Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial ☆

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ABSTRACT

Mindfulness-based stress reduction (MBSR) is a structured 8-week group program teaching mindfulness meditation and mindful yoga exercises. MBSR aims to help participants develop nonjudgmental awareness of moment-to-moment experience. Fibromyalgia is a clinical syndrome with chronic pain, fatigue, and insomnia as major symptoms. Efficacy of MBSR for enhanced well-being of fibromyalgia patients was investigated in a 3-armed trial, which was a follow-up to an earlier quasi-randomized investigation. A total of 177 female patients were randomized to one of the following: (1) MBSR, (2) an active control procedure controlling for nonspecific effects of MBSR, or (3) a wait list. The major outcome was health-related quality of life (HRQoL) 2 months post-treatment. Secondary outcomes were disorder-specific quality of life, depression, pain, anxiety, somatic complaints, and a proposed index of mindfulness. Of the patients, 82% completed the study. There were no significant differences between groups on primary outcome, but patients overall improved in HRQoL at short-term follow-up ($P = 0.004$). Post hoc analyses showed that only MBSR manifested a significant pre-to-post-intervention improvement in HRQoL ($P = 0.02$). Furthermore, multivariate analysis of secondary measures indicated modest benefits for MBSR patients. MBSR yielded significant pre-to-post-intervention improvements in 6 of 8 secondary outcome variables, the active control in 3, and the wait list in 2. In conclusion, primary outcome analyses did not support the efficacy of MBSR in fibromyalgia, although patients in the MBSR arm appeared to benefit most. Effect sizes were small compared to the earlier, quasi-randomized investigation. Several methodological aspects are discussed, e.g., patient burden, treatment preference and motivation, that may provide explanations for differences.

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1. Introduction

Fibromyalgia is a frequently diagnosed pain disorder primarily affecting women and showing high comorbidity with other functional somatic disorders and depression [47]. So far, no distinct cause or pathology has been identified. Recent research indicates that fibromyalgia patients may manifest dysfunctional pain processing of central origin [1] and, possibly, impaired cardiovascular autonomic regulation [36]. Pharmacological treatment of the disorder has proved difficult, perhaps because of its nonspecific pathophysiology. Thus, central nervous agents, such as tricyclic antidepressants [25], selective serotonin, and norepinephrine reuptake inhibitors [3,41] or pregabalin [16], have been found to be moderately successful, but only for relatively short periods of time [15]. Only a few nonpharmacological interventions appear to confer even moderate benefits, i.e., mainly cardiovascular exercise, cognitive–behavioral therapy and patient education [18], or a combination of these [23]. However many of these benefits are also short-lived.

Another proposed behavioral intervention for fibromyalgia is *mindfulness-based stress reduction* (MBSR), an 8-week, structured group program using mindfulness meditation techniques and mindful yoga exercises [27]. MBSR aims to help participants to develop nonjudgmental awareness of moment-to-moment experience, importantly within a context of openness, kindness, tolerance, and acceptance of perceptible sensory, mental, and emotional phenomena. A body of evidence indicates that MBSR can improve coping and health-related quality of life (HRQol) in many chronic conditions, including chronic pain [20,37].

So far, 8 trials have assessed MBSR, specifically, or mindfulness-based techniques in combination with other educational/behavioral techniques among patients with fibromyalgia. Studies in the latter category were either uncontrolled [14] or did not find significant differences in the primary outcome [4,33]. Of the 5 trials directly evaluating MBSR, one showed clinical improvement but was uncontrolled [29]; a later trial with a nonrandomized wait-list control group reported significant differences on several fibromyalgia-related visual analogue scales (VAS), the Fibromyalgia Impact Questionnaire (FIQ, $P = 0.05$) and the symptom checklist SCL90 ($P = 0.0001$) [19]. A third randomized investigation with wait-list controls showed significant improvements in depression [42], and a fourth uncontrolled trial study provided indications of significant changes in psychophysiological variables [32]. Finally, the fifth study is the direct forerunner of the current investigation [21]. In a quasi-randomized design, 39 female fibromyalgia patients received MBSR; 13 control patients were assigned to an active control procedure designed to match for nonspecific effects of MBSR. MBSR showed strong effects in comparison to the control group for HRQoL (effect sizes ranged from $d = 0.52–1.12$), pain ($d = 1.10$), depression (0.39), anxiety (0.67), and coping abilities (0.34–0.88). In a 3-year observational follow-up, the MBSR group of patients maintained significant improvement in all these variables, compared with preintervention. On the basis of these positive findings, we decided to replicate and extend this study, adding an additional control group.

Health-related quality of life (HRQoL) was chosen in this trial as the primary outcome, because severely impaired HRQoL is a central feature of fibromyalgia for some people, and relatively strong effects on HRQoL have been observed in earlier studies of MBSR and fibromyalgia [21].

2. Methods

2.1. Design

A 3-armed randomized trial was conducted in which female patients were randomly assigned to (1) MBSR, (2) an active control intervention aimed at equating the nonspecific features of MBSR, or (3) a wait-list control group. The primary endpoint was a measure of HRQoL (see also below) at short-term follow-up, 8 weeks postintervention.

We hypothesized that (1) active treatments, i.e., MBSR and active control, would yield greater improvement than wait-list control, and (2) MBSR patients would manifest greater benefits than patients with the active control intervention. The primary outcome was overall score of HRQoL related, in general, to chronic disorders. Secondary outcomes were disease-specific (fibromyalgia) QoL, sleep quality, anxiety, depression general complaints, and pain sensation. All measures were assessed by means of standardized and validated self-report inventories.

Baseline measurements were completed after determination of eligibility (preintervention *baseline*, 0 weeks), and patients were subsequently allocated to one of the 3 study arms. Patients were again assessed after the 8-week intervention or waiting period (*end of intervention*). Patients were then asked to continue to practice their mindfulness exercises and homework for an additional 8 weeks, and they were evaluated a third time at *short-term follow-up*. Changes in outcome variables from preintervention to short-term follow-up were used for the main outcome analysis.

Sample size was determined on the basis of our meta-analysis of controlled MBSR trials, in which we found a mean effect size of $d = 0.53$ [20]. This effect size results in $1-\beta = 0.89$ ($\alpha = 0.05$) for $N = 60$ patients per group or $N = 180$ patients overall. With maximal attrition assumed to be 20%, the power remains $1-\beta = 0.82$.

2.2. Participants

Women 18–70 years of age who currently had fibromyalgia, as defined by the American College of Rheumatology (ACR) criteria [48], were eligible for the trial. Additional inclusion criteria were command of the German language and motivation to participate. Exclusion criteria were life-threatening diseases, evidence of suppressed immune functioning, or participation in other clinical trials. Participants were recruited via patient self-help groups, news media, and referrals from general practitioners, rheumatologists, and the University of Freiburg Medical Center Interdisciplinary Pain Unit. During an intake examination at the hospital, patients were evaluated for all eligibility criteria and were examined by an experienced physician who used ACR criteria to confirm diagnosis of fibromyalgia.

Informational brochures were then provided that briefly described the 2 interventions as alternative behavioral treatments potentially capable of enhancing the well-being in fibromyalgia patients. No suggestion was made about the superiority of either treatment. Information was collected concerning ongoing medical, pharmacological, psychotherapeutic, or other interventions for the disorder, but patients were not asked to discontinue any treatments. This study was approved by the University of Freiburg Ethics commission, and all patients completed informed consent before enrollment.

2.3. Interventions

Consenting eligible patients were randomly assigned to 1 of 3 study arms: the experimental intervention (mindfulness-based stress reduction [MBSR]), an active control intervention, and a wait-list group. Patients in the intervention arms were told that 2 new innovative treatments were to be compared, one based on the concept of mindfulness (entailing meditation and yoga lessons, as well as homework), and the other based on health support techniques (entailing relaxation and stretching exercises, as well as homework). The active control group was referred to as the relaxation group. All patients participating in one of the 2 active treatment arms were also offered participation in their treatment of choice after completion of the trial.

2.3.1. MBSR

The MBSR intervention was closely based on the original program [26] and was identical to that used in the earlier investigation [21]. The intervention comprised an 8-week structured program with groups of up to 12 patients, taught by a single instructor. Participants took part in one 2.5-h session every week, and an additional 7-h all-day session on a weekend day. Each session covered specific exercises and topics within the context of mindfulness practice and training. These included various types of formal mindfulness practice, mindful awareness of dynamic yoga postures, and mindfulness during stressful situations, and social interactions. The all-day retreat included a combination of previously used and newly introduced mindfulness exercises. Upon enrollment, participants were asked to commit themselves to daily homework assignments of 45–60 min. Instructors were 2 women with university level degrees in educational counseling who had undergone MBSR training provided by the UMass Medical Center for Mindfulness, Worcester, MA. Each had at least 7 years of previous experience teaching MBSR, as well as experience teaching fibromyalgia patients.

Pre- and postintervention 1-h personal interviews were conducted by each instructor to establish rapport and to help patients formulate realistic individual goals for the intervention. Postintervention interviews addressed participants' personal experiences

during the course and assessed the degree to which pretreatment goals had been met.

2.3.2. Active control group

The active control intervention was planned to control for the nonspecific aspects of the MBSR curriculum and was very similar to that used in the predecessor study [21]. It comprised participation in an 8-week group of size and weekly format similar to that of the MBSR program taught by a single instructor. In addition, equivalent amounts of social support and weekly topical educational discussions were provided. Use of Jacobson Progressive Muscle Relaxation training (PMR), and fibromyalgia-specific gentle stretching exercises [7] served as counterparts for mindfulness and yoga elements of the MBSR curriculum. Homework assignments were similar in duration and intensity to those in the MBSR group. Patients received compact discs (CDs) with instructions for daily exercises. Pre- and postintervention interviews were given by individual instructors using the same protocol as with the MBSR group. Instructors were 2 female psychologists with many years of group and relaxation training experience. A manual similar to that used in MBSR was written by 1 of the authors (S.S.).[1] The trainers had an extensive preparation period and were regularly supervised by S.S., who is a trained psychotherapy group supervisor. One notable difference between active interventions was the absence of an all-day session in the active control program.

None of the MBSR and active control group instructors had any other relationship with the study than providing course instruction.

2.3.3. Wait-list control

Patients randomized to this group received no active treatment but were offered their choice of either intervention at conclusion of the short-term follow-up period.

2.4. Primary endpoint[2]

The *Quality of Life Profile for the Chronically Ill* (PLC) is an HRQoL inventory especially designed for patients with chronic conditions [43]. It consists of 40 items and 6 subscales: physical functioning, ability to relax and enjoy life, positive affect, negative affect, social contact, and social integration. Scores of the 6 subscales can be summed to a total score. The inventory is well validated and was used in an earlier MBSR investigation with fibromyalgia patients [21].

2.5. Secondary endpoints

The Fibromyalgia Impact Questionnaire (FIQ) consists of 20 items [9,38]. The first 10 items assess the physical functioning of

the patients and can be combined to a single score. The next 2 items are related to overall well-being and to the capability to work. There are also 7 VAS that assess frequent fibromyalgia symptoms of pain, fatigue, stiffness, and mood.

Depression was assessed by the Center for Epidemiological Studies depression inventory (CES-D) [24,40], a 20-item scale designed for the general population.

Anxiety was measured by the 20-item trait subscale of the State-Trait-Anxiety-Inventory (STAI) [31,45].

Quality of sleep was assessed by the Pittsburgh Sleep Quality Index (PSQI) [5,10,11]. This inventory has 9 items; 1 item consists of 10 sub-items, so that patients filled in information for 18 items overall.

Pain perception was assessed by means of the well validated Pain Perception Scale (PPS) [17]. This questionnaire consists of 2 subscales: sensory and affective pain, with 14 and 10 items, respectively.

Self-attribution of mindfulness was assessed with the 14-item short form of the Freiburg Mindfulness Inventory (FMI) [46].

Physical symptoms were assessed using the well-validated Giessen Complaint Questionnaire (GCQ) [8]. This inventory documents the presence and severity of 57 single symptoms and combines them into different scales. The scale "general complaint level" consists of 24 items.

Co-occurring therapies were evaluated retrospectively every 4 weeks by asking patients about other ongoing therapies, medical appointments, and medication changes.

Diaries were completed by patients during four 1-week periods within the 8-week treatment phase (twice, weeks 3 and 7) and 8-week follow-up period (twice, weeks 3 and 7). During these weeks, patients were asked to keep a diary for a week of all medication taken, as well as the time, duration, and type of daily practice related to the homework. Diaries were sent and returned by mail.

Interview data were also collected pre- and postintervention. At the preintervention interview, patients were asked to formulate 1 to 3 personal goals that they hoped to achieve. At the postintervention interview, patients were asked to quantify the degree to which these goals had been achieved, using an 11-point goal attainment scale, which ranged from −5 (not at all achieved) to +5 (achieved to far greater extent than expected) with the mid-point indicating the goal was reached to the level expected. During each interview, patients were also asked to indicate degree of impairment experienced due to their condition within the last 2 weeks on a VAS.

2.6. Ambulatory psychophysiological data

At baseline, end of intervention and short-term follow-up, patients were also assessed by means of an ambulatory psychophysiological monitor (LifeShirt, Vivometrics, CA), during which they were asked to wear a vest-like garment for 24 h during everyday life, with sensors for respiration, electrocardiography, and physical activity. The recorder also had a touch-sensitive display on which the patients completed a questionnaire at regular intervals during awake hours. Ambulatory results will be reported in a separate publication.

2.7. Clinically meaningful change

According to the current literature [12,22], there are 2 different approaches to determine a clinically meaningful change in a self-rating questionnaire. These are anchor-based and population-based techniques. Although both methods are not completely satisfactory per se, we preferred the anchor-based approach, as this method includes an external reference point analogous to criterion validation. With this approach, a *minimal clinically important difference* of the scale is determined by an external anchor, usually a

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[1] Manuals for both intervention arms are available in German from the first author.

[2] According to our study protocol, the primary endpoint of this trial was the German version of the Fibromyalgia Impact Questionnaire (FIQ-G). However after examining questionnaire data – but before any analysis had been done and before unblinded as to group allocation – we found that due to some misleading instruction in the German translation, several patients had not correctly completed six visual analogue scales which are the backbone of this instrument. Overall, we missed data of 18 patients because of this problem. After considering various imputation procedures for the missing data, we decided that replacement of such a substantial portion of missing data would represent an unsatisfactory approach. We thus decided to replace the primary outcome with one of the secondary outcomes, i.e. The Quality of Life Profile for the Chronically Ill (PLC) a measure of HRQoL. Our external Scientific Advisory Committee of experts otherwise unrelated to this trial, agreed to this decision. The committee consisted of Frank Wilhelm, University of Basel, Wolfgang Langewitz, University Hospital Basel, and Klaus Linde, Technical University Munich. A corresponding amendment was submitted to the ethics committee. We also marked this change in the record of the trial (identifier NCT00106275) on clinicaltrials.gov. This decision was made without any knowledge of the analyzed data or outcome.

single item asking for global change. An anchor-based estimate of minimal clinically important difference was available for only 1 of the 8 scales that we used, i.e., the FIQ [6]. Another way to judge a meaningful clinical change is whether patients cross established thresholds [34]. For 2 other scales, the CES-D [24] and the PSQI (e-mail communication, D.J. Buysse, University of Pittsburgh Medical Center, July 2, 2010), cut-offs have been recommended. Scores above these cut-offs respectively indicate clinical risk of depression or sleeping problems. We considered traversing these cut-off values in either direction as a clinical meaningful change and report the data accordingly.

2.8. Randomization

Patients were randomized in blocks by a computer algorithm [35]. Block size was randomly chosen to be either 3 or 6 patients. Information regarding eligible patients entering the trial was sent to a study manager who otherwise had no contact with the patients. The study manager then determined block size and randomized the patients, but only if there were enough patients to fill the next block. Patients were blinded to the fact that MBSR was the experimental intervention, and the relaxation procedure was the control intervention. All personnel of the study center handling the data or interacting with the patients during the whole course of the trial stayed blinded until the final analysis. Patients were encouraged not to tell the monitoring physician about their group assignment. Despite attempts to remain blinded, the study physician reported that patients occasionally volunteered information regarding allocation, and estimated this to occur in approximately 20% of the sample.

2.9. Statistical analyses

Results are based upon intention-to-treat (ITT) analyses. Missing values of individual items of scales were replaced according to missing replacement procedures of the respective inventories. When not specified, or when more items were missing than allowed for replacement using these procedures, overall scale values were replaced by a regression-based single imputation procedure ("predicted means") by the software SOLAS 2.0 [44]. Predictors for the imputation process were the respective baseline values of age, group, educational background, housing situation, and occupational level.

All analyses were performed by using the general linear model (GLM). Comparisons of groups at baseline were calculated either by 1-way analysis of variance (ANOVA) or χ^2 test, depending on type of variable. For the main outcome (HRQoL measured by the PLC at short-term follow-up), an analysis of covariance (ANCOVA) was calculated for the summed PLC scores at short-term follow-up, using intervention arm as a grouping factor and baseline value as covariate. Our 2 hypotheses were addressed by Helmert contrasts. Contrast 1 compared wait-list control vs both active treatments; contrast 2 compared MBSR vs the active control group. The same procedure was followed for secondary outcomes.

Substantial intercorrelation occurred among secondary variables at baseline. Therefore, to prevent type I errors, we also performed, as supplementary analysis, a single repeated-measures multivariate analysis of covariance using the change scores of 7 secondary health-related inventory measures (factor *time*, 2 levels; level 1: changes from baseline to end of intervention; level 2: changes from baseline to short term follow-up) with a grouping factor (group: 3 levels) and the baseline values of the 7 scales as covariates to control for baseline differences (the mindfulness index was excluded because it is not a demonstrated measure of health-related outcome but a variable to indicate manipulation control).

3. Results

3.1. Participants

Overall, 376 patients contacted us, of whom 330 individuals underwent required preliminary telephone screening (Fig. 1 flowchart). Telephone-reported complaints of 52 individuals were not consistent with eligibility criteria, and an additional 147 individuals declined participation, citing unavailability because of time demands, travel requirements, scheduling problems, lack of interest, or unspecified reasons. Clinic appointments were made with 187 women, and 177 were included in the trial (Fig. 1).

The criteria for inclusion into the ITT sample were randomization and, for those not in the wait-list arm, participation in at least 1 session of a course. This procedure was chosen because intervention instructors were able to exclude patients before commencement of intervention on the basis of new information they had acquired during the intake interview (e.g., suicidal tendencies), which occurred after randomization. The ITT sample consisted of 168 women. The completer sample comprised all patients who had participated in at least 50% of the allocated intervention and provided data at both preintervention and short-term follow-up (*N* = 137, dropout rate, 18%). All patients were recruited between July 2004 and October 2005.

The average age of participants was 52.5 years (SD = 9.6 years); average reported duration of symptoms 14.3 years (SD = 10.2 years); and mean time since diagnosis of 4.0 years (SD = 3.9 years). Demographic information is presented separately for each intervention arm of the study in Table 1. There were no significant baseline differences for sociodemographic or disease-related parameters. Regarding comorbidity, 58% of the patients had a clinically relevant depression score (i.e., score >23 in the German version of the CES-D scale). Furthermore the sample showed an elevated degree of trait anxiety (mean STAI, 50.0, SD = 10.3), higher than that of 89% of women aged 30–59 years and 80% of women aged 60 years or more in the German norm population. Regarding physical symptoms measured by the complaint list (GCP), our sample scored worse than 96% of the German norm population of same sex and age.

3.2. Anaylsis of of primary outcome at short-term follow-up

Using Helmert contrasts within an ANCOVA analyses, adjusting for baseline levels of respective measures, there were no significant differences for any contrasts (contrast 1: wait-list control vs both active treatments; contrast 2: MBSR vs active control group) between groups at short-term follow-up for the primary outcome HRQoL measured by the PLC. The *P*-values were 0.70 and 0.20, respectively (Table 2).

3.3. Multivariate ANCOVA of secondary health-related outcome measures adjusting for baseline differences

This analysis was performed to account for type I errors because of the substantial intercorrelations of secondary variables at baseline. Analyses revealed no effects of *time* (Wilks' lambda = 0.943, *F* = 1.32, df = 7/152, *P* = 0.25) or *group* (Wilks' lambda = 0.883, *F* = 1.40, df = 14/304, *P* = 0.15) but showed a significant *group × times* interaction (Wilks' lambda = 0.851, *F* = 1.82, df = 15/304, *P* < 0.05). Two significant individual contrasts could also be identified (Table 2). The active treatment groups showed greater postintervention reductions in anxiety than the wait-list patients (*P* = 0.04, contrast 1). Patients in the MBSR group rated themselves higher on the mindfulness scale (FMI) than patients allocated to the active control group (*P* = 0.03, contrast 2). There were no significant differences for any other contrasts.
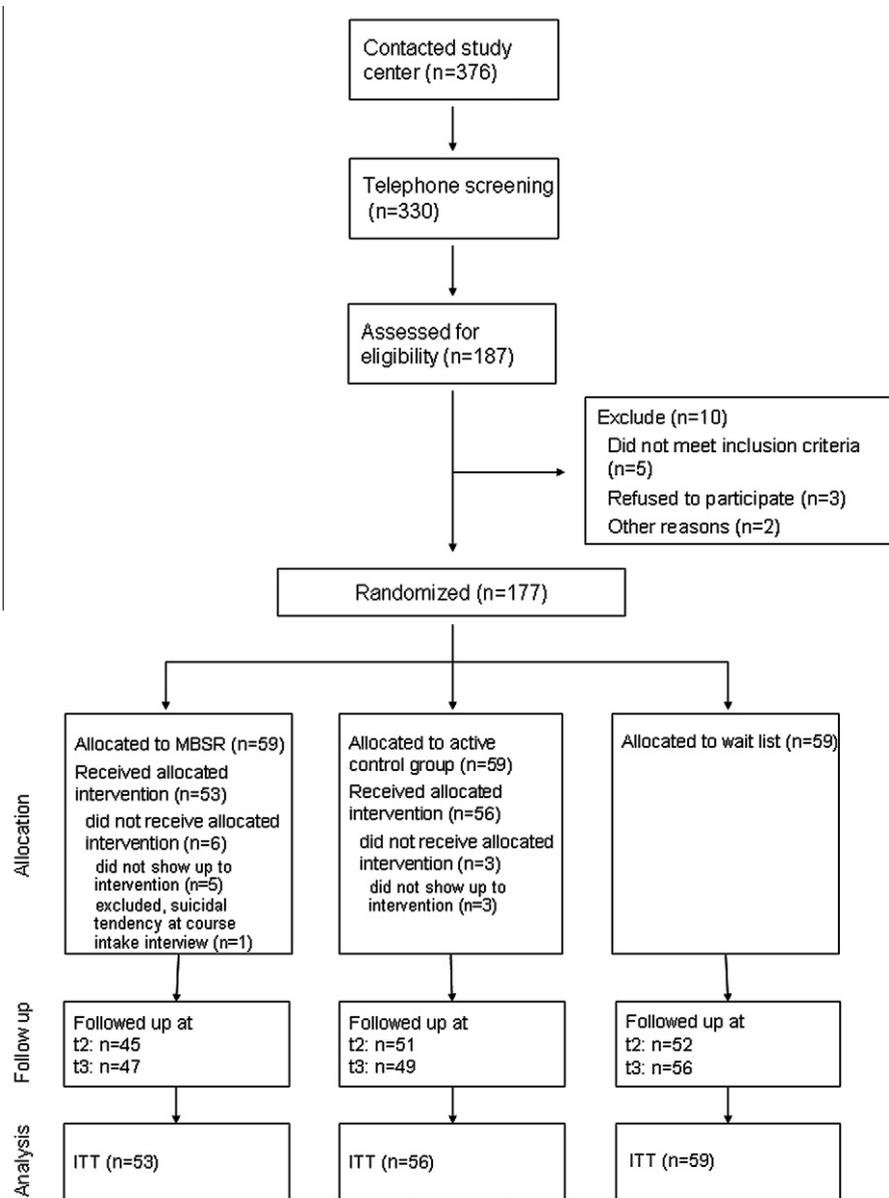
Fig. 1. Patient flow chart according to the revised CONSORT statement [2].

Table 3 reports means of primary and secondary outcome measures for baseline (BL), end of intervention (EOI), and short-term follow-up (STF) for each group and for the whole cohort. *P* values represent within-group effects of these between baseline and short-term follow-up, and the respective effect sizes are provided. The primary outcome HRQoL showed a significant positive change over time for the whole cohort ($P = 0.004$). For within-group analyses, this comparison was also significant for the mindfulness group ($P = 0.02$; within-group pre–post effect size, $d = 0.39$) but not for the active control group or the wait-list condition. For the 8 secondary outcome variables, the following results were found. Overall, patients significantly improved in all variables from baseline to short-term follow-up, except self-attribution of mindfulness. In the wait-list group, 2 variables showed significant within-group pre-to-post-intervention changes (affective pain perception and complaints). For the active control group, 3 of 8 variables showed a significant positive change over time. In the mindfulness group, 5 variables were significant at the $P \leqslant 0.01$ level and 1 at the $P \leqslant 0.05$ level. Effect sizes range from $d = 0.19$ to $d = 0.50$ for the mindfulness group, from $d = -0.09$ to $d = 0.30$ for

the active control group and from $d = -0.08$ to $d = 0.25$ for the wait-list control group.

3.4. Clinically significant changes

Bennett et al. [6] empirically determined a 14% change in the FIQ as a minimal clinically important difference. Overall, 43 patients (26%) showed at least a 14% improvement and 22 (13%) at least an impairment of the same size between baseline and short term follow-up. There were no group differences in improvement or impairment. Improvement rates were 22% for wait list, 25% for active control, and 30% for mindfulness, respectively.

For the German CES-D scale, a score greater than 23 indicates a clinical relevant depression score. A total of 39 patients (23%) showed an improvement by crossing this cut-off point in a positive direction from baseline to short-term follow-up. On the other hand, 17 patients (10%) crossed this threshold in the opposite direction. Improvement rates were unrelated to group allocation with 19% for wait list, 23% for active control, and 28% for MBSR, respectively.

Table 1
Baseline characteristics of the 3 study groups.

Characteristic	Wait list	Active control	MBSR	P value
N	59	56	53	
Mean age, ±SD	52.3 ± 10.9	51.9 ± 9.2	53.4 ± 8.7	0.70
Family status,%				0.053
Married	61.0	58.9	52.8	
Married, living separately	6.8	1.8	1.9	
Widow	0	0	9.4	
Divorced	11.9	17.9	18.9	
Single	20.3	19.6	15.1	
Missing data	0	1.8	1.9	
Work,%				0.94
Working	37.3	41.1	35.8	
Unemployed	10.2	12.5	7.5	
School	1.7	0	0	
Housewife	6.8	8.9	11.3	
Retired	35.6	28.6	37.7	
None of above	6.8	7.1	5.7	
Missing data	1.7	1.8	1.9	
Education level,%				0.25
No school completed	1.7	0	1.9	
9 years	30.5	28.6	34.0	
11 years/GCSE	25.4	39.3	41.5	
A-level/college entry level	42.4	30.4	20.8	
Missing data	0	1.8	1.9	
Duration of FM, months ± SD				
Onset of disease	154.5 ± 117.2	188.0 ± 132.0	173.9 ± 119.1	0.34
Since diagnosis	44.4 ± 47.7	46.0 ± 43.7	54.6 ± 48.7	0.48
Tenderpoint count	15.7 ± 2.3	15.1 ± 2.3	15.2 ± 2.5	0.37

On the PSQI, a score of 5 or less is considered to indicate a good sleeper with no insomnia. Only 19 patients (11%) who scored higher at baseline reached this cut-off at short-term follow-up. In contrast, 9 patients (5%) who reported as being good sleepers at baseline crossed the threshold in the opposite direction. Positive change rates were 10% for wait list, 7% for active control, and 17% for MBSR, respectively.

3.5. Medication

We compared the use of medication with simple dichotomous variables (yes/no) at baseline and at short-term follow-up for antidepressants, pain killers and sleep medication. There were no baseline differences for any of these variables. Only antidepressant medication was reduced significantly from baseline (45.7%) to short-term follow-up (35.0%) ($p = 0.01$, $\chi^2 = 5.94$, $N = 140$, McNemar test), but there was no effect of group.

3.6. Course attendance

Patients showed similarly high attendance rates for both interventions. On average patients in the MBSR arm attended 6.7 of 8

sessions (84%) and 6.2 of 8 (77%) in the active control (no significant difference between groups).

3.7. Role of self-attribution of mindfulness for heath status changes

Associations were examined between change in self-attributed mindfulness (FMI) and changes in the other 8 questionnaire scores for the 2 active groups. In the MBSR arm, positive change in self-reported mindfulness was related to reduced anxiety, improved depressive symptoms, and improved HrQoL ($r = 0.33–0.54$). For the active control group, the same pattern emerged, with 6 of 8 correlations reaching significance (depressive symptoms, HrQoL, FIQ, physical symptoms, and affective pain perception anxiety, $r = 0.27–0.63$).

3.8. Interview data

At the end of the program, patients rated the extent to which they had attained personal goals stated in the preintervention interview (goal attainment scale [30]). In addition, VAS scores of overall impairment at pre- and postintervention were compared. These data were collected exactly as in the forerunner

Table 2
Comparison between groups by analysis of covariance with short-term evaluation results as dependent variable and baseline as covariate.

Variable	Helmert contrast 1: wait list vs both active treatments P value	Helmert contrast 2: MBSR vs active control P value	Main effect for group(df = 2/164) F	Main effect for group(df = 2/164) P value
HRQoL (PLC)	0.70	0.20	0.902	0.41
FIQ	0.95	0.36	0.431	0.65
CES-D	0.41	0.19	1.208	0.30
STAI	0.04[a]	0.19	2.871	0.06
PSQI	0.47	0.74	0.316	0.73
PPSaffective	0.18	0.18	1.805	0.17
PPSsensory	0.89	0.60	0.152	0.86
FMI	0.48	0.03[a]	2.556	0.08
GCQ	0.32	0.22	1.249	0.29

HRQoL, health-related quality of life; PLC, Quality of Life Profile for the Chronically Ill; CES-D, Center for Epidemiological Studies depression inventory; STAI, state-trait-anxiety-inventory; PSQI, Pittsburgh Sleep Quality Index; PPS, Pain Perception Scale; FMI, Freiburg Mindfulness Inventory; GCQ, Giessen Complaint Questionnaire. *Note*: Hypotheses are tested by Helmert contrasts.
[a] $P < 0.05$.

Table 3
Means and standard deviations for all variables per group for all 3 timepoints: baseline (BL), end of intervention (EoI), and short-term follow-up (STF).

| | Wait list (N = 59) | | | | | Active control (N = 56) | | | | | MBSR (N = 53) | | | | | Overall (N = 168) | |
	BL	EoI	STF	P^a	ES^b	BL	EoI	STF	P	ES	BL	EoI	STF	P	ES	P	ES
HRQoL (PLC)	11.67 ± 3.18	11.80 ± 3.48	12.29 ± 3.28	0.11	0.19	11.75 ± 3.27	12.89 ± 3.43	12.16 ± 3.61	0.34	0.13	11.69 ± 2.94	12.64 ± 2.98	12.83 ± 3.06	0.017	0.39	0.004	0.23
FIQ	5.65 ± 1.86	5.32 ± 1.62	5.29 ± 1.66	0.10	0.19	5.50 ± 1.68	5.08 ± 1.57	5.33 ± 1.90	0.49	0.10	5.84 ± 1.37	4.90 ± 1.74	5.23 ± 2.00	0.021	0.45	0.007	0.22
CES-D	25.43 ± 9.26	24.22 ± 10.28	24.00 ± 9.61	0.18	0.15	22.92 ± 10.27	20.90 ± 9.53	22.55 ± 10.13	0.79	0.04	25.19 ± 9.60	23.20 ± 9.04	21.70 ± 9.93	0.012	0.36	0.018	0.18
STAI	48.68 ± 10.68	48.39 ± 9.92	49.18 ± 10.47	0.63	-0.05	49.8 ± 10.91	48.00 ± 8.94	48.44 ± 10.94	0.17	0.12	51.60 ± 9.18	47.65 ± 8.43	47.86 ± 9.12	0.003	0.41	0.022	0.14
PSQI	11.12 ± 4.36	10.68 ± 4.42	10.37 ± 4.06	0.17	0.17	11.37 ± 4.24	10.12 ± 4.21	10.25 ± 4.09	0.015	0.27	11.31 ± 3.45	10.04 ± 3.76	10.01 ± 3.60	0.004	0.38	<0.001	0.26
PPS affective	34.78 ± 7.66	33.09 ± 7.78	32.38 ± 9.07	0.026	0.25	34.74 ± 8.67	31.96 ± 9.02	32.17 ± 8.76	0.027	0.30	35.47 ± 9.38	31.26 ± 8.78	30.79 ± 9.20	<0.001	0.50	<0.001	0.35
PPS																	
Sensory	22.64 ± 5.65	21.17 ± 5.75	21.44 ± 5.34	0.09	0.21	22.85 ± 6.58	22.56 ± 5.93	21.87 ± 5.40	0.17	0.15	22.35 ± 6.12	20.78 ± 4.98	21.16 ± 5.42	0.06	0.19	0.004	0.18
FMI	36.67 ± 6.64	36.00 ± 5.28	36.13 ± 7.27	0.48	-0.08	35.86 ± 7.81	36.99 ± 7.38	35.14 ± 7.61	0.38	-0.09	36.38 ± 6.10	39.20 ± 5.03	37.66 ± 5.15	0.11	0.21	0.95	0.00
GCQ	48.36 ± 14.79	47.41 ± 14.30	45.29 ± 15.04	0.025	0.21	47.02 ± 14.65	43.41 ± 15.76	43.91 ± 15.10	0.022	0.21	48.43 ± 13.53	42.01 ± 10.63	42.63 ± 12.20	<0.001	0.43	<0.001	0.28

For abbreviations, see footnote to Table 2. *Note:* Higher values on the PLC, indicate better health status. For all other scales, lower values indicate greater well-being.
[a] P values represent within-group changes from baseline (BL) to short-term follow-up (STF) as well as for the whole cohort.
[b] Within-group effect sizes reflect differences between (BL) and (STF), calculated by the mean difference divided by the standard deviation at baseline, positive effect sizes indicate improvement.

study [21], in a short questionnaire during the interview, and are reported in Table 4. Because we unexpectedly did not replicate major findings of the earlier study, we compared the goal attainment and VAS findings between the 2 studies (Table 4) to facilitate interpretation of results. Examination of the 95% confidence intervals revealed no differences between studies in either of these measures.

4. Discussion

We conducted a randomized, partially blinded, 3-armed trial, with adequate statistical power, to investigate the effects of an MBSR-based intervention on HRQoL and other parameters of well-being among female fibromyalgia patients. Comparisons were made among MBSR group, an active control intervention group, and a wait-list group. In each set of analyses, no group effects upon HRQoL were found. Therefore the MBSR intervention did not yield the hypothesized effects and did not prove to be better than either a simple wait-list procedure or an active control condition designed to match for nonspecific aspects. On the basis of the results of this trial, MBSR cannot be recommended as an effective treatment for women with fibromyalgia.

An examination of the 8 secondary variables, using 2 comparisons revealed, only 2 significant effects out of 16 contrasts considered. Namely, the active treatment groups showed greater postintervention reductions in anxiety than the wait-list patients. In addition, MBSR patients rated themselves higher on the mindfulness scale than active control patients.

Despite the overall negative findings, examination of within-group pre- to posteffect sizes (Table 3) may nevertheless reveal relevant additional information. On average, patients of all groups showed slight improvements over the course of the trial. Average within-group effect sizes from baseline to short-term follow-up ranged from $d = -0.08$ to 0.25 (mean = 0.14) for wait list, from $d = -0.09$ to 0.30 (mean = 0.14) for active control and from $d = 0.19$ to 0.50 (mean = 0.37) for MBSR. Differences in effect sizes between MBSR (mean = 0.37) and the 2 other treatments (mean = 0.14) were too small to show either statistical or clinical significance. Nevertheless, a multivariate analysis of secondary outcomes adjusting for baseline differences indicated a significant group × time interaction, which reflected the somewhat larger pre-to-post effects of the MBSR group. These post hoc findings are merely informative and in no way should be construed to be at variance with the failure to find differential benefits of MBSR for the primary outcome.

Confronted by the inconsistencies between the current findings and those of the forerunner study, we examined the data for clues that might shed light on why this may have occurred. For example, in the present investigation, the additional quantitative data derived from personal interviews of the 2 active treatments before and after the intervention do not fit the overall picture of the standardized inventories. In the postintervention interviews, patients in the MBSR arm reported substantial improvements, and large effect sizes were found, on a self-rated global scale that estimated perceived lessening of fibromyalgia-related impairment. Patients also indicated that they had achieved personal goals exceeding the level expected at baseline (Table 4). Similar, but smaller, effects were found for the active control group. In general, these quantitative interview data also matched what was found among MBSR participants in the earlier study [21].

It is also striking that results of the main questionnaire data for this trial, especially the primary outcome measure, are in sharp contrast to the outcome of the earlier study [21], which was very similar in design, intervention, outcome variables, and actual MBSR instructors. Although patients in the 2 studies were comparable at baseline levels, only the Grossman et al. study [21] showed a marked improvement after MBSR intervention. The within-group

Table 4
Results for the interview data for this study and the study by Grossman et al. [21].

		Active control				MBSR			
		Mean	SD (95% CI)	ES	n	Mean	SD (95% CI)	ES	n
Impairment by fibromyalgia	This study	10.39	32.11 (−0.10–20.88)	0.49	36	18.83	24.16 (11.52–26.14)	0.86	42
	Grossman et al. [21]	−7.62	29.52 (−23.67–8.43)	−0.32	13	14.87	23.49 (7.51–22.24)	0.73	39
Goal attainment score	This study	0.58	2.13 (−0.10–1.26)		38	1.27	1.34 (0.86–1.68)		42
	Grossman et al. [21]	−1.26	1.91 (−2.3–0.22)		13	1.31	2.27 (.55–2.07)		34

CI, confidence interval. Note: Impairment by FM is the difference between end of intervention and baseline for data from visual analog scales (0–100 mm), positive results indicate an improvement. Goal attainment scores reflect whether goals specified at baseline have been reached at end of intervention. A mean of 0 reflects that the goal has just been reached, whereas values larger than 0 indicate that the result was much better than expected before the intervention. Data from this study are based on the per protocol sample, with 1 data set missing for the mindfulness group.

postintervention effect size for the HrQoL sum score was $d = 0.93$ vs $d = 0.39$ in the current study.

One possible reason for the latter discrepancy could be the fact that the self-report questionnaire data in the current investigation might have been biased because of excessive patient burden. In the present study, questionnaires were usually filled out during the visit to the hospital, after patients had been instrumented with the LifeShirt for later 24-h monitoring and had undergone a calibration procedure (controlled breathing and walking). Indeed, over the course of the study, more and more patients complained of discomfort during this assessment. In addition, some patients felt too exhausted to complete questionnaires during the visit and were allowed to complete inventories at home and return them the next day. This led to inconsistency in the setting and, in retrospect, may have caused significantly greater error variance in results of the current investigation.

Other aspects of the current investigation may have also added to overall patient burden, especially when common symptoms of fibromyalgia are considered (e.g., fatigue, lack of energy and reduced threshold to discomfort). During the LifeShirt assessment, patients were prompted approximately every 45 min to fill in an electronic diary. They were also requested to change equipment batteries, and to connect a pulse oximetry sensor for assessment during sleep. Furthermore, patients were asked to keep diaries of their homework and medications during selected weeks, as well as to complete a questionnaire every 4 weeks about changes in medication and concurrent therapies. On the other hand, in the first study, patient burden was much lower, as no ambulatory or physiological monitoring was performed, and questionnaire completion was less demanding and always performed in the same location.

Other crucial differences between the studies had to do with issues of recruitment and assignment to treatments: In the present study, two-thirds of the sample was randomly assigned to 1 of 2 plausible active, behavioral interventions. Thus, patients were provided information that presented 2 rather vaguely described interventions. Potential benefits were mentioned but not further specified. This approach may have influenced motivation of our patients quite differently from those in the earlier quasi-randomized study.

In the earlier study, patients actively chose mindfulness training upon enrollment, either based on either referrals from physicians who were often enthusiastic about the specific benefits of mindfulness training or after having read a brochure positively describing the program and its potential benefits. Therefore, the treatment preferences of patients in the former study were always concordant with the intervention received.

Potent influences of patient preferences upon effects of treatment have repeatedly been demonstrated [13,28,39]. Patient preference and resulting effects on motivation are important and typically neglected issues in randomized controlled trials of behavioral interventions, especially because such trials commonly require substantial commitment and effort. It seems plausible that these factors may have contributed to the differences between the previous and current trials. Therefore, although the present investigation can be considered a better controlled study because of its stringent randomization procedure and more elaborate methodology, these very features may also have brought with them distinct vulnerabilities that commonly are ignored regarding the ecological and external validity of results.

Indeed, the current trial's failure to find beneficial effects of MBSR in the primary outcome, as well the relatively meager evidence of improvements in secondary measures, are not easy to reconcile with results of the earlier investigation, unless one considers these methodological differences relating to patient burden, recruitment, and randomization procedure. Therefore, when designing trials in the future, it may be important to keep in mind the characteristics of participation in behavioral interventions in real life: Usually, patients deliberately choose to attend an MBSR course and are not merely assigned to a mindfulness program. Furthermore, they are typically not part of an extensive monitoring procedure. In these respects, the earlier investigation conformed more to what occurs under naturalistic conditions.

Two other issues regarding specific limitations of the present investigation should also be mentioned. As previously reported, patients were told before randomization that both active treatments were of equal value; however, patients may not have perceived treatment as equivalent. As a post hoc check of the credibility of this claim, we assessed the post-trial treatment choices of participants who had been randomized to the wait-list group and were later free to choose between interventions. Of 59 patients, 35 chose MBSR, 10 chose the active control group, and 14 did not participate in any treatment. The fact that MBSR was more frequently chosen may indicate that patients deemed it the more promising treatment.

Another point to consider is that fidelity of interventions was not monitored during the study. Both interventions often dealt with personal emotional issues and required an atmosphere of trust. We chose against monitoring because of concerns that it might be disruptive or might influence the intervention in some other undesired manner. Nevertheless, instructors in both arms were carefully supervised and highly experienced in their group intervention techniques. For example, instructors in the experimental intervention (MBSR) had taught for many years, continuously conferred with each other, and followed the same weekly syllabus; however, we cannot be absolutely sure of strict treatment fidelity.

5. Conclusion

In conclusion, despite the current, clearly negative findings, this report may provide additional and valuable information regarding commonly neglected factors likely to influence assessment of behavioral interventions in general and MBSR efficacy in fibromyalgia in particular. We believe that our findings demonstrate the value that can be derived from replicating research with essentially identical interventions and similar patient groups, while at the same time varying methodological aspects. Thus our results do point to the

necessity of further, and even more carefully conceived and executed, trials that take into account the necessity for both methodological stringency and ecological validity.

Conflicts of interest statement

No financial or other conflicts of interest exist for any of the authors.

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