

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

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Scientific summary

Prevention of depressive relapse/recurrence (the PREVENT study)

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Scientific summary

Background

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

Currently, most depression is treated in primary care and maintenance antidepressant medication (m-ADM) is the mainstay approach to preventing relapse/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 on m-ADM for at least 2 years. However, adherence rates tend to be poor, m-ADM is protective only for as long as it is taken and is contraindicated for some groups, patients at higher risk receive less protection from m-ADM and many patients express a preference for psychosocial interventions that provide long-term protection against relapse/recurrence.

Mindfulness-based cognitive therapy (MBCT) was developed as a psychosocial intervention to teach people with recurrent depression the skills to stay well in the long term. A systematic review and meta-analysis of six randomised controlled trials ($n = 593$) suggests that MBCT significantly reduces the rates of depressive relapse/recurrence compared with usual care or placebo, corresponding to a relative risk reduction of 34% [risk ratio 0.66, 95% confidence interval (CI) 0.53 to 0.82]. A key remaining uncertainty is whether MBCT provides an alternative for people wishing to discontinue m-ADM. There is accumulating evidence that MBCT may confer most benefit to patients at greatest risk.

Objectives

The overarching policy aim and research question of the PREVENT trial was to establish whether MBCT with support to taper and/or discontinue antidepressant medication (MBCT-TS) is superior to and more cost-effective than an approach of m-ADM in a primary care setting for patients with a history of recurrent depression followed up over a 2-year period in terms of a primary outcome of preventing depressive relapse/recurrence. Secondary outcomes were depression-free days, residual depressive symptoms, psychiatric and medical comorbidity, quality of life and cost-effectiveness over 24 months. The trial also sought to address whether an increase in mindfulness skills is the key mechanism of change of MBCT and explore barriers to participation in MBCT-TS within the PREVENT study.

Methods

The PREVENT study was a two-arm, multicentre, single-blind superiority trial randomly allocating patients in a 1 : 1 ratio to receive either MBCT-TS or m-ADM. The m-ADM was constant over the 2 years of the study and the psychosocial intervention was a front-loaded, 8-week relapse/recurrence prevention programme. Patients in the MBCT-TS arm received support to taper their antidepressant medication (ADM). The trial included a parallel economic evaluation to examine the cost-effectiveness of MBCT-TS compared with m-ADM. It included a mixed-methods process evaluation to examine the acceptability and mechanism of action of MBCT.

Participants were considered for inclusion if they:

- had had three or more previous major depressive episodes in which depression was the primary disorder and which were not secondary to substance abuse, bereavement or a general medical condition
- were aged ≥ 18 years
- were on a therapeutic dose of ADM in line with *British National Formulary* (BNF) and NICE guidance
- were open either to continue taking antidepressants for 2 years or to take part in a MBCT class and stop their ADM.

Participants were considered unsuitable for inclusion if they:

- were currently depressed
- had a comorbid diagnosis of current substance abuse
- had organic brain damage
- had current/past psychosis, including bipolar disorder
- displayed persistent antisocial behaviour
- engaged in persistent self-injury that required clinical management/therapy
- were undergoing formal concurrent psychotherapy.

Searches were carried out of computerised general practice databases to identify patients who were currently being prescribed a therapeutic dose of ADM in line with BNF and NICE guidance. Subsequent to each participant giving written informed consent, participants were randomly allocated to receive either m-ADM or an 8-week MBCT class that included support to taper/discontinue their m-ADM (MBCT-TS) using computer-generated random permuted blocks and stratified by recruitment locality (four sites) and participants' symptomatic status (asymptomatic vs. partially symptomatic).

- *MBCT-TS*. MBCT is a manualised, group-based skills training programme designed to enable patients to learn skills that prevent the recurrence of depression.
- *m-ADM*. Patients in the m-ADM arm received support from their general practitioner (GP) to maintain a therapeutic level of ADM in line with BNF and NICE guidelines.

Data collection

Participants were assessed at six time points: baseline (prior to randomisation), 1 month after the end of the 8-week MBCT-TS programme, which varied between 12 and 24 weeks post randomisation (or the equivalent time in the m-ADM arm) and 9, 12, 18 and 24 months post randomisation.

The primary outcome measure was time to relapse/recurrence of depression. Relapse/recurrence was defined as an episode meeting *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) criteria for a major depressive episode. At each follow-up we recorded the secondary outcomes: number of depression-free days, residual depressive symptoms, quality of life, health-related quality of life and psychiatric and medical comorbidities.

The economic perspective included all hospital and community health and social services plus productivity losses, known to be a substantial cost in depression.

Mechanisms were examined through an embedded process study in which the hypothesised mechanism (change in mindfulness) was assessed before and after MBCT and outcome was assessed at 24 months' follow-up. Acceptability was examined through an embedded qualitative study that enabled participants to provide their views and experiences of the acceptability of MBCT through interviews and feedback booklets.

Statistical analysis

Statistical analyses were conducted in accord with International Conference on Harmonisation (ICH-9) statistical guidelines for clinical trials and updated Consolidated Standards of Reporting Trials (CONSORT) guidelines for trials. All statistical analyses were undertaken in Stata version 13 (StataCorp LP, College Station, TX, USA) following a predefined analysis plan agreed with the Trial Steering Committee (TSC).

The study was powered to detect a hazard ratio (HR) of 0.63 between the two treatments at 24 months for the primary outcome, with 90% power and a two-sided 5% alpha level, assuming a small clustering effect [intra-class correlation coefficient (ICC) = 0.01] and allowing for 20% loss to follow-up, producing a target sample size of 420 (210 per arm).

The primary analysis was a between-group comparison of time to relapse/recurrence at 24 months using a Cox regression proportional hazards model adjusted for stratification variables.

Secondary outcomes were compared across all time points 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. Between-group inference for secondary outcome analyses was based on the complete case and imputed data sets are reported.

Interaction terms were used to undertake predefined exploratory subgroup analyses on the primary outcome, across the stratification variables (recruitment centre and baseline depression severity) and reported levels of childhood abuse. Participants with a more abusive childhood reported experiencing childhood physical or sexual abuse and/or scored above the median score for the Measure of Parenting Scale (MOPS) abuse subscale. Participants completed the MOPS at baseline as part of an embedded process–outcome study. 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 to me', 'parent made me feel unsafe'. Participants were categorised as either in the lower abusive childhood group (i.e. scored below the median score for the MOPS abuse subscale and did not report childhood physical or sexual abuse) or in the higher abusive childhood group (i.e. scored above the median score for the MOPS abuse subscale or did report childhood physical or sexual abuse).

Differences in mean costs were analysed using standard parametric *t*-tests with the validity of results confirmed using bias-corrected, non-parametric bootstrapping (repeat resampling). The primary economic analysis compared MBCT-TS and m-ADM from the health and social care perspective preferred by NICE; secondary analyses included productivity losses.

Results

Between 23 March 2010 and 21 October 2011 we recruited 424 patients, of whom 212 were allocated to receive MBCT-TS and 212 were allocated to receive m-ADM. Primary outcome data were collected for 90% (383/424) of the participants. The remaining participants' data were censored at their last follow-up. We retained 86% (366/424) of participants over the 24-month follow-up period, with 5% (20/424) lost to contact and 8% (34/424) withdrawing consent for further follow-up; in addition, 1% (4/424) died during the trial. The pattern of primary outcome missing data was identical across trial arms (14% in each arm).

With respect to the primary outcome, primary intention-to-treat analysis showed no evidence of a reduction in the hazard of relapse/recurrence with MBCT-TS compared with m-ADM (HR 0.89, 95% CI 0.67 to 1.18; $p = 0.43$), with 44% (94/212) of the MBCT-TS patients relapsing compared with 47% (100/212) of the m-ADM patients [log-rank $\chi^2(1) = 0.67$; $p = 0.41$].

There was no difference in treatment effect on the primary outcome across either stratification variable subgroup of severity of depression at baseline or recruitment centre. However, there was evidence of a significant interaction between severity of reported childhood abuse and treatment group (HR 0.53, 95% CI 0.29 to 0.95; $p = 0.03$). Specifically, compared with m-ADM, MBCT-TS reduced the risk of relapse/recurrence for participants with a higher severity of reported childhood abuse (47% vs. 59%) whereas there was a slightly higher risk of relapse/recurrence with MBCT-TS compared with m-ADM in the lower severity of childhood abuse subgroup (42% vs. 35%). Given their non-randomised nature, these secondary analyses are prone to selection bias and confounding.

With respect to the secondary outcomes, there was no evidence of MBCT-TS's superiority over m-ADM.

Over 24 months' follow-up, group attendance in the MBCT-TS arm was estimated to cost £112 per participant and the average cost of antidepressants was £40.10 in the MBCT-TS group and £69.79 in the m-ADM group. Use of other health and social care services differed little between groups and hence there was no significant difference in the total health and social care cost per participant between the MBCT-TS group (£2484.52) and the m-ADM group (£2360.41; mean difference £124, 95% CI £-749.98 to £972.57; $p = 0.80$). The results including patient costs (productivity losses and out-of-pocket expenditure) were also non-significant (mean difference £449, 95% CI £-842.18 to £1286.26; $p = 0.68$). There were no significant differences in quality-adjusted life-years (QALYs) over follow-up and the cost-utility and cost-effectiveness analysis did not support the hypothesis that MBCT-TS is cost-effective compared with m-ADM.

To examine MBCT's mechanism of action, meditational analyses were conducted, which showed that, although changes in mindfulness were specific to MBCT (and not m-ADM), they did not predict outcome in terms of relapse/recurrence at 24 months.

In terms of acceptability, the qualitative analyses suggest that many people have views about (dis)continuing their ADM, which can serve as a facilitator or a barrier to taking part in a trial that requires either continuation for 2 years or discontinuation. The most commonly cited reasons for non-participation in the PREVENT trial were related to the treatment interventions provided. Together these accounted for 40% of all reasons given. Within this, the largest category related to use of ADM (19% of all responses). Most commonly, people reported that they did not want to stop taking ADM (49% of ADM reasons). Other reasons were that people were no longer taking ADM (24%), were currently coming off ADM (9%) and were happy with their current ADM use (11%).

Discussion

There was no evidence for the superiority of MBCT-TS over m-ADM for patients with recurrent depression in terms of the primary outcome of time to depressive relapse/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 m-ADM in terms of either relapse/recurrence or QALYs.

Relapse/recurrence rates in people with three or more previous episodes can be as high as 80% over 2 years. Moreover, meta-analyses consistently suggest that m-ADM reduces the odds of relapse/recurrence by two-thirds compared with placebo, a halving of the absolute risk. Therefore, it is likely that MBCT would provide benefits over and above either no treatment or pill placebo.

Across both treatment arms, outcomes were comparatively good over the 2 years of follow-up in terms of relapse/recurrence (MBCT-TS 44%, m-ADM 47%), residual symptoms and quality of life.

MBCT is hypothesised to work through teaching mindfulness, a skill that enables people to recognise and respond resiliently in the face of early warning signs of depressive relapse/recurrence. Using a meditational design and a self-report measure of mindfulness we found that, although changes in mindfulness are specific to MBCT, they do not predict relapse/recurrence at 24 months. However, we used a self-report measure and it is possible that alternative approaches to establishing mechanisms of action are needed.

The main barrier to participation in the PREVENT trial at the point of recruitment appears to be expectations surrounding m-ADM use. This applied to both arms of the trial. For most people, their concerns centre on being randomised to MBCT-TS, as they do not consider themselves to be in a position to taper their m-ADM. For a smaller group of people, reluctance to participate relates to being randomised to the m-ADM arm, as this carries an expectation of continuing on m-ADM for 2 years, a prospect that may not be acceptable.

Consistent with an emergent pattern of findings, MBCT may confer most benefit to patients at greatest risk of relapse/recurrence. A reported history of abuse and adversity is associated with worse outcomes among those who suffer from depression. Perhaps MBCT confers resilience in this group at highest risk because patients learn skills that address some of the underlying mechanisms of relapse/recurrence, a question that 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 action of MBCT for those at differing levels of risk of relapse/recurrence, with robust measures of risk.

Implications for practice and directions for future research

1. MBCT-TS is not superior to m-ADM over 2 years of follow-up for patients with recurrent depression.
2. Benchmarked against epidemiological data, both treatments were associated with enduring positive outcomes in terms of relapse/recurrence, residual depressive symptoms and quality of life.
3. This study provides important evidence that MBCT-TS may confer ongoing protection for patients who would like an alternative to m-ADM.
4. For patients at low risk, m-ADM, which requires less patient commitment and is less costly, may be indicated, whereas, for patients at highest risk, more intensive treatments such as MBCT may be indicated. However, studies have tended to operationalise risk in somewhat different ways (e.g. early adversity, unstable remission, a higher number of 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.

Trial registration

This trial is registered as ISRCTN26666654.

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