Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis – a systematic review and meta-analysis

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Abstract

Background

Physical wellbeing is commonly impaired in people with multiple sclerosis (PwMS). This study aims to update our previous systematic review (2014) and conduct a meta-analysis on the efficacy of Mindfulness-based interventions (MBIs) for improving physical symptoms in PwMS.

Methods

In November 2017 we carried out systematic searches for eligible randomised controlled trials (RCTs) in seven major databases, updating our search in July 2018. We used medical subject headings and key words. Two independent reviewers used pre-defined criteria to screen, data extract, quality appraise, and analyse studies. The Cochrane Collaboration risk of bias tool was used to determine study quality. Physical wellbeing was the main outcome of interest. We used the random effects model for meta-analysis, reporting effect sizes as Standardised Mean Difference (SMD). This study is registered with PROSPERO: CRD42018093171.

Results

We identified 10 RCTs as eligible for inclusion in the systematic review (including 678 PwMS), whilst seven RCTs (555 PwMS) had data that could be used in our meta-analyses. In general, comorbidity, disability, ethnicity and socio-economic status were poorly reported. MBIs included manualised and tailored interventions, treatment duration 6-9 weeks, delivered face-to-face and online in groups and also individually. For fatigue, against any comparator SMD was 0.24 (0.08 – 0.41), I^2=0%; against active comparators only, SMD was 0.10 (-0.14 – 0.34), I^2=0%. For pain SMD was 0.16 (-0.46 – 0.79), I^2=77%. Three adverse events occurred across all studies.

Conclusions

MBIs appear to be an effective treatment for fatigue in PwMS. The optimal MBI in this context remains unclear. Further research into MBI optimisation, cost- and comparative-effectiveness is required.

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Keywords
Multiple sclerosis
Fatigue
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Meta-analysis

1.1 Background

Multiple sclerosis (MS) is a complex, poorly understood chronic inflammatory and neurodegenerative condition [1]. Common physical symptoms include difficulties with vision, speech, swallow, bowel, bladder and sexual function, chronic pain, spasticity and limited mobility [1]. Comorbidity, or the presence of an additional long-term condition besides MS, is common among people with multiple sclerosis (PwMS) [2]. Physical comorbidities in MS are associated with more CNS lesions on Magnetic Resonance Imaging (MRI), greater levels of disability, increased hospitalisations, and higher mortality rates [3]. Furthermore, having additional physical conditions in MS is associated with more stress and worse quality of life (QoL); as the number of additional physical conditions increase, so does the prevalence of mental health impairment [2].

Among physical comorbidities in PwMS, hypertension, hyperlipidaemia and chronic lung disease predominate [4]. Specific care guidelines for managing these physical comorbidities in PwMS do not exist [3]. Fatigue and chronic pain are among the commonest symptoms reported by PwMS [5 6]. The UK National Institute for Care and Clinical Excellence (NICE) recommends offering PwMS cognitive behavioural therapy (CBT), aerobic exercise, yoga, or amantadine for fatigue, as well as avoiding stress and treating comorbid anxiety and depression [7]. For chronic pain in PwMS, NICE recommends the application of generic treatment approaches [7].

Mindfulness-based interventions (MBIs) fit the UK Medical Research Council criteria for complex interventions [8], with multiple potential active components. Originally introduced in North America in the 1980s as a treatment for people with chronic pain [9], MBIs characteristically include a range of meditation practices, group exercises, psychoeducation and home practices [10 11]. MBIs have been applied and researched in a range of health conditions and found to be effective treatments for anxiety, stress, recurrent depression and somatisation disorders [12 13]. In a previous systematic review of the effectiveness of MBIs in PwMS in 2014 [14] we found limited evidence from two randomised controlled trials (RCTs) and a controlled trial to support MBIs as a potential treatment for

comorbid fatigue and comorbid pain in the condition, as well as improving standing balance [14]. Since 2014, several more RCTs have been published and it is important to determine more definitively whether MBIs are effective treatments for fatigue and pain in PwMS, besides other commonly encountered physical symptoms.

The aim of this review is to conduct a meta-analysis of RCTs testing the efficacy of MBIs in improving physical symptoms in PwMS.

2.1 Methods

2.2 Protocol and registration

Our protocol was registered prospectively with the Centre for Reviews and Dissemination, University of York, Prospero ID: CRD42018093171. This body of work also included a meta-analysis of MBI effects on mental wellbeing in PwMS, reported separately [15].

2.3 Eligibility for inclusion

We based eligibility on the Study design, Participants, Interventions, Outcomes (SPIO) model (deriving from PICOS) [16]. To be eligible for inclusion, studies had to be RCTs, (comparing MBI vs active comparator or care as usual), with no limit placed on sample size. Participants had to be PwMS (of any phenotype), aged 18 years or older. The intervention(s) being tested had to be a recognisable MBI that included core practices of mindful breathing, mindful body awareness, and mindful movement; Mindfulness-based stress reduction (MBSR) and Mindfulness-based cognitive therapy (MBCT) served as reference guides in this regard. Outcomes had to be appropriately validated and report on a definable aspect of physical wellbeing experienced by PwMS (e.g. symptoms such as fatigue, pain, standing balance).

2.4 Search strategy

We employed a search strategy from our previous systematic review for use in: Allied and Complementary Medicines Database (AMED), Cochrane Central

Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), and PsycINFO. As our previous systematic review found the first study in this area was published in 2000, we set our 'years' delimiter to 2000 – 2018. In addition, we also searched ProQuest Dissertations & Theses, reviewed key references from identified studies, searched the grey literature, and approached experts in the field. We carried out our initial search in November 2017 and repeated this in July 2018. Our search strategy as used in MEDLINE is available in Appendix A.

2.5 Study selection, storage and screening

We imported search results into COVIDENCE, a data storage package for systematic reviews. Title/abstracts were screened by two reviewers (RS, SS) for potential eligibility using keywords like 'mindfulness' and 'multiple sclerosis'. Selected studies were then assessed against SPIO criteria by two reviewers (JB, RS) to assess ultimate eligibility. A senior, third party reviewer (SM) was available to arbitrate any disagreements.

2.6 Data collection/data items

Data from the final list of included studies was extracted guided by CONSORT [17] and TIDieR [18] checklist categories (Appendix B).

2.7 Quality appraisal

We used the Cochrane Collaboration's tool for assessing risk of bias (RoB) [19] to summarise risk for individual outcomes in selected studies, graded as high, unclear, or low risk. This assessed generation of sequence, concealment of allocation, blinding of participants, outcome assessors and personnel, incomplete outcomes, selective reporting of outcomes, and any other bias. Finally, as outlined by Higgins et al. (2011)[19], an overall RoB within each trial was determined based on the number of individual outcomes falling in to the high, unclear, and low risk categories:

Low = Low RoB for all key domains

Unclear = Low or unclear RoB for all key domains

High = High RoB for one or more key domains

2.8 Principal summary measures

The main outcome for this study was impact of MBI on physical symptoms. Main outcome measures were all reported as continuous with mean, standard deviation (SD) values and the number of participants for each treatment group extracted. "Effect size" is reported as the unbiased standardised mean difference (SMD), a positive SMD indicating a finding in support of the intervention having a positive treatment effect (TE). The standardised mean difference was calculated by difference in means between the MBI and the control group at last point of follow-up divided by the pooled last point of follow-up SD. Where effect estimates were reported from adjusted regression models, we extracted these as the SMD with their corresponding SD.

2.9 Synthesis of results

Throughout this study we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] guidance. We used a random-effects meta-analysis, with an inverse variance method for pooling [21] to determine SMD, as outcome measures were known to vary widely. We report estimates with corresponding 95% confidence intervals (CI) and 'p' values. We used the I^2 statistic to determine variability between studies [22]; I^2 representing the percentage of total variability in effect size estimates due to heterogeneity. An I^2 of 0% indicates that all heterogeneity is consistent with sampling error, whilst an I^2 of 100% suggests all variability may be attributable to studies being truly heterogenous.

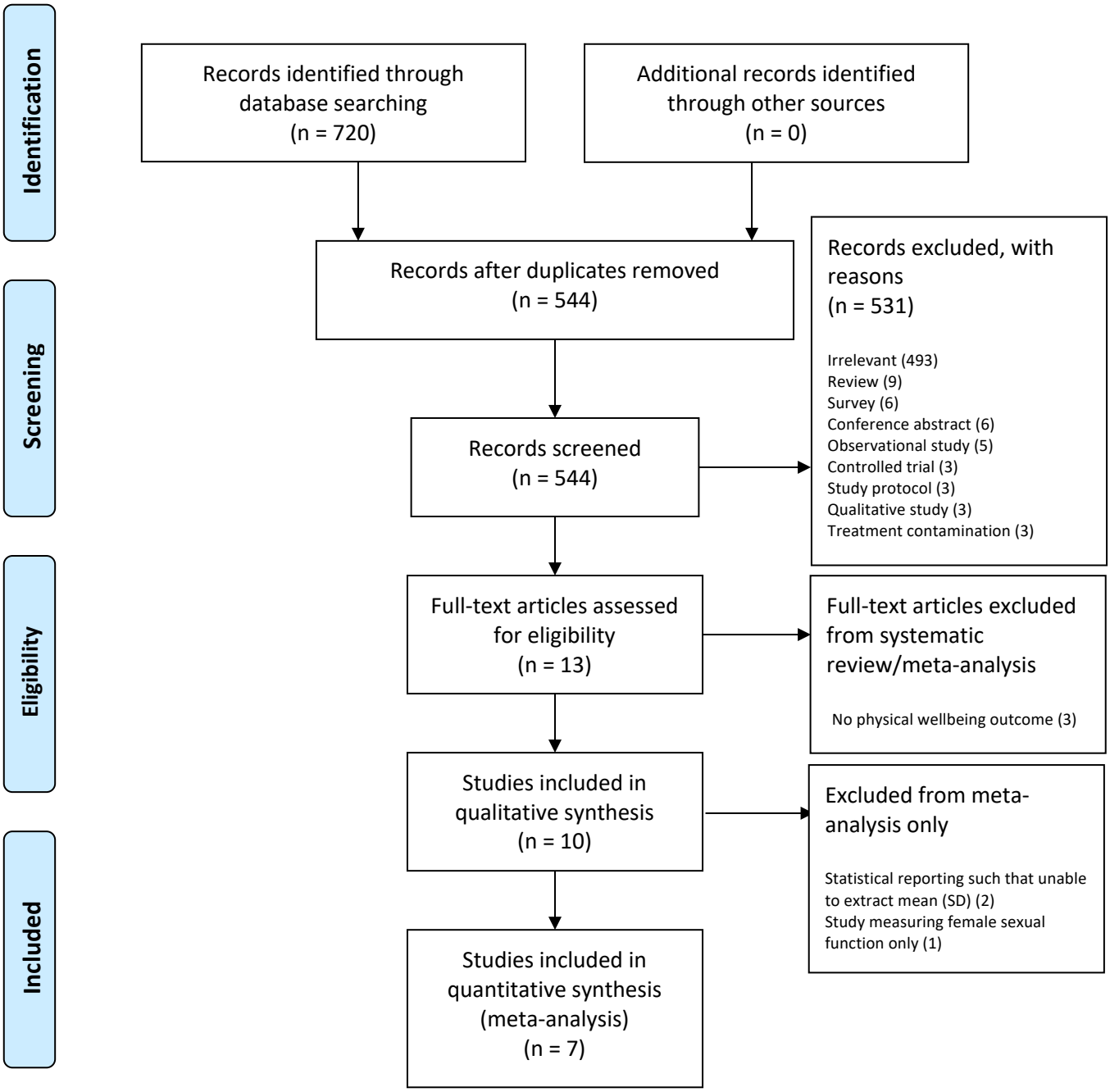
To assess for evidence of publication bias, we undertook Funnel plots and Egger's Test for asymmetry [23] [24].

We carried out all statistical analyses in R version 3.4.0 and using the meta package [25].

3.1 Results

We identified ten RCTs as eligible for inclusion in the systematic review, with seven studies reporting endpoint data usable in meta-analysis (Figure 1). We sought additional information from several study authors; one [26] replied.

Figure 1 – PRISMA flow diagram



3.2 Systematic review

3.2.1 Study characteristics

Three studies took place in Iran [27-29], three in the UK [30-32], two in Italy [26 33], one each in the USA [34] and Switzerland [35]. Four studies tested a MBI against treatment as usual [30-32 35], four versus an active comparator (three a psycho-education control [26 33 34], one pelvic floor muscle exercises [29]), and in two the control condition was not clearly specified [27 28]. Four study sample sizes were based on statistical power calculations [26 33-35]. Number of study participants ranged from 24 – 150 (median 62). Eight studies reported measuring outcomes at three points in time (baseline, immediately post MBI, and at further follow-up, which varied from 1 month post MBI to 1 year later) [26 29-35], whilst two studies took measures twice, pre and post MBI [27 28] (Table 1).

Table 1- Study characteristics

Study	Country	Study design	Powered (Y/N/ unclear)	Comparator	Sample size (n)	Study attrition (%)	Outcome measures (others)	Data collection
Mills & Allen (2000)	Wales (UK)	Randomised controlled trial	N	Treatment as usual	24	33	Profile of Mood States, Standing balance, Symptom rating questionnaire	○ Baseline ○ Post MBI ○ 3 months post MBI
Grossman et al. (2010)	Switzerland	Randomised controlled trial	Y	Treatment as usual	150	5	Center for Epidemiological Studies Depression, Spielberger Trait Anxiety Inventory, Modified Fatigue Impact Scale, Hamburg Quality of life Questionnaire in Multiple Sclerosis, Profile of health-related Quality Of Life in Chronic disorders, Goal setting, Neuropsychology assessment	○ Baseline ○ Post MBI ○ 6 months post MBI
Bogosian et al. (2015)	England (UK)	Randomised controlled trial	N	Treatment as usual	40	5	General Health Questionnaire, Hospital Anxiety and Depression Scale, Multiple Sclerosis Impact Scale-29, EuroQol, Fatigue Severity Scale, Numerical Rating Scale (Pain)	○ Baseline ○ Post MBI ○ 3 months post MBI
Mahdavi et al. (2016)	Iran	Randomised controlled trial	N	Indeterminate	24	0	Beck Anxiety Inventory, Beck Depression Inventory, Fatigue Severity Scale, Meta-Worry Questionnaire, Thought Fusion Inventory	○ Baseline ○ Post MBI
Nejati et al. (2016)	Iran	Randomised controlled trial	Unclear	Indeterminate	24	0	Multiple Sclerosis Quality of Life-54, Fatigue Severity Scale	○ Baseline ○ Post MBI
Simpson et al. (2017)	Scotland (UK)	Randomised controlled trial	N	Treatment as usual	50	12	Perceived Stress Scale, EuroQol, Multiple Sclerosis Quality of Life Inventory, Mindful Attention Awareness Scale, Self-Compassion Scale-short form, Emotional Lability Questionnaire	○ Baseline ○ Post MBI ○ 3 months post MBI
Carletto et al. (2017)	Italy	Randomised controlled trial	Y	Psycho-education	90	21	Beck Anxiety Inventory, Beck Depression Inventory, Perceived Stress Scale, Brief Illness Perception Questionnaire, Functional Assessment of Multiple Sclerosis, Fatigue Severity Scale	○ Baseline ○ Post MBI ○ 6 months post MBI
Cavalera et al. (2018)	Italy	Randomised controlled trial	Y	Psycho-education	139	39	Multiple Sclerosis Quality of Life-54, Hospital Anxiety and Depression Scale, Medical Outcomes Sleep Scale, Modified Fatigue Impact Scale	○ Baseline ○ Post MBI ○ 6 months post MBI
Mosalanejad et al. (2018)	Iran	Randomised controlled trial	Unclear	Pelvic floor muscle exercises	75	7	Female Sexual Function Index	○ Baseline ○ Post MBI ○ 1-month post MBI
Senders et al. (2018)	USA	Randomised controlled trial	Y	Psycho-education	62	16	Perceived Stress Scale, Patient-Reported Outcomes Information System, Connor-Davidson Resilience Scale, Paced Auditory Serial Attention Task	○ Baseline ○ Mid-intervention ○ Post MBI ○ 4 months post MBI ○ 8 months post MBI ○ 12 months post-MBI

3.2.2 Participant characteristics

There were 678 participants between the 10 RCTs included in the systematic review, versus 555 participants in the seven studies included in the meta-analysis. Participant ethnicity was described in three studies [30 32 34], most were Caucasian. Between all 10 RCTs, the majority were female (76%; n=517). The extractable mean participant age was 46.0 years (not reported in [27]). One study reported on socioeconomic status (SES) using post-code derived data [32]. Three studies described negligible data on employment status of participants [31-33]. Seven studies reported education status [26-28 30 32 34 35], most having school level education as a minimum. The majority (a minimum of 414 or 61%) had a relapsing-remitting phenotype, a minimum of 112 (17%) a secondary progressive phenotype, and a minimum of 27 (4%) had a primary progressive phenotype. Degree of disability was reported in five studies [30 32-35], using the Expanded Disability Status Scale (EDSS) with a range of 2.3 – 6.5. Comorbidity (mental and physical) count was described in one study [32] (mean 2.3, SD 1.7). Four studies [26 32 34 35] described use of psychotropic and/or MS disease modifying drugs (Table 2).

Table 2 – Participant characteristics

Study/ demographic	Mills & Allen (2000)	Grossman et al. (2010)	Bogosian et al. (2015)	Mahdavi et al. (2016)	Nejati et al. (2016)	Simpson et al. (2017)	Carletto et al. (2017)	Cavalera et al. (2018)	Mosalanejad et al. (2018)	Senders et al. (2018)
Ethnicity	Not reported	Not reported	90% British Caucasian	Not reported	Not reported	100% British Caucasian	Not reported	Not reported	Not reported	97% Caucasian
Number of participants (% F)	16 (80%)	150 (80%)	40 (55%)	24 (100%)	24 (46%)	50 (92%)	90 (71%)	139 (65%)	75 (100%)	67 (78%)
Mean age (SD)	49.8 (6.8)	47.3 (10.3)	52.2 (9.1)	NR	32.3 (5.1)	45 (10.9)	44.6 (9.4)	42.7 (8.7)	37.5 (6.5)	52.94 (11.37)
Socio-economic status	Not reported	Not reported	Not reported	Not reported	Not reported	Postcode derived; controlled in analyses	Not reported	Not reported	Not reported	Not reported
Employment status	4 employed (25%)	Not reported	Not reported	Not reported	Not reported	20 employed (40%)	59 employed (65%)	Not reported	Not reported	Not reported
Education status (SD)	Not reported	Mean (SD) 14.1 (1.9) years of education	31 (77.5) college education at least	Completed high school	Completed high school	(56%) university	Not reported	11% elementary school; 52% completed high school; 38% university	Not reported	60% college education at least
Disease phenotype (%)	Secondary progressive 16 (100%)	Relapsing 123 (82%) Secondary progressive 27 (18%)	Secondary progressive 23 (57.5%) Primary progressive 17 (42.5%)	Not reported	Not reported	Relapsing 40 (80%) Secondary progressive 16 (32%) Primary progressive 4 (8%)	Relapsing 79 (88%) Secondary progressive 7 (8%) Primary progressive 2 (2%)	Relapsing 131 (93%) Secondary progressive 8 (7%)	Not reported	Relapsing 41 (67%) Secondary progressive 15 (25%) Primary progressive 4 (6%) Unknown 2 (3%)
EDSS score	Not reported	Mean (SD) 3.0 (1.1)	Mean (SD) 6.5 (1.5)	Not reported	Not reported	4.4 (1.8)	2.3 (1.7)	Median 3.0	Not reported	4.6 (1.93)
Comorbidities	Not reported	Not reported	Not reported	Not reported	Not reported	Mean 2.4 (2.0); Range 0-9	Not reported	1 participant had severe depression on HADS	Excluded if comorbid conditions	Not reported
On DMDs	Not reported	91 (60.1%)	Not reported	Not reported	Not reported	26 (52%)	Not reported	104 (85%)	Not reported	34 (55%)
Psychotropic medication(s)	Not reported	30 (20%)	Not reported	Not reported	No	23 (46%)	Not reported	9 (6%)	Not reported	35 (56%)

3.2.3 Intervention characteristics

MBSR was explicitly used as the MBI in four studies [26 32 34 35] and the loose basis in a further two [28 33], two explicitly used MBCT [27 30], one described the intervention as 'Mindfulness of Movement' [31], and in the remaining case the foundation for the MBI was unclear [29]. Five studies reported on what course materials were provided to those taking part [26 28 30-32]. An interview was compulsory prior to taking part in three studies [27 28 35]. Two studies required evidence of impaired mental wellbeing (stress, anxiety) at baseline in order to take part [30 34]. Six studies reported on what MBI sessions comprised [27 28 30 32 34], three provided scant information in this regard [31 33 35], and in another this information was available in a separate publication, via the study protocol [26]. Home practices were prescribed in six studies [30-35]. Teacher characteristics (training/certification/experience) were outlined in seven studies [26 29 30 32-35], but details were sparse in one [29]. MBIs were delivered as groups in nine studies [26-30 32-35], the remaining study delivered a one-to-one MBI[31]. An online platform was used to deliver the MBI in two studies [26 30]. Four studies reported where the MBI took place [26 29 30 32]. The majority of studies used eight MBI sessions [26-30 32-34], there were nine in one study [35], another used six [31]. Weekly MBI session lengths varied between 1-3 hours. There were between five to 25 participants per MBI class across the studies, sessions being administered by 1-2 MBI instructors. The core MBI components were delivered in all studies. However, in six studies the MBI was tailored for PwMS [26 30-33 35], mostly in advance, but reflexively in one case [32], where mindful movement was simplified to accommodate high levels of disability. Another study pre-emptively removed mindful movement following stakeholder consultation [30]. Home practice completion and/or session attendance was used to determine treatment adherence in six studies [26 30-32 34 35]. Intervention fidelity was appraised in three studies [26 30 32], in one case by an independent observer checking session content against referenced standards [30]. The day retreat, characteristically part of week six in MBSR, was included in three studies [33-35] (Table 3 outlines intervention characteristics using the Template for Intervention Description and Replication checklist).

Table 3 – Template for Intervention Description and Replication (TIDieR) checklist

Study/ checklist item	Mills & Allen 2000	Grossman et al. 2010	Bogosian et al. 2015	Mahdavi et al. 2016	Nejati et al. 2016	Simpson et al. 2017	Carletto et al. 2017	Cavalera et al. 2017	Mosalanejad et al. 2018	Senders et al. 2018
1. Brief name?	Mindfulness of Movement	Mindfulness-based stress reduction (MBSR)	Mindfulness-based cognitive therapy	Mindfulness-based cognitive therapy	MBSR and Conscious Yoga	Mindfulness-based stress reduction	Modified MBSR – 'Body Affective Mindfulness'	Mindfulness-based stress reduction	'Mindfulness'	Mindfulness-based stress reduction
2. Why (stated rationale/ theory/ goal)?	Develop moment to moment awareness of breath, posture, movement with compassion	Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior	Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/ reacting to them automatically	Adaptation of MBSR. Focus on negative thinking, engaging low mood, changing relationship with thoughts, feelings, sensations, no longer avoiding/ reacting to them automatically	Facilitate the compliance with and adaptation to medical conditions. Pay attention to being present in a non-judgmental manner	Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior	Cultivation of mindful awareness, loving kindness, enrichment of listening, self-compassion, sensorimotor psychotherapy principles 'window of tolerance'	Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior	Non- judgmental present moment awareness	Cultivate interested, accepting, non-judgmental attitude to experience, including difficult sensations, emotions, thoughts and behavior
3. What - Materials provided to participants?	Written handout, audio and video aids	Not reported	Headset, webcam, compact discs for home practice	Not reported	Leaflets for each session and compact discs for home practice	Course manual, compact discs for home practice Book - *Full Catastrophe Living*	Not reported	Dedicated website with online multimedia for home practices	Not reported	Not reported
4. What - Procedures - Pre-session?	Had to make a commitment to regular practice	Personal intake interview; goal planning	Screened for evidence of distress on General Health Questionnaire	Personal intake interview	Personal intake interview	Not reported	Not reported	Not reported	Not reported	Score of at least 1ten on Perceived Stress Scale
4. What - Procedures – In session?	**General description only** - Body awareness, breath awareness,	**General description only** - Observation of sensory, cognitive and affective	**Session content reported in paper –** Raisin exercise, Mindful awareness, body scan, sitting	**Session outline reported in paper –** Sustained attentional focus on the	**Session outline reported in paper –** Body awareness, raisin	**Session content reported in paper –** Raisin exercise, Mindful	**General description in trial protocol –** Emphasis on sensorimotor resources: grounding,	**General description only -** Based on original Mindfulness-based stress	**Session content reported in paper –** Mindful breathing, body scan, sitting mediation, mountain	**Session content reported in paper –** Mindful breathing, body scan,

	mindful movement, Tui Na self-massage	experience in lying, siting, and dynamic yoga postures	practice, three-minute breathing space, psycho-education, cognitive exercises	body and breath, decentered view of thoughts as passing mental events	exercise, three-minute breathing, yoga, sitting meditation, psycho-education on stress, mountain meditation	breathing, body scan, mindful movement, psycho-education	centring, self-soothing, psycho-education on stress, self-compassion, body scan, breath meditation, walking meditation, yoga exercises	reduction protocol	meditation, mindful eating, choice-less awareness, loving kindness, psycho-education	mindful movement, loving kindness, sitting meditation, push- pull exercise, psycho-education on stress
4. What – Procedures - Home practice?	Thirty minutes per day	Forty minutes per day	Ten-twenty minutes per day	Not reported	Not reported	Forty-five minutes per day	Forty-five minutes per day	Not reported	Not reported	Forty-five minutes per day
4. What - Procedures – Post-course?	Not reported	Post course interviews for all participants	Post course interviews for some participants	Not reported	Not reported	Post course interviews for some participants	Not reported	Not reported	Not reported	Not reported
5. Who provided?	Not reported	Two experienced (over nine years), certified teachers	Study author. Had completed MBI teacher training	Not reported	Not reported	Two experienced (seven and a half years), certified physician teachers	Trained clinical psychologists, used to working with people with multiple sclerosis	Expert MBSR trainer	Study author	Certified MBSR teacher with sixteen years of experience
6. How - Mode of delivery?	One-to-one, face-to-face	Group, face-to-face, ten-fifteen per group	Group, via Skype, up to five per group	Group, twelve per group	Group, twelve per group	Group, face-to-face, twenty-five per group	Group, number per group not reported	Group, via Skype, average of five per group	Not reported	Group, number per group not reported
7. Where - Intervention location?	Unclear	Unclear	Participants' own homes	Unclear	Unclear	NHS Centre for Integrative Care	Unclear	In patients own homes	University hospital out- patient clinic	Not reported
8. When and how much?	Six weekly sessions	Nine weekly two and a half hour sessions Seven-hour practice day at week six	Eight weekly one hour sessions	Eight weekly two hour sessions	Eight weekly two hour sessions	Eight weekly two and a half hour sessions	Eight weekly three hour sessions Seven-hour practice day	Eight weekly sessions (? duration)	Eight weekly ninety minute sessions	Eight weekly two hour sessions Six-hour practice day at week six
9. Tailoring?	Individualised application of core techniques	Exercises did not exceed level of function	Developed with people with multiple sclerosis. MBCT manual adapted for Progressive	Not reported	Not reported	Developed with people with multiple sclerosis, informed MBSR	Protocol reports tailoring to needs of participants, but not reported in paper	Music meditations and acceptance of multiple sclerosis	Not reported	Not reported

			multiple sclerosis issues Mindful-movement removed			optimisation for future iteration		symptoms introduced		
10. In study modifications?	Not reported	Not reported	Not reported	Not reported	Not reported	Mindful movement simplified	Not reported	Not reported	Not reported	Not reported
11. How well - Treatment adherence?	Average thirty-two minutes home practice per day	Ninety-two percent session attendance; Average twenty-nine-point two minutes home practice per day	Ninety-five percent completed four or more sessions. Home practice not reported	Not reported	Not reported	Sixty percent session attendance; Average thirty-two and a half minutes home practice per day	Not reported	Seventy-nine percent session attendance	Not reported	Eighty-five percent attended six or more sessions. Median home practices thirty-eight minutes per day
12. How well - Fidelity assessment?	Not reported	Not reported	Senior clinical psychologist listened to session recordings for every session	Not reported	Not reported	Based on National Institutes of Health (2004)	Not reported	Treatment integrity monitored, but not reported in what way	Not reported	Not reported

3.2.4 Outcome characteristics

Seven studies measured the impact of MBI on fatigue [26 28 30 32-35], three on pain [30 32 34], one on standing balance [31], one on sleep [26], and one on female sexual function [29]. As all three studies that reported on pain also reported on fatigue, fatigue was thus chosen as the main outcome for our analysis.

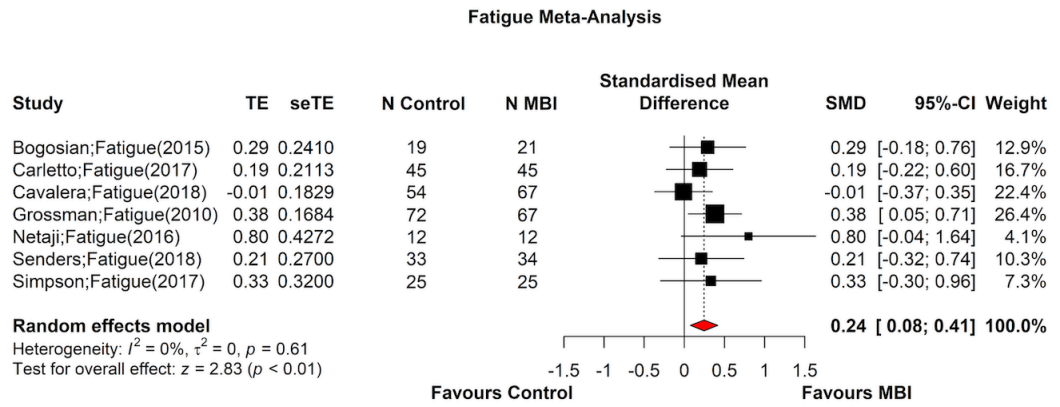
Average home practice was reported in three studies (32, 29.2, 32.5 minutes) [31 32 35]; whilst one study reported median value/ minimum-maximum range (38 minutes/day; 14 – 80) [34]. Attrition ranged from 0-39% across the ten studies; those with no attrition were pre-post- studies with small sample sizes [27 28].

3.3 Meta-analysis

3.3.1 *Effect of MBIs on physical symptom measures*

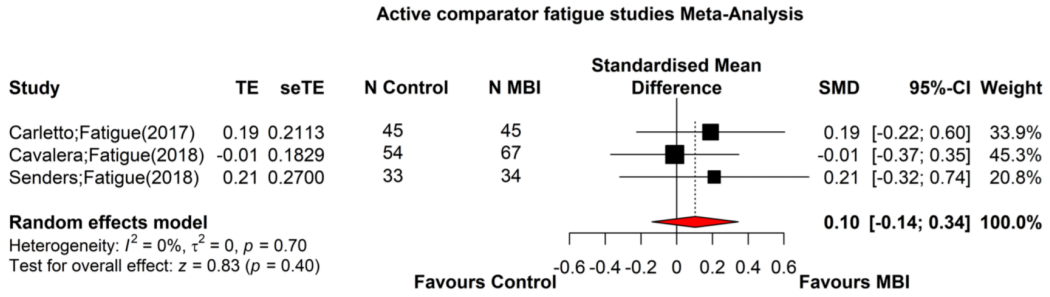
The effect of a MBI on physical symptoms was measured in 10 studies [26-35]; seven reported endpoint data usable in the meta-analysis [26 28 30 32-35]. Seven studies evaluated MBI effect on fatigue [26 28 30 32-35], where the SMD against any comparator was 0.24 (0.08 – 0.41) p<0.01, I^2=0% (low heterogeneity) (Figure 2); against active comparators only the SMD for fatigue was 0.10 (-0.14 – 0.34), p=0.40, I^2=0% (low heterogeneity) (Figure 3). Three studies also evaluated MBI effect on pain (besides fatigue) [30 32 34], where the SMD was 0.16 (-0.46 – 0.79), p=0.61, I^2=77% (substantial heterogeneity) (Figure 4).

Figure 2 SMD for fatigue vs any comparator



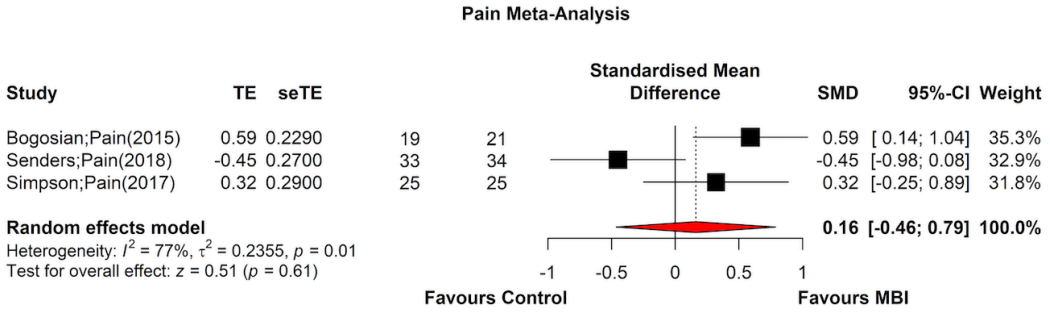
TE - Treatment effect; seTE - standard error of the TE; SMD – Standardised mean difference; 95%CI - 95% confidence interval; Weight - weight contributed by each study

Figure 3 SMD for fatigue vs active comparators



TE - Treatment effect; seTE - standard error of the TE; SMD – Standardised mean difference; 95%CI - 95% confidence interval; Weight - weight contributed by each study

Figure 4 SMD for pain vs any comparator

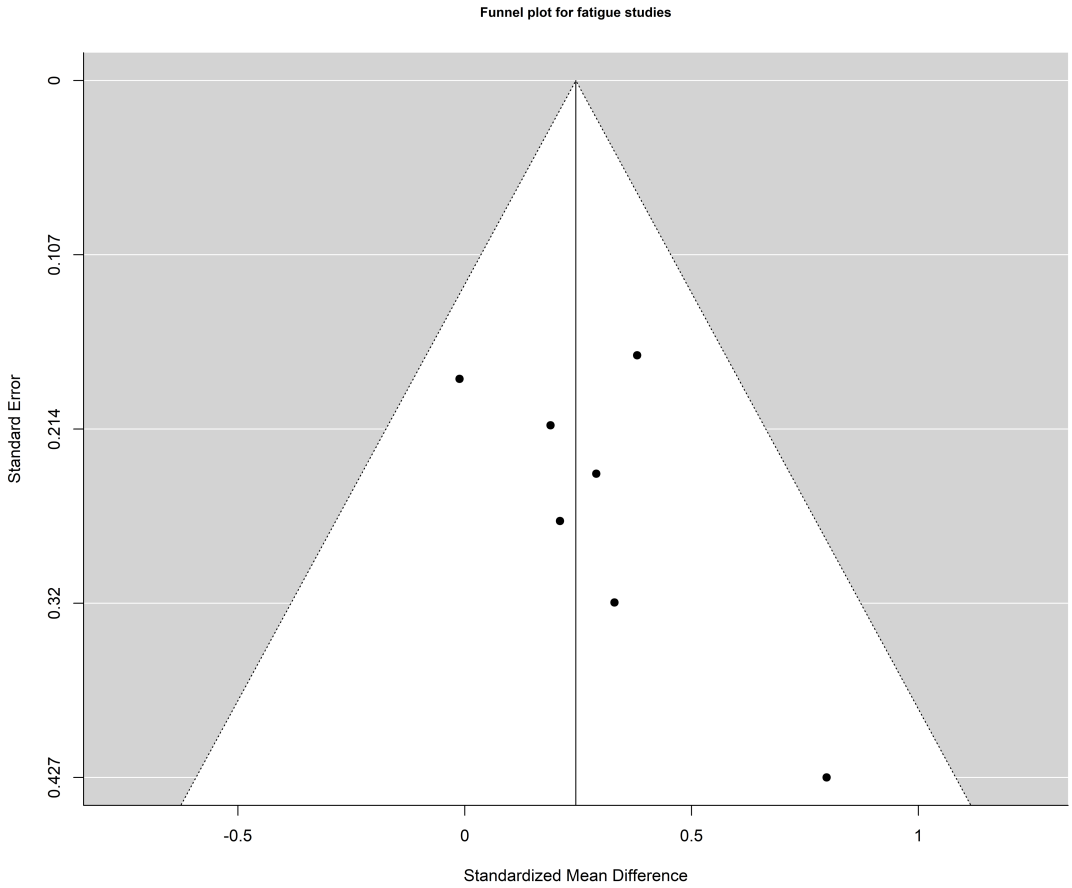


TE - Treatment effect; seTE - standard error of the TE; SMD – Standardised mean difference; 95%CI - 95% confidence interval; Weight - weight contributed by each study

3.3.2 *Heterogeneity and publication bias*

Using the I^2 statistic, heterogeneity was low for fatigue (0%), but substantial for pain (77%). The funnel plot for fatigue identified no evidence of publication bias (Figure 5). The p-value from Egger's Test of asymmetry from fatigue studies was 0.256.

Figure 5 - Funnel plot for fatigue studies



3.3.3 *Outcomes by intervention type*

Where MBSR was used (four studies [26 32 34 35]; n=401), SMD for fatigue was 0.22 (0.01 – 0.42), p=0.04, I^2=0%; for pain (two studies [32 34]) SMD was -0.07 (-0.83 – 0.68), p=0.85, I^2=74%. Outcomes for MBCT came from a single pilot study [30] (n=40) versus usual care, where effect size for fatigue was 0.29 (-0.18 – 0.76), p=0.30 and the effect size for pain was 0.59 (0.14 – 1.04), p<0.05. Compared to a psychoeducation control, a study using Body-Affective Mindfulness (n=90) [33] had an effect size of 0.19 (-0.22 – 0.60), p=0.37 for effect on fatigue.

3.4 Study quality

Study quality was highly variable. Assessment was frequently made challenging by scanty reporting. For unclear reasons, those studies of highest quality (lowest RoB) originated from European countries and the United States. Eight studies

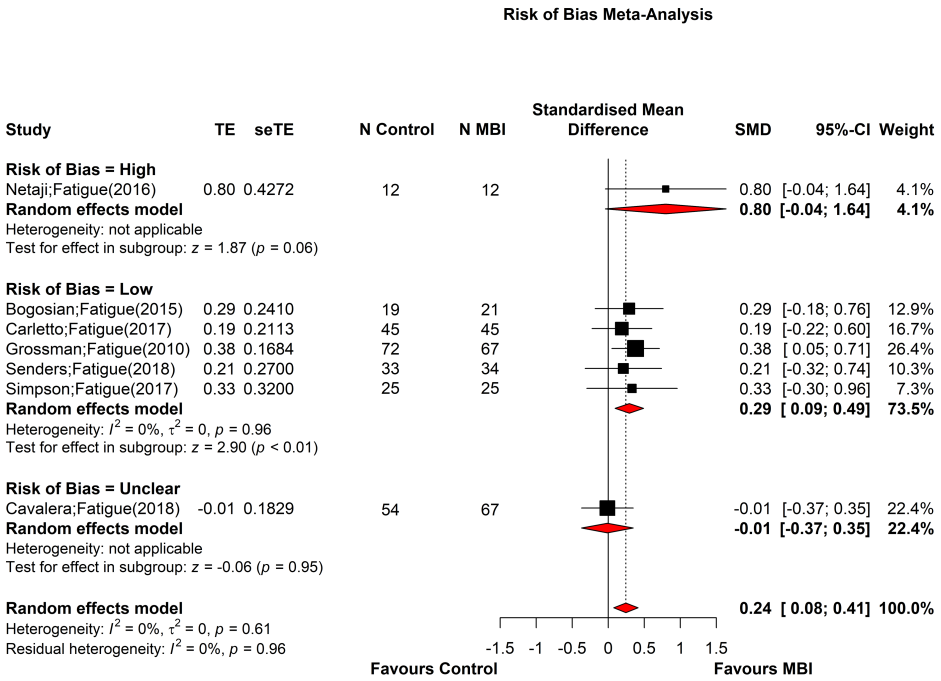
outlined random sequence generation [26 28-30 32-35]. Five studies were adjudged low risk for allocation concealment [30 32-35], with the remainder unclear [26-29 31]. Blinding of assessors was outlined in six studies [29 30 32-35], as was outcome assessor blinding [29 30 32-35]. Five studies were deemed low risk when assessing reporting of outcomes as incomplete [30 32-35]. One study was assessed as at high risk for selective reporting of outcomes [31]. In terms of overall *within* trials RoB assessments, five studies were deemed low risk [30 32-35], two unclear [29], and three as high [27 28 31]. *Across* trials, overall RoB was low for random sequence allocation, unclear for allocation concealment, low for assessor blinding, low for blinding of outcome assessment, unclear for incomplete outcome assessment, low for selective outcome reporting, and low for other sources of bias. Overall, there is an unclear RoB across trials. (Table 4). Appendix C details rationale for RoB assessments.

As all the pain studies were in the low RoB group, Figure 6 illustrates only the SMD for all trials able to be analysed for fatigue, arranged by RoB categories (low, unclear and high). Low RoB (n=5) SMD was 0.29 (0.09 – 0.49): I^2=0% (low heterogeneity); p<0.01. Unclear RoB (n=1) SMD was -0.01 (-0.37 – 0.35); p=0.95. High RoB (n=1) SMD was 0.80 (-0.04 – 1.64); p=0.06. Effect estimates did not vary significantly between RoB allocation in the overall RoB analysis, p=0.15. The low RoB studies are most likely to approximate the true effect of an MBI on PwMS who have fatigue, with (generally) larger sample sizes, a higher standard of trial procedures and hence less chance of inadvertent bias.

Table 4 – Risk of Bias

	Mills & Allen (2000)	Grossmann et al. (2010)	Bogosian et al. (2015)	Mahdavi et al. (2016)	Nejati et al. (2016)	Simpson et al. (2017)	Carletto et al. (2017)	Cavelera et al. (2018)	Mosalanejad et al. (2018)	Senders et al. (2018)	Across trials – overall RoB
Random sequence generation	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low
Allocation concealment	Unclear	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Unclear
Blinding of assessors	Unclear	Low	Low	Unclear	Unclear	Low	Low	Unclear	Low	Low	Low
Blinding of outcome assessment	High	Low	Low	Unclear	Unclear	Low	Low	Unclear	Low	Low	Low
Incomplete outcome data addressed	Unclear	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Unclear
Selective outcome reporting	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Other sources of bias	Unclear	Low	Low	High	High	Low	Low	Low	Low	Low	Low
Within trials overall RoB	High	Low	Low	High	High	Low	Low	Unclear	Unclear	Low	Unclear

Figure 6 Risk of Bias Forest plot for fatigue studies



TE - Treatment effect; seTE - standard error of the TE; SMD – Standardised mean difference; 95%CI - 95% confidence interval; Weight - weight contributed by each study

3.5 Adverse events

Two studies reported on adverse events associated with MBI exposure [32 34]. In one study that used MBSR a participant reported an episode of increased spasticity during mindful body awareness [34]. In the same study another participant described increased anxiety following the MBSR retreat [34]. In another study using MBSR one participant with chronic pain reported increased symptoms following the raisin exercise [32].

4.1 Discussion

4.2 Summary of main findings

Ten RCTs that assessed the effects of an MBI on physical symptom outcomes in PwMS were eligible for inclusion in our systematic review; seven of these had data extractable for use in our meta-analysis. Four studies tested an MBI against an active comparator, four tested against treatment as usual, whilst the control condition was unclear in the remaining two studies. Intervention fidelity was reliably assessed in only one study. Sample sizes were frequently small. Follow-ups took place from immediately post-MBI to up to 1 year following course completion.

Six hundred and seventy-eight PwMS were included in these studies. Most (58%) had relapsing phenotypes. Most participants were female; mostly of Caucasian ethnicity. In general, comorbidity and disability levels were poorly reported.

Four studies used MBSR, two were loosely modeled on MBSR; two explicitly used MBCT, one 'Mindfulness of Movement', and in one case the basis for the MBI was unclear. Most interventions were provided as groups (n=5-25), delivering core MBI practices in and between sessions. Level of teacher training and experience were not well reported. MBI session attendance +/- home practice (treatment adherence) was described in six studies. Rates of attrition varied considerably (0-39%). Although very few adverse events were described from MBI training, few studies explicitly reported on this outcome.

Five RCTs were categorised as overall low RoB using the Cochrane Collaboration tool, three as high and two as unclear, signifying an overall improvement in study quality since we last assessed this in 2014 [14].

Our meta-analysis indicates that MBIs are modestly effective treatments for fatigue in PwMS, but evidence to support improvements in pain is inconsistent. No MBI is clearly optimal for treating impairment of fatigue in PwMS.

4.3 Comparison with existing literature

In this study we found MBIs moderately effective for improving fatigue (SMD 0.24; 0.08 – 0.41), but inconsistent with regards to effects on pain (SMD 0.16; -0.46 – 0.79) in PwMS.

A 2018 meta-analysis [36] of psychological interventions for treating fatigue in PwMS reported CBT to be moderately effective (SMD 0.32; 0.01 – 0.63) and MBIs to be considerably more effective (SMD 0.62; 0.12 – 1.12), but only included two [30 35] of the seven [26 28 30 32-35] RCTs identified in our current review, likely reflecting an earlier search cut-off date in their study (April 2017).

No previous meta-analysis has assessed the impact of MBI training on pain in PwMS, but in chronic pain populations at large, several meta-analyses have been conducted. A 2014 meta-analysis [37] reported moderate overall treatment effects (Cohen's d) from MBI training (0.33; 0.03 – 0.62), a finding that diminished to a null effect when examining the effect against active comparators. A 2015 meta-analysis [38] comprising painful musculoskeletal conditions reported small effects (Hedge's g) versus usual care following MBI training on pain intensity (0.16; 0.03 – 0.36; the effect attenuated when compared against active comparators to 0.09; -0.13 – 0.31), moderate effects on perceived pain control (0.58; 0.23 – 0.93), but larger effects on pain acceptance versus usual care (1.58; -0.57 – 3.74). Finally, a 2017 meta-analysis [39] found small overall effects against any comparator, SMD 0.32 (0.09 – 0.54), but included a wide variety of clinical syndromes.

4.4 Strengths of this review

Guided by the PRISMA checklist [20], the TIDieR checklist [18] and the Cochrane Collaboration tool [19], our multidisciplinary team of experienced reviewers used robust search, appraisal and analysis techniques for extracting and analysing data in this systematic review and meta-analysis.

4.5 Limitations of this review

Although we assessed quality using a reference standard, the Cochrane Collaboration RoB tool, we did not estimate the strength of any recommendation

for use of MBIs in PwMS. Future studies could do so by applying the GRADE criteria [40].

Meta-analyses of RCTs by design exclude other potentially relevant data, such as that deriving from observational or qualitative research. When considering intervention feasibility, such as acceptability, accessibility and implementability, these alternate study designs can provide important insights into how and why interventions succeed or fail in a given context. However, in this current study, the use of SPIO, the TIDieR checklist and Cochrane Collaboration tool for RoB, means that our evidence synthesis has covered other, related aspects of trial feasibility and execution.

4.6 Strengths and Limitations of the included studies

When considering the strength of evidence for the use of MBIs in PwMS, most studies which assessed impact on fatigue (n=5/7) and all that assessed impact on pain (n=3) were adjudged low RoB. However, despite all studies being RCTs, participant numbers were low (n=<50) in four. Although all MS phenotypes were represented, most participants had relapsing-remitting MS. Furthermore, mean sample age was relatively low (46.0), whilst ethnicity, SES and comorbidity were poorly covered, limiting the generalisability of findings. To complicate matters, several studies tailored their MBIs with minimal/absent prior justification. Only four compared an MBI against an active comparator condition. Observed effects were mostly small, with a wide range of confidence intervals. Heterogeneity, overall, was low.

Given the well documented high levels of physical comorbidity in PwMS, it is notable that our meta-analysis has only been able to quantify the effects of MBI training on two, albeit common, facets of physical wellbeing, namely fatigue and pain. Other aspects of physical wellbeing were measured in individual studies (e.g. standing balance, sleep and sexual function), where beneficial effects were reported, but meta-analysis was not possible. Future studies could address this evidence gap by measuring the impact of MBI training on other common physical symptoms associated with MS, for example dysarthria, dysphagia, bowel and

bladder dysfunction, dynamic balance, in-coordination and spasticity. Although MBSR and MBCT both appear to be effective treatments for fatigue, it is not currently possible to recommend one approach over the other.

4.7 Implications for research

The quality of evidence for MBIs as effective treatments for fatigue in PwMS has improved considerably since our systematic review in 2014. However, adherence to CONSORT [17] reporting was poor in several studies included in the meta-analysis, with three studies assessed overall as high risk and two as unclear according to the Cochrane Collaboration [19] tool. In addition, MBI description was often sparse in detail. Were researchers to adhere more closely to the CONSORT [17] and TIDieR [18] checklists when reporting studies of MBIs for PwMS, the knowledge base in this area could be further enhanced, helping to clarify where further research efforts should focus.

It remains unclear which type of MBI may be best for PwMS with impaired physical wellbeing in general, or fatigue or pain more specifically. Future research could test either MBSR or MBCT against established treatments in this area; by involving people affected with the condition in this endeavor, the co-design, delivery and ongoing development of an optimised MBI course for PwMS could take place [8].

4.8 Implications for clinical practice

MBIs appear to be modestly effective at improving fatigue in PwMS.

5.1 Conclusions

Meta-analytic evidence supports the use of MBIs in PwMS to improve fatigue. Evidence to support the use of MBIs for treating pain in this population is inconsistent. Although the quality of study reporting has become better, room still exists for enhanced reporting in this area. No clear optimal MBI exists for improving impaired physical wellbeing in PwMS.

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.

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