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Mindfulness-based cognitive therapy for prevention and time to depressive relapse: systematic review and network meta-analysis

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Short title: Network meta-analysis on the effectiveness of MBCT

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Abstract

Objective: To perform a network meta-analysis (NMA) to compare the long-term effectiveness of mindfulness-based cognitive therapy (MBCT) with available strategies for prevention and time to depressive relapse.

Methods: Seven electronic databases were searched up to June 2019. Studies evaluated MBCT for the management of depression related outcomes and follow-up assessments occurred at 12-months or longer.

Results: Twenty-three publications were included, 17 of which were randomised controlled trials (RCTs). Data from 14 RCTs including 2077 participants contributed to meta-analysis (MA) and NMA to assess relapse of depression and 13 RCTs with 2017 participants contributed to MA and NMA for time to relapse of depression. NMAs showed statistically significant advantages for MBCT over treatment as usual (TAU) for relapse of depression (RR=0.73, 95%CI 0.54 to 0.98) and for MBCT over TAU and placebo for time to relapse of depression (MCBT vs TAU: HR=0.57, 95%CI 0.37 to 0.88; MCBT vs placebo: HR=0.23, 95%CI 0.08 to 0.67). Subgroup meta-analysis of relapse of depression by previous number of depressive episodes showed similar results between subgroups. Subgroup meta-analysis by the use or not of booster sessions suggests these may lead to improved effectiveness.

Conclusions: MBCT is more effective than TAU in the long-term in preventing relapse of depression and has statistically significant advantages over TAU and placebo for time to relapse of depression. No statistically significant differences were observed between MBCT and active treatment strategies for rate of relapse or time to relapse of depression.

Summations

Our results show that mindfulness-based cognitive therapy has advantages when compared to treatment as usual and placebo.

Subgroup meta-analysis based on previous number of depressive episodes showed very similar results for relapse of depression between the subgroups.

Booster sessions may be advantageous, but the results are uncertain due to heterogeneity and lack of published information of timings, frequency and attendance at booster sessions.

Limitations

The data available was limited for some of the comparisons in the meta-analysis and network meta-analysis and there was some heterogeneity in some of the analyses.

Introduction

Mindfulness-based cognitive therapy (MBCT) is a pragmatic (but theoretically and experimentally derived) manualised treatment approach developed to address a common but specific clinical problem: frequent recurrence of depressive illness (1). A multi-centre randomised controlled trial (2) followed by a replication trial (3) provided confirmation of the efficacy of MBCT in significantly reducing relapse rates in recurrent depression when compared to treatment as usual. The evidence led to the inclusion of MBCT in the UK National Institute for Health and Care Excellence (NICE) guideline for depression and the recommendation of "mindfulness-based cognitive therapy for people who are currently well but have experienced three or more previous episodes of depression" p.34 (4). Subsequent widespread clinical employment of MBCT encouraged further research fuelling systematic reviews and meta-analyses (5-7) that drew supportive general conclusions regarding efficacy in preventing depressive relapse when compared to usual care, albeit with degrees of equivocation and a consensus that there remained a need for further research to resolve uncertainties. However, conventional pairwise meta-analyses can only compare two interventions at a time, cannot efficiently include data from studies with more than two treatment arms and can consider only direct evidence. Network meta-analysis (NMA) can combine direct and indirect evidence, incorporating all relevant data from studies with more than two treatment arms and therefore allow assessment of the relative effectiveness of MBCT when compared to alternative treatments.

Aim of the study

An NMA evaluating the effectiveness of MBCT has not been performed. The aim of this study was to compare the long-term effectiveness of MBCT with available strategies for prevention and time to depressive relapse.

Material and Methods

The systematic review methods followed the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care (8). This article is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9). The protocol for the review was registered with PROSPERO as CRD42018099375.

Search strategy

Potentially eligible studies were identified by searching electronic databases and by reference list trawling. We searched electronic databases CINAHL, Cochrane Central Register of

Controlled Trials (CENTRAL) & Cochrane Database of Systematic Reviews, Embase, MEDLINE, PsycINFO, and Web of Science initially from inception up to 26 July 2018 and updated the searches up to 28 June 2019. The search strategy used for the MEDLINE database is presented in Supplementary material 1 of this manuscript. The MEDLINE search strategy was adapted to enable similar searches of the other relevant electronic databases. Literature search results were managed using EndNote X8.2 software.

Study selection

Titles and abstracts were screened independently by two reviewers. Those identified as meeting the eligibility criteria (Supplementary material 2) were retained, and all other papers were excluded. If sufficient detail to enable such a decision was not clearly available in the title or abstract, then a full text version of the paper was acquired and reviewed before a decision was made. Full text versions of all retained papers were obtained and screened independently by two reviewers. Any disagreements regarding study eligibility were resolved by discussion and when necessary by consultation with a third reviewer. As MBCT was primarily designed as an intervention for depressive illness, this review only considers studies which have depression related outcomes. There is no accepted definition of what period would constitute “long-term” so for the purpose of this review it was considered to be 1 year or longer.

Data extraction

A standardised form was used for data extraction. The following data fields were included: authors, year, study design, control, setting, population (incl. demographics), baseline health data, follow-up and drop-out rates, outcome measures used and summary statistics of results. Table 1 summarises the characteristics of studies included and key data extracted. Data was extracted by the lead reviewer and then examined for accuracy by an independent reviewer. Any disagreements regarding data extraction were resolved by discussion and when necessary by consultation with a third reviewer.

Risk of bias assessment

Risk of bias of RCTs was assessed according to the Cochrane risk of bias tool.(10) The Downs and Black checklist (11) was used for the assessment of non-randomised trials (Supplementary material 3). Risk of bias assessment was performed by one reviewer and checked for agreement by a second independent reviewer. Any disagreements regarding risk of bias assessment were resolved by discussion and when necessary by consultation with a third reviewer.

Data analysis

Meta-analysis (MA) and NMA for the outcomes 'Relapse of Depression' (expressed as a pooled risk ratio (RR) and 95% confidence interval (CI)) and 'Time to Relapse of Depression' (expressed as a pooled hazard ratio (HR) and 95% CI) were conducted.

Two of the included RCTs (12, 13) had three treatment arms (MBCT and two control arms) which causes complexity for meta-analysis.(14) Two analysis approaches were taken to account for this complexity:

- Control groups were broadly categorised into three subgroups (treatment as usual (TAU), placebo, maintenance antidepressant medication (mADM) and other active controls). MAs of MBCT versus control were conducted separately by control group. This approach allows both of the control groups from the three-armed studies(12, 13) to be included within meta-analysis. An additional meta-analysis by control group subgroups was conducted splitting the TAU control subgroup by whether study eligibility required remission and being off antidepressant medication at baseline or whether the use of antidepressant or mood stabilisers was permitted at baseline.
- A network of MBCT and all control treatments was constructed (Figure 1) and NMA was also performed. This approach is the most appropriate method to take account of the different control treatments while also taking account of the trials with three treatment arms and the correlations between the pairwise treatment comparisons in these trials.

[Insert Figure 1 here]

Subgroup meta-analysis was performed for the outcome 'Relapse of Depression' according to the previous number of depressive episodes required for inclusion within the RCT (at least 3 previous episodes for inclusion vs less than 3 episodes required for inclusion) and by whether booster sessions were used during follow-up. To allow the two RCTs (12, 13) with three treatment arms to be included within this subgroup meta-analysis, the results of control arms within the two RCTs were pooled by adding together the number of participants and number of events (i.e. relapses of depression) in the two control arms. These two RCTs could not be included within subgroup meta-analysis for 'Time to Relapse of Depression' as it was not possible to combine the published HRs for the control arms within the two RCTs; access to individual participant data would be required to accurately pool time-to-event data for the two control arms.

MAs were performed using the inverse-variance method via the *metan* command (15) in Stata version 14.1. NMA was performed under a multivariate meta-analysis framework (16) with an

exchangeable variance-covariance structure via the *network* command in Stata version 14.1.(17) Both MA and NMA were conducted with random-effects due to anticipated heterogeneity between trials.

The underlying assumption of NMA is that any indirect evidence is consistent with the direct evidence where a comparison exists (known as the consistency assumption).(18) To investigate inconsistency within the NMA, direct treatment effect estimates from individual trials or MA were compared to treatment estimates calculated via NMA and a 'design-by-treatment' inconsistency model, a method which evaluates both loop and design inconsistencies, particularly within multi-arm trials (19) was fitted via the *network* command in Stata version 14.1.(17)

Due to variability of outcome definitions, follow-up times and variability of reported results for other outcomes within the RCTs, it was not possible to combine results for other outcomes in MA or NMA. Results for other outcomes reported in the RCTs and results of the non-randomised studies are summarised narratively.

Results

Searches identified a total of 2092 publications. Removal of duplicates and application of eligibility criteria resulted in 23 studies included in the systematic review (Figure 2). The publications by Huijbers et al (20, 21) and Spinhoven et al (22) were part of the Dutch multicentre MOMENT study involving a total of 317 participants; publications by Michalak et al (23, 24) used data from the same German group of 29 participants; and publications by Shallcross et al (25, 26) were sequential long-term follow-up studies of the same group of 92 participants.

[Insert Figure 2 here]

Study characteristics

Seventeen of the 23 studies were RCTs (Table 1). Four of the RCTs used TAU,(2, 3, 27, 28) and two used waiting list as a control.(29, 30) TAU was defined as participants being told to seek help from their family doctor of other sources as they normally would, should they encounter symptomatic deterioration or other difficulties over the course of the study (2, 3, 27) or weekly handouts.(28) In a study with two control groups, TAU was not specified but the therapist informed participants they should seek treatment as needed from their usual health care provider throughout the trial duration.(13) Two of the RCTs employed cognitive behaviour therapy (CBT)(31) or cognitive therapy (CT)(32) as a comparator intervention, two RCTs used

an active control condition (ACC)(25, 26) and one used depression relapse active monitoring (DRAM).(33) The comparator group in three RCTs was mAMD.(20, 34, 35) The comparator intervention in one RCT was MBCT in addition to mADM.(21) Two RCTs included two control groups; one compared MBCT to mAMD and to placebo pills with clinical management (12), and one RCT compared MBCT to cognitive psychological education (CPE) and to TAU (13). Eight of the 17 RCTs reported that booster sessions were provided. Three RCTs indicated that booster sessions were provided at regular three-month intervals up to 12 months follow-up.(27, 34, 35) The timings and frequency of booster sessions varied in the remaining studies.(2, 3, 12, 13, 33) Two studies stated that booster sessions were optional.(12, 33) The proportion of participants that attended booster sessions was not reported in any of the included studies. Only one of the RCTs clearly reports in the discussion that booster sessions were not provided.(26)

Eight of the 23 studies employed a follow-up period of one year. The longest follow-up in the RCTs included was 26 months (26, 33) and for the non-RCTs the longest mean follow-up was 49 months (36).

[Insert Table 1 here]

Participant demographics

The studies recruited participants who had a recurrent depressive disorder and were either in remission or had residual depressive symptoms. For the majority of studies (12, 13, 20-27, 29, 30, 32), criteria for depression was based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)(37) and assessed using the Structured Clinical Interview for DSM-IV (SCID) Axis 1 Disorders (38). Some studies mentioned using DSM-IV criteria (3, 34, 35, 39, 40), DSM-IV criteria on the computerised version of the Composite International Diagnostic Interview (CIDI-AUTO) (31), CIDI 2.1 (33) or DSM-III-R (2) to diagnose depression but did not specify how it was assessed. The criteria were unclear in one study (36). The population in one study (28) comprised people with bipolar affective disorder based on DSM-IV criteria (unclear how assessed), however, the primary outcome of this study was time to recurrence of a major episode including a depressive episode and also assessed the number of depressive relapses. In all but one study the majority of participants were female (range 58% to 80%). The mean age of participants in each study ranged from 35 to 54 years.

Quality assessment

Details of the risk of bias assessment for included RCTs and quality assessment of non-RCTs are presented in Supplementary material 4. All studies were judged to have low or unclear risk

of bias for the domains random sequence generation, allocation concealment, selective reporting or other bias. Participant blinding is not possible with a group-delivered psychotherapy such as MBCT, therefore all studies were judged to have a high risk of bias for the blinding of participants and/ or personnel domain. Three studies were judged to have a high risk of bias for the blinding of outcome assessors domain as the research assistants conducting the assessments were not blind to the intervention delivered.(20, 21, 29) One study was judged to have a high risk of bias for the incomplete outcome data domain as only data from participants that completed the trial were included in the analysis.(31)

Relapse of depression

Rate of relapse or time to relapse during the follow-up period was the primary outcome measure in 15 RCTs and change in depressive symptoms the primary outcome measure in 2 RCTs. Studies in which the primary outcome measure was relapse, this was assessed based on DSM-IV criteria for major depressive episode using the depression module of the SCID (38) in 12 of the publications (12, 13, 20, 21, 25-28, 30, 32, 34, 35) or Structured Clinical Interview for DSM–III–R (41) in two publications (2, 3). One study (33) assessed relapse based on CIDI 2.1 12-month version depression module (42).

Meta-analysis and network meta-analysis results

Results of 14 RCTs (2, 3, 12, 13, 20, 21, 26-28, 30, 32-35) including 2077 participants could be combined in MA and NMA for 'relapse of depression' and results of 13 RCTs (2, 3, 12, 13, 20, 21, 26, 28, 30, 32-35) including 2017 participants could be combined in MA and NMA for 'time to relapse of depression'. The data extracted which has contributed to the analysis is presented in Supplementary material 5. Six RCTs compared MBCT to TAU, four RCTs compared MBCT to mADM and one RCT compared MBCT to each of placebo, ACC, CPE, CT, DRAM or MBCT added to mADM.

Results of MA and NMA are presented in Table 2 for MBCT compared to all control treatments. MA results by control group are shown in Figure 3A and 3B and NMA results are shown in Figure 3C and Figure 3D.

[Insert Table 2 here]

[Insert Figure 3 here]

Both MA and NMA showed a statistically significant advantage for MBCT over TAU for relapse of depression (meta-analysis RR from MA 0.72, 95% CI (0.55 to 0.93); network meta-analysis RR 0.73, 95% CI (0.54 to 0.98), Table 2).

Both MA and NMA also showed a statistically significant advantage for MBCT over both TAU and placebo for time to relapse of depression (MCBT vs TAU: HR from MA 0.52, 95% CI (0.30 to 0.90); HR from NMA 0.57, 95% CI (0.37 to 0.88); MCBT vs placebo: HR from MA 0.26, 95% CI (0.09 to 0.79); HR from NMA 0.23, 95% CI (0.08 to 0.67, Table 2).

MA with TAU control subgroups split according to study eligibility criteria showed a statistically significant advantage for MBCT over TAU for relapse of depression (RR 0.73, 95% CI (0.59 to 0.90) but not for time to relapse of depression, where remission was required at baseline. There were no differences between MBCT and TAU for relapse or time to relapse of depression where antidepressant medication or mood stabilisers were permitted at baseline, however the results of the two studies of MBCT compared to TAU permitting antidepressant medication or mood stabilisers showed substantially different results (Supplementary material 6).

No differences between MBCT and mADM, ACC, CPE, CT or DRAM were shown in MA or NMA for either outcome (Table 2). There were also no differences for either outcome in MA for MBCT vs other active controls considered together (Figure 3A and Figure 3B).

A statistically significant advantage for MCBT added to mADM was shown over MCBT alone in MA for both outcomes (relapse of depression RR 1.39 95% CI (1.05 to 1.83) and time to relapse of depression HR 1.59 95% CI (1.09 to 2.31), Table 2) but this advantage was not shown within NMA (Table 2, Figure 3C and Figure 3D).

Overall, results of MA and NMA (except for the comparison of MCBT added to mADM was shown over MCBT alone) were very similar and reached the same conclusions (Table 2). Heterogeneity was observed in MA, with I^2 values of around 30% to 60% observed within the MAs of MBCT compared to TAU or placebo and MBCT compared to other active controls (Figure 3A and Figure 3B). Some HRs extracted from published RCT reports for the outcome 'Time to Relapse of Depression' reflected only the treatment comparison of MBCT versus the control while other HRs were also adjusted for other factors such as number of depressive episodes and severity of depression at baseline. This may have been a source of heterogeneity. CIs of results from NMA were generally wider than CIs of results from MA which likely reflects the heterogeneity present within the network as well as the sparse data, often

from only a single study within some links of the network, resulting in wider CIs from conducting a random-effects NMA. Despite the different conclusions which could be drawn for the comparison of MCBT added to mADM was shown over MCBT alone from direct evidence (i.e. the MA) and from NMA, there was no evidence of inconsistency present according to the 'design-by-treatment' inconsistency model (p-value = 0.768 for NMA of relapse of depression and p-value=0.546 for NMA of time to relapse of depression).

Subgroup meta-analysis of relapse of depression and time to relapse of depression by the previous number of depressive episodes (i.e. less than three previous episodes or at least three previous episodes) required for inclusion within the RCT showed very similar results and no difference in conclusions between the subgroups (Supplementary material 7).

Subgroup meta-analysis showed a statistically significant advantage for MBCT over control where booster sessions were used during follow-up (RR for relapse of depression 0.80, 95% CI 0.71 to 0.89 and HR for time to relapse of depression 0.65, 95% CI 0.47 to 0.91). No difference was shown between MBCT and control where booster sessions were not used during follow-up. However, substantial heterogeneity between the studies without booster sessions was present and confidence intervals were wide (Supplementary material 8), therefore it is uncertain whether the use of booster sessions influences the treatment effect of MBCT over control. Further uncertainty stems from the limited detail provided in the included studies on the timing of booster sessions, frequency and attendance (i.e. the proportion of participants who actually received the booster sessions).

Two non-RCTs that included depressive relapse as an outcome measure observed that post-MBCT mindfulness scores (23) and levels of rumination (24) were predictors of depressive relapse.

Other outcome measures

One RCT (involving 130 participants) that assessed depressive symptoms as a primary outcome (rather than depressive relapse) showed a significant benefit of MBCT compared to waiting list (29). One other RCT (involving 69 participants) assessing depressive symptoms as a primary outcome showed that both MBCT and CBT significantly improved symptoms, but that there was no significant difference between the two interventions (31). Statistically significant improvements in depressive symptoms and quality of life (QoL) following MBCT were observed in RCTs comparing MBCT with TAU (30) and mADM.(34) No statistically significant differences were observed for depressive symptoms or QoL in other RCTs with an active control (i.e. mADM and ACC).(20, 21, 26, 35) One RCT observed that patients receiving

MBCT had statistically significantly fewer days with a major depressive episode than those in the active monitoring control group.(33)

Two non-RCTs observed statistically significant improvements in depressive symptoms between baseline post-treatment (36) and up to follow-ups of 13 to 34 months.(39) One study observed statistically significant improvements before and after intervention for ruminative thinking, mindfulness and state and trait anxiety and no differences between post-treatment and average follow-up of 49 months.(36) Statistically significant improvements in ruminative thinking,(40) mindfulness scores and personality facets were also observed.(22)

Discussion

MA and NMA shows that MBCT is more effective than TAU in preventing relapse of depression and has statistically significant advantage over TAU and placebo for time to relapse of depression. Booster-sessions at regular intervals may result in higher effectiveness of MBCT to prevent relapse of depression and delay time to relapse in the long-term. Current recommendations are for four follow-up sessions in the 12 months after the end of treatment (4). The use of booster sessions, timing, frequency and attendance should be clearly reported.

The first two major studies of MBCT found positive benefits for reducing risk of relapse, but suggested this was limited to those patients who had suffered three or more previous episodes (2, 3). Indeed, the results of those studies also suggested a tendency to increased risk of relapse following MBCT in participants who had a history of fewer than 3 previous episodes. However, our subgroup MA based on previous number of depressive episodes found similar results between those with at least 3 previous episodes and those with less than 3 previous episodes. It is a clear point of NICE guidance that MBCT is only recommended for patients who have experienced 3 or more previous episodes of depression. Implications of the findings of our review and further analysis accounting for previous episodes of depression should be considered in future research and guidance development.

Our results are similar to a meta-analysis that evaluated the effectiveness of all psychological interventions to prevent relapse compared with TAU (RR 0.66; 95% CI 0.53 to 0.82) and mADM (RR 0.80; 95% CI 0.60 to 1.08).(43) An individual patient data (IPD) meta-analysis observed that MBCT resulted in a reduced risk of depressive relapse compared with those who did not receive MBCT (HR 0.69; 95% CI 0.58 to 0.82), with any active treatment (HR 0.79; 95% CI 0.64 to 0.97) and with mADM (HR 0.77; 95% CI 0.60 to 0.98).(6) IPD meta-analysis allows for more accuracy in the estimation of the effect of MBCT, while our estimates

are based on the results presented within the included studies. However, the IPD meta-analysis is limited by the unavailability of study data from Meadows et al.(33) This study was included in our quantitative synthesis as well as the study by Perich et al.(28) which evaluates relapse and time to relapse of depression in people with bipolar disorder. Excluding the study by Perich et al. from the pooled analysis within a sensitivity analysis did not change the conclusions (i.e. MBCT would continue to be more effective than TAU, sensitivity analysis results available from the authors on request).

Consistent with the personalised medicine approach being adopted in healthcare services (44), research also appears to be trying to identify other subgroups that may specifically benefit from MBCT, with those who have experienced childhood adversity and other early life trauma identified as one such group (13). It is likely that future research will continue this trend, but there will remain an inherent danger of "data-dredging" and type-1 errors (45) that should be minimised by high quality and transparent study design and rigorous methodology (46).

Further consideration of the enduring effects of TAU on depressive relapse leads to reflection upon those studies in this review that compare MBCT with another specific active intervention as there are practical clinical implications. In all those studies that compared MBCT to antidepressant medication no overall significant advantage to MBCT was demonstrated (12, 20-22, 35) and no advantage was observed by adding MBCT to antidepressant medication (20). However, long term follow-up studies also show that both MBCT and antidepressants can each confer enduring positive effects and thus MBCT may offer an alternative to medication in some cases (12, 34, 35). It should also be recognised that withdrawal of maintenance antidepressants may increase depressive relapse (21). It has been suggested that the key components responsible for part of the effects of psychotherapies for adult depression cannot be dismantled but may be caused by non-specific factors common to all therapies (47).

A driver to the original development of MBCT was the recognition that CBT, whilst effective for acute depressive episodes it did not reliably reduce the rate of future relapse (1). Subsequent studies however, have reported that the acute phase of CBT is effective at reducing the risk of depressive relapse.(48-51) We observed no statistically significant differences between MBCT and CBT in reducing rate or time to relapse. It is of paramount importance to consider the issue of patient choice and involvement in the decisions about which treatment options they choose. This is a progressive issue and active debate for conditions such as psychosis (52, 53). Patient choice can result in an improvement in adherence to treatments and consequently in effectiveness and cost-effectiveness of

treatments.(54) This is of particular relevance for MBCT as recent systematic review of economic evaluations of acceptance and mindfulness-based interventions reported that there is still considerable uncertainty surrounding the cost-effectiveness of MBCT for management of mental health conditions including recurrent depression (55).

Strengths and limitations

Our review followed best practice recommendations for systematic reviews.(8, 9) To our knowledge this systematic review reports the first NMA evaluating the long-term effectiveness of MBCT compared to control treatments in preventing relapse and time to relapse of depression. The focus of the review was MBCT when employed for the management of depressive symptoms rather than treatments of depression in general; as such, an inclusion criterion was that studies had an MCBT group. Moreover, the aim of the review was to investigate how MBCT performed compared to control treatments rather than to rank all available treatments, which is often evaluated within an NMA framework.

The data available was limited for some of the comparisons in the meta-analysis and NMA and there was some heterogeneity in some of the analyses. The CIDI was used in one of the studies included in the quantitative synthesis.(33) It should be noted that the CIDI was developed for epidemiological studies as a screening tool but does not represent a clinical diagnosis. It is possible that the study inclusion criteria that required publications to be in English and to be published in peer-reviewed journals may lead to selection bias and may have caused some relevant studies to be overlooked.

In conclusion, we found that MBCT is more effective than TAU in the long-term in preventing relapse of depression and has statistically significant advantages over TAU and placebo for time to relapse of depression. No statistically significant differences were observed between MBCT and alternative strategies evaluated (i.e. mADM, ACC, CPE, CT or DRAM) both for rate of relapse or time to relapse of depression. Subgroup meta-analysis by number of previous episodes of depression showed very similar results. Use of booster sessions may result in improved outcomes and its use, timings, frequency and attendance should be clearly reported.

Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article

Figure legends

Figure 1. Network plot of MBCT and all control treatments

Figure 2. PRISMA flow chart

Figure 3. Meta-analysis and network meta-analysis of relapse of depression and time to relapse of depression comparing MBCT to control

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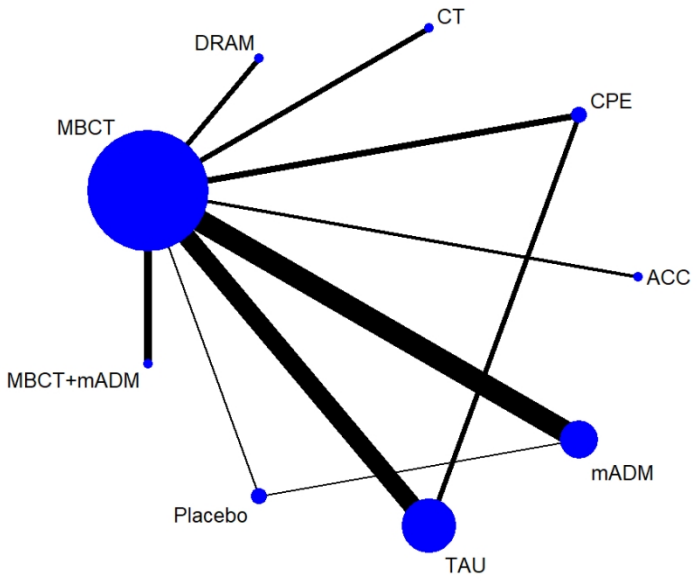


Figure 1. Network plot of MBCT and all control treatments

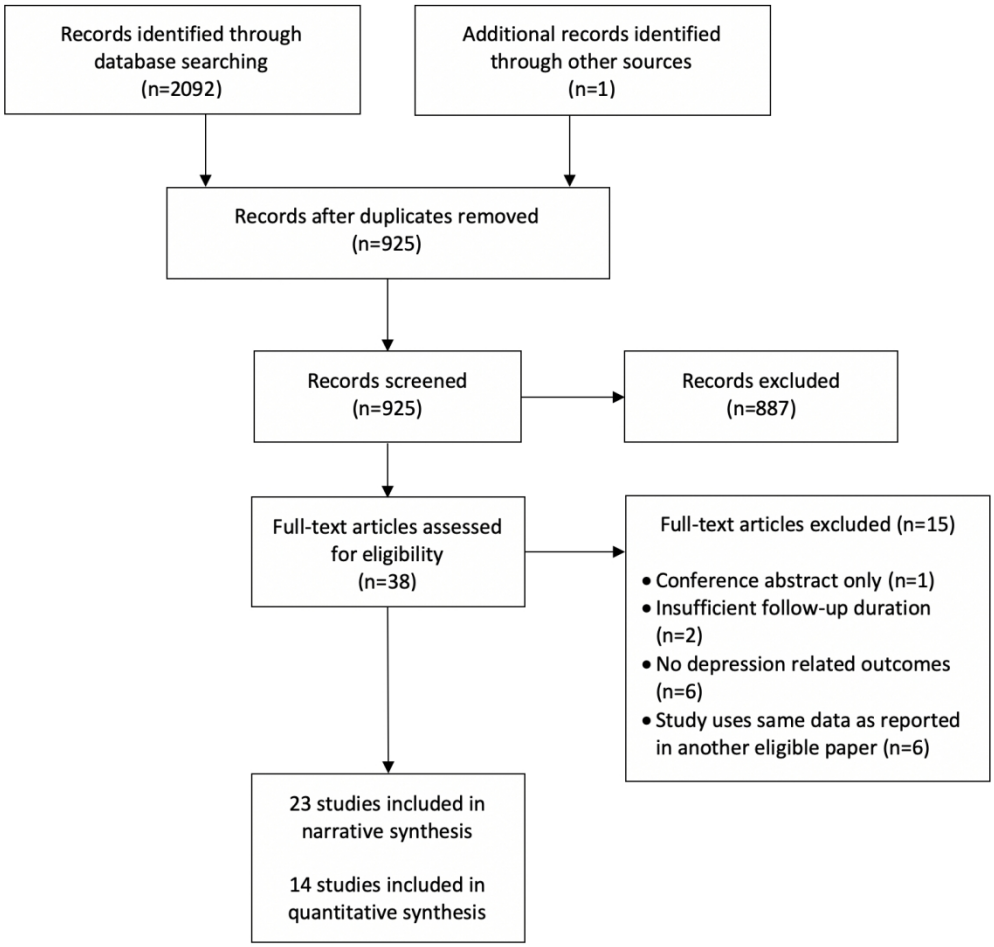
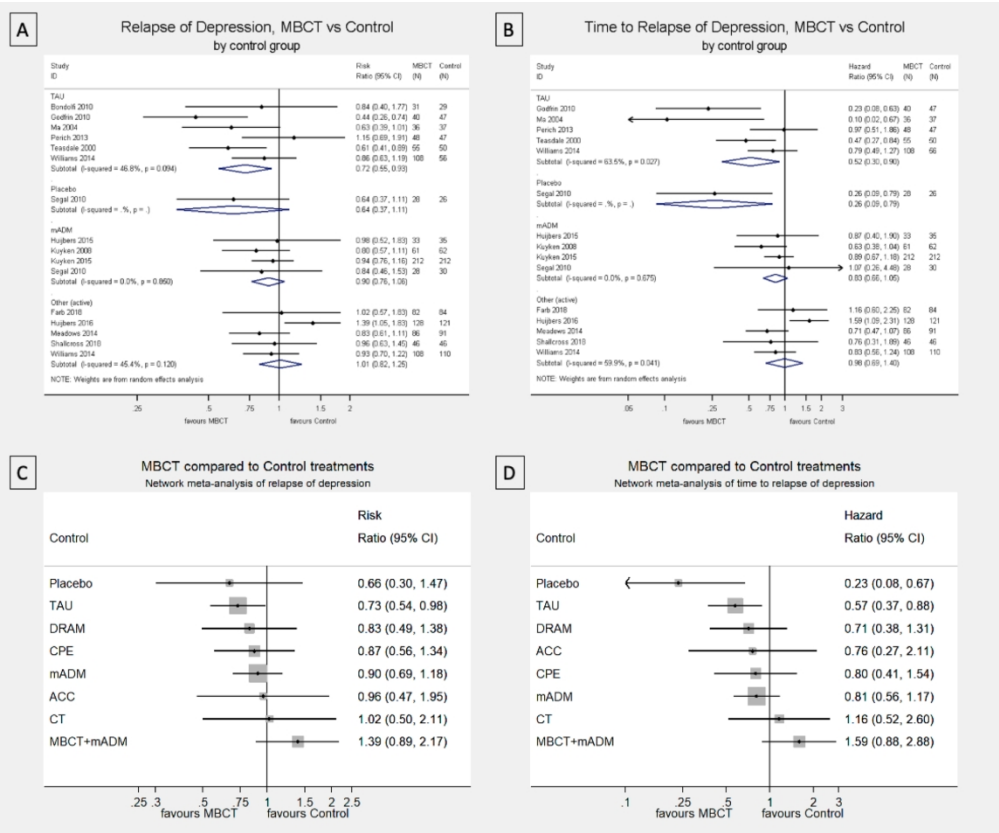


Figure 2. PRISMA flow chart



Meta-analysis and network meta-analysis of relapse of depression and time to relapse of depression comparing MBCT to control

Table 1 Characteristics of studies included in the systematic review

Author (year) and setting	Number in analysis, sex, mean age	Mental health indication	Control	Follow-up duration	Outcomes	Key findings
Randomised controlled trials						
Bondolfi (2010)(27) Switzerland *	MBCT (n=31); control (n=29) 74% female 46 years	Recurrent depressive illness in remission	TAU	14 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Depression severity (MADRS) Severity of depressive symptoms (BDI-II) Mindfulness practice (MBCT group only)	(-) p=0.58 ↑ p=0.006 NR (only assessed at baseline) NR (only assessed at baseline) (-) between relapsers and non-relapsers
Farb (2018)(32) Canada	MBCT (n=82); control (n=84) 66% female 40 years	Major depressive disorder in remission	CT	24 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Depressive symptoms (QIDS) Decentering/ rumination (EQ) Dysfunctional beliefs (DAS)	(-) (-) p=0.55 (-) p=0.85 (-) p=0.69 (-) p=0.37
Geschwind (2012)(29) Netherlands	MBCT (n=64); control (n=66) 49% female 54 years	Residual depressive symptoms	Waiting list	12 months	Depressive symptoms (HRSD) Depressive symptoms (IDS)	(-) p=0.16 (-) p=0.24
Godfrin (2010)(30) Belgium	MBCT (n=40); control (n=47) 81% female 45 years	Recurrent depressive illness in remission	Waiting list	14 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Depressive symptoms (HRSD) Severity of depressive symptoms (BDI-II) Quality of life (QLDS) Mood states (POMS)	↑ p<0.0005 ↑ p<0.001 ↑ p<0.01 ↑ p<0.001 ↑ p<0.001 POMS depressive ↑ p<0.01 POMS angry (-) POMS tired (-) POMS powerful ↑ p<0.05 POMS tense (-)
Huijbers (2015)(20) Netherlands	MBCT (n=33); control (n=35) 72% female 52 years	Major depressive disorder in remission	mADM	15 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Severity of depressive symptoms (IDS-C) Quality of life (WHOQOL)	(-) p=0.95 (-) p=0.72 (-) p=0.69 (-) all domains
Huijbers (2016)(21) Netherlands	MBCT (n=128); control (n=121) 67% female 50 years	Recurrent depressive illness in remission	MBCT + mADM	15 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Severity of depressive symptoms (IDS-C) Quality of life (WHOQOL-BREF)	↓ p=0.02 ↓ p=0.01 (-) p=0.66 (-) all domains

Kuyken (2008)(34) UK	MBCT (n=61); control (n=62) 77% female 49 years	Recurrent depressive illness in remission	mADM	15 months	Time to relapse or recurrence Relapse or recurrence (SCID for DSM-IV) Depressive symptoms (HRSD) Severity of depressive symptoms (BDI-II) Quality of life (WHOQOL-BREF)	(-) p=0.07 (-) p=0.21 ↑ p=0.02 (-) p=0.12 WHOQOL-BREF physical ↑ p=0.04 WHOQOL-BREF psychological ↑ p=0.01 WHOQOL-BREF social (-)
Kuyken (2015)(35) UK	MBCT (n=212); control (n=212) 77% female 49 years	Recurrent depressive illness in remission	mADM	24 months	Time to relapse or recurrence Relapse or recurrence (SCID for DSM-IV) Depression free days (SCID) Depressive symptoms (GRID-HAMD) Severity of depressive symptoms (BDI-II) Psychiatric comorbidities (SCID) Medical comorbidities (MSCL) Quality of life (WHOQOL-BREF) HRQoL (EQ-5D-3L)	(-) p=0.43 (-) p=0.10 (-) p=0.66 (-) p=0.76 (-) p=0.18 (-) p=0.91 (-) p=0.42 (-) all domains (-) p=0.13
Ma (2004)(3) UK	MBCT (n=36); control (n=37) 76% female 44 years	Depressive illness in remission	TAU	12 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Dysfunctional parenting (MOPS)	↑ ≥3 episodes p=0.002; 2 episodes p=0.23 (-) p=0.17 MOPS indifference ↑ p<0.001 MOPS overcontrol ↑ p<0.023 MOPS abuse p<0.001
Manicavasgar (2011) (31) Australia	MBCT (n=19); control (n=26) 64% female 46 years	Major depressive disorder	CBT	12 months	Severity of depressive symptoms (BDI-II) Severity of anxiety symptoms (BAI) Functioning and impairment (SOFAS)	(-) (-) (-)
Meadows (2014) (33) Australia	MBCT (n=86); control (n=91) 81% female 48 years	Residual depressive illness	DRAM	26 months	Days in MDE Relapse or recurrence (CIDI) Time to relapse or recurrence	↑ p=0.03 ↑ p=0.03 (-) p=0.05
Perich (2013) (28) Australia	MBCT (n=48); control (n=47) 65% female 42 years	Bipolar affective disorder	TAU	12 months	Time to relapse or recurrence Relapse or recurrence (SCID for DSM-IV) Symptoms of mania (YMRS) Depression severity (MADRS) Depression, anxiety and stress (DASS) State and trait anxiety (STAI) Dysfunctional beliefs (DAS-24) Rumination, coping and risk taking (RSQ)	(-) (-) p=0.936 (-) (-) (-) STAI-state anxiety ↑ p=0.048 STAI-trait anxiety (-) p=0.075 (-) (-)

					Trait mindfulness (MAAS)	(-)	
Segal (2010) (12) Canada	MBCT (n=28); control (n=26 & n=30) 58% female 44 years	Depressive illness in remission	mADM Placebo pills and clinical management	18 months	Time to relapse or recurrence Relapse or recurrence (SCID for DSM-IV)	MBCT vs placebo ↑ ↑	MBCT vs mADM (-) (-)
Shallcross (2015) (25) USA	MBCT (n=46); control (n=46) 76% female 35 years	Depressive illness in remission	ACC	14 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Severity of depressive symptoms (BDI-II) Life satisfaction (SWL)	(-) p=1 (-) p=0.91 (-) p=0.337 (-) p=0.919	
Shallcross (2018) (26) USA	*(as Shallcross 2015* (25)*)*	Depressive illness in remission	ACC	26 months	Relapse or recurrence (SCID for DSM-IV) Time to relapse or recurrence Severity of depressive symptoms (BDI-II) Life satisfaction (SWL)	(-) p=0.99 (-) p=0.55 (-) p=0.30 (-) p=0.84	
Teasdale (2000) (2) UK	MBCT (n=55); control (n=50) 76% female 43 years	Recurrent depressive illness in remission	TAU	12 months	Relapse or recurrence (SCID for DSM-III-R) Time to relapse or recurrence	↑ p<0.01 ↑ p<0.01	
Williams (2014) (13) UK	MBCT (n=108); control (n=110 & n=56) 72% female 43 years	Recurrent depressive illness in remission	CPE TAU	12 months	Time to relapse or recurrence Relapse or recurrence (SCID for DSM-IV)	(-) p=0.56 (-)	
Non-randomised controlled trials							
Mathew (2010) (37) Australia	MBCT (n=39) 77% female 52 years	Major depressive disorder, bipolar affective disorder depressed phase, or dysthymia	-	13 to 34 months	Severity of depressive symptoms (BDI-II) Ruminative thinking (RSS) Trait mindfulness (MAAS)	↑ p<0.05 NR NR	
Michalak (2008) (23) Germany	MBCT (n=24) 79% female 48 years	Recurrent depressive illness in remission	-	12 months	Depressive symptoms (HRSD) Severity of depressive symptoms (BDI) Trait mindfulness (MAAS) Relapse or recurrence (SCID for DSM-IV)	Mindfulness predicted the risk of relapse/recurrence after controlling for numbers of previous episodes and residual depressive symptoms	
Michalak (2011) (24) Germany	*(as Michalak (2008) (23))*	Recurrent depressive illness in remission	-	12 months	Ruminative thinking (RSS) Depressive symptoms (HRSD) Relapse or recurrence (SCID for DSM-IV)	Post-treatment levels of rumination predicted the risk of relapse of major depressive disorder in the 12-month follow-up period even after controlling for numbers of previous episodes and residual depressive symptoms	

Munshi (2013) (36) USA	MBCT (n=18) 77.8% female 54 years	Depressive illness in remission	-	49 months	Severity of depressive symptoms (BDI-II) Ruminative thinking (RSS) Mindfulness (FMI) State and trait anxiety (STAI)	↑ p<0.0001 pre-post (-) p=0.71 post-fu ↑ p=0.004 pre-post (-) p=0.12 post-fu ↑ p=0.023 pre-post (-) p=0.94 post-fu STAI-state ↑ pre-post (-) post-fu STAI-trait ↑ pre-post (-) post-fu
Spinhoven (2017)(22) Netherlands	MBCT (n=138) 68.1% female 51 years	Recurrent depressive illness in remission	-	15 months	Mindfulness (FFMQ) Personality facets (NEO PI-R)	↑ p<0.001 (all subscales) NEO PI-R neuroticism ↑ p<0.001 NEO PI-R extraversion ↑ p=0.03 NEO PI-R conscientiousness ↑ p<0.01 NEO PI-R agreeableness (-) p=0.12 NEO PI-R openness to experience (-) p=0.43
van Aalderen (2015) (38) Netherlands	MBCT (n=146) 72% female 48 years	Recurrent depressive illness in remission and recurrent depressive illness	-	15 months	Severity of depressive symptoms (BDI) Ruminative thinking (RSS) Mindfulness (KIMS) Quality of life (WHOQOL-BREF)	(-) p=0.17 ↑ p<0.001 (-) p=0.20 (-) all domains

ACC=active control condition, BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory II; CBT=cognitive behaviour therapy; CIDI=Composite International Diagnostic Interview; CPE=cognitive psychological education; CT=cognitive therapy; DAS=Dysfunctional Attitudes Scale; DASS=Depression Anxiety Stress Scales; DRAM=depression relapse active monitoring; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; EQ=Experiences Questionnaire; FMI=Freiburg Mindfulness Inventory; gCBT=group cognitive behaviour therapy; GRID-HAMD=GRID Hamilton Rating Scale for Depression; HRSD=Hamilton Rating Scale for Depression; IDS=Inventory of Depressive Symptoms; KIMS=Kentucky Inventory of Mindfulness; mADM=maintenance antidepressant medication; MADRS=Montgomery-Asberg Depression Rating Scale; MAAS=Mindful Attention Awareness Scale; MBCT=mindfulness based cognitive therapy; MDE=major depressive episode; MOPS=Measure of Parenting Style; MSCL=Medical Symptom Checklist; NEO PI-R=NEO Personality Inventory–Revised; NR=not reported; POMS=Profile of Moods Scale; QIDS=Quick Inventory of Depressive Symptomatology; QLDS=Quality of Life in Depression Scale; RSQ=Response Style Questionnaire; RSS=Rumination on Sadness Scale; SCID=Structured Clinical Interview; SOFAS=Social and Occupational Functioning Scale; STAI=State/Trait Anxiety Inventory; SWL=Satisfaction With Life Scale; TAU=treatment as usual; WHOQOL=World Health Organization Quality of Life; YMRS=Young Mania Rating Scale

* Replication trial of studies (2) & (3)

(-) no statistically significant differences between groups (RCTs) or no difference with MBCT (non-RCTs)

↑ statistically significant improvements for MBCT group (RCTs) or statistically significant improvement with MBCT (non-RCTs)

↓ statistically significant improvements for control group (RCTs) or statistically significant deterioration with MBCT (non-RCTs)

Table 2 Results of meta-analysis and network meta-analysis for outcomes relapse of depression and time to relapse of depression: MBCT compared to control treatments

Control group	Number of participants (number of studies)	Relapse of depression: RR (95% CI)[a]		Time to relapse of depression: HR (95% CI)[a]	
		Direct evidence[b]	NMA results	Direct evidence[b]	NMA results
Placebo	54 (1)[c]	0.64 (0.37 to 1.11)	0.66 (0.30 to 1.47)	**0.26 (0.09 to 0.79)**	**0.23 (0.08 to 0.67)**
TAU	584 (6)[d]	**0.72 (0.55 to 0.93)**	**0.73 (0.54 to 0.98)**	**0.52 (0.30 to 0.90)**	**0.57 (0.37 to 0.88)**
DRAM	177 (1)[e]	0.83 (0.61 to 1.11)	0.83 (0.50 to 1.36)	0.71 (0.47 to 1.07)	0.71 (0.38 to 1.31)
CPE	218 (1)[c]	0.93 (0.70 to 1.22)	0.87 (0.56 to 1.34)	0.83 (0.56 to 1.24)	0.80 (0.41 to 1.54)
mADM	673 (4)	0.90 (0.76 to 1.06)	0.90 (0.69 to 1.18)	0.83 (0.66 to 1.05)	0.81 (0.56 to 1.17)
ACC	92 (1)	0.96 (0.63 to 1.45)	0.96 (0.47 to 1.95)	0.76 (0.31 to 1.89)	0.76 (0.27 to 2.11)
CT	166 (1)	1.02 (0.57 to 1.83)	1.02 (0.50 to 2.11)	1.16 (0.60 to 2.25)	1.16 (0.52 to 2.60)
MBCT + mADM	249 (1)	**1.39 (1.05 to 1.83)**	1.39 (0.89 to 2.17)	**1.59 (1.09 to 2.31)**	1.59 (0.88 to 2.88)

Results in bold are statistically significant. There was no evidence of inconsistency present within either NMA according to the 'design-by-treatment' inconsistency model (p-value = 0.768 for NMA of relapse of depression and p-value=0.546 for NMA of time to relapse of depression).

ACC = active control condition; **CI** = confidence intervals; **CPE** = Cognitive Psychological Education; **CT** = cognitive therapy; **DRAM** = depression relapse active monitoring; **HR =** hazard ratio; **mADM** = maintenance antidepressant medication; **MBCT** = mindfulness based cognitive therapy; **NMA** = network meta-analysis; **TAU** = treatment as usual

a. RR or HR less than 1 indicates an advantage to MBCT over the control
b. Direct evidence is the study specific RR and 95% CI where only one RCT included the control (Placebo, DRAM, CPE, ACC, CT and MBCT + mADM) and from meta-analysis were more than one study included the control (TAU and mADM)
c. Within one study (13) of MCBT compared to CPE compared to Placebo, a HR for time to relapse of depression for CPE compared to Placebo was not reported for all participants. To allow NMA to be conducted, a HR for participants with low childhood trauma questionnaire (CTQ) scores was extracted for CPE vs TAU. Sensitivity analysis was conducted using a HR for participants with high CTQ scores; NMA results were very similar and conclusions unchanged (results available on request)
d. A HR could not be extracted or estimated for one study comparing MBCT and TAU,(27) therefore the analyses for 'time to relapse of depression' are based on 524 participants from 5 studies for MBCT vs TAU.
e. A HR was not reported within the trial publication,(33) but could be estimated indirectly using the number of events and log-rank p value according to the methods of Tierney et al.(43)