), as assessed by the Structured Clinical Interview for *DSM–III–R* (SCID; Spitzer, Williams, Gibbon, & First, 1992) administered at bimonthly assessments through the follow-up period and covering the period from the previous assessment. Assessments were made by doctoral-level psychologists and an experienced psychiatric social worker. To maintain blindness of assessors to treatment condition, we instructed patients not to reveal whether they were receiving MBCT or any details that might prejudice blindness. Nonetheless, assessors occasionally became aware of a patient's treatment condition. To overcome such occasional unblinding, and to examine interrater reliability, interviews were audiotaped and all 133 occasions on which patients met the screening criteria for major depression were evaluated by an independent, blind, experienced research psychiatrist (any information potentially revealing patients' treatment allocation was excluded from the taped interview presented to the blind assessor). Only patients responding positively to the screening question were included in this analysis. The kappa for interrater agreement on categorization of presence/absence of major depression was .74, which is indicative of good/excellent agreement. Some of the disagreements arose from the fact that the first raters had wider knowledge of the patients who they were rating and so were more able to place the specific information elicited in the SCID interview in a wider context that sometimes altered the significance of that specific information. Also, of course, the second rater did not have access to the nonauditory information that was available to the rater making the live rating. In cases of disagreement, the blind ratings of the independent psychiatric rater were used for analysis.

Following baseline assessment, interviews were scheduled at points corresponding to the completion of the initial eight MBCT training sessions and bimonthly thereafter over the course of the follow-up year.

Treatment

TAU. Patients were instructed to seek help from their family doctor, or other sources, as they normally would, should they encounter symptomatic deterioration or other difficulties over the course of the study. The treatment that patients in both the TAU and MBCT groups actually received was monitored at the bimonthly assessment sessions and is described in the Results section.

MBCT. MBCT is a manualized group skills-training program (Segal, Williams, & Teasdale, in press). MBCT is based on an integration of aspects of CBT for depression (Beck et al., 1979) with components of the MBSR program developed by Kabat-Zinn and colleagues (e.g., Kabat-Zinn, 1990). It is designed to teach patients in remission from recurrent major depression to become more aware of, and to relate differently to, their thoughts, feelings, and bodily sensations (e.g., relating to thoughts and feelings as passing events in the mind rather than identifying with them or treating them as necessarily accurate readouts on reality). The program teaches skills that allow individuals to disengage from habitual ("automatic") dysfunctional cognitive routines, in particular depression-related ruminative thought patterns, as a way to reduce future risk of relapse and recurrence of depression.

After an initial individual orientation session, the MBCT program is delivered by an instructor in eight weekly 2-hr group training sessions involving up to 12 recovered recurrently depressed patients. During that period, the program includes daily homework exercises. Homework invariably includes some form of guided (taped) or unguided awareness exercises, directed at increasing moment-by-moment nonjudgmental awareness of bodily sensations, thoughts, and feelings, together with exercises designed to integrate application of awareness skills into daily life. Key themes of the program include empowerment of participants and a focus on awareness of experience in the moment. Participants are helped to cultivate an open and acceptant mode of response, in which they intentionally face

and move in to difficulties and discomfort, and to develop a decentered perspective on thoughts and feelings, in which these are viewed as passing events in the mind.

A core feature of the program involves facilitation of an aware mode of being, characterized by freedom and choice, in contrast to a mode dominated by habitual, overlearned, automatic patterns of cognitive–affective processing. For patients, this distinction is often illustrated by reference to the common experience, when driving on a familiar route, of suddenly realizing that one has been driving for miles "on automatic pilot," unaware of the road or other vehicles, preoccupied with planning future activities or ruminating on a current concern. By contrast, "mindful" driving is associated with being fully present in each moment, consciously aware of sights, sounds, thoughts, and body sensations as they arise. When one is mindful, the mind responds afresh to the unique pattern of experience in each moment instead of reacting "mindlessly" to fragments of a total experience with old, relatively stereotyped, habitual patterns of mind. Increased mindfulness is relevant to the prevention of relapse/recurrence of depression as it allows early detection of relapse-related patterns of negative thinking, feelings, and body sensations, thus allowing them to be "nipped in the bud" at a stage when this may be much easier than if such warning signs are not noticed or are ignored. Further, entering a mindful mode of processing at such times allows disengagement from the relatively automatic ruminative thought patterns that would otherwise fuel the relapse process. Formulation of specific relapse/recurrence prevention strategies (such as involving family members in an "early warning" system, keeping written suggestions to engage in activities that are helpful in interrupting relapse-engendering processes, or looking out for habitual negative thoughts) are also included in the later stages of the initial 8-week phase.

Following the initial phase of weekly group meetings, four follow-up meetings were scheduled at intervals of 1, 2, 3, and 4 months.

MBCT sessions were video- or audiotaped, with patients' permission, to allow monitoring of treatment integrity.

Instructors

The three instructors were all experienced cognitive therapists who had, jointly, developed the MBCT program. Each had previously led at least one cohort of recovered depressed patients through the MBCT program.

Results

Intent-to-Treat and Per-Protocol Samples

Results were analyzed separately for an intent-to-treat sample ($n = 145$), comprising all of the patients included in the random allocation, and a per-protocol sample ($n = 132$), comprising (a) all of the patients allocated to the TAU condition ($n = 69$) and (b) those patients allocated to MBCT who received a predetermined "minimum effective dose" of MBCT (at least four of the eight weekly MBCT sessions; $n = 63$). The results from these two samples are complementary: The intent-to-treat sample provides a stringent test of whether the MBCT and TAU groups differed in outcome, reducing possible artifactual selective effects of differential attrition from the two treatment conditions, and the per-protocol sample provides an estimate of the benefits of MBCT among those who actually experienced at least a minimally adequate exposure to that treatment program.

Patient Flow

One hundred forty-nine patients met the inclusion criteria at a baseline screening interview and were invited to participate in the study. Of these, 4 declined, leaving 145 patients to be randomized. Of the 13 patients allocated to MBCT not included in the per-

protocol sample, 6 failed to attend any training sessions and 7 (9% of those allocated to MBCT) dropped out after attending fewer than four sessions.

Complete data on relapse or recurrence were available for 137 (95%) of the 145 patients in the intent-to-treat sample and 128 (97%) of the 132 patients in the per-protocol sample; data were incomplete for 3 TAU patients, 4 "insufficient treatment" MBCT patients, and 1 "adequate treatment" MBCT patient.

Patient Characteristics

Baseline characteristics of the intent-to-treat sample are given in Table 1.

The TAU and MBCT treatment groups were closely similar on each of the baseline variables, with the exception of age. Given the size of this difference in means in relation to standard deviations, age was included as a covariate in all of the comparisons of treatment group outcome. For the sample as a whole, social class distribution (Office of Population Censuses and Surveys, 1991) was as follows (percentages for the general population of England and Wales are given in parentheses for comparison): for Class 1 (e.g., general managers of large corporations), 5% (4%); for Class 2, 40% (21%); for Class 3, 45% (46%); for Class 4, 7% (17%); for Class 5 (e.g., road sweepers), 3% (8%); and for armed services/unclassified, 0% (5%). Class distribution was very similar in the TAU ($M = 2.7$, $SD = 0.9$) and MBCT ($M = 2.6$, $SD = 0.8$) groups. Basic patient characteristics across the three sites were as follows: for Bangor ($n = 45$), mean age was 44.0 years ($SD = 9.5$) and 73% were female; for Cambridge ($n = 54$), mean age was 44.5 years ($SD = 10.6$) and 78% were female; and for Toronto ($n = 46$), mean age was 41.3 years (10.6) and 76% were female.

Comparison of the 13 "insufficient treatment" patients in the MBCT group, who either attended no treatment sessions or dropped out before completing at least four sessions, with the 63 patients who completed four or more sessions revealed no statistically significant differences between these groups on baseline characteristics (smallest $p = .17$).

TAU

The treatment for depression actually received by patients in the TAU condition was monitored at the bimonthly assessment interviews over the follow-up period and is summarized in Table 2. The corresponding data for patients in the MBCT condition are also shown for comparison. There were no statistically significant differences between the TAU and MBCT conditions for any of these measures of treatment received (all $ps > .10$).

Outcome Analysis: Relapse/Recurrence to Major Depression

Time to onset of relapse or recurrence (in weeks) was compared between treatment groups using Cox proportional hazards regression models (SPSS, 1994, pp. 291–328), with treatment condition as a categorical (indicator) variable and TAU as the reference condition. In the results that follow, 95% confidence intervals (CIs) for hazard ratios are provided following Wald and hazard ratio statistics.

To examine whether effects of treatment condition were moderated by either of the stratifying variables used in randomization, it was necessary to conduct preliminary Cox regression analyses that included, separately, each of these variables (recency of last episode of depression [0–12 months vs. 13–24 months] and number of previous episodes of MDD [two vs. more than two]) and its interaction with treatment condition, as covariates, together with treatment condition (MBCT vs. TAU). These analyses revealed a significant effect of the interaction of number of previous episodes and treatment condition in both the intent-to-treat sample, Wald(1)

Table 1

Baseline Characteristics of Treatment as Usual (TAU) and Mindfulness-Based Cognitive Therapy (MBCT) Samples

Variable	TAU ($n = 69$)	MBCT ($n = 76$)
Female (%)	78	74
White (%)	100	97
Age (years)	46.2 ± 9.6	40.7 ± 10.3
Marital status (%)		
Single	12	18
Married/cohabiting	57	55
Divorced/separated/widowed	32	26
Years of education	14.3 ± 3.3	14.9 ± 3.1
Depression		
Median HRSD score (IQR)	3.0 (4.3)	4.0 (5.0)
Median BDI score (IQR)	10.0 (10.0)	10.0 (10.0)
Median previous episodes (IQR)	3.0 (3.8)	3.5 (2.0)
Age of first onset (years)	28.1 ± 10.4	25.7 ± 9.9
Median duration of episodes (weeks)		
Last (IQR)	15.0 (19.0)	17.5 (16.3)
Penultimate (IQR)	22.0 (32.0)	16.0 (22.0)
Previous treatment for depression (%)		
Antidepressant medication	100	100
Hospitalization	17	11
Psychotherapy/counseling	68	73

Note. HRSD = Hamilton Rating Scale for Depression; IQR = interquartile range; BDI = Beck Depression Inventory.

Table 2

Treatment for Depression From Other Sources Received by Patients in Treatment as Usual (TAU) and Mindfulness-Based Cognitive Therapy (MBCT) Over the 60-Week Study Period

Variable	TAU	MBCT
One or more depression-related visits to general practitioner (%)	52	58
Psychiatric treatment (%)		
Outpatient	8	10
Day patient	2	0
Inpatient	2	0
Counseling/psychotherapy/professional mental health support (%)[a]	34	49
Other mental health contacts (%)[b]	21	17
Medication for depression (ADM; %)	40	45
Mean (±SD) duration (weeks)	32.7 ± 21.2	23.3 ± 17.9
Mean (±SD) reported dosage SSRI[c]	20.1 ± 8.6	18.2 ± 3.8

Note. ADM = antidepressant medication.
[a] Includes psychiatric social worker, community psychiatric nurse, community mental health team worker, counselor, psychotherapist, group therapy/support, and marital/family therapy. [b] Includes voluntary mental health organizations (e.g., Samaritans) and health visitor. [c] SSRIs (selective serotonin reuptake inhibitors) were the most commonly prescribed antidepressants; reported dosage is expressed in milligrams of fluoxetine daily dose equivalents.

$= 4.32, p < .05$, and the per-protocol sample, $\text{Wald}(1) = 4.32, p < .05$. That is, differences in outcome between treatment conditions were not the same in participants with three or more previous episodes as in participants with only two previous episodes, thus mandating separate analyses for these two groups.

Figure 1 shows survival (i.e., nonrelapse/nonrecurrence) curves comparing relapse/recurrence over the 60-week study period for MBCT and TAU in participants with a history of three or more episodes of depression. These participants composed 77% (105/137) of the intent-to-treat sample for whom relapse/recurrence data were available and 77% (99/128) of the per-protocol sample for whom relapse/recurrence data were available. Cox regression analyses showed significantly less hazard of relapse/recurrence in MBCT participants, compared with TAU participants, for both the intent-to-treat sample, $\text{Wald}(1) = 6.65, p < .01$, hazard ratio $= .473$, CI $= .267-.836$, and the per-protocol sample, $\text{Wald}(1) = 7.97, p < .005$, hazard ratio $= .419$, CI $= .229-.766$. These treatment effects remained significant when baseline values of the HRSD or the BDI were also entered as covariates. Over the total study period, in the intent-to-treat sample, 40% (22/55) of MBCT participants experienced relapse/recurrence compared with 66% (33/50) of TAU participants, $\chi^2(1, N = 105) = 7.10, p < .01$, a 39% reduction in risk of relapse/recurrence in the MBCT condition. The difference between 66% relapse/recurrence and 40% relapse/recurrence yields an *h* value of .53, which Cohen (1988, p. 185) described as indicating a medium effect size. In the per-protocol sample, corresponding figures were 37% (18/49) relapse/recurrence for the MBCT group and 66% (33/50) relapse/recurrence for the TAU group, $\chi^2(1, N = 99) = 8.49, p < .005$, a 44% reduction in risk of relapse/recurrence in the MBCT condition. The difference between 66% relapse/recurrence and 37% relapse/recurrence yields an *h* value of .59, which Cohen (1988, p. 185) described as indicating a medium effect size.

The data from the per-protocol sample displayed in Figure 1 yield the following cumulative relapse rates (the TAU figure is

presented first, the MBCT figure second): for 10 weeks, 28% versus 8%; for 20 weeks, 38% versus 20%; for 30 weeks, 44% versus 26%; for 40 weeks, 60% versus 31%; and for 50 weeks, 66% versus 35%. These data appear to suggest that the differences in relapse rates between TAU and MBCT become established within the first 10 weeks of the study period, remain much the same until 30 weeks, and then increase again. However, these apparent trends should be interpreted with caution because (a) the relapses from the TAU group are from smaller surviving populations than in the MBCT group so that numerical relapse underestimates probability of relapse in the TAU group and (b) the sample sizes in the two groups mean that estimates of risk have appreciable margins of error.

Participants with a history of two episodes of depression composed 23% (32/137) of the intent-to-treat sample for whom relapse/recurrence data were available and 23% (29/128) of the per-protocol sample for whom relapse/recurrence data were available. Cox regression analyses showed no significant differences in hazard of relapse/recurrence between MBCT participants and TAU participants for either the intent-to-treat sample, $\text{Wald}(1) = 0.82, p > .10$, or the per-protocol sample, $\text{Wald}(1) = 0.67, p > .10$. Over the total study period, in the intent-to-treat sample, 56%

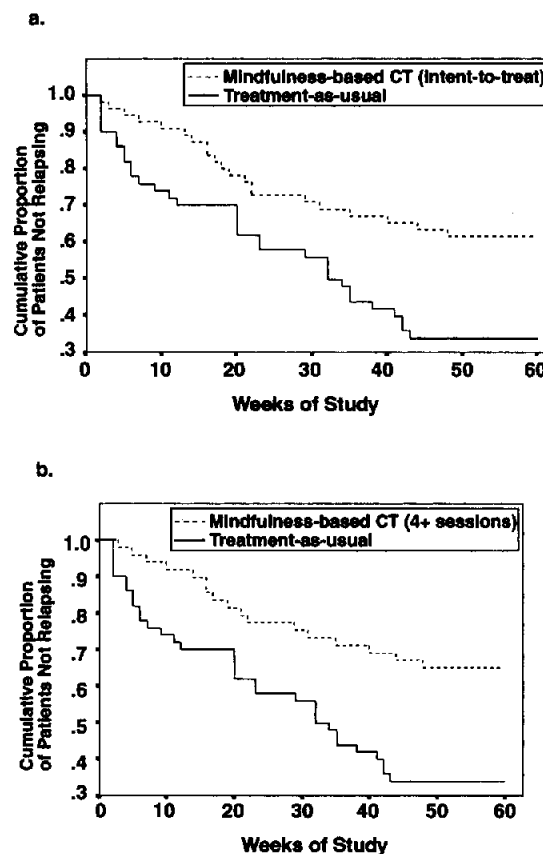*Figure 1.* Survival (nonrelapse/nonrecurrence) curves comparing relapse/recurrence to *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; American Psychiatric Association, 1987) major depression for treatment as usual and mindfulness-based cognitive therapy in patients with three or more previous episodes of major depression: (a) intent-to-treat sample and (b) per-protocol sample. CT = cognitive therapy.

(9/16) of MBCT participants experienced relapse/recurrence compared with 31% (5/16) of TAU participants, $\chi^2(1, N = 32) = 2.03$, $p > .10$. In the per-protocol sample, corresponding figures were 54% (7/13) relapse/recurrence for the MBCT group and 31% (5/16) relapse/recurrence for the TAU group, $\chi^2(1, N = 29) = 1.51, p > .10$.

To examine further the effects of number of previous episodes on differential response to TAU and MBCT, we examined the relationship between number of previous episodes (two vs. more than two) and hazard of relapse/recurrence by separate Cox regression analyses in the TAU and MBCT groups. In the TAU group, there was a significant relationship between number of previous episodes and relapse/recurrence, Wald(1) = 4.08, $p < .05$. Further examination revealed a positive linear relationship between number of previous episodes and risk of relapse/recurrence over the follow-up period: for two episodes, 31% relapse/recurrence (5/16); for three episodes, 56% relapse/recurrence (10/18); and for four or more episodes, 72% relapse/recurrence (23/32), Mantel-Haenszel test for linear association, $\chi^2(1, N = 66) = 7.06$, $p < .025$. In the MBCT group, there was no significant relationship between number of previous episodes and hazard of relapse/recurrence in either the intent-to-treat sample, Wald(1) = 0.38, $p > .10$ (9 of 16 [56%] relapsed in the fewer-than-three-episodes group, and 22 of 55 [40%] relapsed in the more-than-two-episodes group), or the per-protocol sample, Wald(1) = 0.53, $p > .10$ (7 of 13 [54%] relapsed in the fewer-than-three-episodes group, and 18 of 49 [37%] relapsed in the more-than-two-episodes group).

In summary, the main finding was that, in participants with three or more previous episodes of depression (who composed 77% of the sample), an "adequate dose" of MBCT almost halved relapse/recurrence rates over the follow-up period compared with TAU.

Clinical Significance of Outcomes

The observed reduction in rates of relapse/recurrence for patients with more than two previous episodes of major depression was statistically significant, but was it clinically significant? Kendall, Marrs-Garcia, Nath, and Sheldrick (1999) have recently described the use of normative comparisons as a method to evaluate the clinical significance of the changes produced by therapeutic interventions. This approach is particularly useful when applied to patient populations that begin treatment with abnormally elevated symptom scores and are reassessed on those measures following treatment. In this situation, comparison of patients' posttreatment scores with those from normative samples provides a valuable indicator of the clinical significance of the extent of therapeutic gains achieved.

Unfortunately, this elegant method is not applicable in the present study. Unusual among clinical treatment trials, the key outcome of interest in this study was the prevention of a future event (relapse/recurrence) rather than reduction of symptoms present at baseline assessment. Indeed, because it was assumed that depression-related difficulties in concentration would interfere with the implementation of MBCT, selection criteria for the trial were deliberately chosen to exclude patients who were not largely recovered or remitted. For example, at baseline assessment 86% of patients fell in the asymptomatic range on the HRSD (Frank, Prien, et al., 1991). In this situation, it is clearly inappropriate to assess the clinical significance of the outcomes in terms of the numbers of patients falling in the asymptomatic range on posttreatment assessments of severity of depressive symptomatology.

The relapse/recurrence rate in patients with three or more previous episodes treated with "adequate" MBCT (37%) was clearly substantially above the expected annual incidence rate of MDD among those with no prior history of major depression in general population samples. On this basis, it is clear that the intervention did not reduce risks of major depression to the "normal" range. Nonetheless, the halving of relapse/recurrence rates in a group at high risk for relapse/recurrence would appear to be a clinically useful outcome. On this basis, we suggest that the benefits of MBCT to patients with three or more previous episodes were both statistically and clinically significant.

Use of Medication for Depression

To examine whether the reduction in relapse and recurrence in patients with three or more episodes receiving MBCT was secondary to increased use of medications for depression, we compared the proportions of patients in the two treatment groups using such medications at any time over the follow-up period. This procedure showed no significant differences between groups: for the intent-to-treat sample, 40% (19/47) in the MBCT group and 46% (20/44) in the TAU group, $\chi^2(1, N = 91) = 0.24, p > .10$; for the per-protocol sample, 33% (14/42) in the MBCT group and 46% (20/44) in the TAU group, $\chi^2(1, N = 86) = 1.32, p > .10$. (These figures differ from those in Table 2: The table shows figures for the total TAU and MBCT samples, whereas these figures are for patients with more than two previous episodes of depression.) The lack of significant differences between the TAU and MBCT groups in use of medications for depression or other forms of treatment (see Table 2) in the presence of significantly less relapse/recurrence in MBCT is open to a number of possible explanations. The most parsimonious explanation is that these other treatments contributed equally to the outcomes in the MBCT and TAU conditions, the lower relapse in MBCT being attributable to the effects of the MBCT intervention. Alternatively, it is conceivable that MBCT may have made patients more responsive to the effects of other treatments.

Comparison of Patients With Two Previous Episodes With Patients With Three or More Previous Episodes

Exploratory analyses compared patients with two previous episodes of MDD with those with three or more episodes on a range of background variables. The only significant differences observed were on two age-related variables. Those with three episodes or more were older when admitted into the study (for two episodes, $M = 38.88$, $SD = 9.84$; for three or more episodes, $M = 44.58$, $SD = 10.11$), $t(143) = 2.83, p < .01$, and were younger when they experienced their first episode (for two episodes, $M = 33.38$, $SD = 8.65$; for three or more episodes, $M = 25.00$, $SD = 9.84$), $t(143) = 4.36, p < .001$. The difference in age of onset of first episode suggests that these two groups may not simply represent younger and older samples from essentially the same population but may represent distinct populations of patients. Combining these two age-related variables into a single variable ("history") reflecting the total duration of patients' experience with depression (history = age at admission to study minus age of first onset) yielded a mean for those with three or more episodes approxi-

mately four times as great as that for patients with two episodes (for two episodes, $M = 5.50$, $SD = 4.79$; for three or more episodes, $M = 19.58$, $SD = 10.33$), unequal-variances $t(113) = 10.92$, $p < .001$.

Discussion

For patients with recurrent major depression who had experienced three or more previous episodes, MBCT approximately halved rates of relapse and recurrence over the follow-up period compared with patients who continued with TAU. This prophylactic effect could not be accounted for in terms of patients who received MBCT being more likely to use antidepressant medication. The preventative effect of MBCT was achieved for an average investment of less than 5 hr of instructor time per patient, suggesting that offering a group skills-based training program to recovered depressed patients may be a cost-efficient strategy for prevention. It is important to note that MBCT was specifically designed for remitted patients and is unlikely to be effective in the treatment of acute depression, where factors such as difficulties in concentration and the intensity of negative thinking may preclude acquisition of the attentional control skills central to the program. To our knowledge, the results of the present trial provide the first demonstration that a group-based psychological intervention, initially administered in the recovered state, can significantly reduce risk of future relapse/recurrence in patients with recurrent major depression.

The finding that MBCT prevented relapse and recurrence in patients with a history of three or more episodes of depression, but not in patients with only two previous episodes, is of particular interest with respect to the theoretical background to MBCT (Segal et al., 1996; Teasdale et al., 1995). This program was specifically designed to reduce the contribution of patterns of depressive thinking reactivated by dysphoria to the processes mediating relapse and recurrence. Such dysphoria-linked thinking, it was assumed, resulted from repeated associations between the depressed state and characteristic negative thinking patterns within each depressive episode. The strengthening of these associations with repeated episodes was assumed to contribute to the increased risk of subsequent episodes following each episode experienced. In particular, it was assumed that negative thinking reactivated by dysphoria contributed to the increasingly autonomous nature of the relapse/recurrence process with multiple episodes, reflected in the observation that environmental provoking events appear to play a progressively less important role in onset with increasing number of episodes (Post, 1992).

The above account suggests the possibility that, in the present study, (a) the greater risk of relapse/recurrence in those with three or more episodes than in those with only two episodes (apparent in the TAU group) was to a large extent attributable to autonomous relapse/recurrence processes involving reactivation of depressogenic thinking patterns by dysphoria and (b) the prophylactic effects of MBCT arose, specifically, from disruption of those processes at times of potential relapse/recurrence. Consistent with this analysis, MBCT appeared to have no prophylactic effects in those with only two previous episodes, and the rate to which relapse/recurrence was reduced by adequate MBCT in those with three and more episodes (37%) was similar to the rate of relapse/recurrence in those with only two episodes receiving TAU (31%).

The present findings add to a growing body of evidence (Fava et al., 1996, 1998; Frank, Kupfer, et al., 1991) that psychological interventions administered after recovery from the acute symptoms of a depressive episode can substantially alter the future course of MDD. These findings have considerable potential relevance for our understanding of the cognitive and biological processes that mediate the increased vulnerability to subsequent episodes of those who have already experienced depressive episodes. An effective prophylactic intervention offers an opportunity to investigate controlled changes in vulnerability processes, with all the consequent interpretative advantages conferred by experimental, as compared with correlational, designs. However, the design of the present study does not allow us to attribute the benefits of MBCT to the specific skills taught by the program versus nonspecific factors, such as therapeutic attention and group participation. Equally, the present study provides no evidence of the extent to which similar prophylactic effects would be obtained by instructors who had not been actively involved in the development of the program or in samples with different ethnic or educational backgrounds.

To our knowledge, this is the first multicenter randomized clinical trial evaluating a mindfulness-based clinical intervention. Taken with the results from smaller, or less controlled, evaluations suggesting the effectiveness of the generic MBSR program in treating chronic pain, GAD, and panic (Kabat-Zinn et al., 1986, 1992), and the effectiveness of a cognitive–behavioral program incorporating a substantial mindfulness component in reducing self-harm in BPD (Linehan, Armstrong, Suarez, Allmon, & Heard, 1991), the present findings suggest that mindfulness-based clinical interventions may hold considerable therapeutic promise, either alone or in combination with other forms of intervention.

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