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, socio-economic 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), $p<0.01$, $I^2=28\%$; against active comparators only (three studies) SMD was 0.17 (0.01 – 0.32), $p<0.05$, $I^2=0\%$. 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.

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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

Study	Country	Study design	Powered	Comparator	Sample size (n)	Study attrition (%)	Outcome measures (others)	Data collection
1. Mills & Allen (2000)	Wales (UK)	RCT	No	TAU	n=24	33%	POMS, Standing balance, Symptom rating questionnaire	Baseline, post, 3 months follow-up
2. Grossman et al. (2010)	Switzerland	RCT	Yes	TAU	n=150	5%	CES-D, STAI, MFIS, HAQUAMS, PQOLC, (Neuropsychology assessment, goal attainment)	Baseline, post, 6 months follow-up
3. Bogosian et al. (2015)	England (UK)	RCT	No	TAU	n=40	5%	GHQ, HADS, MSIS, FSS	Baseline, post, 3 months follow-up
4. Kolahkaj & Zargar (2015)	Iran	RCT	Yes	TAU	n=48	17%	DASS-21	Baseline, post, 2 months follow-up
5. Amiri et al. (2016)	Iran	RCT	No	Unclear	n=40	0%	STAI, BDI-2, WCST	Baseline, post
6. Mahdavi et al. (2016)	Iran	RCT	No	Unclear	n=24	0%	BAI, BDI-2, FSS, MWQ, TFI	Baseline, post
7. Nejati et al. (2016)	Iran	RCT	Unclear	Unclear	n=24	0%	MSQOL-54, FSS	Baseline, post
8. Bahrani et al. (2017)	Iran	RCT	Yes	TAU	n=56	16%	DASS-21	Baseline, post
9. Simpson et al. (2017)	Scotland (UK)	RCT	No	TAU	n=50	12%	PSS, EQ5D5L, MSQLI, MAAS, SCS-sf, ELQ	Baseline, post, 3 months follow-up
10. Carletto et al. (2017)	Italy	RCT	Yes	Psycho-education intervention	n=90	21%	BDI-2, BAI, PSS, BIPQ, FAMS	Baseline, post-BAM, 6 months post-BAM
11. Cavalera et al. (2018)	Italy	RCT	Yes	Psycho-education intervention	n=139	39%	MSQOL-54, HADS, MOSS, MFIS,	Baseline, post-, 6-months post MBI
12. Senders et al. (2018)	USA	RCT	Yes	Educational control, matched for time and attention	n=62	16%	PSS, PROMIS, CD-RISC, PASAT	Baseline, mid-intervention, immediately post-, 4, 8 and 12-months post-MBI

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. MSQLI – 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 2 – Participant characteristics

Study/ demographic	Mills & Allen (2000)	Grossman et al. (2010)	Bogosian et al. (2015)	Kolahkaj & Zargar (2015)	Amiri et al. (2016)	Mahdavi et al. (2016)	Nejati et al. (2016)	Bahrani et al. (2017)	Simpson et al. (2017)	Carletto et al. (2017)	Cavalera et al. (2018)	Senders et al. (2018)
Ethnicity	NR	NR	90% British Caucasian	NR	NR	NR	NR	NR	100% British Caucasian	NR	NR	97% Caucasian
Number of participants (% female)	16 (80%)	150 (80%)	40 (55%)	48 (100%)	40 (47.5%)	24 (100%)	24 (46%)	56 (100%)	50 (92%)	90 (71%)	139 (65%)	67 (78%)
Mean age (SD)	49.8 (6.8)	47.3 (10.3)	52.2 (9.1)	25.3 (4.1)	25.2 (4.5)	NR	32.3 (5.1)	36.4 (6.6)	45 (10.9)	44.6 (9.4)	42.7 (8.7)	52.94 (11.37)
Socio-economic status	NR	NR	NR	NR	'Average or above average'	NR	NR	NR	Postcode derived; controlled in analyses	NR	NR	NR
Employment status	4 employed (25%)	NR	NR	NR	NR	NR	NR	NR	20 employed (40%)	59 employed (65%)	NR	NR
Education status (SD)	NR	Mean (SD) 14.1 (1.9) years of education	31 (77.5) had at least a college education	21 had high school, and 19 had a bachelor's degree	All high school diploma or university education	School education or above	High school diploma at least	High school diploma at least	(56%) university level education	NR	11% elementary school; 52% high school; 38% university	60% college education or greater
Disease phenotype	SP 16 (100%)	RR 123 (82%) SP 27 (18%)	SP 23 (57.5%) PP 17 (42.5%)	NR	NR	NR	NR	RR (100%)	RR 40 (80%) SP 16 (32%) PP 4 (8%)	RR 74 (82%) SP 7 (8%) PP 2 (2%) PR 5 (6%)	RR 113 (93%) SP 8 (7%)	RR 41 (67%) SP 15 (25%) PP 4 (6%) UK 2 (3%)
EDSS score	NR	Mean (SD) 3.0 (1.1)	Mean (SD) 6.5 (1.5)	NR	Range 0 – 5.5	NR	NR	</=5.5	4.4 (1.8)	2.3 (1.7)	Median 3.0	4.6 (1.93)
Comorbidities	NR	NR	NR	NR	NR	NR	NR	NR	Mean 2.4 (2.0); Range 0-9	NR	1 participant had severe depression on HADS	NR
On DMDs	NR	91 (60.1%)	NR	NR	NR	NR	NR	NR	26 (52%)	NR	104 (85%)	34 (55%)
Psychotropic medication(s)	NR	30 (20%)	NR	NR	NR	NR	No	NR	23 (46%)	NR	9 (6%)	35 (56%)

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] (For TIDieR checklist items, see Supplementary file 3).

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; $p<0.001$), I^2= 28% (low heterogeneity) (Figure 2); against active comparators SMD was 0.17 (0.01 – 0.32), $p<0.05$, I^2=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), I^2=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), I^2=10% (low heterogeneity). Six studies evaluated MBI effect on stress[21-24,28,29], where the SMD was 0.55 (0.25 – 0.85), I^2=48% (moderate heterogeneity).

Heterogeneity and publication bias

Heterogeneity, I^2, 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), I^2=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), I^2=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), I^2=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), I^2=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 3). Justifications for risk of bias scores are available in Supplementary file 4.

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 3 – Risk of Bias

Study/ Risk area	Mills & Allen (2000)	Grossmann et al. (2010)	Bogosian et al. (2015)	Kolahkaj & Zargar (2015)	Amiri et al. (2016)	Mahdavi et al. (2016)	Nejati et al. (2016)	Bahrani et al. (2017)	Simpson et al. (2017)	Carletto et al. (2017)	Cavelera et al. (2018)	Senders et al. (2018)
Random sequence generation (selection bias)	*Unclear*	*Low*	*Low*	*Low*	*Unclear*	*Unclear*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
Allocation concealment (selection bias)	*Unclear*	*Low*	*Low*	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Low*	*Low*	*Low*	*Unclear*	*Low*
Blinding of assessors (performance bias)	*Unclear*	*Low*	*Low*	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Low*	*Low*	*Low*	*Unclear*	*Low*
Blinding of outcome assessment (detection bias) (patient reported outcomes)	*High*	*Low*	*Low*	*Unclear*	*Unclear*	*Unclear*	*Unclear*	*Low*	*Low*	*Low*	*Unclear*	*Low*
Incomplete outcome data addressed (attrition bias)	*Unclear*	*Low*	*Low*	*High*	*High*	*Unclear*	*Unclear*	*Unclear*	*Low*	*Low*	*Unclear*	*Low*
Selective outcome reporting (reporting bias)	*High*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*	*Low*
Other sources of bias (i.e. baseline bias)	*Unclear*	*Low*	*Low*	*High*	*Unclear*	*High*	*High*	*Low*	*Low*	*Low*	*Low*	*Low*
Overall risk of bias	*High*	*Low*	*Low*	*High*	*High*	*High*	*High*	*Unclear*	*Low*	*Low*	*Unclear*	*Low*

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 4)

Table 4 – Meta-regression

Predictors	Estimates	95% CI	p-val
Intervention type(MBI)	-0.03	(-0.33, 0.26)	0.82
Intervention type (MBCT)	0.51	(0.13, 0.88)	0.008
Risk of Bias (High)	0.54	(0.12, 0.96)	0.01
Risk of Bias (Low)	0.18	(-0.13, 0.49)	0.25
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[37,38]. Preliminary RCT evidence supports CBT-based stress management therapy having a potential role in diminishing underlying disease activity in MS (Gadolinium uptake on magnetic resonance imaging). Besides the beneficial effects on perceived stress deriving from CBT, the clinical utility of these findings

remains unclear[39]. However, on the basis of 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 indicated.

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.[40]. However, on the basis of our study and others, it seems prudent to recommend systematic, group-based 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.

CONTRIBUTORSHIP

RS, SWM, NR, ML conceived the design of this project. ML carried out the database searches. RS, SB, JB carried out the literature screening and data extraction. NR and RS carried out the meta-analysis. RS led the writing of the manuscript. All authors read and approved the final version of the manuscript.

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COMPETING OF INTERESTS

None declared

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Figure 1PRISMA 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