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Review

A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome

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ABSTRACT

Objectives: This paper presents a systematic review and meta-analysis of the effectiveness of mindfulness-based stress reduction (MBSR) for FMS.
Methods: The PubMed/MEDLINE, Cochrane Library, EMBASE, PsychINFO and CAMBASE databases were screened in September 2013 to identify randomized and non-randomized controlled trials comparing MBSR to control interventions. Major outcome measures were quality of life and pain; secondary outcomes included sleep quality, fatigue, depression and safety. Standardized mean differences and 95% confidence intervals were calculated.
Results: Six trials were located with a total of 674 FMS patients. Analyses revealed low quality evidence for short-term improvement of quality of life (SMD = −0.35; 95% CI −0.57 to −0.12; P = 0.002) and pain (SMD = −0.23; 95% CI −0.46 to −0.01; P = 0.04) after MBSR, when compared to usual care; and for short-term improvement of quality of life (SMD = −0.32; 95% CI −0.59 to −0.04; P = 0.02) and pain (SMD = −0.44; 95% CI −0.73 to −0.16; P = 0.002) after MBSR, when compared to active control interventions. Effects were not robust against bias. No evidence was further found for secondary outcomes or long-term effects of MBSR. Safety data were not reported in any trial.
Conclusions: This systematic review found that MBSR might be a useful approach for FMS patients. According to the quality of evidence only a weak recommendation for MBSR can be made at this point. Further high quality RCTs are required for a conclusive judgment of its effects.

Contents

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Introduction

The fibromyalgia syndrome (FMS), a chronic condition characterized by chronic widespread pain, fatigue, cognitive disturbances, sleep disorders and a high amount of somatic and psychological distress [1,2] affects between 2.9 and 3.8% of the general population in Europe [3,4], with women being much more frequently affected than men [2]. Due to lack of data only a few complementary therapies can be recommended at the moment, although such therapies are frequently applied by the majority of FMS patients [5]. One treatment modality, which has been used for a variety of chronic pain conditions, is mindfulness-based stress reduction (MBSR).

MBSR has originally been developed as a behavioral medical intervention for patients suffering from chronic pain conditions and stress-related disorders [6] and received increasing attention within the past decade [7]. The original curriculum [6] applies a structured 8-week group program of 2.5 h weekly and an additional all-day silent retreat with the overarching aim of cultivating mindfulness, a special way of paying attention often described as moment-to-moment non-judgmental awareness. Key components of MBSR include different formal mindfulness practices (sitting meditation, walking meditation, body scan, and also yoga exercises) [8], daily homework, and also informal mindfulness practice aiming to increase awareness during routine activities in everyday life [9]. MBSR cannot be considered a causal therapy for any pain disorder; however it might help patients to improve their coping and thereby reduce suffering.

Systematic reviews have already shown that MBSR might be effective for chronic pain conditions [10–12] and for mental problems such as stress, depression and anxiety [13,14] however no review has been undertaken to determine the effects of MBSR for the treatment of FMS in particular. Therefore this systematic review and meta-analysis aimed to determine the short- and long-term efficacy and safety of mindfulness-based stress reduction compared to control interventions for patients suffering from FMS.

Materials and methods

Protocol and registration

This review was planned and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [15], the recommendations of the Cochrane Musculoskeletal Group [16,17] and the GRADE recommendations (Grading of Recommendations Assessment, Development and Evaluation) [18]. The protocol was not registered in any database.

Eligibility criteria

To be eligible for review, studies were required to meet the following conditions:

1) *Types of study designs*: Randomized controlled trials (RCTs) and non-randomized controlled trials (nRCT) were eligible.
2) *Types of participants*: Studies of patients diagnosed with fibromyalgia were eligible, regardless of age, condition's duration or intensity. No restrictions regarding diagnostic procedures were applied.
   If studies included not only FMS patients but also other patients with chronic pain or functional disorders, the authors were asked to provide data for the FMS subsample. This procedure, however, was applied only in studies where at least 20 FMS patients were included.
3) *Types of interventions*: Studies that compared MBSR with either no treatment, usual care or any active treatment were eligible. Studies were included if MBSR was conducted in accordance with the original curriculum developed by Kabat-Zinn [6] or if an adaption was used. However, the intervention had to be of a comparable format, i.e. between 6 and 10 group sessions of 2–4 h with the cultivation of mindfulness as the key element. A cognitive behavioral program on the other hand was not included, when the main component was of psychotherapeutic nature. Co-interventions were allowed, but these studies were then excluded in the subsequent sensitivity analyses.
4) *Types of outcomes*: Studies were eligible if they assessed at least one major patient-centered outcome, namely quality of life or pain. Secondary outcomes were sleep quality, fatigue, depression and safety. Outcomes were chosen because they represent the key symptoms of fibromyalgia.
5) *Length of follow-up*: No restrictions regarding length of follow-up were applied. Short-term effects were defined as measures taken directly after the intervention and long-term effects as measures taken closest to 6 months post-randomization.

6) *Accessibility of data*: Studies were eligible only if they were published as full papers. No language restriction was applied.

Literature search

The following electronic databases were searched from their inception through to September 05, 2013: PubMed/MEDLINE, Scopus, PsycINFO, the Cochrane Library and CAMBASE. The literature search, which was constructed around search terms for 'Mindfulness-based stress reduction' and 'fibromyalgia syndrome', was adapted for each database as necessary. For example, the following search strategy was used on the MEDLINE database:

(Fibromyalgia[MeSH Terms] OR fibromyalgia[Title/Abstract] OR fibrositis[Title/Abstract] OR FMS[Title/Abstract] OR widespread pain [Title/Abstract]) AND (mind body therapies[MeSH Terms] OR mindfulness[Title/Abstract] OR Mindfulness-Based Stress Reduction[Title/Abstract] OR MBSR[Title/Abstract]).

The reference lists of identified original articles or reviews were also searched manually for relevant articles.

Study selection

At first all duplicates were removed from the references. Two reviewers then screened the abstracts of the remaining papers individually and went on to obtain the full papers for potentially eligible studies. The studies were then checked in detail, with eligible papers being included in the systematic review. Papers that provided data on relevant clinical outcomes as defined in the next section were also included in the meta-analysis.

Data collection

Two reviewers independently extracted data on studies' characteristics (participants, interventions, control conditions, co-interventions, outcome measures, results). Disagreements were checked with a third reviewer and resolved by agreement. If data could not be extracted from the original published papers, their authors were contacted.

Outcome measures

To be eligible studies had to measure at least one major outcome, namely:

1) Quality of life, assessed by the Fibromyalgia Impact Questionnaire (FIQ) [19], the Physical Component Summary of the Short Form 36 Health Survey Questionnaire (SF-36) [20] or any other validated instrument. If studies used multiple instruments, the FIQ as the specific instrument was preferred over the others.
2) Pain intensity, measured on a visual analog scale (VAS), a numerical rating scale (NRS), the McGill Pain Questionnaire (MPQ) [21], the pain subscale of the Fibromyalgia Impact Questionnaire (FIQ), which is also a VAS [19] or on another validated specific measure.

Secondary outcomes included:

1) Sleep quality, assessed on a visual analog scale (VAS), a numerical rating scale (NRS), the Pittsburgh Sleep Quality Index (PSQI) [22] or on another validated sleep quality index. If studies used multiple instruments, the PSQI was preferred over the others.
2) Fatigue, measured on a visual analog scale (VAS), a numerical rating scale (NRS), the Multidimensional Fatigue Inventory (MFI) [23] or on another validated fatigue questionnaire. If studies used multiple instruments, the MFI was preferred over the others.
3) Depression was included where this was measured on the Beck Depression Inventory (BDI) [24] or on another validated depression inventory. If studies used multiple instruments, the BDI was preferred over the others.
4) Patients' safety, defined as any adverse event occurring during a study.

Risk of bias in individual studies

The risk of bias at study level was assessed by two independent reviewers using the 2006 Method guidelines for systematic reviews of the Cochrane Musculoskeletal Group [17]. These guidelines recommend the imposition of seven quality criteria, each of which is rated as 'low risk', 'high risk' or 'unclear risk of bias'. These criteria relate to the following risk of bias categories: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and any other bias relating to major study flaws.

The risk of bias within each domain was used to perform sensitivity analyses.

Data analysis

Studies were analyzed separately for their type of intervention (waitlist/usual care vs. active treatments) and for short- and long-term effects.

Assessment of effect size

If at least two studies presented data on an outcome, then meta-analysis was undertaken using Review Manager 5 software (Version 5.2, The Nordic Cochrane Centre, Copenhagen).

Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated as the mean post-intervention group differences divided by the respective pooled standard deviations [16,25]. Where no standard deviations were available, standard errors, confidence intervals or t-values were used to calculate them. A fixed effect model was applied. If significant baseline differences were present and neither corrected post-scores nor difference-scores were reported, pre-post differences were calculated for each group separately. Standard deviations were calculated based on suggestions from the Cochrane handbook using a predefined correlation coefficient of $r = 0.8$ [16].

The magnitude of the overall effect size was classified according to Cohen's categories: a small effect size was defined as a SMD = 0.2 to 0.5: moderate effect size: SMD = 0.5 to 0.8 and large effect size: SMD > 0.8 [26].

A negative standardized mean difference was defined to indicate the beneficial effects of MBSR, as compared to the control interventions, for all outcomes. If outcome measures used opposing scaling then patients' scores of the scales concerned were inverted by multiplication by −1.

Assessment of heterogeneity

Statistical heterogeneity between the reviewed studies was quantified by determination of I^2. $I^2 > 30\%$, $I^2 > 50\%$ and $I^2 > 75\%$ were defined to indicate moderate, substantial and considerable heterogeneity, respectively [16]. A p value ≤ 0.10 from the Chi^2 test was taken to indicate significant heterogeneity [16].

Subgroup and sensitivity analyses

Subgroup analyses were conducted for randomized controlled studies vs. non-randomized controlled studies.

Sensitivity analyses to test the robustness of any significant results were conducted by comparing the results of studies with high risk vs. low risk at the domain selection bias, detection bias, attrition bias and other risks. If statistical heterogeneity was present in the respective meta-analysis, sensitivity analyses were conducted by subsequent exclusion of single studies.

Risk of bias across studies

If at least ten studies were included in a meta-analysis, the risk of publication bias was assessed by visual analysis of funnel plots

generated by Review Manager 5.1 software. Roughly symmetrical funnel plots indicate a low risk of publication bias, while asymmetrical funnel plots indicate a high risk of such bias [27].

Quality of evidence

The quality of evidence for each outcome was judged according to the GRADE recommendations [18] based on the methodological quality and the confidence in the results of the meta-analysis.

1) High quality: Further research is very unlikely to change the confidence in the estimate of effect.
2) Moderate quality: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
3) Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4) Very low quality: Any estimate of effect is very uncertain.

Strength of recommendation

The strength of recommendation for MBSR as a therapeutic option is judged according to GRADE with either "strong" or "weak" [18]. This recommendation takes into account the quality of evidence and the risk of undesirable effects of the intervention.

Results

Study selection

The literature search and cross-reference search retrieved 376 records, of which 110 were duplicates (Fig. 1). After abstract screening, another 242 records were excluded. Of the remaining 24 articles that were assessed as full text, 18 referred to studies that did not fulfill the inclusion criteria since they did not investigate MBSR (N = 7) [28–34] or FMS patients (N = 4) [35–38], did not apply a control group (N = 5) [39–43]; or did not assess relevant outcomes (N = 2) [44,45] (Fig. 1). One study investigated the effects of MBSR on patients with somatization disorder and functional somatic syndromes [46]; however 99 of these patients suffered from fibromyalgia (83%) and the trial author provided separate data for FMS patients, therefore the study was included in this review. In the end, 6 studies with a total of 674 patients could be included in the qualitative and quantitative analysis [46–51].

Study characteristics

The characteristics of the study samples, interventions, outcome measures and results are shown in Table 1.

Setting and participant characteristics

Trials originated from Denmark [46], Germany or Austria [49,50] and the US [47,48,51]. All except one of the studies included patients who had been diagnosed according to the American College of Rheumatology (ACR) diagnostic criteria [47–51], one study [46] used the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview [52]. Three studies included adults of both genders [46–48] whereas three studies included only females [49–51]. Studies were conducted in primary, secondary or tertiary care settings with patients being recruited through adverts and referrals.

Intervention characteristics

MBSR was conducted as group program of 8 weeks [46,47,49–51] or 10 weeks [48] with a single session per week of 2–3.5 hour duration each. Four studies also reported daily home practice of 30 to 45 min [46,49–51]. All but two studies also included an all-day retreat [46,49–51].

The studies' control interventions differed widely. Four studies used a wait-list or usual care group [46,48,50,51], one study applied an educational support group [47] and two other studies used an intervention which was matched to the MBSR program contents [49,50]. Only one study used two comparator groups which were included separately into the meta-analyses [50].

Outcome measures

Pain was assessed as an outcome measure in all but one study using either a VAS [48,49], the sensory component of the Pain Perception Scale [50] or the pain scale of the SF-36 [46,47]. Quality of life was measured using the FIQ [47,48,50,51], the SF-36 [46] or

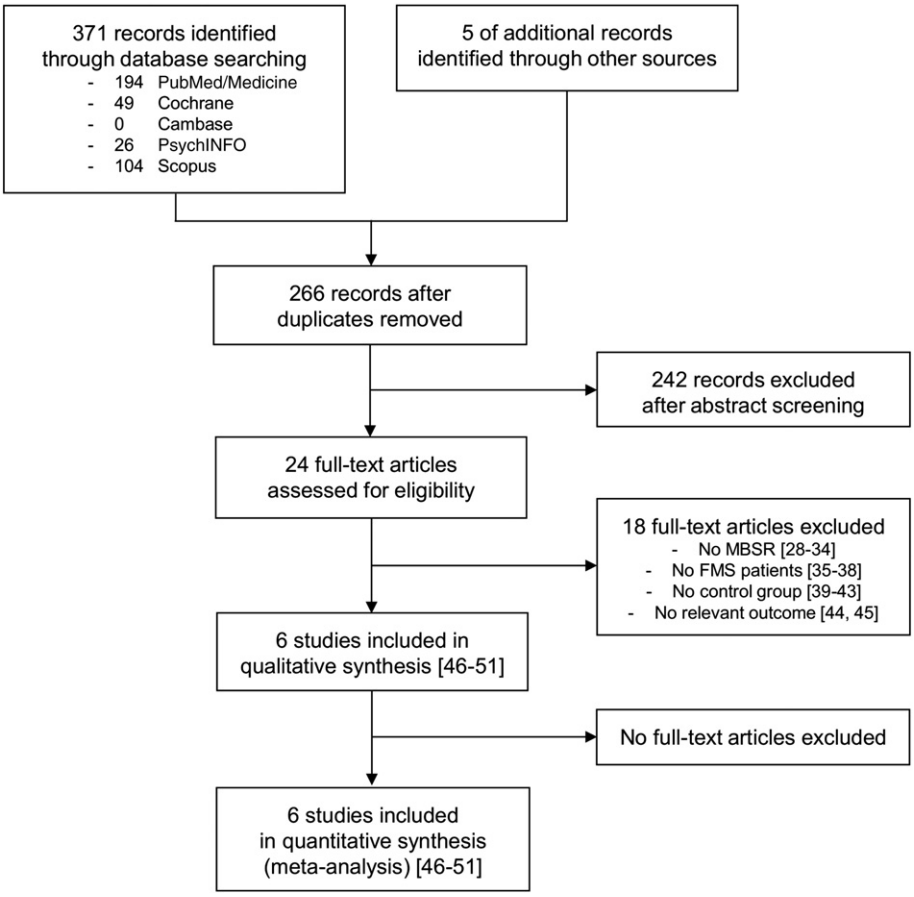

Fig. 1. Flow chart of results of literature search.

Table 1
Characteristics of the included studies

Reference	Patients (N, age, diagnosis)	Co-interventions	Intervention groups (program length, frequency, duration)		Short-term and long-term follow-up	Outcome measures	Results	
			Treatment	Control		1) Pain 2) Quality of life (disease specific, generic) 3) Sleep quality 4) Fatigue 5) Depression 6) Safety	Short-term	Long-term
Astin et al., 2003 [47]	128 patients with fibromyalgia according to the ACR criteria Mean age: 47.7 ± 10.6 years Gender: 63/1 f/m (MBSR) 64/0 f/m (education)	Not reported	MBSR (N = 64) (Mindfulness meditation and qigong) 8 weeks once weekly 2.5 h each (90 min mindfulness meditation 60 min qigong)	Education (N = 64) (Education and support group) 8 weeks once weekly 2.5 h each	8 weeks 24 weeks	1) Pain (SF-36 pain scale) 2) Quality of life (FIQ) 5) Depression (BDI)	1) Sign. improvement in MBSR and education 2) Sign. improvement in MBSR and education 5) Sign. improvement in MBSR and education	1) Sign. improvement in MBSR and education 2) Sign. improvement in MBSR and education 5) Sign. improvement in MBSR and education
Fjorback et al., 2013 [46]	99 patients with fibromyalgia (in a sample of 119 patients with somatoform disorders assessed by the SCAN interview) Mean age: 37.0 ± 9.5 (MBSR) 39.4 ± 7.9 (usual care) Gender: 37/11 f/m (MBSR) 39/12 f/m (usual care)	Individual treatment plan	MBSR (N = 48) (MBSR according to Kabat-Zinn [6] and elements of CBT) 8 weeks once weekly 3.5 h each + follow up session + silent retreat + homework Individual treatment plan (medication, psychoeducation, graded exercise)	Usual care (N = 51) (enhanced treatment as usual) Individual treatment plan (medication, psychoeducation, graded exercise)	3 months 15 months	1) Pain (SF-36 pain scale) 2) Quality of life (SF36) — Physical Scale 5) Depression (SCL-8)	1) No sign. group difference, sign. improvement in MBSR and usual care 2) No sign. group difference, sign. improvement in MBSR 5) No sign. group difference, sign. improvement in MBSR and usual care	1) No sign. group difference, sign. improvement in MBSR and usual care 2) No sign. group difference, sign. improvement in MBSR and usual care 5) No sign. group difference, sign. improvement in MBSR and usual care
Goldenberg et al., 1994 [48]	129 patients with fibromyalgia according to the ACR criteria Mean age: 46.0 ± 9.9 (MBSR) 47.2 ± 11.8 (Control) Gender: 71/8 f/m (MBSR) 41/1 f/m (Control)	Medication (analgesics, antidepressants)	MBSR (N = 79) (MBSR modeled after Kabat-Zinn [6]) 10 weeks once weekly 2 h each (30 min each for meditation, discussion, education and final meditation)	Control (N = 42) (wait-list patients and patients who were not interested in MBSR)	10 weeks 6 months	1) Pain (VAS) 2) Quality of life (FIQ) 3) Sleep quality (VAS) 4) Fatigue (VAS)	1) Sign. group difference favoring MBSR 2) No sign. group difference 3) No sign. group difference 4) Sign. group difference favoring MBSR	1) N.R. 2) N.R. 3) N.R. 4) N.R.

Grossmann et al., 2007 [49]	58 female patients with fibromyalgia according to the ACR criteria Mean age: 54.4 ± 8.3 (MBSR) 48.8 ± 9.1 (Control) Gender: female only	Not reported	MBSR (N = 31, those patients enrolled first) (MBSR according to Kabat-Zinn [6]) 8 weeks once weekly 2.5 h each + all-day retreat + daily home practice of 45 min	Active control (N = 15) (education, support, relaxation, stretching, discussion) 8 weeks once weekly 2.5 h each	8 weeks 36 months (only MBSR)	1) Pain (VAS) 2) Quality of life (PLC — functional status) 5) Depression (HADS)	1) Sign. group difference of pre-post differences favoring MBSR 2) Sign. group difference of pre-post differences favoring MBSR 5) Sign. group difference of pre-post differences favoring MBSR	1) Sign. improvement compared to baseline 2) Sign. improvement compared to baseline 5) Sign. improvement compared to baseline
Schmidt et al., 2011 [50]	177 female patients with fibromyalgia according to the ACR criteria Mean age: 53.4 ± 8.7 (MBSR) 51.9 ± 9.2 (usual care) 52.3 ± 10.9 (active control) Gender: female only	Usual care, not specified	MBSR (N = 53) (MBSR according to Kabat-Zinn [6]) 8 weeks once weekly 2.5 h each + all-day retreat + daily home practice of 30-45 min	Usual care (N = 59) (no specific treatment) Active control (N = 56) (education, support, relaxation, stretching, discussion) 8 weeks once weekly 2.5 h each	8 weeks 16 weeks	1) Pain intensity (PPS) 2) Quality of life (PLC, FIQ) 3) Sleep quality (PSQI) 5) Depression (CES-D)	1) No sign. group differences 2) PLC: no sign. group differences FIQ: no sign. group differences 3) No sign. group differences 5) No sign. group differences	1) No sign. group differences 2) PLC: no sign. group differences FIQ: no sign. group differences 3) No sign. group differences 5) No sign. group differences
Sephton et al., 2007 [51]	91 female patients with fibromyalgia according to the ACR criteria Mean age: 48.4 ± 8.9 (MBSR) 47.6 ± 11.5 (usual care) Gender: female only	Usual care, not specified	MBSR (N = 51) (MBSR according to Kabat-Zinn [6]) 8 weeks once weekly 2.5 h each + all-day retreat + daily home practice of 30–45 min	Usual care (N = 40) (no specific treatment)	8 weeks 16 weeks	1) Pain intensity (VAS) 2) Quality of life (FIQ) 3) Sleep quality (SDQ) 5) Depression (BDI)	1) N.R. 2) N.R. 3) N.R. 5) Sign. group difference of pre-post differences favoring MBSR	1) N.R. 2) N.R. 3) N.R. 5) Sign. group difference of pre-follow-up differences favoring MBSR

Abbreviations: ACR: American College of Rheumatology; BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies depression inventory; FIQ: Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; MBSR: mindfulness-based stress reduction; PLC: Quality of Life Profile for the Chronically Ill; PPS: Pain Perception Scale; PSQI: Pittsburgh Sleep Quality Index; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCL-8: Symptom Check List; SDQ: Sleep Disorders Questionnaire; SF-36: Short Form 36 Health Survey; Sign.: significant.

the Quality of Life Profile for the Chronically Ill (PLC) [49], however one study failed to report the results of that outcome [51]. Sleep quality was assessed in only two studies using a VAS [48] or the PQSI [50]; and fatigue was measured in only one study using a VAS [48]. Depression was measured in five studies, two of them using the BDI [47,51], and one each using the subscale depression of the Hamilton Anxiety and Depression Scale (HADS) [49], the Symptom Checklist (SCL-8) [46] and the Center for Epidemiologic Studies Depression Scale (CES-D) [50]. Safety was assessed and reported in none of the trials.

Short- and long-term effects were assessed in all studies with time frames ranging from 4 to 36 months post-randomization; however one study failed to report the follow-up data [48] and another one reported outcomes only for the intervention group [49].

Risk of bias in individual studies

Two studies had to be rated to have serious risk for bias since they were CCTs without randomization [48,49] (Table 2). The studies' risk of selection bias was mixed, with three out of six studies having low risk at random sequence generation and allocation concealment [46,47,50]. All other studies had unclear [51] or high risk of selection bias [48,49].

The risk of performance bias was low in only one study [50], unclear in three studies, [46,47,51] and high in two studies [48,49]. Two studies each had a low [47,50], an unclear [46,51] and a high risk of detection bias [48,49]. Attrition bias was mixed with three out of six studies having a low risk [47,50,51], one with an unclear risk [49,47] and two with high risk [47,48]. Selective reporting was observed in only one study [51], all the other studies had a low risk of reporting bias [46–50].

Analyses of effects of MBSR vs. waitlist/usual care

Major outcomes:

1) Quality of life: A significant small short-term effect was found for MBSR on quality of life (SMD = −0.35; 95% CI −0.57 to −0.12; P = 0.002; heterogeneity: I^2 = 0%; Chi^2 = 0.83; P = 0.66) (Fig. 2). No long-term effects were found (SMD = 0.00; 95% CI −0.29 to 0.29; P = 1.0).
2) Pain: A significant small short-term effect was found for MBSR on pain intensity (SMD = −0.23; 95% CI −0.46 to −0.01; P = 0.04; heterogeneity: I^2 = 14%; Chi^2 = 1.13; P = 0.57) (Fig. 2) compared to usual care. No long-term effects were found (SMD = −0.01; 95% CI −0.30 to 0.27; P = 0.93).

Secondary outcomes:

1) Sleep quality: No effect was found for short-term effects on sleep quality (SMD = −0.07; 95% CI −0.33 to 0.20; P = 0.63) (Fig. 3). No long-term comparisons could be made since data from only one study [48] were available with no effect (SMD = −0.09; 95% CI −0.46 to 0.28; P = 0.62).
2) Fatigue: Only one study assessed the influence of MBSR on fatigue [48]. Results showed a significant group difference of 12.8 mm VAS (95% CI: 2.2 to 23.3) favoring MBSR (p = 0.02). No long-term effects could be assessed.
3) Depression: No effect was found for depression, neither on the short- (SMD = −0.15; 95% CI −0.38 to 0.08; P = 0.21) nor on the long-term (SMD = −0.19; 95% CI −0.43 to 0.04; P = 0.11).

Subgroup and sensitivity analyses of MBSR vs. waitlist/usual care

Subgroup analyses for RCTs revealed that after exclusion of the non-randomized trial [48] the effects on quality of life (SMD = −0.27; 95% CI −0.55 to 0.01; P = 0.06) and pain intensity (SMD = −0.11; 95% CI −0.39 to 0.17; P = 0.43) disappeared.

The same results were found in the sensitivity analyses, since the non-randomized trial was also the high risk trial. No considerable heterogeneity was found; therefore no further analyses were necessary.

Quality of evidence

The quality of evidence according to GRADE was judged low for quality of life and pain. The quality of evidence was downgraded because of serious issues regarding risk of bias (−1) and imprecision due to small sample size (−1).

Analyses of effects of MBSR vs. active treatment

Major outcomes:

1) Quality of life: A significant small short-term effect was found for MBSR on quality of life (SMD = −0.32; 95% CI −0.59 to −0.04; P = 0.02; heterogeneity: I^2 = 86%; Chi^2 = 13.88; P = 0.001) (Fig. 2). No long-term effects were found (SMD = −0.10; 95% CI −0.40 to 0.20; P = 0.50).
2) Pain: A small short-term effect was found for MBSR on pain (SMD = −0.44; 95% CI −0.73 to −0.16; P = 0.002; heterogeneity: I^2 = 85%; Chi^2 = 12.99; P = 0.002), but no effect was found or long-term effects (SMD = −0.07; 95% CI −0.37 to 0.23; P = 0.54) compared to active treatments on pain intensity (Fig. 2).

Secondary outcomes:

1) Sleep quality: No meta-analyses were possible to determine short- or long-term effects for sleep quality. The only RCT [50] found no group differences (SMD = −0.02; 95% CI −0.40 to 0.36; P = 0.85 and SMD = −0.06; 95% CI −0.44 to 0.31; P = 0.75 respectively).
2) Fatigue: No study assessed effects on fatigue.
3) Depression: No effects were found for depression on the short (SMD = −0.13; 95% CI −0.40 to 0.15; P = 0.36) (Fig. 3) or long term (SMD = −0.13; 95% CI −0.42 to 0.17; P = 0.41).

Subgroup and sensitivity analyses of MBSR vs. active treatment

Subgroup analyses for RCTs revealed that after exclusion of the non-randomized trial [49] the effects on quality of life (SMD = −0.10; 95% CI −0.39 to 0.20; P = 0.53) and pain intensity (SMD = −0.22; 95% CI −0.53 to 0.08; P = 0.15) disappeared.

The same results were found in the sensitivity analyses, since the non-randomized trial [49] was also the high risk trial. The before mentioned trial [49] was also the cause of heterogeneity in both analyses.

Quality of evidence

The quality of evidence according to GRADE was judged low for quality of life and pain. The quality of evidence was downgraded because of serious issues regarding risk of bias (−1) and imprecision due to small sample size (−1).

Safety

None of the studies reported adverse events; therefore it is not possible to evaluate the safety profile of MBSR. As indicated by the reasons for drop-outs [46,50,51] and given the nature of MBSR it can be assumed that MBSR might not associated with serious adverse events.

Strength of recommendation

According to GRADE, only a weak recommendation could be made for the use of MBSR for FMS, mainly due to the small number of studies and low quality of evidence.

Risk of bias across studies

As less than ten studies were included in each meta-analysis, funnel plots were not analyzed.

Discussion

Summary of main results

This meta-analysis found low quality evidence for small effects of MBSR on quality of life and pain intensity in patients with fibromyalgia syndrome, when compared to usual care control groups or active control groups. Effects however were not robust against bias. Finally, data on safety were not reported in any study.

Applicability of evidence

The reviewed trials were conducted in different care settings through Europe and the US. Most patients were adults in their 40's and 50's, female and diagnosed with FMS according to the ACR 1990 classification criteria [53]. While co-interventions were not reported or specified in the majority of studies in one study all patients received an individual treatment plan consisting of medication, psychoeducation and exercise [46]. It can be assumed that in the other studies patients received usual care treatment including medication. Assuming that fibromyalgia is more frequently diagnosed in middle-aged females [2], this review's results may apply to many patients with FMS, however it may be difficult to apply the results to the total FMS population, especially to male and younger/older patient samples.

Quality of evidence

The overall quality of evidence for the primary outcomes quality of life and pain was low and the effects were not robust against bias.

Agreements and disagreements with other systematic reviews

A thorough literature search located no other review of MBSR for fibromyalgia, but several reviews were found on the effects of MBSR on physical or mental conditions.

The most recent review assessed the effects of MBSR on chronic low back pain [11] and found promising evidence of its efficacy with a moderate effect size regarding pain intensity. Other reviews for pain in general [10,12] found that although MBSR might be effective for pain intensity, its effect was not superior to other active treatments and therefore not distinguishable from non-specific treatment effects. Reviews that assessed its influence on mental health found that it may be effective in reducing stress and anxiety [12,14,54] but it was not

Table 2
Risk of bias summary: review authors' judgments about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Astin et al., 2003 [47]	+	+	?	+	–	+	+
Fjorback et al., 2013 [46]	+	+	?	?	+	–	+
Goldenberg et al., 1994 [48]	–	–	–	–	–	+	–
Grossmann et al., 2007 [49]	–	–	–	?	?	+	–
Schmidt et al., 2011 [50]	+	+	+	+	+	+	+
Sephton et al., 2007 [5151]	?	?	?	?	+	–	+

Legend: "+" means low risk, "−"means high risk,"?" means unclear risk of bias.

superior to cognitive behavioral therapy (CBT), which itself provides a small incremental benefit for FMS patients [55].

There are also reviews available on the effects of mindfulness-based therapies [56] or meditation-based therapies [57], which include MBSR. The most recent review by Lakhan and Schofield [56] investigated the effects of MBSR, mindfulness based cognitive therapy (MBCT) and other mindfulness-based therapies on somatization disorders, including FMS. The authors concluded that those therapies may be effective in treating some aspects of somatization disorders, however contrary to the present review the one by Lakhan and Schofield [56] did not only include MBSR,

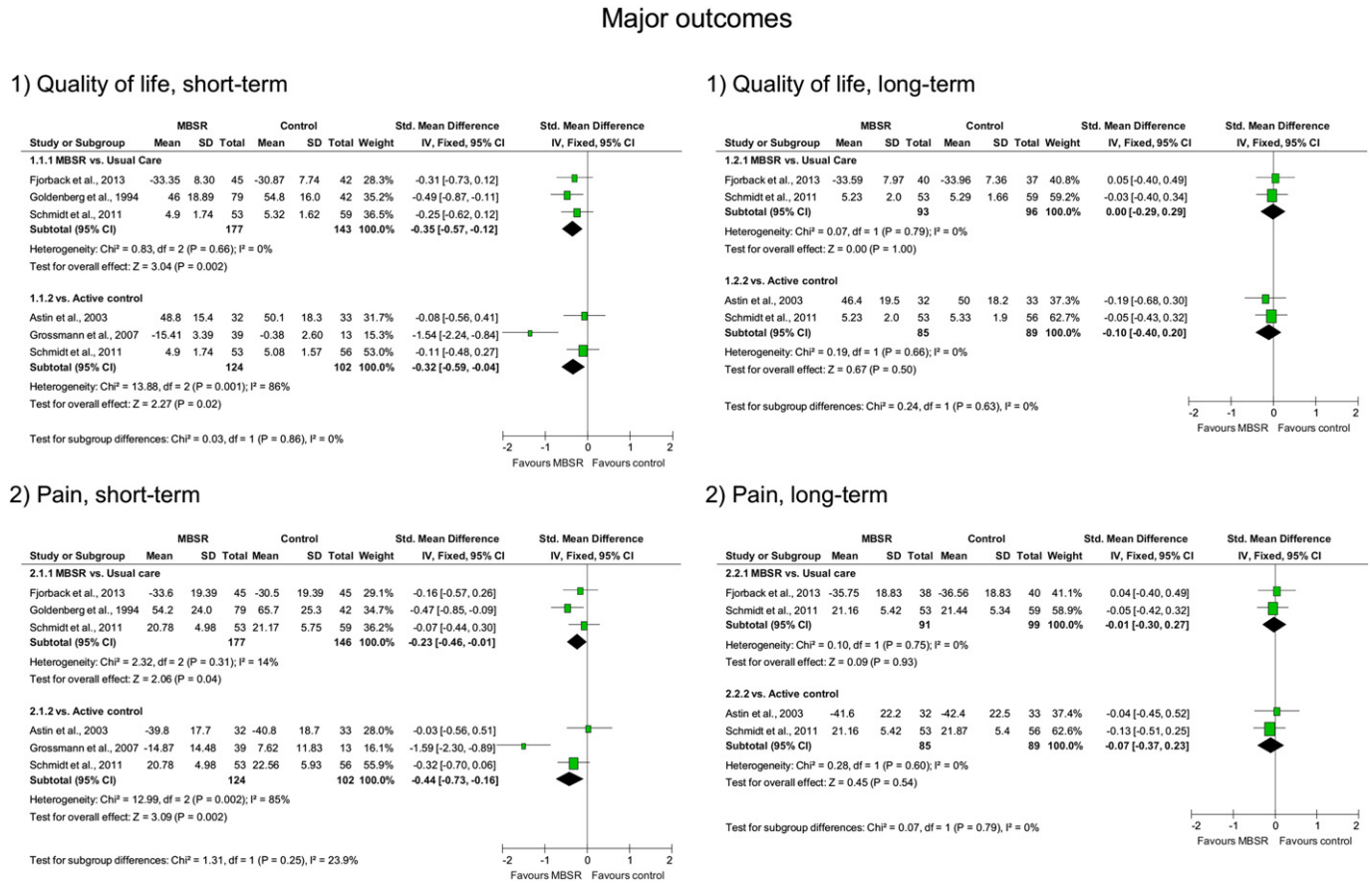

Fig. 2. Forest plots for short- and long-term effects on major outcomes.

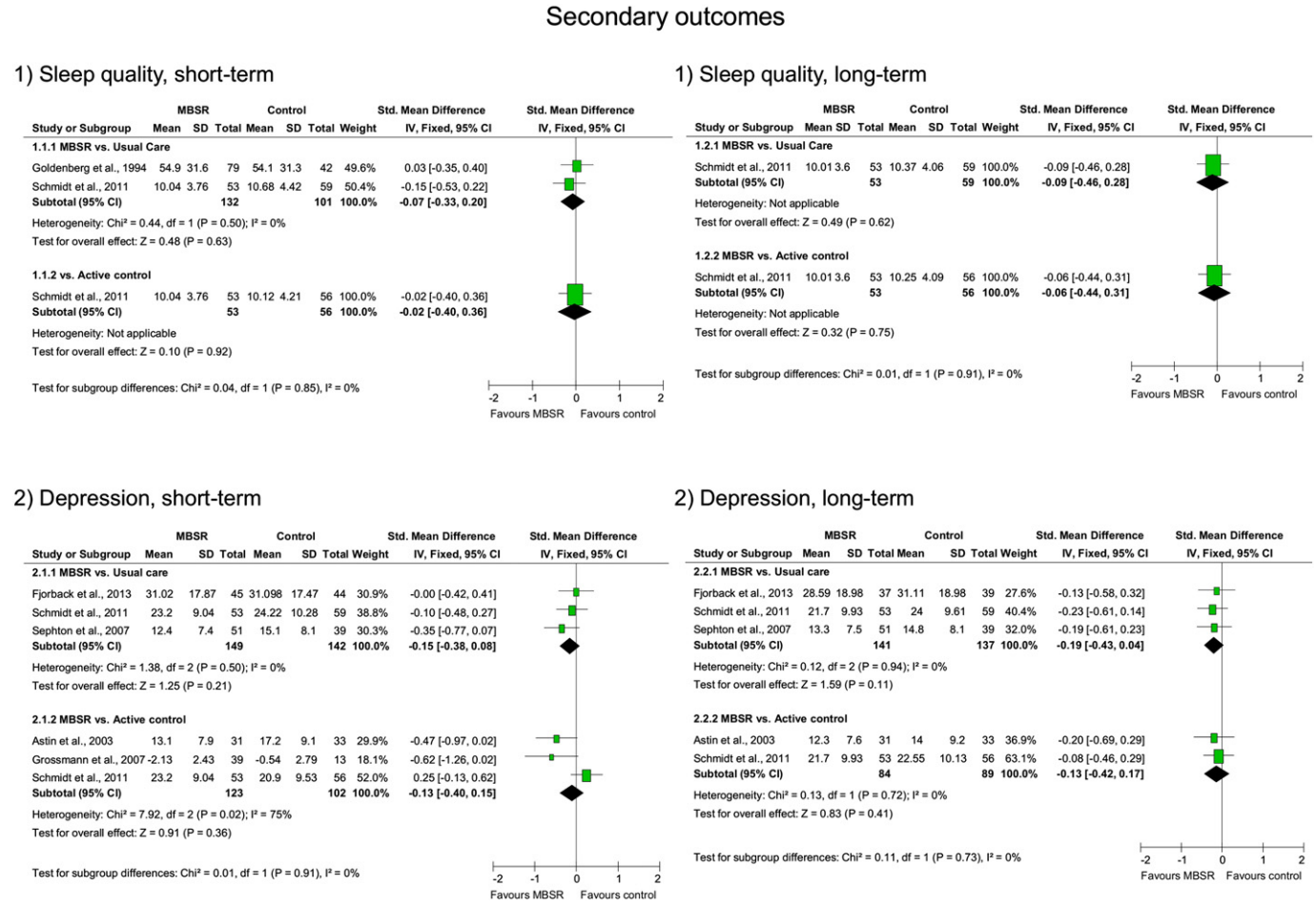

Fig. 3. Forest plots for short- and long-term effects on secondary outcomes.

but also MBCT, or comprehensive yoga programs; and they did not conduct subgroup analyses regarding types of control groups. They also did not utilize risk of bias assessment or recommendation tools for judging the effects of mindfulness-based therapies.

Another review by Kozasa et al. [57] was also reporting on effects of meditation-based interventions on fibromyalgia. However compared to the present review it was not as comprehensive and systematic, it also did not focus on MBSR alone. Finally it did not contain a meta-analytic approach to estimate effect sizes.

Because of its focus and methodological rigor the present review does allow for more differentiated recommendations regarding the effects of MBSR in the treatment of the fibromyalgia syndrome.

Given the six controlled studies included in this review and the evidence found for effects of MBSR compared to both usual care and active controls, the review suggests that MBSR might be effective on the short-term. However results might not be robust against bias, the effect sizes found in this review are small, no long-term effects have been found and no reliable conclusions regarding safety can be made at this point.

Compared to findings from prior uncontrolled trials on MBSR [40–44], which showed significant improvement of pain [40,41,43], quality of life [40–43], sleep [40,43], fatigue [40,43] and depression [41], the recent review found only low evidence for pain reduction and increase in quality of life, which were not robust against bias. This illustrates the need for high quality RCTs in order to minimize risk of bias.

Strengths and weaknesses

This review and meta-analysis was conducted in accordance to the recommendations with the Cochrane Musculoskeletal Group [17].

The review's primary limitation is the paucity of eligible trials, which rendered further subgroup analyses impossible. In particular low risk studies comparing MBSR to other active therapies and studies investigating long-term effects are urgently needed.

Another limitation is the diversity of MBSR programs with variable time frames. At least, all MBSR interventions were based on the original curriculum [6] and only slightly modified. For future trials a more comprehensive description of the program and control interventions would be beneficial.

Limiting factors are not only based on the study designs, but also on the reporting of details on how the studies were conducted and the results. Only three of the RCTs reported adequate randomization and allocation concealment, and only one study had low risk at participant blinding. Blinding, however, is virtually impossible in trials on mindfulness as it is also for most other non-pharmacological or mind/body interventions. One trial on the other hand dealt adequately with this issue by introducing a well matched control group [50] and was therefore judged to have a low risk in that domain. It could be recommended that future studies might apply such approach in their study planning. Incomplete outcome data were an issue in three studies and at least two studies showed signs of selective reporting. Some of the studies also used statistical within group comparisons but not between group comparisons despite the randomized controlled study design. Future studies should consider these issues which are of utmost importance for conclusive judgment of the effects of MBSR.

Strength of recommendation

According to GRADE only a weak recommendation for MBSR can be made at this point.

Implication for further research

One major implication for future research is that researchers should bear in mind that MBSR primarily aims to establish a mindful and accepting pain coping style rather than to reduce the intensity of pain or other complaints. Therefore researchers are encouraged to select custom outcomes such as awareness, acceptance or coping rather than intensity of symptom which might not reflect the intention of the intervention. Only two trials measured coping, however, only one of them actually reported results and the other one [47] did not provide data but stated that besides catastrophizing there were no significant group differences. Results of the trial by Grossmann et al. [49] on the other hand indicated significant improvements on several subscales, which could be worth further investigations.

Further high quality RCTs comparing MBSR to established therapies (e.g. defined drug treatment, cognitive behavioral therapy) are also required for the conclusive judgment.

Conclusion

This systematic review found low quality evidence for a small short-term improvement of pain and quality of life after MBSR for fibromyalgia, when compared to usual care or active control interventions. No evidence was found for long-term effects.

Conflict of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that (1) Dr. Lauche, Dr. Cramer, Prof. Langhorst and Prof. Dobos received a grant from the Rut- and Klaus-Bahlsen-Foundation, but this funding source had no influence on the review's planning, organization, management or publication. (2) Prof. Schmidt was involved in one of the reviewed trials. He was not, however, involved in the extraction or analysis of the reviewed data or the risk of bias assessment.

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