Examining What Works for Whom and How in Mindfulness-Based Cognitive Therapy (MBCT) for Recurrent Depression: A Moderated-Mediation Analysis in the PREVENT Trial

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Abstract

Background: Personalized management of recurrent depression, considering individual patient characteristics, is crucial. **Aims**: This study evaluates the potentially different mediating role of mindfulness skills in managing recurrent depression using mindfulness-based cognitive therapy (MBCT) among patients with varying depression severity. **Method**: Data from the PREVENT trial, comparing MBCT (with antidepressant medication (ADM) tapering support, MBCT-TS) vs. maintenance-ADM, was used. The study included pre, post, 9-, 12-, 18-, and 24-month follow-ups. Adult patients with ≥3 previous major depressive episodes, in full/partial remission (below threshold for a current episode), on ADM, were assessed for eligibility in primary care practices in the UK. Patients were randomized (1:1) to MBCT-TS or maintenance-ADM. We used the Beck Depression Inventory-II to evaluate depressive symptom

changes over the six time points. Pre-post treatment, we employed the Five Facets of Mindfulness Questionnaire to gauge mindfulness skills. Baseline symptom and history variables were used to identify patients with varying severity profiles. We conducted Latent Profile Moderated-Mediation Growth Mixture Models. **Results**: A total of 424 patients (mean (SD) age=49.44 (12.31) years; with 325 (76.7%) self-identified as female) were included. A mediating effect of mindfulness skills, between trial arm allocation and the linear rate of depressive symptoms change over 24 months, moderated by depression severity, was observed (moderated-mediation index=-0.27, 95%CI=-0.66, -0.03). Conditional indirect effects were -0.42 (95%CI=-0.78, -0.18) for higher severity (expected mean BDI-II reduction=10 points), and -0.15 (95%CI=-0.35, -0.02) for lower severity (expected mean BDI-II reduction=3.5 points). **Conclusions**: Mindfulness skills constitute a unique mechanism driving change in MBCT (vs. maintenance-ADM). Patients with higher depression severity may benefit most from MBCT-TS for residual symptoms. It is unclear if these effects apply to those with a current depressive episode. Future research should investigate individuals who are not on medication. This study provides preliminary evidence for personalized management of recurrent depression. **Trial Registration**: ISRCTN26666654.

Introduction

Depression causes significant disability to individuals and a high economic burden to societies. There is a growing call to move beyond treatment to secondary prevention, focussing on the broader societal impact.[1,2] Maintenance antidepressant medication (m-ADM) is the leading approach to preventing depressive relapse.[3] But they don't work for everyone and can have contraindications, side-effects, and some experience unpleasant withdrawal effects if they taper or

discontinue.[4] A recent study in the UK and USA showed a 15% benefit for antidepressant medication compared to no treatment after two months. Only one in three people accepted antidepressants given the side-effects, and two in three expected greater treatment benefits than they experienced.[5] Thus, there is a need for alternatives to m-ADM that support recovery without these costs.[6] There is now compelling evidence that psychological interventions are comparably effective to m-ADM (hazard ratio = 0.86; 95%CI = 0.60, 1.23).[7] Mindfulness-based cognitive therapy (MBCT) is one such psychological intervention in which people with a history of depression learn mindfulness skills to stay well,[8] with proven effectiveness, including as an alternative to m-ADM.[9] However, further knowledge is needed to better tailor these interventions to individual patients and maximise their effectiveness.

Translational science enhances our understanding of who benefits most from which treatment, and through which mechanisms different treatments operate. This enables us to innovate the treatments themselves by better targeting the mechanisms and also ensuring that treatments most likely to be effective are offered to people most likely to benefit. A recent scoping review suggests improvements in mindfulness skills (which include present-moment attention, and non-judgmental acceptance) as a potential target mechanism of mindfulness-based programs across different mental health strategies (e.g., treatment, and prevention). This supports theoretical assumptions on how these programs work by helping people to break established cognitive patterns that maintain and

enhance depressive symptoms. However, more studies are required to determine whether this potential mechanism is shared across, or unique to, different subgroup populations.[10] This review also offers additional conceptual guidelines for analysing mediation, recommending the use of high-quality randomized controlled trials (RCTs), active comparators targeting different mechanisms, and innovative statistical approaches within the context of an embedded process evaluation framework.[11]

Objective

The present study explores potential moderated-mediation effects in the management of recurrent depression following treatment with m-ADM compared to MBCT. A moderated-mediation analysis offers an opportunity to better understand for whom and why MBCT (vs. m-ADM) may have different effects on depressive patients. Building on previous research suggesting that MBCT may be especially helpful in the context of entrenched depression, we hypothesized that the putative mediating effects of improvements in mindfulness skills are specific to MBCT and are stronger in the subgroup of patients with a more severe history of depression.[12]

Method

This study is a post-hoc extension on planned secondary analysis of the PREVENT trial.[13] PREVENT was a single-blind, parallel RCT, examining m-ADM vs. MBCT (with ADM tapering support, MBCT-TS) for patients with recurrent depression. Results of the PREVENT trial showed that both treatments were associated with enduring positive

outcomes. To better tailor treatments to patients and maximise their effectiveness, the PREVENT trial was envisioned to explore process-outcome relationships of mindfulness skills beyond the overall effectiveness and cost-effectiveness findings.[13,14]

Participants

The sample consisted of adult participants aged 18 years or older, with a diagnosis of recurrent depression, who were taking m-ADM. Participants were not currently experiencing a depressive episode at the time of the study. They were recruited from various locations within the South-West region of England (Bristol, North Devon, East Devon, and Mid Devon), totalling 424 participants. The sample size was not established a priori for moderated-mediation analyses, thus the secondary analyses reported in the current paper were exploratory.[14] Nevertheless, the exploration of mindfulness skills as a potential mechanism of MBCT to be tested was already established in the protocol,[14] and we carried out sensitivity analysis to control for potential confounding effects.

Randomisation and Masking

The 424 participants were randomly assigned (1:1) to m-ADM or MBCT-TS and stratified by recruitment site and symptomatic status (asymptomatic, or partially symptomatic) via computer-generated random permuted blocks, using a password-protected website externally hosted by the Peninsula Clinical Trial Units. Researchers working on the PREVENT were blind to treatment allocation.

However, given the nature of the interventions, patients were aware of their treatment group assignment.

Procedures

Recruitment

Patients were recruited and received treatment in Primary Care settings. The inclusion/exclusion criteria were refined during a feasibility trial,[15] to maximize real-world applicability for the Primary Care patient population, who experience recurrent depression and are treated with m-ADM and interested in exploring a psychological approach. Inclusion criteria for study participation required individuals to have a diagnosis of recurrent Major Depressive Disorder (MDD) in full or partial remission as per DSM-IV,[16] with a history of three or more previous MDD episodes, to be 18 years or older, and on a therapeutic dose of m-ADM, following the British National Formulary (BNF) and NICE guidelines.[17] Exclusion criteria included a current depressive episode; concurrent substance misuse; organic brain damage; current or past psychosis (including bipolar disorder); antisocial behaviour; ongoing self-injury requiring clinical management and/or therapy; and receiving concurrent psychotherapy. Participants provided written informed consent after receiving a description of the study.

Interventions

MBCT is a manualised group program aimed at teaching skills to prevent depression relapse. The goal of MBCT is to increase patients'

awareness of bodily sensations, thoughts, and feelings linked to depressive relapse and to help them respond to these experiences in a constructive manner. Participants practice mindfulness exercises during sessions and through homework, with therapists supporting them in developing adaptive responses to potential triggers of depression. The original MBCT program was adapted, placing emphasis on developing a relapse and recurrence signature and response plan, which involved participants considering the reduction or discontinuation of m-ADM (Supplement S1).[8] The MBCT-TS program consisted of eight 2.25-hour group sessions, typically held over consecutive weeks, with up to four booster sessions offered in the year following the end of the 8-week program. Participants in the MBCT-TS arm were encouraged to taper and discontinue their m-ADM towards the end of the 8-week program. The research team provided information for general practitioners (GPs) and participants, regarding typical tapering and discontinuation regimens and potential withdrawal effects. A total of 21 MBCT-TS groups (around 10 individuals per group) were led by four experienced MBCT teachers. Teachers were mental health professionals (two clinical psychologists, and two occupational therapists), with extensive training and experience in leading MBCT groups (≥4 years) and a long-standing ongoing personal mindfulness practice (≥7 years). An independent check on competency was established before teachers progressed to running trial groups. For that, an experienced MBCT therapist independent of the trial rated at least two videotapes of MBCT-TS

sessions and, using the Mindfulness-Based Interventions–Teacher Assessment Criteria (MBI-TAC), made an overall judgement about whether the teachers were competent. During the trial, MBCT teachers received 3-hour supervision biweekly. Trial groups were videotaped for checks on therapist competence and adherence. Randomly selected samples of two sessions (42 sessions in total) were assessed by a MBCT expert independent of the trial. Transcription coding of the MBCT-TS trial sessions indicated that the teachers delivered the groups at or above the required levels of competence (Supplement S2). The mean (SD) total adherence score in the trial was 23.6 (4.30) –potential range 0-34– indicating acceptable adherence to protocol, with no differences found between teachers.[13]

The m-ADM arm consisted of maintenance of the ADM treatment. Participants were monitored and treated by GPs in a Primary Care setting in line with standard clinical practice. Primary Care physicians were asked to meet with patients regularly to review their medication. Changes in medication sometimes occurred but physicians and participants were asked to ensure that the dose remained within therapeutic limits. The trial GPs and trial psychiatrist provided materials for all participants and participating GPs on m-ADM and ongoing support as required.

Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the

Helsinki Declaration of 1975, as revised in 2013. All procedures involving human patients in the PREVENT trial were approved by the UK National Health Service South-West Research Ethics Committee (09/H0206/43), obtained research governance approval from local Primary Care trusts or health boards, and were overseen by a data monitoring and ethics committee, and the PREVENT trial steering committee.

Measures

Supplement S3 provides details on the measures and their corresponding references. The following sociodemographic information was collected prior to trial randomization at baseline: age, self-identified gender, self-identified ethnicity, level of education, relationship status, and employment status.

Informed by previous theoretical and empirical research describing factors that predict whether MBCT could offer superior relapse prevention for recurrent depression compared to m-ADM,[12,18-23] we used a series of baseline-measured variables to define different latent profiles (LPs) characterized by distinct severity of clinical history. For that, we considered (i) markers of symptoms intensity and clinical history, (ii) cognitive and emotional factors, and (iii) relational and social variables (all assessed prior to randomization). Symptoms intensity and clinical history variables included clinician-rated residual symptoms of depression (Hamilton Depression Rating Scale (HAMD)); childhood abuse (Measure of Parenting Scale (MOPS)); age of first onset of depression (years); number of previous depressive

episodes; severity of last episode (number of symptoms present from the Structured Clinical Interview for DSM-IV (SCID); potential range: 5-9); chronicity of last episode (months); previous suicide attempt (yes, no); and number of comorbid DSM-IV Axis I diagnoses.[16] Cognitive and emotional factors involved cognitive rumination (negative and un-resolution rumination, from the Cambridge-Exeter Repetitive Thought Scale (CERTS)); self-blame and lack of acceptance (Cognitive Emotion Regulation Questionnaire (CERQ)); ability to recognise early warning signs of depression (bespoke single item); acting with awareness (Five Facet Mindfulness Questionnaire (FFMQ)); self-efficacy (General Self-Efficacy Scale (GSE)); and positive affect (contentment and joy, from the Dispositional Positive Emotion Scale (DPES)). Relational and social factors covered relationship satisfaction (bespoke 7-items) and stigmatisation (bespoke 7-items). We used quality-of-life at baseline (WHOQOL-BREF) as a distal measure (not included in the analytical processes of identifying/confirming the LPs) to assist in understanding the observed LPs.

We focused on mindfulness skills as a potential MBCT-TS mediator because it has been widely supported empirically, despite variable effects. Variations suggest that the influence of mindfulness skills might depend on participant characteristics, warranting further investigation.[10] Mindfulness skills were measured at baseline and one month after the MBCT-TS training (or the equivalent in the m-ADM

arm) using the FFMQ total score to examine improvements in mindfulness skills as a hypothesised mechanism.

We selected the total score of the Beck Depression Inventory (BDI-II), taken as a continuous variable, as our primary measure to monitor changes in the intensity of depressive symptomatology over time (from baseline to one month after the end of the MBCT-TS training, and at 9, 12, 18, and 24 months after baseline). The BDI-II is one of the most widely used instruments for assessing the presence and intensity of depressive symptoms. It is a self-reported measure composed of 21 items covering cognitive, emotional, and somatic domains associated with depression. It aligns with diagnoses from the DSM-IV and has demonstrated strong concordance with clinical diagnoses of depression. The BDI-II inquiries about the preceding two weeks and requires participants to rate symptom levels ranging from 0 ('not present') to 3 ('severe'), with a total score ranging from 0 to 63 (0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; 29-63: severe depression). It demonstrates high convergent validity with other depression rating scales, such as the Hamilton Depression Rating Scale, and exhibits robust psychometric properties, including strong internal consistency and test-retest reliability. Its comprehensive coverage ensures a nuanced evaluation of depressive symptoms, making it an invaluable tool for monitoring shifts in symptom severity throughout the course of treatment. A clinically relevant improvement generally depends on the initial levels of depression and is usually established at around a 15%

improvement.[24] However, NICE guidance suggests that a change of three or more BDI-II points is clinically significant. This BDI-II change has, in fact, been demonstrated to be relevant for service use patients with average BDI-II scores of 14 points.[24]

Statistical analyses

A moderated-mediation growth mixture model was used to evaluate the indirect effects (IEs) at varying levels of the moderator (i.e., the LPs). Moderated-mediation analyses examine the conditional IE of a potential moderating variable on the relationship between a predictor variable and an outcome, through a potential mediator. The predictor was the allocation group (m-ADM vs. MBCT-TS). The outcome was the linear growth (β_1) of the latent change trajectory of depressive symptoms (BDI-II) across all trial time points (from baseline to 24 months later), as a measure of the rate of change of depressive symptoms over time.[25] The potential mediator was the change in mindfulness skills (ΔFFMQ) from baseline to one month after the end of the MBCT training. The potential moderator was the LP variable, reflecting distinct subgroups of individuals with recurrent depression in remission, characterized by a distinct degree of clinical severity. Details of the LP and latent growth curve model (LGCM) analyses are provided in Supplement S4.

We tested the potential moderating effect of the LP on the predictor-to-mediator path (*a*-path), on the mediator-to-outcome path (*b*-path), and on the predictor-to-outcome direct path after controlling for the IE (c'-path). We used the index of moderated-mediation (i.e.,

the difference in the IEs across levels of the potential moderator) to test the significance of the moderated-mediation.[26] Significant effects are supported by the absence of zero within the bootstraped 95% confidence intervals (CIs).[27] Sensitivity analyses were conducted whereby the moderated-mediation model was adjusted to account for the potential confounding effects of the amount of home-based formal meditation practice (‘not at all’, ‘sometimes’, ‘regularly’, ‘more days than not’) and discontinuation of antidepressant intake (i.e., whether they remained on a therapeutic dose of antidepressants for the duration of the trial). A graphical representation and more details of the moderated-mediation analyses are provided in Supplement S5.

We examined missing data and applied Full Information Maximum Likelihood assuming missingness at random.[28,29] We used 2-tailed tests with an alpha level of 0.05 and 95% bootstrapped CIs for the IEs. Due to the exploratory nature of this study, we opted not to correct for multiple testing. Analyses were performed using Mplus v8.10.

Results

Descriptive statistics for baseline sociodemographic, quality-of-life, and depressive symptoms variables are presented by trial arm in Table 1. In the MBCT-TS arm, 176 participants (83.0%) completed four or more MBCT-TS sessions. Additionally, 140 participants (66.1%) engaged in home-based formal meditation practices (‘sometimes’, ‘regularly’, or ‘more days than not’), and 133 participants (62.7%) did not remain on a therapeutic dose of antidepressant medication for the

duration of the trial (m-ADM use in patients who attended ≥4 sessions of MBCT-TS can be seen elsewhere).[13] In the m-ADM arm, 23 participants (10.8%) practiced home-based formal meditation exercises, and 50 participants (23.6%) did not remain on a therapeutic dose of antidepressant medication for the duration of the trial (Supplement S6). Details on antidepressant use according to participants' self-reports, and the number of visits registered in the GP record by group can be seen in Supplements S7-8. Of the participants recruited to the trial, 348 (82.1%) provided data on the BDI-II at one month after the end of the MBCT-TS training; 293 (69.1%) provided data at 9 months after baseline; 324 (76.4%) at 12 months; 291 (68.6%) at 18 months; and 336 (79.3%) at 24 months. Participant baseline characteristics by trial arm and follow-up status are presented in Supplements S9-S13.

Latent profiles

Supplement S14 presents the model selection, LP interpretation, and patient classification according to the LP analysis. A two-level model (LP1: 'lower severity of depression'; LP2: 'higher severity of depression') was estimated. Figure 1A includes a graphical representation of the distribution of predictor variables between LPs. LP2 did not differ from LPI in any sociodemographic data but had significantly worse values of a moderate-to-large effect size in history of abuse, number of previous episodes of depression and suicide, stigmatization, self-blame, negative and un-resolution rumination, residual symptom severity at intake, and in the distal quality-of-life

variables. Supplements S15 and S16 provide details on the LPs and their baseline characteristics by trial arm.

Latent growth curve

Supplement S17 provides details of the LGCM analysis. The quadratic (heteroscedastic auto-correlated) LGCM outperformed both the intercept-only and the linear models, indicating a curvilinear trend with a decreasing initial phase that diminishes and may eventually turn into an increase of symptoms (Figure 1B). The LGCM suggested individual variability in the initial level of residual depressive symptoms (BDI-II Mean=13.64, which is around the cutoff that differentiates mild from minimal depression).[41] However, there was no significant variability either in the linear rate of change (BDI-II Mean=-0.30, suggesting an average decrease of 0.3 BDI-II points per unit of time, i.e., per month) or in the quadratic rate of change (BDI-II Mean=0.01).

Moderated-mediation

Descriptive statistics for the change in mindfulness skills during the intervention by trial arm and LP are provided in Supplement S18. As shown in Table 2 and Figure 2, a significant moderation effect was observed between trial arm and LP in the *a*-path, from trial arm to change in mindfulness skills (coefficient=8.84; 95%CI=0.26, 17.32; p=0.043) (Supplement S19). The conditional effect from trial arm to change in mindfulness skills was most pronounced for higher severity of depression (LP2: a_2=13.87; 95%CI=7.80, 20.20; p<0.001) but was also significant for lower severity of depression (LP1: a_1=5.03;

95%CI=0.26, 10.09; p=0.045). The effect from change in mindfulness skills to the linear slope of depressive symptoms over time was *b*=-0.03 (95%CI=-0.25, -0.02; p<0.001). This effect was not moderated by the LPs (coefficient=-0.001; 95%CI=-0.04, 0.04; p=0.949) (Supplement S20). The index of moderated-mediation was significant (coefficient=-0.27; 95%CI=-0.66, -0.03), providing evidence for the LPs to moderate the mediating effect of change in mindfulness skills between trial arm and rate of change in depressive symptoms. The conditional IE for higher severity of depression (LP2) was the strongest (IE=-0.42; 95%CI=-0.78, -0.18). For lower severity of depression (LP1), it was weaker but significant (IE=-0.15; 95%CI=-0.35, -0.02). For the direct effect from trial arm to the linear slope of depressive symptoms over time, there was no significant moderation between trial arm and LP (coefficient=-0.02; 95%CI=-1.08, 1.02; p=0.965). The direct effect from trial arm to the linear slope of depressive symptoms over time, after controlling for the IEs, was not significant (c'=0.37; 95%CI= -0.04, 0.77; p=0.080), and in the opposite direction to the total effects (c=-0.20; 95%CI=-0.68, 0.25; p=0.398). Around 10% of the variance in the linear slope of change in depressive symptoms over time was explained by trial arm and change in mindfulness skills. Within this variance, the IE explained a small amount in LP1 (2%) and an intermediate amount in LP2 (18%).

Descriptive data for m-ADM discontinuation and home-based formal meditation practice, by trial arm and LP, are presented in

Supplement S21. Results for the moderated-mediation sensitivity analysis, are provided in Supplement S22. After adjusting for the potential confounders, a significant moderation effect was observed between trial arm and the LPs in the *a*-path from trial arm to change in mindfulness skills (coefficient=14.00; 95%CI=3.00, 25.96; p=0.016). The index of moderated-mediation after adjusting for the potential confounders was significant (coefficient=-0.37; 95%CI=-0.89, -0.08). This provided further evidence for the LPs to moderate the mediating effect of change in mindfulness skills between trial arm and rate of change in depressive symptoms, favouring the higher severity of depression profile (LP2).

Discussion

We know that both m-ADM and MBCT are effective treatments for recurrent depression,[3,7,9,30] but there is a need to better understand which works best for which patient profile, as well as how MBCT provides its benefits. This understanding is crucial for personalizing prevention efforts, thereby increasing acceptability, and optimizing their effectiveness. In line with previous research,[31,32] we found two relevant subgroups of patients with recurrent depression in remission, that can be differentiated in terms of the severity of their clinical history, psychological characteristics, and impairment. This heterogeneity was also evident in the starting point (i.e., intercept) of the time series for residual depressive symptoms, showing clear differences between both subgroups.

We found evidence that mindfulness skills is a potential mediator through indirect mediation only (i.e., significant IEs were observed, but neither the direct effect, after controlling for the IEs, nor the total effects were significant).[33] This suggests that mindfulness skills is a unique mechanism of action to this MBCT-TS intervention (vs. m-ADM) for treating residual depressive symptoms in recurrent depression. This finding aligns with the originally hypothesized theoretical framework,[8] and supports the conclusions of recent reviews.[10,34] As expected,[12,18-23] the mediating effect was stronger in the subgroup of patients with a more severe history of depression. Our results suggest this is because these patients are learning mindfulness skills. Other variables such as rumination, self-criticism, or positive affect, which define severity profiles, might also act as mechanisms of change in MBCT. This dual role requires further investigation.

The impact of MBCT through mindfulness skills (i.e., the IE) was three times more pronounced in the more severe subgroup of patients with recurrent depression. This resulted in a clearly clinically relevant expected mean reduction of around 10 points on the BDI-II for the more severe profile, suggesting large effects and a potential shift from a mild-to-moderate baseline level of depressive symptoms to a minimal level of depressive symptoms at 24-month follow-up. However, for the less severe profile, the expected mean reduction was around 3.5 points on the BDI-II, reflecting small-to-moderate effects and a potential (clinically relevant) shift within the minimal range of symptoms. These findings suggest that the subgroup of patients with

recurrent depression and a more severe profile should be the optimal target population for MBCT. However, we do not know if effects would hold with those having a current depressive episode, although there is evidence for the efficacy of MBCT in reducing current depressive symptoms.[35] For patients with a less severe profile, other evidence-based approaches such as cognitive therapy, physical exercise, and lifestyle changes might be beneficial.[36] There is also preliminary evidence, showing that innovations in cognitive therapy and MBCT that focus on lifestyle changes and enhancing positive affectivity can confer benefits (e.g., MBCT Finding Peace, MBCT For Life, MBCT Taking it Further).[37-39]

Strengths and Limitations

This study offers a unique opportunity to examine MBCT's pathways of change by using a large RCT with process elements and innovative statistical approaches to answer for whom and how MBCT leads to the management of depressive symptoms in recurrent depression. Although mediation can be difficult to detect,[40] we have utilized a sophisticated analytical approach that considers moderated-mediation to shed light on this process. Further strengths include the use of an evidence-based active control group (m-ADM), which effectively addresses depressive symptoms through different mechanisms, and our 24-month follow-up period. Nevertheless, the representativeness of the study sample (which included patients with recurrent depression fully or partially remitted, predominately female, and white British), and in turn, generalisability of our findings, are key

limitations. We did not have enough numbers to address gender-based analyses, which is a limitation. In addition, we carried out exploratory analyses without adjusting for multiple comparisons. Whilst the use of 95% CIs provides an indication of the precision and stability of our findings, future replication studies are needed. The m-ADM group received less attention compared to the MBCT-TS group. Consequently, effects might be attributed to increased contact with services. Finally, although moderated-mediation effects persisted after controlling for the discontinuation of antidepressant medication, future studies need to incorporate interaction analyses to determine whether the effects of MBCT vary depending on whether or not patients are taking medication.

Conclusions

Patients with recurrent depression and a more severe history of depression, partially remitted with mild-to-moderate residual symptoms, may benefit most from MBCT-TS in the management of residual depressive symptoms by the acquisition of mindfulness skills. Enhancing MBCT to focus on the acquisition and use of mindfulness skills might lead to further improvements. Here we provide initial evidence for the benefit of a more personalised approach to the management of recurrent depression, that may be informed by patient treatment preferences and clinical characteristics.

Declaration of interests: WK is director of the University of Oxford Mindfulness Research Centre. SB is a member of the British Journal of

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Transparency Declaration: Dr Montero-Marin and Dr Kuyken had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Montero-Marin and Dr Kuyken claim that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained throughout the manuscript. Authors were not precluded from accessing data and they accept responsibility to submit for publication.

Data Availability: The de-identified baseline data and codebook from the PREVENT trial, and analytic codes and research materials are available from Dr Kuyken (willem.kuyken@psych.ox.ac.uk) upon reasonable request (release of data is subject to an approved proposal and a signed data access agreement).

Consents: The PREVENT study was approved by the UK National Health Service South West Research Ethics Committee (09/H0206/43), and it obtained research governance approval from the local primary care trusts or health boards. Participants gave informed consent to participate in the study before taking part (available upon request).

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Table 1: Baseline characteristics of participants by allocation group

	m-ADM (n = 212)	**MBCT (n = 212)**
Demographic characteristics		
Age, *years*, M (SD)	48.71 (12.73)	50.16 (11.85)
Gender, *Women*, n (%)	174 (82.1)	151 (71.2)
Ethnicity, *White*, n (%)	210 (99.1)	210 (99.1)
Marital status		

Single, n (%)	38 (17.9)	42 (19.8)
Married, cohabiting, civil partnership, n (%)	140 (66.0)	125 (59.0)
Separated, divorced, widowed, n (%)	33 (15.6)	44 (20.8)
Education		
No educational qualification, n (%)	10 (4.7)	10 (4.7)
O levels or GCSEs, n (%)	45 (21.2)	36 (17.0)
AS and A levels or vocational qualification, n (%)	92 (43.4)	84 (39.6)
University training, n (%)	61 (28.8)	77 (36.3)
Employment status		
Not working, n (%)	82 (38.7)	98 (46.2)
Part time, n (%)	70 (33.0)	53 (25.0)
Full time, n (%)	59 (27.8)	59 (27.8)
Quality-of-life		
Quality-of-life rating (range: 1-5), M (SD)	3.72 (0.83)	3.66 (0.80)
Health satisfaction (range: 1-5), M (SD)	3.07 (0.99)	2.92 (1.03)
Physical (range: 4-20), M (SD)	14.41 (5.06)	14.47 (5.51)
Psychological (range: 4-20), M (SD)	12.32 (2.59)	12.61 (2.62)
Social (range: 4-20), M (SD)	13.12 (3.42)	13.39 (3.41)
Environment (range: 4-20), M (SD)	15.08 (2.56)	15.03 (2.39)
Mindfulness skills		
FFMQ (range: 39-195), M (SD)	117.94 (17.22)	119.26 (18.69)
Depressive symptoms		
BDI-II (range: 0-63), M (SD)	14.45 (10.07)	13.77 (10.21)

m-ADM = maintenance antidepressant medication. MBCT = mindfulness-based cognitive therapy (with support to taper or discontinue antidepressant medication). GCSE = general certificate of secondary education. FFMQ = Five Facets of Mindfulness Questionnaire (higher scores mean higher levels of mindfulness skills). Quality-of-life was measured using the WHO Quality-of-Life instrument (WHO-QOL-BREF, with higher scores meaning better quality-of-life). BDI-II = Beck Depression Inventory-II (higher scores mean higher levels of depressive symptoms). In m-ADM, 1 participant did not provide data on marital status, 4 participants did not provide data on education, 2 participants did not provide data on employment status, 7 participants did not provide data on any quality-of-life measure, 10 participants did not provide data on FFMQ, and 6 participants did not provide data on BDI-II. In MBCT, 1 participant did not provide data on marital status, 5 participants did not provide data on education, 2 participants did not provide data on employment status, 3 participants did not provide data on any quality-of-life measure, 5 participants did not provide data on FFMQ, and 2 participants did not provide data on BDI-II.

Table 2: Moderated-mediation of mindfulness skills

Direct effects	**coefficient**	**SE**	**Boot 95% CI**	**p**
Allocation group * LP -> ΔFFMQ	8.84	4.38	0.26, 17.32	0.043
Allocation group -> ΔFFMQ (LP1)	5.03	2.52	0.26, 10.09	0.045
Allocation group -> ΔFFMQ (LP2)	13.87	3.20	7.80, 20.20	<0.001
ΔFFMQ * LP -> β_1(BDI-II)	-0.001	0.02	-0.04, 0.04	0.949
ΔFFMQ -> β_1(BDI-II)	-0.03	0.01	-0.25, -0.02	<0.001
Allocation group * LP -> β_1(BDI-II)	-0.02	0.53	-1.08, 1.02	0.965
Allocation group -> β_1(BDI-II)	0.37	0.21	-0.04, 0.77	0.080
Total	-0.20	0.24	-0.68, 0.25	0.398
Indirect effects	**coefficient**	**SE**	**Boot LLCI**	**Boot ULCI**
LP1	-0.15	0.08	-0.35	-0.02
LP2	-0.42	0.15	-0.78	-0.18
Difference (index of moderated-mediation)	-0.27	1.92	-0.66	-0.03

Allocation group = m-ADM (maintenance antidepressant medication) vs. MBCT (mindfulness-based cognitive therapy) with support to taper or discontinue ADM. SE = standard error. Boot LLCI = Bootstrap Lower Limit of (95%) Confidence Interval. Boot 95% CI = Bootstrap 95% Confidence Interval. Boot ULCI = Bootstrap Upper Limit of (95%) Confidence Interval. LP = latent profile. ΔFFMQ = pre-post (T0-T1) change in mindfulness skills. β_1 (BDI-II) = linear slope of depressive symptoms over time (T0-T5). Difference (index of moderated-mediation) = indirect effects difference by LP. Coefficients are not standardized, and therefore maintain the original units of the variables involved in the regression. R^2 (M) = 0.02; R^2 (Y) = 0.10. LP2: R^2 (M) = 0.15; R^2 (Y) = 0.10.

Figure 1: Latent Profiles and Individual Trajectories

A: Latent Profiles Graphical Representation. Profile 1: latent profile 1 (i.e., less severe history of depression). Profile 2: latent profile 2 (i.e., more severe history of depression). Total sample N = 424. Due to the different scaling of the continuous and dichotomous items included in the latent profile analysis, all mean scores and proportions for each predictor were standardized and z-scores were used to present the distribution between mean scores and proportions for each profile. We used a range of potential predictor variables to define latent profiles demarcated by a different depression severity. These variables fall into three categories: (1) *Symptoms intensity and Clinical History* (Clinician-rated residual symptoms of depression (HAMD), Childhood abuse (MOPS), Age of first depression onset, Number of previous episodes of depression, Severity of the last episode (SCID), Chronicity of the last episode, Previous suicide attempt, Number of comorbid DSM-IV axis I psychiatric diagnoses (SCID)); (2) *Cognitive and Emotional Factors* (Rumination (negative and un-resolution rumination from CERTS), Self-blame and lack of acceptance (CERQ), Ability to recognize early warning signs of depression (bespoke single item), Acting with awareness (FFMQ), Self-efficacy (GSE), Positive affect (contentment and joy from DPES); (3) *Relational and Social Variables* (Relationship satisfaction (bespoke 7-item questionnaire), Stigmatization (bespoke 7-item questionnaire). These variables were measured at baseline (T0) and were selected based on theoretical and empirical research.[20]

B: Individual Trajectories and Estimated Means of Depressive Symptoms Over Time. The colored lines represent the observed individual trajectories, with this representation including a subset of n = 250 randomly selected participants. The thick black line represents the mean estimated by the quadratic latent curve growth model for the total group (N = 424). BDI-II = Beck Depression Inventory-II (range: 0-63). Participants were assessed on the BDI-II at baseline (0 months), and then post-treatment (3 months, i.e., one month after the end of the mindfulness-based cognitive therapy (with support to taper or discontinue antidepressant medication) training, or the equivalent time in the maintenance antidepressant medication arm. Follow-up measures include 9, 12, 18, and 24 months after randomization.

Figure 2: LPs moderating the mediation of change in mindfulness skills on depressive symptoms.

MBCT = mindfulness-based cognitive therapy with support to taper or discontinue antidepressant medication. m-ADM = maintenance antidepressant medication. LPs = latent profiles. LP1 = latent profile 1 (less severe history of depression). LP2 = latent profile 2 (more severe history of depression). ΔFFMQ = baseline to one month after the end of the MBCT training (T0-T1) change in mindfulness skills. β_1 (BDI-II) = linear slope of depressive symptoms (i.e., rate of change in depressive symptoms) over time from baseline to two-years follow-up (T0-T5). a_1 = allocation group -> ΔFFMQ path for LP1. a_2 = allocation group -> ΔFFMQ path for LP2. b = ΔFFMQ -> β_1 (BDI-II) path (this is shared across LPs, as there were no moderating effects in this path). IE_1 = indirect effect for LP1. IE_2 = indirect effect for LP2. 95% CI = bootstraped 95% Confidence Interval for the indirect effect. c' = direct effect of allocation group on β_1 (BDI-II) after adjustment for the mediating effects (this is shared across LPs, as there were not moderating effects in this path). c = total effects. Coefficients are not standardized, and therefore, are shown in the original units of the variables used in the moderated-mediation model. The color transition of IEs represents a potential large shift from a mild-to-moderate baseline level of depressive symptoms (BDI-II mean = 19.37) to a minimal level of depressive symptoms at the 24-month follow-up (BDI-II mean = 9.29) for LP2. For LP1, it indicates a small-to-moderate effect in the minimal range of depressive symptoms (BDI-II mean = 10.71) between baseline and 24-months follow-up (BDI-II mean = 7.11).[30.] * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Image created with support of Delphine Perrot.