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Mindfulness-based interventions for mental wellbeing among people with multiple sclerosis – a systematic review and meta-analysis of randomised controlled trials

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Abstract

Objective
Impairment of mental wellbeing (anxiety, depression, stress) is common among people with multiple sclerosis (PwMS). Treatment options are limited, particularly for anxiety. The aim of this study was to update our previous systematic review (2014) and evaluate via meta-analysis the efficacy of Mindfulness-based interventions (MBIs) for improving mental wellbeing in PwMS.

Methods
Systematic searches for eligible randomised controlled trials (RCTs) were carried out in seven major databases (November 2017, July 2018), using medical subject headings and key words. Studies were screened, data extracted, quality appraised, and analysed by two independent reviewers, using predefined criteria. Study quality was assessed using the Cochrane Collaboration risk of bias tool. Mental wellbeing was the primary outcome. Random effects model meta-analysis was performed, with effect size reported as Standardised Mean Difference (SMD). PROSPERO registration: CRD42018093171.

Results
Twelve RCTs including 744 PwMS were eligible for inclusion in the systematic review, eight had data extractable for meta-analysis; n=635. Ethnicity, socioeconomic status, comorbidity and disability were inconsistently reported. MBIs varied from manualised to tailored versions, lasting 6-9 weeks, delivered individually and via groups, both in person and online. Overall SMD for mental wellbeing (eight studies) was 0.40 (0.28 – 0.53), p<0.01, I²=28%; against active comparators only (three studies) SMD was 0.17 (0.01 – 0.32), p<0.05, I²=0%. Only three adverse events were reported.

Conclusions
MBIs are effective at improving mental wellbeing in PwMS. More research is needed regarding optimal delivery method, cost- and comparative-effectiveness.
Funding
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Abstract word count: 246

BACKGROUND
People with multiple sclerosis (PwMS) often describe the condition as stressful.[1]. Mental health comorbidity is common[2]; anxiety and depression three times as frequent compared to population norms[2] and are associated with higher levels of somatic symptoms, increased suicidality, lower quality of life (QoL) and greater social problems.[3].

Very little evidence exists on the optimal treatment for impaired mental wellbeing in PwMS. Systematic review and meta-analytic evidence supports cognitive behavioural therapy (CBT) for both stress and depression in PwMS, but effective treatments for anxiety are lacking. [4,5].

Mindfulness-based interventions (MBIs) are complex interventions [6] increasingly used in healthcare. MBIs have high quality evidence for treating stress, anxiety and recurrent depression in the general population [7] and thus might also help PwMS with impaired mental wellbeing. In 2014, our previous systematic review found preliminary evidence from two randomised controlled trials (RCTs) and a controlled trial to support MBIs as a potential treatment for anxiety and depression in PwMS.[8]. Due to heterogeneity between study type, populations, interventions and outcomes, meta-analysis was not possible, nor was the optimal MBI for PwMS clear. Since 2014 several more RCTs have been published.

The aim of this review is to undertake a meta-analysis of RCT evidence for MBIs in improving mental wellbeing in people with MS.
METHODS

Protocol and registration
Our study protocol was prospectively registered with Prospero:
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=93171

Eligibility for inclusion
Based on the Study design, Participants, Interventions, Outcomes (SPIO) model (a derivative of PICOS)[9], eligibility included: RCTs of patients with any diagnosis of MS, aged =/>18, any type of MBI (including core components of mindful breath awareness, body awareness, and mindful movement), with outcomes focused primarily on impact on mental wellbeing.

Search strategy
We used our previous systematic review search strategy in: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, AMED, and PsycInfo. The 'years' delimiter was 2000 – 2018; our previous systematic review found the first study in this area was in 2000. We also searched ProQuest Dissertations & Theses Database, reference lists from key papers, contacted relevant experts, and searched the grey literature. The initial search was in November 2017, updated in July 2018. Supplementary file 1 contains the search strategy formatted for MEDLINE.

Study selection, storage and screening
Search results were first imported into COVIDENCE, a systematic review data storage software package. Two independent reviewers (RS, SS) screened study title/abstracts for potential eligibility using keywords like 'mindfulness' and 'multiple sclerosis'. Selected studies were then assessed further by two independent reviewers (RS, JB) against SPIO criteria to determine definitively eligibility. A third-party senior reviewer adjudicated any disagreements (SM).
Data collection/data items
Once the final list of studies for inclusion was agreed, data was extracted and expanded to ensure all CONSORT [10] and TIDieR [11] checklist items were included (Supplementary file 2).

Quality appraisal
The Cochrane Collaboration’s assessment tool [12] was used to summarise the risk of bias for major outcomes in selected studies for individual outcomes, graded as high, unclear, or low risk, assessing sequence generation, allocation concealment, participant blinding, personnel and outcome assessor blinding, completeness of outcome data, selective outcome reporting, and any other sources of bias. Overall risk of bias for each study was also graded as:
Low = Low risk of bias for all key domains
Unclear = Low or unclear risk of bias for all key domains
High = High risk of bias for one or more key domains

Principal summary measures
The ‘Primary outcome’ was identified as mental wellbeing (anxiety +/- depression +/- stress). The main outcome measure was taken as the last follow-up at which data was reported for that outcome. All main outcome measures were reported as continuous measures and their mean, standard deviation (SD) and number of subjects for each treatment group were extracted. The unbiased standardised mean difference (SMD) was calculated, whereby a positive SMD reflects a difference in favour of MBI. Where papers reported effect estimates from adjusted regression models, these were extracted as the SMD.

Synthesis of results
We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13] guidance. Due to the wide variety of outcome measures identified and known heterogeneity, random-effects meta-analysis regression model [14] was used to derive SMD. Estimates are reported along with their corresponding 95% confidence intervals (CI) and p values. The $I^2$ statistic was used to assess the variability between studies.[15] $I^2$ describes the percentage of
total variability in the estimates effect size that is attributable to heterogeneity. $I^2$ varies from 0% (all heterogeneity is due to sampling error) to 100% (all variability due to true heterogeneity between studies).

Funnel plots and Egger's Test for asymmetry were undertaken to test for publication bias and ‘trim and fill’ method was undertaken to assess the impact of the bias. [16-19]

All statistical analyses were carried out in R version 3.4.0 and using the meta package.[20]

**RESULTS**

Twelve RCTs were identified as eligible for inclusion in the systematic review. [21-32] However, only eight studies reported endpoint data that could be included in the meta-analysis. [21–24,28–30,32] (Figure 1). Further details were sought from study authors [29,31,32], but only one [32] responded.

**Study characteristics**

Five studies took place in Iran, [23,25-27,29], three in the UK, [22,28,31], two in Italy[24,32], one each in Switzerland[30] and the USA.[21]. Six studies reported assessing a MBI against usual care [22,23,28-31], in three this was not specified [22-24], whilst three used an active comparator (psycho-education control,[21,24,32]). Six studies were powered. [21,23,24,29,30,32] Sample sizes ranged from 24 – 150 (median 49). Eight studies measured outcomes at three time points (baseline, post MBI and at follow-up; range 1 month – 1 year), [21,22,24,28-32], whilst four were pre-post-measurements only. [23,25-27] (Table 1).
Table 1: Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Powered</th>
<th>Comparator</th>
<th>Sample size (n)</th>
<th>Study attrition (%)</th>
<th>Outcome measures (others)</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mills &amp; Allen (2000)</td>
<td>Wales (UK)</td>
<td>RCT</td>
<td>No</td>
<td>TAU</td>
<td>n=24</td>
<td>33%</td>
<td>POMS, Standing balance, Symptom rating questionnaire</td>
<td>Baseline, post, 3 months follow-up</td>
</tr>
<tr>
<td>2. Grossman et al. (2010)</td>
<td>Switzerland</td>
<td>RCT</td>
<td>Yes</td>
<td>TAU</td>
<td>n=150</td>
<td>5%</td>
<td>CES-D, STAI, MFIS, HAQAMS, PQOLC, (Neuropsychology assessment, goal attainment)</td>
<td>Baseline, post, 6 months follow-up</td>
</tr>
<tr>
<td>3. Bogosian et al. (2015)</td>
<td>England (UK)</td>
<td>RCT</td>
<td>No</td>
<td>TAU</td>
<td>n=40</td>
<td>5%</td>
<td>GHQ, HADS, MSIS, FSS</td>
<td>Baseline, post, 3 months follow-up</td>
</tr>
<tr>
<td>4. Kolahkaj &amp; Zargar (2015)</td>
<td>Iran</td>
<td>RCT</td>
<td>Yes</td>
<td>TAU</td>
<td>n=48</td>
<td>17%</td>
<td>DASS-21</td>
<td>Baseline, post, 2 months follow-up</td>
</tr>
<tr>
<td>5. Amiri et al. (2016)</td>
<td>Iran</td>
<td>RCT</td>
<td>No</td>
<td>Unclear</td>
<td>n=40</td>
<td>0%</td>
<td>STAI, BDI-2, WCST</td>
<td>Baseline, post</td>
</tr>
<tr>
<td>6. Mahdavi et al. (2016)</td>
<td>Iran</td>
<td>RCT</td>
<td>No</td>
<td>Unclear</td>
<td>n=24</td>
<td>0%</td>
<td>BAI, BDI-2, FSS, MWQ, TFI</td>
<td>Baseline, post</td>
</tr>
<tr>
<td>7. Nejati et al. (2016)</td>
<td>Iran</td>
<td>RCT</td>
<td>Unclear</td>
<td>Unclear</td>
<td>n=24</td>
<td>0%</td>
<td>MSQOL-5,4, FSS</td>
<td>Baseline, post</td>
</tr>
<tr>
<td>8. Bahrani et al. (2017)</td>
<td>Iran</td>
<td>RCT</td>
<td>Yes</td>
<td>TAU</td>
<td>n=56</td>
<td>16%</td>
<td>DASS-21</td>
<td>Baseline, post</td>
</tr>
<tr>
<td>9. Simpson et al. (2017)</td>
<td>Scotland (UK)</td>
<td>RCT</td>
<td>No</td>
<td>TAU</td>
<td>n=50</td>
<td>12%</td>
<td>PSS, EQ5D-SI, MSQOL, MAAS, SCS-sf, ELQ</td>
<td>Baseline, post, 3 months follow-up</td>
</tr>
<tr>
<td>10. Carletto et al. (2017)</td>
<td>Italy</td>
<td>RCT</td>
<td>Yes</td>
<td>Psycho-education intervention</td>
<td>n=90</td>
<td>21%</td>
<td>BDI-2, BAI, PSS, BIPQ, FAMS</td>
<td>Baseline, post-BAM, 6 months post-BAM</td>
</tr>
<tr>
<td>11. Cavalera et al. (2018)</td>
<td>Italy</td>
<td>RCT</td>
<td>Yes</td>
<td>Psycho-education intervention</td>
<td>n=139</td>
<td>39%</td>
<td>MSQOL-5,4, HADS, MOSS, MFIS,</td>
<td>Baseline, post-6-months post MBI</td>
</tr>
<tr>
<td>12. Senders et al. (2018)</td>
<td>USA</td>
<td>RCT</td>
<td>Yes</td>
<td>Educational control, matched for time and attention</td>
<td>n=62</td>
<td>16%</td>
<td>PSS, PROMIS, CD-RISC, PASAT</td>
<td>Baseline, mid-intervention, immediately post-, 4, 8 and 12-months post-MBI</td>
</tr>
</tbody>
</table>
1. RCT - Randomised controlled trial; 2. TAU - Treatment as usual; 3. POMS - Profile of mood states; 4. CES-D - Center for epidemiological studies depression scale; 5. STAI - Spielberger trait anxiety inventory; 6. MFIS - Modified fatigue impact scale; 7. PQOLC - Profile of health related quality of life in chronic disorders (German); 8. HAQUAMS - Hamburg quality of life questionnaire in multiple sclerosis (German); 9. GHQ - General health questionnaire; 10. HADS - Hospital anxiety and depression scale; 11. MSIS - Multiple sclerosis impact scale; 12. FSS - Fatigue severity scale; 13. DASS-21 - Depression, Anxiety, and Stress Scale-21; 14. BDI-2 - Beck depression inventory-2; 15. WCST - Wisconsin card sorting test; 16. BAI - Beck anxiety inventory; 17. MWQ - Meta worry questionnaire; 18. TFI - Thought fusion inventory; 19. MSQOL-54 - Multiple sclerosis quality of life - 54; 20. PSS - Perceived stress scale; 21. EQ-5D-5L - EuroQol; 22. MQOLI - Multiple sclerosis quality of life inventory; 23. MAAS - Mindful attention awareness scale; 24. SCS-sf - Self-compassion scale-short form; 25. ELQ - Emotional lability questionnaire; 26. BIPQ - Brief illness perception questionnaire; 27. FAMS - Functional Assessment of Multiple Sclerosis; 28. MOSS - Medical Outcomes Sleep Scale; 29. PROMIS - Patient-Reported Outcomes Information System; 30. CD-RISC - Connor-Davidson Resilience Scale; 31. PASAT - Paced Auditory Serial Attention Task
**Participant characteristics**

Across the 12 RCTs, the total number of participants was 744, those in the meta-analysis 635. Three studies reported ethnicity [21,22,28], mostly Caucasian. Overall, 76% (n=565) of study participants were female. Where reported, overall mean age of participants was 41.4 years (age not reported in one study [26]). Only two studies included details on socio-economic status (SES) [22,25], three minimal details on employment status.[22,24,31]. Ten studies included details on education status [21-23,25-30,32], with the majority in nine studies[21-23,25-30,32] having completed at least school level education. Most (at least 447 or 60%) had relapsing-remitting MS (RRMS), at least 112 (15%) had secondary progressive MS (SPMS), and at least 30 (4%) had primary progressive MS (PPMS). Mean Expanded Disability Status Scale (EDSS) was reported in five studies [21,22,24,28,30], ranging from 2.3 – 6.5. Only one study reported on number of comorbid conditions (mean 2.3, SD 1.7) [22], with four studies reporting on the active use of disease modifying drugs and/or psychotropic medications[21,22,30,32] (Table 2).
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>NR</td>
<td>NR</td>
<td>90% British Caucasian</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100% British Caucasian</td>
<td>NR</td>
<td>NR</td>
<td>97% Caucasian</td>
<td></td>
</tr>
<tr>
<td>Number of participants (% female)</td>
<td>16 (80%)</td>
<td>150 (80%)</td>
<td>40 (55%)</td>
<td>48 (100%)</td>
<td>24 (100%)</td>
<td>24 (46%)</td>
<td>56 (100%)</td>
<td>50 (92%)</td>
<td>90 (71%)</td>
<td>139 (65%)</td>
<td>67 (78%)</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>49.8 (6.8)</td>
<td>47.3 (10.3)</td>
<td>52.2 (9.1)</td>
<td>25.3 (4.1)</td>
<td>25.2 (4.5)</td>
<td>NR</td>
<td>32.3 (5.1)</td>
<td>36.4 (6.6)</td>
<td>45 (10.9)</td>
<td>44.6 (9.4)</td>
<td>42.7 (8.7)</td>
<td>52.94 (11.37)</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>‘Average or above’</td>
<td>NR</td>
<td>NR</td>
<td>Postcode derived; controlled in analyses</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td>4 employed (25%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>20 employed (40%)</td>
<td>59 employed (65%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Education status (SD)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Disease phenotype</td>
<td>SP 16 (100%)</td>
<td>RR 123 (82%)</td>
<td>SP 23 (57.5%)</td>
<td>PP 17 (42.5%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>RR 40 (80%)</td>
<td>RR 41 (67%)</td>
<td>SP 15 (25%)</td>
<td>PP 4 (6%)</td>
<td>UK 2 (3%)</td>
</tr>
<tr>
<td>EDS5 score</td>
<td>NR</td>
<td>Mean (SD) 14.1 (1.9)</td>
<td>Mean (SD) 31 (77.5)</td>
<td>had at least a college education</td>
<td>21 had high school, and 19 had a bachelor’s degree</td>
<td>All high school diploma or university education</td>
<td>School education or above</td>
<td>High school diploma at least</td>
<td>(56%) university level education</td>
<td>NR</td>
<td>11% elementary school; 52% high school; 38% university</td>
<td>60% college education or greater</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean 2.4 (2.0); Range 0-9</td>
<td>NR</td>
<td>1 participant had severe depression on HADS</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>On DMDs</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>104 (85%)</td>
<td>34 (55%)</td>
<td>NR</td>
</tr>
<tr>
<td>Psychotropic medication(s)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Key: 1. NR – Not reported; 2. RR – Relapsing remitting; 3. SP – Secondary progressive; 4. PP – Primary progressive; 5. PR – Primary relapsing
**Intervention characteristics**

Five studies used Mindfulness-Based Stress Reduction (MBSR) [21,22, 29,30,32], two based on MBSR[24,27], three Mindfulness-Based Cognitive Therapy (MBCT)[25,26,28], one Mindfulness-integrated CBT (MiCBT)[23], and one Mindfulness of Movement.[31]. Six studies reported on participant materials. [22,23,27,28,31,32]. Three studies required a personal intake interview to take part [26,27,30], two sought baseline evidence of impaired mental wellbeing. [21,28] Eight studies reported session content [21-23,25-29], three gave minimal description[30-32], one referred to the study protocol.[24]. Seven studies described home practices. [21-24,28,30,31]. Seven studies reported teacher characteristics [21-24,28-30], but in two detail was minimal [23,29]. Eleven studies delivered group MBIs [21-30,32], one was individual.[31]. Two studies used online MBIs [28,32]. Four studies reported intervention delivery location [22,28,29,32]. Three studies had nine MBI sessions [21,24,30], eight had eight [22,23,25-29,32], one had six.[31]. Session length ranged from 1-3 hours. Class sizes ranged from five to 25, either one or two instructors present. Six studies modified the MBI for PwMS[22,24,28,30-32], one study during the course[22], simplifying mindful movement. Seven studies monitored treatment adherence (session attendance +/- home practice) [21,22,25,28,30-32], four considered fidelity assessment[22,25,28,32], two recording/checking sessions. [25,28]. Ten studies delivered core MBI components. [21-25,27-31] One study removed mindful movement.[28]. Three included an MBSR day retreat at week six. [21,24,30] (Table 3).
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Brief name</td>
<td>Mindfulness of Movement</td>
<td>MBSR</td>
<td>MBCT</td>
<td>MBSR</td>
<td>MBCT</td>
<td>MBSR and Conscious Yoga</td>
<td>MCBT</td>
<td>MBSR</td>
<td>Modified MBSR - Body Affective Mindfulness</td>
<td>MBSR</td>
<td>MBSR</td>
<td></td>
</tr>
<tr>
<td>2. Why? (rationale/ theory/goal)</td>
<td>Develop moment to moment awareness of breath, posture, movement with compassion</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/reacting to them automatically</td>
<td>Facilitate the compliance with and adaptation to medical conditions. Pay attention to being present in a non-judgmental manner</td>
<td>Attention regulation, emotion regulation, interpersonal relations, empathy, relapse prevention. Trained in awareness of body movement, behavior, emotions and mental contents</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td>Cultivation of mindfulness, loving kindness, enrichment of listening, self-compassion, sensorimotor psychotherapeutic principles 'window of tolerance'</td>
<td>Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. What - Materials provided to participants</td>
<td>Written handout, audio and video aids</td>
<td>headset, webcam, Audio CDs for home practice</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Leaflets for each session and home practice CDs</td>
<td>Audio CDs, 25 page booklet on sessions and instructions on mindful exercises</td>
<td>Course manual, home practice CDs, Book - Full Catastrophe Living</td>
<td>NR</td>
<td>Dedicated website with online multimedia for home practice</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>4. What - Procedures pre session</td>
<td>Had to make a commitment to regular practice</td>
<td>Personal intake interview; goal planning</td>
<td>Screened for evidence of distress on GHQ</td>
<td>NR</td>
<td>Screened for above average anxiety,</td>
<td>Personal intake interview</td>
<td>Personal intake interview</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Score of at least 10 on PSS</td>
</tr>
<tr>
<td>4. What - Procedures –</td>
<td>General description</td>
<td>General description</td>
<td>Session content</td>
<td>Session content</td>
<td>Session content</td>
<td>Session outline</td>
<td>Session outline</td>
<td>Session outline</td>
<td>Session content</td>
<td>General description</td>
<td>General description</td>
<td>Session content</td>
</tr>
<tr>
<td>in session</td>
<td>only -</td>
<td>only -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>in trial protocol -</td>
<td>n only -</td>
<td>reported in paper -</td>
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<tr>
<td>4. What - Procedures for home practice</td>
<td>only -</td>
<td>only -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>reported in paper -</td>
<td>in trial protocol -</td>
<td>n only -</td>
<td>reported in paper -</td>
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<tr>
<td>30 minutes daily</td>
<td>40 minutes daily</td>
<td>10-20 minutes daily</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>15 – 45 minutes daily</td>
<td>45 minutes daily</td>
<td>45 minutes daily</td>
<td>NR</td>
<td>45 minutes daily</td>
<td></td>
</tr>
<tr>
<td>4. What - Procedures - post course</td>
<td>NR</td>
<td>Post course interviews for all participants</td>
<td>Post course interviews for some participants</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Post course interviews for some participants</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>5. Who provided</td>
<td>NR</td>
<td>Two experienced (&gt;9 years), certified teachers</td>
<td>Study author: Had completed MBI teacher training</td>
<td>Trained psychologist</td>
<td>NR</td>
<td>NR</td>
<td>Clinical psychologist</td>
<td>Two experienced (7.5 years), certified physician teachers</td>
<td>Trained clinical psychologists, used to working with PwMS</td>
<td>Expert MBSR trainer</td>
<td>Certified MBSR teacher with 16 years experience</td>
<td></td>
</tr>
<tr>
<td>6. How - Mode of delivery</td>
<td>One-to-one, face-to-face</td>
<td>Group, face-to-face, 10-15 people per group</td>
<td>Group, via Skype, max 5 people per group</td>
<td>Group, face-to-face, 20 people per group</td>
<td>Group, 20 people per group</td>
<td>Group, 12 people per group</td>
<td>Group, 28 people per group</td>
<td>Group, face-to-face, 25 people per group</td>
<td>Group, number per group NR</td>
<td>Group, via Skype, average of 5 people per group</td>
<td>Group, number per group NR</td>
<td></td>
</tr>
<tr>
<td>7. Where - Intervention location</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Participant’s own homes</td>
<td>Ahvaz MS Society</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>NHS Centre for Integrative Care</td>
<td>Unclear</td>
<td>Unclear</td>
<td>In patients own homes</td>
<td>NR</td>
</tr>
<tr>
<td>8. When and how much</td>
<td>6 weekly sessions</td>
<td>9 weekly 2.5 hour sessions</td>
<td>8 weekly 2 hour sessions</td>
<td>8 weekly 2 hour sessions</td>
<td>8 weekly 2 hour sessions</td>
<td>8 weekly 2.5 hour sessions</td>
<td>8 weekly 3 hour sessions</td>
<td>8 weekly sessions (?) duration</td>
<td>8 weekly 2 hour sessions 6 hour practice day at week 6</td>
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<tr>
<td>9. Tailoring</td>
<td>Individualised application of core techniques</td>
<td>Exercises did not exceed level of function</td>
<td>Developed with PwMS, MBCT manual adapted for Progressive MS issues Mindfulness movement removed</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Developed with PwMS, informed MBSR optimisation for future iteration</td>
<td>Protocol reports tailoring to needs of participants, but not reported in paper</td>
<td>Music meditation and acceptance of MS symptoms introduced</td>
<td>NR</td>
</tr>
<tr>
<td>10. In study modification</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Mindfulness movement simplified</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>11. How well - Treatment adherence</td>
<td>Average 32 minutes home practice/day (&gt;100%)</td>
<td>92% session attendance; Average 29.2 minutes home practice/day</td>
<td>18/19 (95%) completed ≥4 sessions, Home practice NR</td>
<td>NR</td>
<td>88% session attendance</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>60% session attendance; Average 32.5 minutes home practice/day</td>
<td>NR</td>
<td>79% session attendance</td>
<td>85% attended ≥6/8 sessions; median home practices 38 minutes/day (range 14-80 minutes); only 55% practiced as assigned</td>
</tr>
<tr>
<td>12. How well - Fidelity assessment</td>
<td>NR</td>
<td>NR</td>
<td>Senior clinical psychologist listened to session recordings</td>
<td>NR</td>
<td>All sessions recorded and assessed as consistent with protocol</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>As per NIH guidance (2004) minus session observation</td>
<td>NR</td>
<td>Treatment integrity monitored, but NR why</td>
<td>NR</td>
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</table>

For every session.
Outcome characteristics
Eleven studies measured MBI effect on anxiety [21-26,28-31], eleven on depression[21-26,28-31], six on stress. [21-24,28,29]. One assessed likely cost-effectiveness, finding 87% probability of savings on service costs and improved outcomes.[28]. Three studies reported mean daily home practice (32, 29.2, 32.5 minutes [22,30,31]); another median (38 minutes/day; range 14 – 80[21]). Study attrition ranged from 0-39%.

Meta-analysis
Effect of MBIs on mental wellbeing measures
Eleven studies investigated MBI effect on mental wellbeing [21-26,28-32], however only eight[21-24,28-30,32] reported extractable endpoint data. Meta-analysis showed an overall SMD of 0.40 (0.28 – 0.53; p<0.001), I²= 28% (low heterogeneity) (Figure 2); against active comparators SMD was 0.17 (0.01 – 0.32), p<0.05, I²=0% (low heterogeneity) (Figure 3). Eight studies evaluated MBI effect on anxiety [21-24,28-30,32], where the SMD was 0.35 (0.15 – 0.55), I²=25% (low heterogeneity). Eight studies evaluated MBI effect on depression [21-24,28-30,32], where the SMD was 0.35 (0.17 – 0.53), I²=10% (low heterogeneity). Six studies evaluated MBI effect on stress [21-24,28,29], where the SMD was 0.55 (0.25 – 0.85), I²=48% (moderate heterogeneity).

Heterogeneity and publication bias
Heterogeneity, I², among the studies was at 28% (low heterogeneity).
There was no evidence of publication bias from the funnel plot (Figure 4) and Egger’s Test of asymmetry confirmed that there was no evidence of asymmetry in the funnel plot. However, this was exactly on the threshold at p=0.05. When the trim and fill method was implemented, the estimated number of missing studies was seven. After adjustment for ‘missing’ studies, the pooled SMD estimate was 0.27 (0.12 - 0.42; p<0.001).

Outcomes by intervention type
The largest overall effects were reported for MiCBT [23], SMD 0.80 (0.48 – 1.12), I²=0%, but this was a pre- post- RCT (n=56), versus usual care. Overall effects for
MBCT versus usual care came from a small study [28] (n=40), where SMD was 0.78 (0.45, 1.11), I²=0%. In another study [24] (n=90), compared to a psychoeducation control, Body-Affective Mindfulness (BAM) had an overall SMD of 0.24 (0.00 – 0.48), I²=0%. From the five studies[21,22,29,30,32] with extractable endpoint data that used MBSR (total n=449), overall SMD was 0.29 (0.15 – 0.42), I²=0%, three studies[22,29,30] comparing MBSR against usual care, two [21, 32] against psychoeducation controls.

Study quality
Study quality varied widely. Poor reporting frequently hampered assessment. The highest quality studies derived from Europe and North America. Random sequence generation was well described in nine studies. [21-24,27-30,32]. Allocation concealment was assessed low risk in six studies [21-24,28,30], and unclear in the remaining six[25-27,29,31,32]. Six studies described blinding of assessors [21-24,28,30], while six reported outcome assessor blinding[21-24,28,30]. Five studies were adjudged low risk of bias for incomplete outcome reporting [21,22,28,30,32], whilst selective outcome reporting was adjudged high risk in one[31]. Overall, five studies were adjudged low risk of bias [21,22,24,28,30], two unclear[23,32], five high[25-25,29,31]. (Table 4). Justifications for risk of bias scores are available in Supplementary file 3.

When results were pooled, studies adjudged high risk of bias reported the largest overall treatment effects. Figure 5 shows the SMD for all analysable trials grouped by their risk of bias (high, unclear and low) ratings. High risk of bias (N=3) SMD was 0.64 (0.31 – 0.98; p=0.002), low risk of bias (N=28) SMD was 0.32 (0.24 – 0.41; p<0.0001) and unclear risk of bias (N=7) SMD was 0.35 (0.08 – 0.62; p=0.01). The overall risk of bias analysis showed effect estimates did not significantly differ between risk of bias groups, p=0.20.
Table 4 – Risk of Bias

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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
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<td>Unclear</td>
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<td>Low</td>
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<tr>
<td>Blinding of assessors (performance bias)</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) (patient reported outcomes)</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Incomplete outcome data addressed (attrition bias)</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Selective outcome reporting (reporting bias)</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Other sources of bias (i.e. baseline bias)</td>
<td>Unclear</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
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</table>
Meta-regression

A meta-regression was fitted to analyse the association between predictors and effect estimate. A backward manual selection process was used with intervention type, risk of bias, mean age, gender and EDSS scores as covariates in the model. Covariates were sequentially excluded based on p values (significance level at 5%) to obtain a final model. MBCT and high risk of bias were found to be significant predictors of the effect estimate (Table 5)

Table 5 – Meta-regression

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Estimates</th>
<th>95% CI</th>
<th>p-val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention type (MBI)</td>
<td>-0.03</td>
<td>(-0.33, 0.26)</td>
<td>0.82</td>
</tr>
<tr>
<td>Intervention type (MBCT)</td>
<td>0.51</td>
<td>(0.13, 0.88)</td>
<td>0.008</td>
</tr>
<tr>
<td>Risk of Bias (High)</td>
<td>0.54</td>
<td>(0.12, 0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Risk of Bias (Low)</td>
<td>0.18</td>
<td>(-0.13, 0.49)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Reference for intervention type: MBSR, reference for risk of bias: Unclear

Adverse events

Discreet adverse events were described in two studies[21,22]; an exacerbation of chronic neuropathic pain during the ‘Raisin Exercise’[22]; spasticity during guided progressive muscle relaxation[21]; anxiety following the MBSR retreat.[21].

DISCUSSION

Summary of main findings

This systematic review and meta-analysis identified twelve RCTs that assessed MBI effect on mental wellbeing in PwMS. Only three studies compared an MBI against active comparators, six against usual care, and in three this was unclear. Two studies explicitly measured intervention fidelity. Most studies had small sample sizes, but six were powered to detect meaningful effects, follow-up ranging from immediately post-MBI – one year later.
In total, 744 PwMS took part in these studies, the slight majority (60%) having a relapsing phenotype. Where reported, the majority ethnic group was Caucasian, and most participants female. Reporting on levels of comorbidity and disability was mostly poor.

Five studies used MBSR explicitly, two based on MBSR; three MBCT, one MiCBT, one Mindfulness of Movement. The majority of studies were delivered in face-to-face groups. Most studies reported delivering core MBI components and home practices. Class sizes varied. Mostly, teacher characteristics were poorly described. Treatment adherence was reported in seven studies, variably as session attendance +/- home practice. Attrition ranged widely (0-39%). Adverse events appear infrequent but were rarely reported.

Generally, study quality has improved since our last review[8]; in this current study, five of the RCTs score a low risk of bias on all items in the Cochrane Collaboration tool.

Meta-analysis demonstrated that MBIs are moderately effective for improving mental wellbeing in PwMS. At present, there is insufficient evidence to recommend any particular MBI over another for PwMS.

**Comparison with existing literature**

In this study we found MBIs moderately effective for treating anxiety (SMD 0.35; 0.15 – 0.55), depression (SMD 0.35; 0.17 – 0.53), and stress (SMD 0.55; 0.25 – 0.85) in PwMS. A 2004 meta-analysis[33] on the use of MBIs in diverse chronic medical conditions reported overall effect sizes (Cohen’s d) for mental health of d=0.50 (0.43 – 0.56). A 2010 meta-analysis[34] on MBSR effects on mental health in patients with varied chronic medical conditions reported smaller effect sizes (Hedge’s g): g=0.27 (0.19 – 0.35) for depression; g=0.24 (0.10 – 0.38) for anxiety; and g=0.32 (0.13 – 0.50) for psychological distress. A 2016 meta-analysis[4] of interventions for anxiety and depression in PwMS reported small effect sizes for psychological treatments (mostly CBT, n=9, none testing a MBI) (SMD 0.45; 0.16 – 0.74), medium effects for pharmacological treatments (SMD 0.63; 0.20 – 1.07).
in improving depression, but limited evidence for effective treatments for anxiety.

When compared with our own analysis, accumulating evidence suggests that MBIs are at least moderately effective for treating anxiety, depression and stress in PwMS, effect sizes comparable with CBT, but marginally less effective than medication for treating depression.

**Strengths of this review**

We adopted rigorous search, appraisal and analysis strategies, using a multi-disciplinary team of experienced reviewers for data extraction and a statistician for our meta-analysis. Our methods were guided by the PRISMA checklist\[13\], the TIDieR checklist\[11\] and the Cochrane Collaboration tool for assessing risk of bias.\[12\].

**Limitations of this review**

This study only included RCTs, necessarily excluding other important sources of data, such as observational and qualitative studies, particularly useful when considering intervention feasibility, acceptability, and accessibility. However, by using validated methods such as SPIO, the TIDieR checklist and Cochrane Collaboration tool for risk of bias, various ‘qualitative’ aspects of feasibility, replicability and trial conduct were covered.

**Strengths and Limitations of the included studies**

All studies included in this review were RCTs. However, six had small sample sizes (n=<50), only six were powered to detect statistical significance on outcome measures, and only three tested an MBI against an active comparator. One study did not report on participant age \[26\]; the extractable mean (SD) age from the remaining studies was relatively low (41.4). This potentially indicates a pooled sample skewed towards lower levels of disability \[35\]. Although seven studies stipulated EDSS as an inclusion criterion, only five reported mean (SD) values, making it difficult to determine what role a given MBI may have relative to disability level. Whilst all MS phenotypes featured among the included studies,
only two evaluated MBI effects on specific phenotypes[23,31], limiting analysis to pooled data, meaning no recommendations can be made for people with a particular type of MS. Participant SES was poorly covered; important because there is an established link between lower SES and higher incidence of depression in those with MS [36]. Both MBSR and MBCT appear effective, with no clear optimal MBI. Several studies altered the manualised MBSR or MBCT courses, often with little/no justification, although most included core MBI components.

**Implications for research**

Generally, the quality and weight of evidence supporting MBIs to improve mental wellbeing in PwMS has improved since our previous systematic review. However, many of the RCTs in this meta-analysis did not clearly follow the CONSORT [12] criteria and scored unclear or high on the Cochrane Collaboration risk of bias[10] tool. Furthermore, several lacked in clarity when it came to describe the MBI used. By using validated, evidence-based tools such as the CONSORT [12] and TIDieR[11] checklists, study authors could improve reporting in this area and help identify key gaps in knowledge and future research priorities.

The optimal MBI for PwMS remains unclear. As per the MRC guidance on complex interventions [6], PwMS should help design an optimised MBI and this should then be tested in a definitive RCT against current ‘gold-standard’ treatment(s). In PwMS who have stress or depression, this would mean testing against a matched group CBT course and usual care.

An additional consideration for future research in this area could be how MBI training may impact on disease activity in PwMS. Systematic review and meta-analytic data suggest a link between perceived stress and MS relapse [38,39]. Preliminary RCT evidence supports CBT-based stress management therapy having a potential role in diminishing disease activity in MS (relapse rate and Gadolinium uptake on magnetic resonance imaging). However, beneficial effects for CBT appear limited to duration of active therapy [40]. Given the beneficial
effects on perceived stress identified in this meta-analysis, an RCT study examining the effects of MBI training on disease activity in PwMS may now be justified.

Implications for clinical practice
MBIs effectively improve mental wellbeing in PwMS. It remains unclear where an MBI might ‘fit’ in the bigger picture of managing comorbid mental health conditions in PwMS, where patient characteristics and clinical severity may vary widely, and stepped care models increasingly predominate.[35]. However, on the basis of our study and others, it seems prudent to recommend systematic MBI training with regular home practice [41] and follow-up[42].

CONCLUSIONS
A substantial body of RCT evidence now exists supporting the use of MBIs in PwMS to improve mental wellbeing. Study quality is improving, but significant scope for improvement still exists in study design and reporting. What constitutes the optimal MBI for PwMS remains unclear.

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

Competing interests
We declare no competing interests.

Acknowledgements
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29. Kolahkaj B, Zargar F. Effect of Mindfulness-Based Stress Reduction on Anxiety, Depression and Stress in Women With Multiple Sclerosis. *Nursing and Midwifery Studies* 2015;4(4)


Figure 1 PRISMA flow diagram

Figure 2 Mental wellbeing (all comparators) forest plot

Figure 3 Mental wellbeing (active comparators only) forest plot

Figure 4 Funnel plot, Trim and fill

Figure 5 Risk of Bias forest plot