Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial

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Summary

Background Individuals with a history of recurrent depression have a high risk of repeated depressive relapse or recurrence. Maintenance antidepressants for at least 2 years is the current recommended treatment, but many individuals are interested in alternatives to medication. Mindfulness-based cognitive therapy (MBCT) has been shown to reduce risk of relapse or recurrence compared with usual care, but has not yet been compared with maintenance antidepressant treatment in a definitive trial. We aimed to see whether MBCT with support to taper or discontinue antidepressant treatment (MBCT-TS) was superior to maintenance antidepressants for prevention of depressive relapse or recurrence over 24 months.

Methods In this single-blind, parallel, group randomised controlled trial (PREVENT), we recruited adult patients with three or more previous major depressive episodes and on a therapeutic dose of maintenance antidepressants, from primary care general practices in urban and rural settings in the UK. Participants were randomly assigned to either MBCT-TS or maintenance antidepressants (in a 1:1 ratio) with a computer-generated random number sequence with stratification by centre and symptomatic status. Participants were aware of treatment allocation and research assessors were masked to treatment allocation. The primary outcome was time to relapse or recurrence of depression, with patients followed up at five separate intervals during the 24-month study period. The primary analysis was based on the principle of intention to treat. The trial is registered with Current Controlled Trials, ISRCTN26666654.

Findings Between March 23, 2010, and Oct 21, 2011, we assessed 2188 participants for eligibility and recruited 424 patients from 95 general practices. 212 patients were randomly assigned to MBCT-TS and 212 to maintenance antidepressants. The time to relapse or recurrence of depression did not differ between MBCT-TS and maintenance antidepressants over 24 months (hazard ratio 0·89, 95% CI 0·67–1·18; p=0·43), nor did the number of serious adverse events. Five adverse events were reported, including two deaths, in each of the MBCT-TS and maintenance antidepressants groups. No adverse events were attributable to the interventions or the trial.

Interpretation We found no evidence that MBCT-TS is superior to maintenance antidepressant treatment for the prevention of depressive relapse in individuals at risk for depressive relapse or recurrence. Both treatments were associated with enduring positive outcomes in terms of relapse or recurrence, residual depressive symptoms, and quality of life.

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Introduction

Depression typically has a relapsing and recurrent course.[1] Without ongoing treatment, individuals with recurrent depression have a high risk of repeated depressive relapses or recurrences throughout their life with rates of relapse or recurrence typically in the range 50–80%.[2] Major inroads into the substantial health burden attributable to depression could be offset through interventions that prevent depressive relapse or recurrence in people at highest risk. If the factors that make people susceptible to depressive relapse or recurrence can be attenuated, the recurrent course of depression could potentially be broken.

Currently, most depression is treated in primary care, and maintenance antidepressants are the mainstay approach for the prevention of relapse or recurrence. The UK's National Institute for Health and Care Excellence (NICE) recommends that, to stay well, people with a history of recurrent depression should continue maintenance antidepressants for at least 2 years.[3] However, adherence rates tend to be poor, maintenance antidepressant treatment is only protective for as long as it is taken[4] and is contraindicated for some groups, and many patients express a preference for psychosocial interventions that provide long-term protection against

relapse or recurrence. Patients at increased risk of relapse show less protection from maintenance antidepressants than do patients at low risk and many patients express a preference for psychosocial interventions that provide long-term protection against relapse or recurrence.

Mindfulness-based cognitive therapy (MBCT) was developed as a psychosocial intervention for teaching people with recurrent depression the skills to stay well in the long term.[5] A systematic review and meta-analysis[6] of six randomised controlled trials (n=593) suggests that MBCT significantly reduces the rates of depressive relapse or recurrence compared with usual care or placebo, corresponding to a relative risk reduction of 34% (risk ratio 0·66, 95% CI 0·53–0·82). Evidence is accumulating that MBCT might confer most benefit to patients at greatest risk, for example those reporting childhood adversity.[7,8] A key remaining uncertainty is whether MBCT provides an alternative for people wishing to discontinue antidepressants.[9] On the basis of our pilot trial,[10] we tested whether MBCT with support to taper or discontinue antidepressant treatment (MBCT-TS) was better than maintenance antidepressants in terms of: a primary outcome of prevention of depressive relapse or recurrence over 24 months; and secondary outcomes of depression-free days, residual depressive symptoms, psychiatric and medical comorbidity, quality of life, and cost-effectiveness over 24 months.

Method

Study design and participants

PREVENT was a multicentre, pragmatic, single-blind, parallel randomised controlled trial examining MBCT-TS versus maintenance antidepressants. The study design and procedures are presented in full in in the published trial protocol.[11,12]

Participants were recruited from general practices in urban and rural settings in four UK centres: Bristol, Exeter and east Devon, north and mid Devon, and south Devon. Inclusion criteria were a diagnosis of recurrent major depressive disorder in full or partial remission according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV); three or more previous major depressive episodes; age 18 years or older; and on a therapeutic dose of maintenance antidepressant drugs in line with the British National Formulary (BNF)[13] and NICE guidance. Exclusion criteria were a current major depressive episode, comorbid diagnoses of current substance misuse; organic brain damage; current or past psychosis, including bipolar disorder; persistent antisocial behaviour; persistent self-injury needing clinical management or therapy; and formal concurrent psychotherapy. All participants gave written informed consent.

Most participants were identified through searches of computerised general practitioner (GP) practice databases to identify patients who were currently being prescribed a therapeutic dose of antidepressants. PREVENT was also advertised locally and interested patients could self-refer. GPs had the opportunity to exclude patients they felt would be unsuitable and a letter of invitation was sent to the remaining identified patients. Patients who expressed an interest in the trial were screened over the telephone to establish potential eligibility and if suitable were invited to attend a baseline interview.

The study was approved by the UK National Health Service South West Research Ethics Committee (09/H0206/43) and we obtained research governance approval from the local primary care trusts or health boards. The trial was conducted and reported in accordance with CONSORT guidelines.[14,15]

Randomisation and masking

Participants were randomly allocated (in a 1:1 ratio) to receive either maintenance antidepressant treatment or an 8-week MBCT class that included support to taper or discontinue their maintenance antidepressant medication (MBCT-TS).

Patients were randomly assigned to the two groups with a computer-generated random number sequence stratified according to recruitment centre and participants' symptomatic status at randomisation using the GRID-Hamilton Rating Scale for Depression (GRID-HAMD)[16] cutoff of less than 8 being asymptomatic and greater than or equal to 8 being partially symptomatic.[17] Allocation was undertaken using a password-protected website maintained by the Peninsula Clinical Trials Unit, independent of the trial. The trial administrator informed participants of the outcome of randomisation via a letter; research assessors remained masked to treatment allocation for the duration of the follow-up period. The fidelity of this masking was moderate with assessors correctly guessing allocation for 56% of assessments. In view of the nature of the interventions, patients and clinicians were aware of treatment allocation.

Procedures

MBCT is a manualised, group-based skills training programme designed to enable patients to learn skills that prevent the recurrence of depression.[18] It is derived from mindfulness-based stress reduction, a programme with proven efficacy in ameliorating distress in people with chronic disease, and cognitive-behavioural therapy for acute depression, which has shown efficacy in prevention of depressive relapse or recurrence. MBCT is intended to enable people to learn to become more aware of their bodily sensations, thoughts, and feelings associated with depressive relapse or recurrence and to relate constructively to these experiences. Participants learn mindfulness practices and cognitive-behavioural skills both in session and through homework assignments. Therapists provide support to patients in learning to respond adaptively to thoughts, feelings, and experiences that might otherwise have triggered depressive relapse. The programme consists of eight 2·25 h group sessions, normally over consecutive weeks, with four refresher sessions offered roughly every 3 months for the following

year. Four therapists delivered 21 MBCT-TS groups in various settings including research clinical facilities, hospital sites, and the community.

Before therapists progressed to running trial groups, an independent check on their competency was established. An experienced MBCT therapist independent of the trial rated at least two videotapes for every potential therapist using the Mindfulness-Based Interventions Teacher Assessment Criteria[19] and MBCT Adherence Scale (MBCT-AS).[20] She made an overall judgment as to whether the therapists were competent and adhered to the MBCT manual, and therapists only progressed once competency in all domains was clearly established. During the trial, the same rater assessed two sessions from each of the 21 MBCT-TS courses using the MBCT-AS, which indicated that the MBCT teaching was at required competency or adherence levels and above. The sessions second rated were randomly selected by the trial team before the start of the intervention, and therapists were unaware which of their sessions would be assessed. During the trial, therapists received group supervision every 2 weeks for 3 h.

Patients in the MBCT-TS group received support to taper or discontinue their maintenance antidepressants both from the MBCT-TS therapist and their GPs. The study team provided guideline information to GPs and patients about typical tapering or discontinuation regimens and possible withdrawal effects. The guidelines recommended that patients began a tapering regimen after 6 weeks of treatment; however, GPs and patients determined the tapering or discontinuation regimen. Letters signed by the chief investigator and trial GP (RB) were sent to patients' GPs and copied to the patient, prompting the GP to have a discussion with the patient about a suitable tapering or discontinuation regimen after 4–5 weeks of the MBCT-TS group sessions. At the end of the eight MBCT-TS sessions, another letter was sent reminding the GP to ensure a tapering or discontinuation regimen was in place.

Patients in the maintenance antidepressant group received support from their GPs to maintain a therapeutic level of antidepressant medication in line with BNF[13] and NICE guidelines for the 2-year follow-up period.

As described fully in the trial protocol,[11,12] we encouraged all participants to adhere to medication for the full length of the trial by writing to all trial participants and their GPs after every follow-up reminding them that the trial was seeking to compare staying on antidepressants for 2 years with taking part in mindfulness classes and tapering or discontinuation of antidepressant treatment. However, patients remained in the trial whatever treatment choices they made.

Participants were assessed at six timepoints: baseline (before randomisation), 1 month after the end of the 8-week MBCT-TS programme (or the equivalent time in the maintenance antidepressant group), which varied between 12 and 24 weeks post-randomisation, and at 9, 12, 18, and 24 months post-randomisation.

Outcomes

The primary outcome measure was time to relapse or recurrence of depression, with patients followed up at five separate intervals during the 24-month period of study. We assessed the time between assessments retrospectively according to the depression module of the Structured Clinical Interview for DSM–IV (SCID).[21] We defined relapse or recurrence as an episode meeting DSM-IV criteria for a major depressive episode.[11,21]

The secondary outcomes were number of depression-free days, residual depressive symptoms, psychiatric and medical comorbidity, quality of life, and cost-effectiveness. At each follow-up we recorded the number of depression-free days based on episode duration as assessed by the SCID, residual depressive symptoms as assessed by the GRID-HAMD[22] and the 21-item self-report Beck Depression Inventory (BDI),[23] psychiatric comorbidity using the relevant SCID modules and medical comorbidities using the Medical Symptom Checklist (MSCL), quality of life using the WHO Quality of Life instrument (WHOQOL-BREF),[24] and health-related quality of life using the EQ-5D-3L (three level version).[25,26]

The economic perspective included all hospital and community health and social services, plus productivity losses, known to be a substantial cost in depression.[27] We obtained MBCT group data from therapist records. We obtained data on indirect time related to MBCT delivery, including preparation and supervision, from trial therapists. We obtained data on drugs and use of all other services using the Adult Service Use Schedule (AD-SUS) at each follow-up, modified and successfully used in our previous MBCT trial.[10] We confirmed ADM prescriptions and GP contacts via GP records. We measured productivity losses as a result of time off work or reduced productivity at work due to illness using the absenteeism and presenteeism questions of the WHO's Health and Work Performance Questionnaire (HPQ).[28]

All unit costs were for the financial year 2011–12, and costs and quality-adjusted life-years (QALYs) incurred in the second year were discounted by 3·5% as recommended by NICE.[29] We calculated the cost of MBCT-TS directly from salaries using a micro-costing approach used in our previous trial.[10] We applied national UK unit costs to medication and all other health and social services. We calculated productivity losses using the friction cost approach for absenteeism[30] and using the method set out by Kessler and colleagues[28] for presenteeism. The appendix shows full details of all unit costs.

See Online for appendix

At an early Trial Management Group Meeting we decided on the final list of measures to assess these constructs, and the WHOQOL was selected as secondary outcome measure quality of life (Aug 19, 2009). An oversight meant that this change was not included in the published protocol or in the ISRCTN register (ISRCTN26666654), although the full list of primary and secondary outcomes were logged at the first Trial Steering Committee (Dec 1, 2009) and in the CONSORT diagram

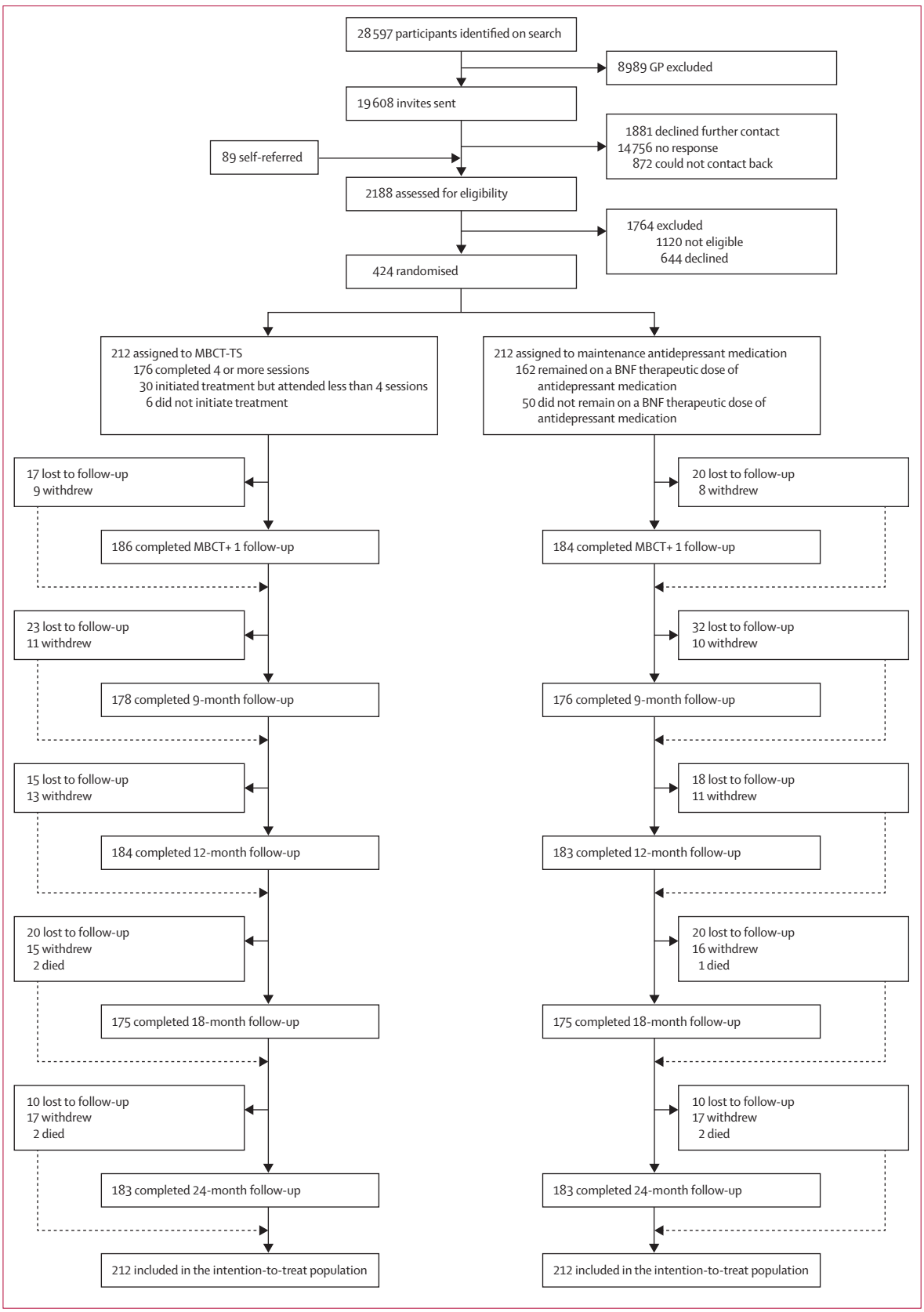

Figure 1: **Trial profile**
GP=general practitioner. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication.

reported in the Data Monitoring Committee (DMC) charter (dated May 24, 2010), which was signed by all DMC members. There is therefore a discrepancy between the published protocol that does not list the WHOQOL as a secondary outcome (Kuyken et al, 2010) and this outcome paper, which does report it. This discrepancy has no impact on the interpretation of the findings.

Statistical analysis

The study was powered to detect a hazard ratio of 0·63[10] between the two treatments at 24 months for the primary outcome, with 90% power, two-sided 5% α level, assuming a small clustering effect (intraclass correlation=0·01) and allowing for 20% loss to follow-up, producing a target sample size of 420 (210 per group). All analyses were prespecified in a detailed statistical analysis plan that was reviewed by the independent Trial Data Monitoring and Steering Committees. Analyses were undertaken according to the intention-to-treat principle except where stated.

The primary analysis was a between group comparison of time to relapse or recurrence at 24 months using a Cox regression proportional hazards model adjusted for stratification variables. We did two predefined secondary analyses of the primary outcome comparing groups according to whether participants had received an adequate dose of treatment and adhered to treatment as invited. We defined an adequate dose of treatment for MBCT-TS as attending four or more group sessions and for maintenance antidepressants as a BNF therapeutic dose of antidepressants during the 24-month follow-up period. We defined adherence to treatment as invited for MBCT-TS as attending four or more classes and at some point discontinuing or reducing antidepressants; for maintenance antidepressants, we defined adherence as a BNF therapeutic dose throughout the 24-month follow-up.

We compared secondary outcomes across all timepoints using repeated measures mixed regression models. Missing data were assumed missing at random and sensitivity analysis examined the effect of missing data using multiple imputations.[31] We report between group inference for secondary outcome analyses based on complete case and imputed datasets.

We used interaction terms to undertake predefined exploratory subgroup analyses on the primary outcome, across the stratification variables (recruitment centre and baseline depression severity) and reported childhood abuse.[12,32] Participants in the high abuse group reported experiencing childhood physical or sexual abuse or scored above the median score for the Measure of Parenting Scale (MOPS)[33] abuse subscale. Participants completed the MOPS at baseline as part of an embedded process-outcome study.[11] The abuse subscale asks participants to indicate how true they felt certain statements about their parents' behaviour were: for example, "parent was physically violent or abusive of me; parent made me feel unsafe". Participants in the low reported childhood abuse group scored below the median score for the MOPS abuse

	MBCT-TS (n=212)	m-ADM (n=212)
Demographic characteristics		
Women	151 (71%)	174 (82%)
White ethnic origin	210 (99%)	210 (99%)
Age, years		
Mean (SD)	50 (12)	49 (13)
Range	22–78	20–79
Marital status		
Single	42 (20%)	38 (18%)
Married, cohabiting, or civil partnership	125 (59%)	140 (66%)
Separated, divorced, or widowed	44 (21%)	33 (16%)
Missing	1 (<1%)	1 (<1%)
Education		
No educational qualification	10 (5%)	10 (5%)
O levels or GCSEs	36 (17%)	45 (21%)
AS and A levels or vocational qualification	84 (40%)	92 (43%)
University training	77 (36%)	61 (29%)
Missing	5 (2%)	4 (2%)
Religion		
Christian	133 (63%)	139 (66%)
Other	10 (5%)	4 (2%)
None	68 (32%)	68 (32%)
Missing	1 (<1%)	1 (<1%)
Salary (£)		
Mean (SD)	£19 930 (13 387)	£18 024 (13 582)
Range	£1200–£72 000	£792–£80 000
Social class		
Class 0	96 (45%)	76 (36%)
Class 1	53 (25%)	52 (25%)
Class 2	22 (10%)	38 (18%)
Class 3	5 (2%)	6 (3%)
Class 4	0	2 (1%)
Class 5	35 (17%)	37 (17%)
Not classified	1 (<1%)	1 (<1%)
Stratification variables		
Depressive symptomology at randomisation		
Asymptomatic	163 (77%)	162 (76%)
Symptomatic	49 (23%)	50 (24%)
Recruitment site		
Bristol	33 (16%)	31 (15%)
Exeter and east Devon	72 (34%)	76 (36%)
North and mid-Devon	55 (26%)	54 (25%)
South Devon	52 (25%)	51 (24%)
Psychiatric characteristics		
Current depressive symptomology GRID-HAMD	4·8 (4·3)	4·6 (4·3)
Current depressive symptomology BDI-II score	13·8 (10·2)	14·5 (10·1)
Previous major depressive episodes		
<6 episodes	120 (57%)	106 (50%)
≥6 episodes	92 (43%)	106 (50%)
Age (years) at first depression onset	24·4 (11·5)	25·4 (13·3)
Time (months) since last depressive episode	21·2 (27·0)	17·1 (23·0)
Number of comorbid DSM-IV axis I psychiatric diagnoses	0·5 (0·9)	0·7 (0·9)

(Table 1 continues on next page)

	MBCT-TS (n=212)	m-ADM (n=212)
(Continued from previous page)		
Received outpatient psychiatric or psychological treatment	103 (49%)	108 (51%)
Attempted suicide	48 (23%)	53 (25%)
Number of previous attempts	1·7 (1·1)	1·9 (1·5)
Severity of reported childhood abuse		
High	105 (50%)	111 (52%)
Low	105 (50%)	101 (48%)
Missing	2 (1%)	0
Quality of life		
How would you rate your quality of life?	3·7 (0·8)	3·7 (0·8)
How satisfied are you with your health?	2·9 (1·0)	3·1 (1·0)
Physical	14·5 (6·5)	14·4 (5·1)
Psychological	12·6 (2·6)	12·3 (2·6)
Social	13·4 (3·4)	13·1 (3·4)
Environment	15·0 (2·4)	15·1 (2·6)
Health-related quality of life (EQ-5D tariffs)	0·760 (0·268)	0·778 (0·211)

Data are number of participants (%) or mean (SD), unless otherwise specified. Quality of life assessed using the WHO quality of life assessment with higher scores indicating a higher quality of life. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication. m-ADM=maintenance antidepressant medication. GCSE=general certificate of secondary education. GRID-HAMD=Hamilton Rating Scale for Depression set out in a grid. BDI-II=Beck Depression Inventory-II. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edn.

Table 1: **Baseline characteristics of participants for the intention-to-treat population**

	Number of patients (%)
m-ADM treatment adherence	
Remained on therapeutic dose	162 (76%)
Did not remain on therapeutic dose	50 (24%)
MBCT-TS treatment adherence	
Participants who did not initiate MBCT treatment	6 (3%)
Participants who initiated MBCT treatment	206 (97%)
Mean number of sessions attended	6
Mode number of sessions attended	8
Standard deviation sessions attended	2·4
Completed four or more MBCT sessions	176 (83%)
ADM use in patients who attended four or more sessions of MBCT-TS	
No reduction to their ADM dose	23 (13%)
Reduced their ADM	29 (17%)
Discontinued their ADM	124 (71%)

m-ADM=maintenance antidepressant medication. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressants.

Table 2: **Adherence to treatment in each trial group**

subscale and did not report childhood physical or sexual abuse.

We analysed differences in mean costs using standard parametric *t* tests with the validity of results confirmed using bias-corrected, non-parametric bootstrapping (repeat re-sampling).[34,35] The primary economic analysis compared MBCT-TS and maintenance antidepressant treatment from the health and social care perspective preferred by NICE;[29] secondary analyses included productivity losses. Cost-effectiveness was explored using the net benefit approach[36] with effectiveness measured in terms of the primary outcome measure (depressive relapse or recurrence) and QALYs calculated with the EQ-5D. Uncertainty around the cost and effectiveness estimates was represented by cost-effectiveness acceptability curves.[37] All analyses were undertaken using Stata v.13.[38]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, interpretation of data, or writing of the paper. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 23, 2010, and Oct 21, 2011, of 2188 participants assessed for eligibility, we recruited 424 patients from 95 general practices. Of these, 212 participants were allocated to receive MBCT-TS and 212 participants to maintenance antidepressant treatment (figure 1). Primary outcome data were obtained for 189 (89%) participants in the MBCT-TS group and 194 (92%) participants in the maintenance antidepressants group; the remaining participants' data were censored at their last follow-up. We retained 366 (86%) of 424 participants over the 24-month follow-up period. At 24 months, we obtained secondary outcome data for 173 (82%) participants in the MBCT-TS group and for 175 (83%) in the maintenance antidepressants group. The pattern of collected secondary outcomes was similar for each group throughout the whole follow-up period, 84% MBCT-TS and 83% maintenance antidepressants. The data available for analysis were comfortably within the margin required by the power calculation.

Baseline characteristics were balanced between the two groups with the possible exception of gender (table 1). Because no evidence exists that patients' gender moderates MBCT treatment outcome,[10] we did not add gender in the primary analysis model. Table 2 shows treatment adherence and the extent to which patients followed invitations to discontinue maintenance antidepressants; more than 75% of patients adhered to treatment as intended.

We observed little or no clustering in primary or secondary outcomes by therapist. Because model results accounting for clustering by therapist were identical to those obtained for the primary intention-to-treat analysis, we report outcome findings without consideration of therapist clustering.

Primary analysis of the primary outcome showed no evidence of a reduction in the hazard of relapse or recurrence with MBCT-TS compared with maintenance antidepressant treatment in the intention-to-treat analysis (hazard ratio [HR] 0·89, 95% CI 0·67–1·18, p=0·43), with 94 (44%) of 212 patients in the MBCT-TS group relapsing compared with 100 (47%) of 212 in

the maintenance antidepressants group, log-rank c^2 (1)=0·67, p=0·41 (figure 2).

Another assessor rated every first actual or borderline relapse or recurrence and we recorded 90% agreement between the raters (κ=0·62, 95% CI 0·48–0·77, p<0·0001). A subset of 112 SCID interviews were also second rated by an experienced rater who was independent of the trial with 96% agreement being recorded (κ=0·90, 0·82–0·98, p<0·0001).

Secondary analyses on our primary outcome exploring the effect of adherence to treatment showed a non-significant reduction in the hazard of relapse or recurrence with MBCT-TS compared with maintenance antidepressant treatment at 24 months in participants who received an adequate dose of treatment (HR 0·79, 95% CI 0·58–1·08, p=0·14), with 81 (46%) of 176 patients in the MBCT-TS group relapsing compared with 80 (49%) of 162 in the maintenance antidepressants group, log-rank c^2(1)=2·3, p=0·13 (appendix). There was a non-significant reduction in the hazard of relapse or recurrence with MBCT-TS compared with maintenance antidepressant treatment at 24 months in participants who followed the invited treatment with respect to use of antidepressants (HR 0·77, 0·56–1·06, p=0·10), with 70 (46%) of 153 patients in the MBCT-TS relapsing compared with 80 (49%) of 162 in the maintenance antidepressants group, log-rank c^2(1)=2·7, p=0·10 (appendix). In view of their non-randomised nature, these secondary analyses are prone to selection bias and confounding (appendix).

We did not note a difference in treatment effect on the primary outcome across either stratification variable subgroup of depression severity at baseline or centre (table 3). However, we noted a significant interaction between severity of reported childhood abuse and treatment group. Specifically, compared with maintenance antidepressant treatment, MBCT-TS reduced the risk of relapse or recurrence for participants with high severity of reported childhood abuse (49 [47%] of 105 *vs* 65 [59%] of 111) whereas there was a slightly higher risk of relapse with MBCT-TS in the low severity of childhood abuse subgroup (44 [42%] of 105 *vs* 35 [35%] of 101) compared with the maintenance antidepressants group (table 3). We noted several differences in the baseline characteristics of participants with high and low severity of reported childhood abuse. Individuals who reported a more abusive childhood had had more previous psychiatric treatments including more hospital admissions, had had more previous episodes of depression and made more suicide attempts, had a greater chance of a family history of both suicide and mental illness, and were more likely to smoke than were participants who reported a less abusive childhood (appendix).

With respect to our secondary outcomes, we noted no evidence of the superiority of MBCT-TS over maintenance antidepressants (table 4). Furthermore, none of the secondary outcome treatment effects at any follow-up points exceeded a standardised mean difference of 0·4.

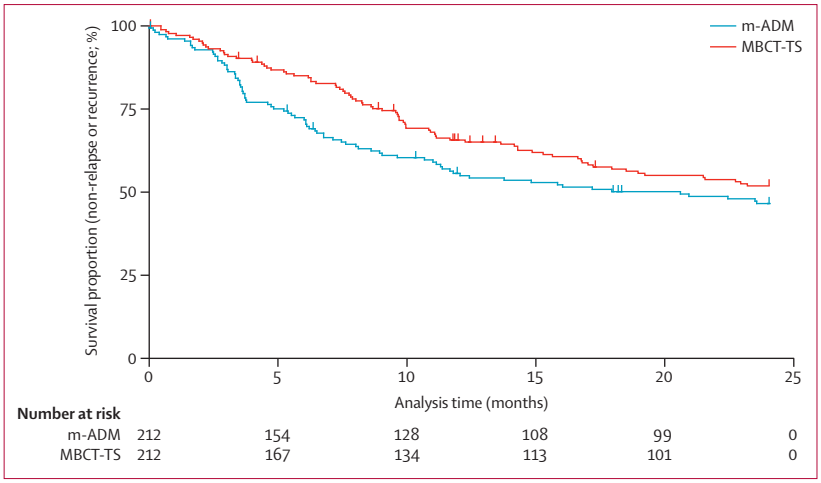

Figure 2: **Survival curves (of not relapse or recurrence) over a 24-month follow-up period for the intention-to-treat population**
m-ADM=maintenance antidepressant medication. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication.

	MBCT-TS	Maintenance antidepressants	Stratified HR (95% CI)	Interaction HR (95% CI); p value
Depression severity				
Asymptomatic (HRSD <8)*	163 (77%)	162 (76%)	0·83 (0·60–1·15)	
Symptomatic (HSRD ≥8)	49 (23%)	50 (24%)	1·06 (0·62–1·18)	1·27 (0·68–2·39); 0·46
Centre				
South Devon*	52 (25%)	52 (24%)	0·61 (0·33–1·13)	
Bristol	33 (16%)	31 (15%)	1·60 (0·54–2·12)	1·75 (0·70–4·39)
Exeter and east Devon	72 (34%)	76 (36%)	1·10 (0·68–1·81)	1·81 (0·83–3·96)
North and mid-Devon	55 (26%)	54 (25%)	0·84 (0·49–1·43)	1·37 (0·61–3·08); 0·47†
Childhood abuse				
Lower risk*	105 (50%)	101 (48%)	1·31 (0·83–2·04)	
Higher risk	105 (50%)	111 (52%)	0·69 (0·47–1·00)	0·53 (0·29–0·95); 0·03

Data are number of participants (%) unless otherwise stated. HR=hazard ratio. HRSD=Hamilton Rating Scale for Depression. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressants. *Reference subgroup. †p value for treatment-centre interaction across centres.

Table 3: **Subgroup analyses of treatment effect on days to relapse**

MBCT-TS group attendance was estimated to cost £112 per participant (table 5). Use of other health-care and social care services differed little between groups (appendix) and hence total health and social care cost per participant did not differ significantly between the MBCT-TS and the maintenance antidepressants group (mean difference £124, 95% CI –749·98 to 972·57, p=0·80). Results including patient costs (productivity losses and out of pocket expenditure) were also non-significant (table 5).

Cost-effectiveness analysis (appendix) suggests a trade-off between MBCT-TS and maintenance antidepressants when effects are measured in terms of relapse (costs higher and outcomes better), implying improve-

	Baseline		MBCT + 1 month		9 months		12 months		18 months		24 months		p value*	p value†
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N		
Depression														
Depression-free days													0·66	0·63
m-ADM	..	..	..	..	..	..	..	..	..	..	607·4 (196·4)	212		
MBCT-TS	..	..	..	..	..	..	..	..	..	..	607·4 (203·7)	212		
Residual depressive symptoms														
BDI													0·18	0·21
m-ADM	14·4 (10·1)	206	13·9 (10·9)	174	10·5 (9·7)	142	11·3 (9·2)	157	11·3 (10·7)	149	11·9 (10·7)	167		
MBCT-TS	13·8 (12·4)	210	9·9 (9·7)	174	11·0 (10·5)	151	10·7 (10·0)	167	11·7 (10·6)	142	11·6 (10·9)	169		
GRID-HAMD													0·76	0·55
m-ADM	4·6 (4·3)	212	7·4 (6·3)	183	5·6 (6·4)	175	4·7 (5·2)	181	5·3 (6·1)	174	4·7 (5·7)	183		
MBCT-TS	4·8 (4·3)	212	6·3 (5·6)	186	6·0 (5·5)	177	5·7 (5·7)	184	5·7 (5·7)	174	4·7 (4·8)	183		
Psychiatric and medical comorbidity														
Psychiatric comorbidities													0·91	0·90
m-ADM	0·7 (1·0)	212	..	..	..	..	0·1 (0·4)	196	..	..	0·3 (0·6)	183		
MBCT-TS	0·5 (0·9)	212	..	..	..	..	0·1 (0·3)	196	..	..	0·3 (0·7)	183		
MSCL													0·42	0·43
m-ADM	21·7 (13·8)	206	..	..	..	..	19·3 (13·7)	156	..	..	21·7 (16·3)	167		
MBCT-TS	22·8 (14·0)	210	..	..	..	..	21·0 (14·0)	167	..	..	22·2 (14·6)	169		
Quality of life														
WHO-QoL: Q1—overall perception of quality of life													0·07	0·03
m-ADM	3·7 (0·8)	205	3·8 (0·9)	173	3·9 (0·8)	141	3·9 (0·9)	157	3·9 (0·9)	149	3·8 (1·0)	167		
MBCT-TS	3·7 (0·8)	209	3·8 (0·8)	174	3·7 (0·9)	151	3·7 (0·9)	166	3·7 (0·9)	141	3·7 (0·9)	169		
WHO-QoL: Q2—overall perception of health													0·97	0·90
m-ADM	3·1 (1·0)	205	3·2 (1·0)	173	3·2 (1·0)	141	3·3 (1·0)	157	3·3 (1·1)	149	3·2 (1·0)	167		
MBCT-TS	2·9 (1·0)	209	3·1 (1·0)	174	3·1 (1·1)	151	3·2 (1·1)	166	3·2 (1·0)	141	3·1 (1·0)	169		
WHO-QoL physical health domain													0·07	0·02
m-ADM	12·3 (2·6)	205	14·3 (3·0)	173	14·8 (3·2)	141	14·7 (3·3)	157	14·7 (3·3)	149	14·9 (5·5)	167		
MBCT-TS	12·6 (2·6)	209	14·3 (3·3)	174	14·2 (3·3)	151	14·1 (3·4)	166	13·9 (3·5)	141	13·9 (3·5)	169		
WHO-QoL psychological domain													0·55	0·68
m-ADM	12·3 (2·6)	205	12·6 (2·8)	173	13·4 (2·7)	141	13·3 (2·7)	157	13·3 (3·0)	149	13·1 (3·0)	167		
MBCT-TS	12·6 (2·6)	209	13·4 (2·6)	174	13·3 (3·0)	151	13·3 (2·9)	166	12·9 (2·8)	141	13·1 (2·9)	169		
WHO-QoL social relationships domain													0·96	0·81
m-ADM	13·1 (3·4)	205	13·3 (3·4)	173	14·0 (3·4)	141	14·2 (3·3)	157	14·2 (3·4)	148	13·9 (3·5)	167		
MBCT-TS	13·4 (3·4)	209	13·8 (2·9)	174	13·7 (3·4)	151	13·9 (3·5)	166	14·0 (3·4)	141	13·7 (3·3)	169		
WHO-QoL environment domain													0·14	0·04
m-ADM	15·1 (2·6)	205	15·3 (2·5)	173	15·7 (2·3)	141	15·6 (2·6)	157	15·7 (2·6)	149	15·7 (2·7)	167		
MBCT-TS	15·0 (2·4)	209	15·21 (2·4)	174	15·4 (2·6)	151	15·2 (2·6)	166	15·3 (2·6)	141	14·9 (2·6)	169		
EQ-5D tariff													0·13	0·07
m-ADM	0·778 (0·211)	202	0·760 (0·226)	173	0·773 (0·234)	142	0·764 (0·248)	156	0·768 (0·243)	149	0·757 (0·266)	166		
MBCT-TS	0·760 (0·268)	209	0·727 (0·295)	174	0·735 (0·256)	151	0·721 (0·293)	167	0·723 (0·282)	142	0·715 (0·310)	169		

m-ADM=maintenance antidepressant medication. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication. BDI=Beck Depression Inventory. GRID-HAMD=GRID Hamilton Rating Scale for Depression. MSCL=medical symptom checklist. WHO-QoL=WHO Quality of Life. *p values reported are the treatment group-time interaction contrasts of marginal linear predictions for observed data. †p values reported are the treatment group-time interaction contrasts of marginal linear predictions for including imputed data. All models adjusted for baseline depression severity category on Hamilton scale and centre.

Table 4: **Intention-to-treat repeated measures analyses at 1 month after treatment, and follow-up at 9, 12, 18, and 24 months for secondary outcomes**

	MBCT-TS (n=181)	Maintenance antidepressants (n=180)	Mean difference (95% CI)*	p value*
MBCT	112·00 (0·00)	0·00 (0·00)		
Antidepressants	40·10 (72·13)	69·79 (168·48)		
Hospital and community services	2332·43 (4065·88)	2290·62 (4190·65)		
Total health-care PSS	2484·52 (4077·31)	2360·41 (4205·58)	124·11 (–749·98 to 972·57)	0·800
Out of pocket costs to patients	56·76 (168·29)	83·33 (283·12)		
Productivity losses (n=265)	504·26 (1881·49)	310·54 (761·06)		
Societal costs (n=252)	3204·05 (4011·91)	2754·92 (4465·07)	449·14 (–842·18 to 1286·26)	0·681

Data are mean (SD) unless otherwise stated. MBCT-TS=mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication. MBCT=mindfulness-based cognitive therapy. PSS=personal social services. *Adjusted for stratification variables.

Table 5: **Mean cost per participant over the 24-month follow-up period (£)**

ments in the percentage of participants who relapse can only be gained with additional expenditure. In terms of QALYs, MBCT-TS is dominated by maintenance antidepressant treatment (MBCT-TS costs higher and outcomes poorer, on average, than maintenance antidepressant treatment). Irrespective of measure of effect, exploration of statistical uncertainty suggests that the probability of MBCT-TS being more cost effective than maintenance antidepressants does not rise above 52%.

Serious adverse events were monitored and a total of ten serious adverse events were reported, four of which resulted in the death of the participant. These adverse events were evenly split between the two trial groups (three non-fatal and two fatal serious adverse events in each group) and reported to the Trial Steering and Data Monitoring Committees who concluded that there was no reason to believe that any of the serious adverse events were related to either the intervention or the trial.

Discussion

We noted no evidence for the superiority of MBCT-TS compared with maintenance antidepressants for patients with recurrent depression in terms of the primary outcome of time to depressive relapse or recurrence over 24 months or any of the secondary outcomes. Cost-effectiveness analysis does not support the hypothesis that MBCT-TS is more cost effective than maintenance antidepressants, in terms of either relapse or recurrence or QALYs.

Before this study, only two small studies[10,39] had compared MBCT-TS with maintenance antidepressants (panel). In our pilot trial,[10] MBCT-TS (n=62) was compared with maintenance antidepressant treatment (n=61) over a 15-month follow-up, and relapse or recurrence rates were 47% for MBCT-TS, compared with 60% for maintenance antidepressants.[10] In the second study,[39] 84 patients with recurrent depression who had remitted on antidepressants were randomly assigned to MBCT-TS, maintenance antidepressants, or pill placebo. Relapse or recurrence rates noted over 18 months of follow-up did not differ for MBCT-TS (28%, n=5/18) and maintenance antidepressants (27%, n=3/11), but both were lower than with placebo (71%, n=10/14).[39]

Relapse or recurrence rates in people with three or more previous episodes are as high as 80% over 2 years.[2] Moreover, results from meta-analyses consistently suggest that maintenance antidepressant treatment reduces the odds of relapse by two-thirds or a halving of absolute risk compared with usual care or placebo.[4] Future research should therefore examine the hypothesis that MBCT-TS would provide benefits over and above either usual care, no treatment, or pill placebo.

Across both treatment groups, outcomes were comparatively good over the 2 years of follow-up in terms of relapse or recurrence, residual symptoms, and quality of life (table 4).

Consistent with an emergent pattern of findings,[7] MBCT might confer most benefit to patients at greatest risk of relapse. A randomised trial[7] of patients with a history of three or more episodes of depression (n=274) compared MBCT, psycho-education, and usual care over a 12-month follow-up. MBCT provided significant protection against relapse or recurrence for participants with increased risk due to history of childhood abuse, but showed no significant advantage over the whole group.[7] Findings from trials of psychosocial approaches have shown that more intensive psychosocial treatments confer protection for those most at risk. For example, in a two-arm randomised trial over a 21-month follow-up, relapse or recurrence rates were 51% for maintenance cognitive behavioural therapy (CBT) and 60% for psycho-education, but in those at greatest risk, CBT conferred greater protection than did psycho-education.[40] A reported history of abuse and adversity is associated with worse outcomes in people who have depression.[41] Perhaps MBCT confers resilience in this group at highest risk because patients learn skills that address some of the underlying mechanisms of relapse or recurrence, a question we will explore in a subsequent publication from this trial. Studies are needed that have the primary aim of establishing the effectiveness and mechanism of MBCT for those at differing levels of risk of relapse, with robust measures of risk.

This largest trial of any mindfulness-based approach to date answered an important clinical question of high relevance to GPs and patients at risk for depressive relapse

Panel: Research in context

Systematic review

A 2011 meta-analysis identified two small trials comparing the effectiveness of mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication (MBCT-TS) with maintenance antidepressants in prevention of relapse or recurrence, following up participants for 60 weeks.[6] We did some searches of electronic databases (Embase, PubMed, PsycINFO, Web of Science, Scopus, and the Cochrane Controlled Trials Register) from the first available year to Nov 22, 2014, using keywords (mindfulness-based cognitive therapy) OR (mindfulness based cognitive therapy) OR (MBCT) AND depress*). No language or other limitations were imposed. We screened abstracts to retrieve full-text articles for assessment of eligibility. We also checked reference lists of relevant studies and reviews for additional references to potentially relevant studies. This search identified no further published trials. The combined relative risk ratio of MBCT-TS versus maintenance antidepressants was 0·80 (95% CI 0·60–1·08, z=1·45, p=0·15), corresponding to a non-significant risk reduction of 20%. We extended these findings with a large pragmatic superiority trial of MBCT-TS compared with maintenance antidepressants for people with a history of three or more previous episodes of depression. The primary outcome was relapse or recurrence over 2 years of follow-up. MBCT-TS was not superior to maintenance antidepressant medication in terms of time to depressive relapse or recurrence over the 24 months (hazard ratio 0·89, 0·67–1·18). We pooled our trial data with the equivalent MBCT-TS and maintenance antidepressant medication groups of the previous two randomised controlled trials (n=123[10] and n=54[39]), and used the equivalent 60-week follow-up point available across all three studies. The combined relative risk ratio of MBCT-TS versus maintenance antidepressants was 0·76 (95% CI 0·59–0·98), a risk reduction of 24%. There was no evidence of statistical heterogeneity.

Interpretation

We found no evidence that MBCT-TS is superior to maintenance antidepressant treatment for the prevention of depressive relapse. However, when considered in the context of the totality of randomised controlled data, we found evidence from this trial to support MBCT-TS as an alternative to maintenance antidepressants for prevention of depressive relapse or recurrence at similar costs. It allows such individuals to stay well and maintain good quality of life. In patients who report childhood abuse, MBCT-TS might confer greater benefit than maintenance antidepressants in prevention of depressive relapse or recurrence.

or recurrence. The internal validity of the trial was established through the fidelity of MBCT-TS delivery, high rates of treatment adherence, excellent retention, and through masked outcome assessment. The external validity was maximised by the relatively long follow-up (24 months), and good adherence rates in both treatment groups.

The study had several limitations. The sample consisted of a group of people at high risk of depressive relapse or recurrence,[42] currently taking antidepressants, and who were open both to considering a group-based psychosocial treatment and to discontinuing or continuing antidepressant medication. This characteristic is both a strength and limitation of the study. The findings are therefore only generalisable to the subgroup of individuals in equipoise about type of preventive treatment. Moreover, our recruitment strategy consisted of searching primary care databases and inviting patients who were currently taking maintenance antidepressants rather than recruiting patients who were discussing their options for preventing relapse or recurrence with their GP.

The design included neither a usual care nor an attention control group. The absence of an attention control group means any effects of MBCT cannot be inferred to be specific to MBCT; ongoing studies of mechanisms of action in MBCT from our group will address this question. Finally, the pragmatic nature of the trial means that a subgroup of patients in both groups did not comply with the study invitation to discontinue antidepressant medication. This characteristic is both a strength (pragmatism and generalisability) and limitation (the antidepressant medication was not fully controlled).

In a large rigorous, yet pragmatic randomised trial we have shown that MBCT-TS is not superior to maintenance antidepressants over 2 years of follow-up for patients with recurrent depression. Benchmarked against epidemiological data, both treatments were associated with enduring positive outcomes in terms of relapse or recurrence, residual depressive symptoms, and quality of life. This study, combined with previous studies, provides important evidence that MBCT-TS might confer ongoing protection for patients who would like an alternative to maintenance antidepressant medication. The results further suggest that psychosocial treatments such as MBCT and CBT[7,40,43] offer added value for patients who need them most (ie, those at highest risk of depressive relapse or recurrence). However, studies have tended to operationalise risk in somewhat different ways (such as early adversity, unstable remission, more previous episodes, early age of onset) and although these risk factors overlap, future research should examine how and through what mechanism risk is conferred and resilience learned. In the interim, the implication is that for patients at low risk, treatments such as psycho-education or maintenance antidepressants, which require less patient commitment and cost, might be indicated, whereas for patients at highest risk, more intensive treatments such as MBCT could be indicated. This implication has substantial potential to improve prevention by maximising the delivery of treatments through stratified approaches, which also have the potential to improve patient choice.

Contributors

WK, SB, RB, TD, GL, RST, EW, PL, DK, and NM were responsible for the original proposal, securing funding for the trial, and drafting the original protocol. WK as chief investigator had overall responsibility for the management of the study and the Exeter site, and as co-investigators GL and DK had responsibility for the Bristol site. Trish Bartley, AE, and WK provided training and supervision for the trial therapists (CB, SC, AE, and JW). RB also provided support for intervention development and delivery. JC, AC, FG, RH, SK, JR, PS, HS, RV, AW, and MW were responsible for data collection. RH, WK, RST, and SB wrote the statistical analysis plan. AC, BB, RH, PS, and MW did the data cleaning and BB and RST did the analyses. SB, RH, WK, and RST wrote the initial draft of the manuscript. All authors contributed to, and approved, the final manuscript.

Declaration of interests

WK and AE are co-directors of the Mindfulness Network Community Interest Company and teach nationally and internationally on MBCT. The other authors declare no competing interests.

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