Research Paper

PAIN®

A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: the EUDAIMON study

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Abstract

Fibromyalgia (FM) syndrome represents a great challenge for clinicians and researchers because the efficacy of currently available treatments is limited. This study examined the efficacy of mindfulness-based stress reduction (MBSR) for reducing functional impairment as well as the role of mindfulness-related constructs as mediators of treatment outcomes for people with FM. Two hundred twenty-five participants with FM were randomized into 3 study arms: MBSR plus treatment-as-usual (TAU), FibroQoL (multicomponent intervention for FM) plus TAU, and TAU alone. The primary endpoint was functional impact (measured with the Fibromyalgia Impact Questionnaire Revised), and secondary outcomes included "fibromyalginess," anxiety and depression, pain catastrophising, perceived stress, and cognitive dysfunction. The differences in outcomes between groups at post-treatment assessment (primary endpoint) and 12-month follow-up were analyzed using linear mixed-effects models and mediational models through path analyses. Mindfulness-based stress reduction was superior to TAU both at post-treatment (large effect sizes) and at follow-up (medium to large effect sizes), and MBSR was also superior to FibroQoL post-treatment (medium to large effect sizes), but in the long term, it was only modestly better (significant differences only in pain catastrophising and fibromyalginess). Immediately post-treatment, the number needed to treat for 20% improvement in MBSR vs TAU and FibroQoL was 4.0 (95% confidence interval [CI] = 2.1-6.5) and 5.0 (95% CI = 2.7-37.3). An unreliable number needed to treat value of 9 (not computable 95% CI) was found for FibroQoL vs TAU. Changes produced by MBSR in functional impact were mediated by psychological inflexibility and the mindfulness facet acting with awareness. These findings are discussed in relation to previous studies of psychological treatments for FM.

Keywords: Fibromyalgia, Mindfulness-based stress reduction, Mediational models, RCT

1. Introduction

Fibromyalgia (FM) is a disabling syndrome of unknown etiology that affects approximately 2% of the general population worldwide.[9] It is mainly characterized by chronic widespread pain, fatigue, stiffness, sleep problems, perceived cognitive dysfunction, and distress.[24,32] FM is associated with high health care and societal costs industrialized countries.[46,73]

Clinicians prescribe medications as the usual treatment for FM despite their limited benefits.[61,67] In fact, clinical guidelines are inconsistent regarding recommendations for pharmacotherapy for

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 160 (2019) 2508–2523

http://dx.doi.org/10.1097/j.pain.0000000000001655

treating FM.[81] In addition, aerobic exercise, multicomponent therapy, psychoeducation, and cognitive-behavior therapy (CBT) have proven their effectiveness in randomized controlled trials (RCTs), obtaining small to medium effect sizes.[6,7,37,43,51,52,61] At the same time, there are treatment developments that represent extensions of, and perhaps innovations within, CBT. These treatments do not include symptom improvement as their primary objective; they emphasize nondidactic and experiential methods, focus on contextual change, and de-emphasize change in the content or intensity of thoughts and feelings as therapeutic mechanisms. Of course, each of these features is not unique from other forms of CBT but a matter of emphasis.[22,34,62] Mindfulness-based stress reduction (MBSR)[39] is conceived as part of this group of therapies because it does not directly aim for symptom reduction. Instead, it aims to fundamentally alter how symptoms, and stressful thoughts and feelings, are experienced, so that they are addressed with greater awareness and acceptance rather than with ignoring and resistance. Mindfulness-based stress reduction maintains that by using awareness and acceptance, one can decrease emotional reactivity and enhance psychological flexibility, thereby improving overall health and functioning, in the context of continued FM symptoms. Mindfulness-based stress reduction was developed as a transdiagnostic treatment for people suffering from chronic conditions, with the aim of relieving suffering through the practice of mindfulness techniques. In the particular case of FM, some studies have found that MBSR achieved significant improvements in some core FM symptoms.[11,17,26,70,73] However, to better understand the benefits and limitations of mindfulness for managing FM, additional RCTs are needed that include methodological refinements such as active control groups, larger sample sizes, and longer-term follow-up to test durability of effects.[38]

The main objective of this 3-armed RCT was to analyze differential efficacy and short- and long-term outcomes of MBSR vs another validated multicomponent treatment called FibroQoL vs treatment-as-usual (TAU) for people with FM. The primary outcome of this RCT was functional impact, and additional measures were included to examine potential therapeutic processes of change, ie, potential mediators of primary and secondary outcomes.

Our previous hypotheses were as follows: hypothesis 1 (clinical outcomes): We expected greater statistical and clinically significant improvement in functional impact for (1) both MBSR and FibroQoL (vs TAU) and (2) for MBSR (vs FibroQoL) at post-treatment and 12-month follow-up. Both MBSR and FibroQoL are practically equivalent in terms of structure, but functionally different, which provides a comparison of MBSR with an active control that matches MBSR in nonspecific factors but does not contain mindfulness methods nor presumed mindfulness processes. Hypothesis 2 (mediators): We expected that changes in mindfulness facets and self-compassion would mediate the impact of MBSR on the primary and secondary outcomes at follow-up[27] as both are processes addressed in the MBSR program. Although MBSR is not based on the psychological flexibility model,[23] we expected that positive outcomes obtained from it may also be mediated by psychological flexibility. This is because facets of psychological flexibility appear widely applicable to different psychological treatments for chronic pain,[2,75] and because MBSR addresses overlapping processes, particularly acceptance and awareness, which are primary components of psychological flexibility.[30]

2. Method

2.1. Design

The study is posted at Clinicaltrials.gov under registration number NCT02561416. A 12-month RCT was performed with random allocation of participants to 3 arms (using a computer-generated randomization list): MBSR + TAU; FibroQoL + TAU; and TAU alone. A detailed description of the study protocol can be found elsewhere.[21] In summary, all recruited participants provided written informed consent and engaged voluntarily in the RCT. This included 3 assessments: baseline, post-treatment (or 2 months after baseline, in the case of the participants allocated in the TAU condition), and 12 months (48 weeks) after randomization. The assessments included the battery of measures described below.

The study was approved by the Ethics Committee at the Sant Joan de Déu Foundation (PIC-102-15) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and subsequent updates.

2.2. Sample size

Following Schmidt et al.'s protocol,[74] sample size was established on the basis of a previous meta-analysis of controlled MBSR trials[29] in which a mean effect size of $d = 0.53$ was found. This effect size results in a statistical power of $(1 - b) = 0.80$ for N = 75 patients per group (225 patients overall) assuming a dropout of 25%.

2.3. Participants

We followed a multistage recruitment process. A total of 225 patients with FM participated in the study between January 2016 and April 2018. All participants were recruited from the Rheumatology Service of Sant Joan de Déu Hospital (Sant Boi de Llobregat, Spain) and underwent a phone screening to assess the inclusion criteria: (1) age between 18 and 65 years; (2) able to understand Spanish language; and (3) providing informed consent to participate, as well as the exclusion criteria: (1) participation in a concurrent treatment trial; (2) presence of cognitive impairment according to the Mini-Mental State Examination[47] (score <27); (3) participation in psychological treatment during the last 12 months; (4) previous experience in meditation or other mind-body therapies; (5) presence of comorbid severe mental or medical disorders which could interfere with treatment; (6) pregnancy; and (7) involvement in ongoing litigation relating to FM. Those participants meeting the eligibility criteria were scheduled for a first face-to-face interview in the hospital with a trained clinical psychologist blind to treatment allocation. At that time, inclusion and exclusion criteria were checked again, a battery of self-report measures (see below) was administrated, and a diagnostic interview was conducted based on the Structured Clinical Interview for DSM-IV-Axis I Depressive disorders (SCID-I).[78] Participants were also informed of confidentiality procedures and that they could freely withdraw from the study at any time.

2.4. Interventions

2.4.1. Mindfulness-based stress reduction

Mindfulness-based stress reduction is a transdiagnostic mindfulness-based intervention originally developed by Kabat-Zinn[39] to help people with chronic pain and other stress-related

conditions. Mindfulness is defined as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience."[41] Intensive and structured training in mindfulness is provided to help people to relate to their physical and psychological conditions in more accepting and nonjudgmental ways[42]; this program explicitly teaches participants that physical relaxation is not an aim of meditation practice.[40] We used the MBSR protocol developed at the University of Massachusetts Medical School (USA) with minimal adaptations for our participants with FM. Our program consisted of 8 weekly 2-hour long sessions, instead of the usual 2.5-hour sessions, to avoid exhaustion or withdrawal from the study. In addition, although we offered the participants with FM the usual one half-day of silent MBSR retreat (a 6-hour long session that was scheduled between weeks 6 and 7), it was optional. A variety of meditation exercises were practiced during treatment sessions (Hatha yoga, sitting and walking meditation, body scan, etc), and audiotapes were provided to facilitate practice at home. Home practice was recorded by participants in a practice log, and the practice experiences were reviewed, discussed, and reinforced during treatment sessions throughout the program. The intervention was delivered in a group format (approx. 15 patients per group), and following Ost's recommendations,[63] we randomized patients to MBSR therapists (5 properly trained MBSR instructors) to enable an analysis of possible instructor effects on the outcome. All sessions were videotaped, and 2 authors (A.F.-S. and J.V.L.) checked adherence to the treatment manual and therapist competence using the Mindfulness-Based Interventions: Teaching Assessment Criteria (MBI:TAC),[16] a validated instrument that measures 6 domains: (1) coverage, pacing, and organization; (2) relational skills; (3) embodiment of mindfulness; (4) guiding of mindfulness practices; (5) conveying course themes; and (6) holding the group learning environment. An outline of the MBSR sessions can be found in **Table 1**. The patients allocated in the active treatment arms were not asked to discontinue their regular pattern of medication and recorded their usual care over the course of the RCT.

2.4.2. FibroQoL

The FibroQoL program is a multicomponent intervention developed by expert multidisciplinary groups in Catalonia between 2006 and 2007. It was used as an active treatment comparator because it had previously demonstrated cost–utility compared with TAU for FM.[53,54] Mindfulness-based stress reduction and FibroQoL were practically equivalent in terms of structure (ie, one 2-hour long weekly session for 8 weeks delivered in a group format), such as in time and attention. FibroQoL is a credible treatment in its own right. It thus provides a comparison of MBSR to an active control that matches MBSR in nonspecific factors, but does not contain mindfulness methods, and does not address mindfulness processes. The FibroQoL protocol consists of 8 weekly 2-hour long sessions divided in 2 parts: 4 sessions of psychoeducation in which patients receive information about the pathophysiology, diagnosis, and management of FM symptoms and another 4 sessions of training in self-hypnosis to generate a state of deep relaxation through the exploration of the sensations produced by one's own body with the objective of achieving control over the body and pain (a focus that is inconsistent with mindfulness) and to imagine the one's life in the future without pain.[66] Audiotapes were provided to facilitate practice at home. The intervention was delivered in a group format (15 patients per group), with sessions conducted by 1 or 2 members of the FibroQoL team (2 psychologists—1 of which oversaw the 4 sessions of training in self-hypnosis, 3 family physicians, and a rheumatologist). The professionals in charge of each FibroQoL session are indicated in **Table 1**. The FibroQoL sessions were also video recorded, but no formal assessment of treatment fidelity was conducted. Delivery was assumed to be adequately consistent with the original design because the intervention was delivered by the same team of professionals who developed FibroQoL. An outline of the FibroQoL sessions can be found in **Table 1**. The patients allocated in the active treatment arms were not asked to discontinue their regular pattern of medication and recorded their usual care over the course of the RCT.

2.4.3. Treatment-as-usual

Participants randomized to this arm received no additional active treatment over the study period but continued with their regular pattern of medication (if any). Standard treatment of FM typically includes analgesics, anxiolytics, opioids, antidepressants, and/or anti-inflammatories and recommendations for practicing aerobic exercise regularly. For ethical reasons, participants were offered participation in the MBSR program at the conclusion of the study.

2.5. Study measures

Along with a sociodemographic questionnaire, the participants completed the following as part of a paper-and-pencil battery of measures:

2.5.1. Primary outcome measure

The *Revised Fibromyalgia Impact Questionnaire* (FIQR)[5] was our primary outcome at post-treatment (primary endpoint) and 12-month follow-up. The FIQR includes 21 items that are answered on a 0 to 10 numerical scale where higher scores indicate greater functional impact. The questionnaire asks about the previous 7 days, and the items are distributed into 3 associated domains: physical impairment, overall impact, and severity of symptoms (ie, pain, energy, stiffness, sleep quality, depression, memory issues, anxiety, pain to the touch, balance problems, and increased sensitivity to noises, lights, smells, or temperatures). The total score is obtained by adding the 3 subscales' scores and can range from 0 to 100 with higher scores indicating greater impact. The FIQR is currently considered the "gold standard" for assessing functioning in patients with FM. The Spanish version of the FIQR is multidimensional, has high internal consistency ($\alpha = 0.91$-0.95), adequate test–retest reliability ($r = 0.82$), and good construct validity.[49]

2.5.2. Secondary outcome measures

The *Fibromyalgia Survey Diagnostic Criteria* (FSDC)[11,33] is a 6-item self-report measure of the key symptoms of FM according to the latest revision of the American College of Rheumatology (ACR) criteria. It includes 2 subscales: the Widespread Pain Index to identify the presence of pain in 19 body areas in the last week and the Symptom Severity scale, in which the 3 major symptoms, fatigue, "fibrofog," and waking up tired, are assessed along with 3 additional symptoms, pain in lower stomach, depression, and headache. A total "fibromyalginess" score is obtained by adding the 2 subscales and ranges from 0 to 31, where higher scores indicating greater FM severity.

Table 1

Outline of the interventions MBSR and FibroQoL

Session	MBSR	FibroQoL
1	The norms are presented, and the objective of the intervention is clarified: to change the reaction to pain. The groups' expectations are discussed. Techniques: the raisin-eating task, the inquiry, and the body scan. Homework: lecture and exercise self-registrations. Patients receive the printed version of the book "*Con rumbo propio*" + 3 CDs	General information: The family physician offers updated information regarding the physiological mechanisms of pain, the usual course of FM, and comorbid medical conditions. The impact of FM on quality of life is discussed. Patients receive the printed version of the *Beginner's guide to fibromyalgia* (http://www.fibro.info/guideen.pdf). Conducted by a family physician.
2	Review of the homework. Techniques: conscious movements, the 9-point exercise, and brief sitting meditation. The importance of open-to-experience, nonjudgmental attitude is underlined. Homework: lecture and exercise self-registrations.	Answers about expectations are compared with find similarities among the patients and to check progress through the sessions. The psychologist explains differences between physical and emotional pain, clarifies differences between hypnosis and self-hypnosis, and administers a hypnotizability test. Technique: "*safe place*" hypnosis. Conducted by a clinical psychologist (specialist in self-hypnosis training).
3	Review of the homework. Techniques: walking meditation and practicing sitting meditation. A dynamic explanation of the emotions is given. Homework: lecture and exercise self-registrations.	Diagnosis and treatment: The family physician explains the diagnostic criteria and the pharmacological and nonpharmacological approaches and their evidence, the prognosis and the current health care model in Catalonia. A list of units specializing in the treatment of FM in Catalonia is provided. Conducted by a family physician.
4	Review of the homework. Techniques: sitting and walking meditation. Discussion of the relationship between stress and pain, introducing the Buddhist concept of "the 2 arrows": suffering = pain × resistance. Homework: reflecting on stressful situations and feelings of distress.	This session focuses on the discussion of personal goals and the obstacles to reaching them, emphasizing common personality characteristics, and highlighting problem's exception. Technique: "*candle and bubbles*" hypnosis. Conducted by a clinical psychologist (specialist in self-hypnosis training).
5	Review of the homework. Technique: sitting meditation. Discussion on how to cope with stress and different styles of dealing with stressful situations. Homework: registering stressful events and reactions to them, in addition to meditation exercise.	Strategies to increase self-esteem and regulate emotions are discussed. Special emphasis is given to the experience of pain and recurrent invalidation. The importance of social support (family and friends) is discussed. Conducted by a clinical psychologist.
6	Review of the homework. Technique: sitting meditation and the *metta* exercise Indications about the silent retreat day are given. Part of the session is dedicated to talking about communicative styles and more adaptive approaches (to avoid vs to attack vs being open and assertive). Homework: registering situations related with communication.	Possible changes are explored, and the difference between acute and chronic pain is discussed. Technique: "*imagination of a journey*" hypnosis. Conducted by a clinical psychologist (specialist in self-hypnosis training).
Voluntary Retreat	A 6-hour long retreat for practicing the abilities learnt so far in the program while cultivating a sense of presence and attention to the present.	—
7	Review of the homework. Technique: meditation, *metta*, and the conscious eating task. Discussion of the thoughts resulting from the 6-hour long retreat. Homework: writing a letter to share feelings about the process with the rest of the group.	Review of goals achieved; it is asked about a new possible change and commitment to consolidation of the changes. Technique: "*look at a photo album*" hypnosis. Conducted by a clinical psychologist (specialist in self-hypnosis training).

(*continued on next page*)

Table 1 (*continued*)

Session	MBSR	FibroQoL
8	Review of the homework. This final session is built around discussion of what has been learned through the course, what expectations have and have not been met, and what conclusions can be drawn from the whole experience. The intervention assessment (Treatment opinion Scale, Satisfaction survey) is conducted.	The role of specialized care: A rheumatologist conducts this session using a specialized care approach for FM, explains the work of specialized units dedicated to FM, resolves doubts, and holds a discussion concerning the strengths and weaknesses of the intervention. It is asked specifically if the expected changes were achieved and how could they be maintained. Finally, a Decalogue about how to live with FM is handed out and the intervention assessment (treatment opinion scale and satisfaction survey) is conducted. Conducted by a rheumatologist and a family physician.

MBSR, mindfulness-based stress reduction.

The *Hospital Anxiety and Depression Scale* (HADS)[85] is a 14-item measure of anxiety and depression symptoms during the previous week. The total score ranges from 0 to 42, and each subscale (HADS-Anxiety and HADS-Depression) includes 7 items with scores ranging from 0 to 21. Higher scores indicate higher symptom severity. The Spanish version has sound psychometric properties in the general population and also in patients with FM, presenting a high internal consistency ($\alpha = 0.80$-0.85).[50,80]

The *Pain Catastrophising Scale* (PCS)[79] is a 13-item measure of the frequency of thoughts about perceived catastrophic consequences of pain. It contains 3 dimensions: rumination (tendency to focus excessively on pain sensations), magnification (tendency to magnify the threat value of pain sensations), and helplessness (tendency to perceive oneself as unable to control the intensity of pain). The PCS total score and subscale scores are computed as the sum of ratings for each item. This study used the total score, which can vary from 0 to 52 with higher scores indicating greater pain catastrophising. The Spanish version of the PCS[26] has high test–retest reliability ($r = 0.84$), internal consistency ($\alpha = 0.79$), and sensitivity to change.

The *Perceived Stress Scale* (PSS-10)[15] consists of 10 items which measure the degree to which a subject appraises situations as stressful during the last month. Scores range from 0 to 40, with higher scores reflecting higher perceived stress. The Spanish version[71] has demonstrated adequate internal consistency ($\alpha = 0.81$), test–retest reliability ($r = 0.73$), validity, and sensitivity to change.

The *Multidimensional Inventory of Subjective Cognitive Impairment* (MISCI)[44] is a 10-item measure of subjective cognitive dysfunction (ie, "fibrofog") in FM. Each item is scored from 1 ("never") to 5 ("very often"), and the total score ranges from 10 to 50, where lower scores indicate higher cognitive dysfunction. The MISCI showed excellent internal reliability, low ceiling/floor effects, and good convergent validity with a similar measure. The Spanish version of the MISCI was recently validated[24] and shows excellent internal consistency ($\alpha = 0.91$).

2.5.3. Process measures

The *Five Facets of Mindfulness Questionnaire* (FFMQ)[3] consists of 39 items that capture 5 facets of mindfulness: (1) Observing includes noticing or attending to internal and external experiences such as sensations, thoughts, or emotions; (2) describing refers to labelling internal experiences with words; (3) acting with awareness involves focusing on one's activities in the here and now as opposed to behaving automatically or habitually; (4) nonjudging of inner experience refers to taking a nonevaluative stance toward thoughts and feelings; and finally, (5) nonreactivity to inner experience refers to allowing thoughts and feelings to come and go, without getting caught up or carried away by them. Each subscale ranges from 8 to 40 (except for nonreact, which ranges from 7 to 35), with higher scores indicating higher presence of the mindfulness facet. The Spanish version[1] shows good internal consistency for every subscale (ω ranging from 0.82 to 0.92).

The *Self-Compassion Scale—short form* (SCS-12)[70] comprises 12 items designed to assess overall self-compassion and 3 dimensions: common humanity, mindfulness, and self-kindness. For this study, only the total score is used; it ranges from 1 to 5, with higher scores indicating a higher level of self-compassion. The Spanish version of the SCS-12 shows good internal consistency ($\alpha = 0.86$) and very high convergence with the long form (26-item version) of the scale ($r \geq 0.97$).[25]

The *Psychological Inflexibility in Pain Scale* (PIPS)[84] is a 12-item scale designed to measure psychological inflexibility in people with chronic pain. It includes 2 subscales: avoidance and cognitive fusion related to pain. All the items are rated on a 7-point Likert-type scale (1 = "never true" and 7 = "always true"), with higher scores indicating more psychological inflexibility towards pain. For this study, only the total score is used; it ranges from 12 to 84, with higher scores indicating higher level of psychological inflexibility. The Spanish version of the PIPS[72] shows good test–retest reliability ($r = 0.97$) and internal consistency ($\alpha = 0.90$).

2.5.4. Other measures

The *Patient Global Impression of Change* (PGIC) and the *Pain-Specific Impression of Change* (PSIC)[76] are self-reported measures frequently used as indicators of meaningful change in treatments for chronic pain. They are scored on a 7-point Likert scale (from 1 = "much better" to 7 = "much worse"). The PGIC is 1 item referred to the perception of global improvement, whereas the PSIC asks about the impression of change in more specific domains: physical and social functioning, work-related activities, mood, and pain. These scales were completed by the participants who were assigned to the active study arms.

The adapted version of the *Credibility/Expectancy Questionnaire* (CEQ)[18] is a 6-item questionnaire for measuring treatment expectancy and credibility for use in clinical outcome studies. The questionnaire shows overall high internal consistency ($\alpha = 0.84$-0.85). We used an adapted version that evaluates expectancy (at the end of the first treatment session) and opinion (at the end of the last treatment session) about MBSR or FibroQoL.

The adverse events of the intervention checklist is an ad hoc measure to check for potential adverse events (eg, headaches, dizziness, sleep problems, etc) across the interventions and follow-up.

The frequency of practice of MBSR exercises during the intervention was assessed through self-reported daily logs in which participants described the frequency and duration of all practiced mindfulness exercises. At the beginning of every MBSR session, the logs of the previous week were collected and difficulties regarding the practice were addressed.

2.6. Statistical analyses

First, we examined baseline between-group differences in sociodemographic and clinical characteristics, applying the Student *t* test for continuous variables and the χ^2 test with continuity correction (or the 2-sided Fisher exact test when appropriate) for categorical data.

The primary between-group analysis to assess the treatment effect was performed on an intention-to-treat (ITT) basis with FIQR total score as a continuous variable,[56] and we assumed missing data were missing at random. This involved using linear mixed-effects models in which restricted maximum likelihood regression was used to account for the correlation between repeated measures for each individual. Restricted maximum likelihood regression produces less biased estimates of variance parameters when using small sample sizes or unbalanced data.[20] A study clearly showed that for all types of missing data (missing completely at random, missing at random, and missing not at random), multiple imputation is not necessary before computing longitudinal mixed model analysis.[82] Regression coefficients (*B*) and 95% confidence intervals (95% CIs) were calculated for the group × time interaction between groups at post-treatment and 12-month follow-up. We reported the effect size (Cohen's *d*) for each pairwise comparison, using the pooled baseline SD to weight the differences in the pre–post mean values and to correct for the population estimate.[59] The rule of thumb is usually that an effect size of 0.20 is small, 0.50 is medium, and 0.80 is large. Separate models were estimated for each of the secondary outcomes using the same analytical strategy. We applied the Benjamini–Hochberg correction for multiple comparisons, a procedure to detect false discovery designed to overcome the limitations that other tests typically used have shown.[27] The Benjamini–Hochberg procedure generates local significance levels where the first statistical test (smallest *P*-values in the ordered sequence) is assigned the local significance level that corresponds to the Bonferroni correction. The 3 pairwise comparisons between the 3 study arms are considered to be part of the multiple testing problem, and therefore, alpha/3 is the lowest significance level, while the other 2 hypotheses are tested locally against 2/3 × alpha and 3/3 × alpha, respectively.[4] Only the total score of each scale was taken into account to keep the statistical analyses as parsimonious as possible. These analyses were replicated using a per-protocol approach, considering only those patients who attended at least 6 treatment sessions (out of 8).

In addition, to assess clinical significance of the improvement on the primary outcome (FIQR), we classified participants into 2 categories (responders vs nonresponders to treatment) using 2 different criteria: (1) ≥ 20% reduction in the pre–post FIQR total score.[5] This classification was used to compute the number needed to treat (NNT) in MBSR compared with FibroQoL and TAU arms. Number needed to treat refers to the estimated number of patients who need to be treated with the new proposed treatment (ie, rather than the control comparison treatment) for 1 additional patient to benefit. A 95% CI for each NNT was calculated. This index allows findings from RCTs to be more meaningful to clinicians. (2) Considering the recent 4-cluster FIQR classification,[65] in which each cluster is associated with a different level of severity, a second NNT was calculated taking as a criterion changing to a less severe cluster compared with the one in which the patient was allocated in the baseline assessment.

The differences regarding participant global and pain-specific impressions of change (PGIC and PSIC) were calculated using the χ^2 test with continuity correction, and the differences regarding expectancies and opinion (CEQ) were calculated using the Student *t* test. The possible effect of the frequency of practice during the intervention (measured in mean days per week) on clinical outcomes was measured using univariate analysis of variance and controlling by baseline levels of the dependent variables.

Finally, we examined whether the effect of MBSR on primary and secondary outcomes at 12-month follow-up was mediated through pre–post changes in mindfulness facets (FFMQ), psychological flexibility (PIPS), and self-compassion (SCS-12). We calculated pre–post change in the total scores of the FFMQ facets, the PIPS, and the SCS-12 and pre–follow-up change scores in the primary and secondary outcomes. Bivariate Pearson correlations were computed between the pre–post change in the process variables and the pre–follow-up change in the outcomes to detect potential significant relationships. We explored the direct and indirect associations between the treatment condition (MBSR vs TAU as independent variable), FFMQ, PIPS, and SCS-12 (mediators), and primary and secondary outcomes (dependent variables) using path analyses. The direct paths between the treatment condition and clinical outcomes and the indirect effect path through the FFMQ facets, the PIPS, and the SCS-12 were tested in all the models. Participants with missing data were excluded for this analysis. Regression coefficients (*B*) of bias-corrected bootstrapped indirect effects were calculated as well as their SEs and 95% CIs.[48] Parameters of indirect effects were considered statistically significant when the 95% CI did not include 0.

Data analyses were computed using SPSS v22, MPlus v7, and STATA 13 software. A 5% significance level was used in all two-tailed tests.

3. Results

3.1. Participants flow and compliance

Of the 567 potential participants who were eligible, 328 were excluded at the screening phone interview, and 14 were excluded for not meeting screening criteria at the face-to-face interview with a clinical psychologist. The final sample, consisting of 225 patients, was randomized into the 3 study arms, with 75 individuals per arm (**Fig. 1**). The mean number of sessions attended in the MBSR group was 5.00 (SD = 2.74), while in the FibroQoL group, it was 5.33 (SD = 2.76), which was not a statistically significant difference (F = 0.55, $P = 0.46$). The retention rate for MBSR was 77% and 65% at post-treatment and follow-up, respectively. In the case of FibroQoL, the retention rate was 80% and 68% at post-treatment and follow-up, respectively. Finally, TAU had 73% of retention rate at post-treatment and 65% at follow-up. Thus, the ratio of dropouts was very similar in the 3 groups, both post-treatment ($\chi^2 = 1.13$, $P = 0.57$) and at 12-month follow-up ($\chi^2 = 0.28$, $P = 0.87$). Data analyses indicated that dropouts had lower education level than completers ($\chi^2 = 15.09$, $P = 0.01$; 75% of completers vs 25% of dropouts had university studies). Regarding treatment fidelity and therapist

competence, the MBSR instructors received an average score of 5.22 (SD = 0.48) on the 1 to 6 scale of the MBI:TAC, which corresponds to a "proficient" level.

3.2. Baseline sociodemographic and clinical characteristics

As can be seen in **Table 2**, most patients were women, middle-aged, married, and most of them had at least completed primary education. A third of the sample had paid employment at baseline. No significant differences were found for sociodemographic characteristics between the 3 study arms. However, 2 marginal tendencies were observed in diagnoses of "current episode of major depression" and "previous episode of major depression" based on the SCID-I; these trends indicated that the MBSR group had fewer participants currently depressed compared with the other 2 groups, which was significant in the pairwise comparisons ($\chi^2 = 3.86$, $P = 0.050$). On the other hand, the TAU group had more participants with previous episodes of major depression, and this was significantly higher compared with the FibroQoL group ($\chi^2 = 5.51$, $P = 0.02$). Most patients were taking medication daily, mostly anxiolytics, antidepressants, opioids, anti-inflammatories, and analgesics. There were no significant differences in medication between the 3 study arms (nor in the 12-month follow-up assessment, $P \geq 0.15$ in all cases). Taking these results into account, subsequent analyses were adjusted for current episode of depression and baseline scores of each outcome.

3.3. Expectations about mindfulness-based stress reduction and FibroQoL

Data analyses of the CEQ indicated that MBSR was expected to be very logical (M = 8.29, SD = 1.79), satisfactory (M = 8.52, SD = 1.45), recommendable (M = 8.58, SD = 1.68), useful for treating other problems (M = 8.18, SD = 1.58), useful in the personal case (M = 7.88, SD = 1.82), and nonaversive (M = 0.92, SD = 2.27). FibroQoL did not receive such high ratings on expectations (all items presented significant differences, $P < 0.05$ in all cases), but it was rated as being logical, satisfactory, useful, recommendable (M ranging between 6.89 and 7.55), and nonaversive (M = 2.35, SD = 2.89). Although treatment expectations were significantly different in the 2 groups, they were not associated with treatment outcomes. Therefore, the following linear mixed models were computed excluding this variable as covariate.

3.4. Effects on functional impairment (primary outcome)

Table 3 shows descriptive statistics and between-group analyses for the FIQR data. Mindfulness-based stress reduction achieved a significantly greater reduction on functional impact than TAU post-treatment ($B = -14.28$, 95% CI −19.59 to −8.97, $d = 1.11$) and at 12-month follow-up ($B = -10.45$, 95% CI −16.64 to −4.26, $d = 0.80$). Compared with FibroQoL, it was superior post-treatment ($B = -10.90$, 95% CI −16.13 to −5.67, $d = 0.86$) but not at follow-up ($B = -4.56$, 95% CI −10.69 to 1.57, $P = 0.15$, $d = 0.35$). FibroQoL did not obtain a greater reduction on FIQR total scores compared with TAU post-treatment, although a marginally significant tendency was observed at follow-up ($B = -5.89$, 95% CI −12.04 to 0.26, $P = 0.06$, $d = 0.45$).

3.5. Effects on fibromyalginess, anxiety–depression, pain catastrophising, perceived stress, and cognitive dysfunction (secondary outcomes)

Mindfulness-based stress reduction was superior to TAU for reductions in fibromyalginess (FSDC) both post-treatment

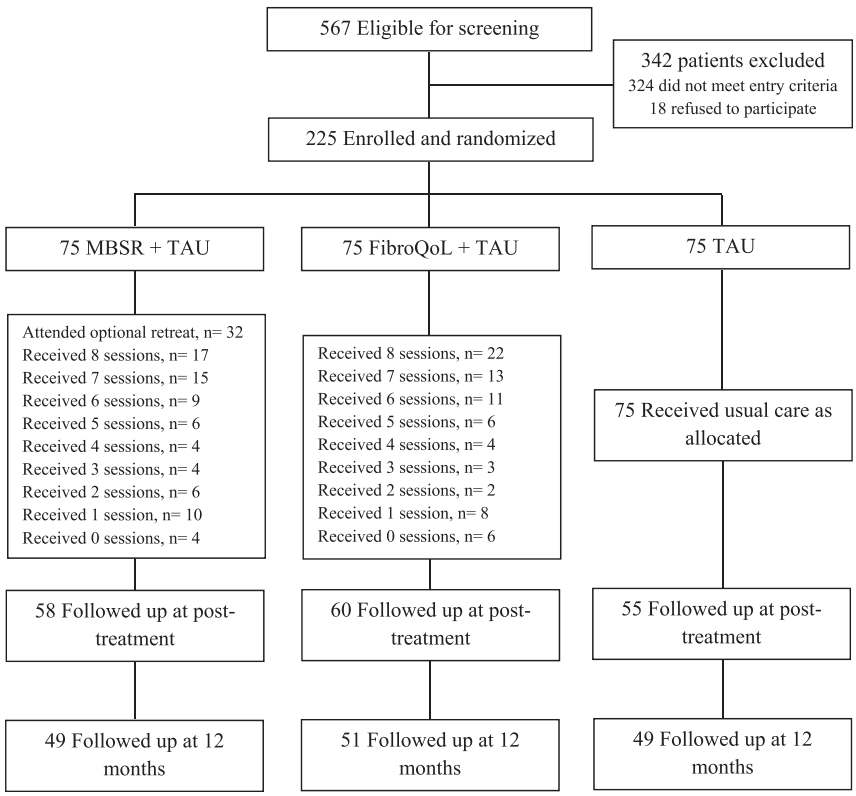

Figure 1. Flow chart of participants in the randomized controlled trial.

Table 2

Baseline characteristics of patients with FM by treatment group.

	MBSR (n = 75)	FibroQoL (n = 75)	TAU (n = 75)	*P*
Sex (No. females, %)	73 (97.3)	74 (98.7)	74 (98.7)	0.78
Age, mean (SD)	52.96 (7.98)	54.21 (7.41)	52.65 (8.52)	0.45
Marital status, n (%)				0.35
Single	3 (4)	5 (6.7)	1 (1.3)	
Married/living with a partner	57 (76)	54 (72)	60 (80)	
Separated/divorced	13 (17.3)	10 (13.3)	12 (16)	
Widowed	2 (2.7)	6 (8)	2 (2.7)	
Living arrangement, n (%)				0.69
Living alone	4 (5.3)	3 (4)	3 (4)	
Living with partner	71 (94.7)	72 (96)	72 (96)	
Education level, n (%)				0.37
Illiterate	0 (0)	1 (1.3)	1 (1.3)	
Did not graduate from primary school	5 (6.7)	2 (2.7)	4 (5.3)	
Primary school	35 (46.7)	41 (54.7)	35 (46.7)	
Secondary school	34 (45.3)	26 (34.7)	32 (42.7)	
University	0 (0)	5 (6.7)	3 (4)	
Others	1 (1.3)	0 (0)	0 (0)	
Employment status, n (%)				0.66
Homemaker	10 (13.3)	11 (14.7)	6 (8)	
Paid employment	22 (29.3)	23 (30.7)	21 (28)	
Paid employment but in sick leave	7 (9.3)	4 (5.3)	4 (5.3)	
Unemployed with subsidy	9 (12)	9 (12)	10 (13.3)	
Unemployed without subsidy	9 (12)	17 (22.7)	10 (13.3)	
Retired/pensioner	9 (12)	5 (6.7)	11 (14.7)	
Temporal disability	2 (2.7)	2 (2.7)	2 (2.7)	
Others	7 (9.3)	4 (5.3)	11 (14.7)	
Clinical variables				
Years of diagnosis, mean (SD)	13.95 (8.96)	11.20 (7.04)	13.10 (9.73)	0.19
Current episode of depression, n (%)	29 (38.7)	41 (54.7)	41 (54.7)	0.08
Previous episode(s) of depression, n (%)	27 (36)	22 (29.3)	36 (48)	0.06
Dysthymia, n (%)	15 (20)	10 (13.3)	8 (10.7)	0.25
Daily FM-related medication*				
Analgesics, n (%)	21 (30.9)	21 (30.4)	15 (22.1)	0.78
Anti-inflammatory, n (%)	17 (25)	17 (24.6)	24 (35.3)	0.67
Opioids, n (%)	25 (36.8)	21 (30.4)	17 (25)	0.68
Antiepileptic, n (%)	13 (19.1)	11 (15.9)	14 (20.6)	0.96
Muscle relaxant, n (%)	2 (2.9)	5 (7.2)	3 (4.4)	0.82
Antidepressants, n (%)	35 (51.5)	30 (43.5)	26 (37.7)	0.64
Anxiolytics, n (%)	30 (44.1)	33 (47.8)	31 (45.6)	0.99

The pairwise comparison showed some statistically significant differences: between the MBSR and the other 2 groups in "Current episode of Major Depression" ($\chi 2 = 3.86$, $P = 0.050$), and between TAU and FibroQoL in "Previous episode of Major Depression" ($\chi^2 = 5.51$, $P = 0.019$).

* The sample size per study arm was lower in this variable (MBSR = 68, FibroQoL = 69, TAU = 68).

MBSR, mindfulness-based stress reduction; TAU, treatment-as-usual.

($B = -3.84$, 95% CI −5.58 to −2.11, $d = 0.97$) and at follow-up ($B = -4.11$, 95% CI −6.03 to −2.18, $d = 1.04$); the same pattern was observed in perceived cognitive dysfunction (MISCI) post-treatment ($B = 7.64$, 95% CI 3.64-11.64, $d = 0.86$) and at follow-up ($B = 9.16$, 95% CI 4.26-14.05, $d = 0.99$). For the other secondary outcomes, large effects of MBSR vs TAU were observed post-treatment (d ranging from 0.84 to 1.07), but only moderate effects were found at follow-up (d ranging from 0.58 to 0.73).

Mindfulness-based stress reduction achieved significant moderate-to-large effects compared with FibroQoL on several secondary measures post-treatment: anxiety–depression (HADS, $B = -2.96$, 95% CI −5.57 to −0.34, $d = 0.49$), pain catastrophising (PCS, $B = -4.35$, 95% CI −8.13 to −0.56; $d = 0.65$), perceived stress (PSS-10, $B = -5.42$, 95% CI −8.45 to −2.38, $d = 0.77$), and cognitive dysfunction (MISCI, $B = 7.91$, 95% CI 4.45-11.37, $d = 0.95$). By contrast, the only significant differences between MBSR and FibroQoL at follow-up were found on fibromyalginess (FSDC, $B = -3.34$, 95% CI −5.29 to −1.40, $d = 0.82$) and pain catastrophising (PCS, $B = -4.35$, 95% CI −8.13 to −0.56, $d = 0.58$).

Finally, FibroQoL was superior to TAU post-treatment for the reduction of fibromyalginess (FSDC, $B = -2.16$, 95% CI −3.89 to −0.42, $d = 0.54$), whereas significant effects were found on anxiety–depression (HADS, $B = -3.61$, 95% CI −6.70 to −0.51, $d = 0.57$) and cognitive impairment (MISCI, $B = 5.56$ 95% CI 0.60-10.51, $d = 0.65$) at follow-up.

3.6. Effects on mindfulness facets, psychological inflexibility, and self-compassion (process variables)

Table 4 displays descriptive statistics and between-group analyses for the process variables. Compared with TAU, patients

Table 3

Descriptive statistics and between-group analyses for primary and secondary outcomes (ITT approach).

	TAU, Mean (SD)	FibroQoL, Mean (SD)	MBSR, Mean (SD)	TAU vs FibroQoL			TAU vs MBSR			FibroQoL vs MBSR		
				d	*t* (*P*)	*B* (95% CI)	*d*	*t* (*P*)	*B* (95% CI)	*d*	*t* (*P*)	*B* (95% CI)
Primary outcome												
FIQR (0-100)*												
Baseline	61.37 (19.70)	62.77 (17.98)	63.51 (19.03)									
Post-treatment	60.73 (21.28)	59.75 (18.15)	47.99 (19.50)	0.25	−1.26 (0.209)	−3.38 (−8.66 to 0.26)	1.11	**−5.29 (<0.001)**	−14.28 (−19.59 to −8.97)	0.86	**−4.09 (<0.001)**	−10.90 (−16.13 to −5.67)
Follow-up	63.75 (18.88)	60.42 (20.11)	53.98 (22.00)	0.45	−1.88 (0.060)	−5.89 (−12.04 to 0.26)	0.80	**−3.32 (0.001)**	−10.45 (−16.64 to −4.26)	0.35	−1.46 (0.145)	−4.56 (−10.69 to 1.57)
Secondary outcomes												
FSDC (0-31)*												
Baseline	22.37 (5.08)	22.28 (4.42)	22.23 (5.32)									
Post-treatment	22.57 (5.28)	20.48 (5.79)	17.93 (6.55)	0.54	**−2.45 (0.015)**	−2.16 (−3.89 to −0.42)	0.97	**−4.35 (<0.001)**	−3.84 (−5.58 to −2.11)	0.41	−1.90 (0.058)	−1.68 (−3.41 to-0.05)
Follow-up	22.71 (4.43)	22.59 (5.60)	18.18 (7.21)	0.20	−0.77 (0.438)	−0.76 (−2.69 to 1.17)	1.04	**−4.19 (<0.001)**	−4.11 (−6.03 to −2.18)	0.82	**−3.37 (0.001)**	−3.34 (−5.29 to −1.40)
HADS (0-42)*												
Baseline	19.68 (9.05)	19.55 (8.44)	18.64 (7.88)									
Post-treatment	20.16 (9.41)	18.62 (10.06)	14.31 (9.09)	0.36	−1.65 (0.100)	−2.22 (−4.86 to 0.42)	0.84	**−3.83 (<0.001)**	−5.17 (−7.83 to −2.52)	0.49	**−2.22 (0.027)**	−2.96 (−5.57 to −0.34)
Follow-up	21.12 (10.00)	18.02 (9.92)	15.69 (9.21)	0.57	**−2.29 (0.022)**	−3.61 (−6.70 to −0.51)	0.67	**−2.59 (0.010)**	−4.12 (−7.24 to −1.00)	0.10	−0.33 (0.745)	−0.51 (−3.61 to 2.59)
PCS (0-52)*†												
Baseline	22.29 (12.97)	23.77 (12.68)	23.79 (13.75)									
Post-treatment	19.55 (14.39)	18.65 (12.41)	12.93 (10.49)	0.37	−1.84 (0.066)	−3.59 (−7.43 to 0.24)	0.84	**−4.01 (<0.001)**	−7.94 (−11.84 to −4.04)	0.65	**−2.26 (0.025)**	−4.35 (−8.13 to −0.56)
Follow-up	18.61 (12.34)	18.00 (14.17)	11.43 (11.08)	0.15	−0.78 (0.434)	−1.71 (−5.99 to 2.58)	0.73	**−3.19 (0.002)**	−7.06 (−11.41 to −2.70)	0.58	**−2.45 (0.015)**	−4.35 (−8.13 to −0.56)
PSS-10 (0-40)*												
Baseline	23.11 (9.96)	23.28 (10.32)	23.05 (9.17)									
Post-treatment	23.47 (9.55)	21.60 (10.65)	15.60 (9.10)	0.30	−1.37 (0.172)	−2.13 (−5.20 to 0.94)	1.07	**−4.81 (<0.001)**	−7.55 (−10.63 to −4.46)	0.77	**−3.50 (0.001)**	−5.42 (−8.45 to −2.38)
Follow-up	23.33 (11.37)	21.22 (10.18)	18.94 (10.82)	0.36	−1.44 (0.149)	−2.56 (−6.04 to 0.92)	0.58	**−2.30 (0.022)**	−4.10 (−7.61 to −0.60)	0.21	−0.87 (0.383)	−1.54 (−5.01 to 1.93)
MISCI (10-50)*												
Baseline	28.90 (10.40)	30.08 (7.46)	28.92 (7.92)									
Post-treatment	28.61 (11.06)	30.45 (10.74)	36.81 (9.65)	0.01	0.13 (0.894)	0.27 (−3.73 to 4.27)	0.86	**3.77 (<0.001)**	7.64 (3.64 to 11.64)	0.95	**4.50 (<0.001)**	7.91 (4.45 to 11.37)
Follow-up	26.81 (9.19)	30.11 (9.86)	33.68 (11.17)	0.65	**2.21 (0.028)**	5.56 (0.60 to 10.51)	0.99	**3.68 (<0.001)**	9.16 (4.26 to 14.05)	0.41	1.66 (0.098)	3.60 (−0.66 to 7.86)

We controlled for current episode of depression and baseline level of the variable. Mean and SD are not adjusted. When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, all significant effects were maintained. The number of participants varied across assessment periods due to dropouts (see flow chart). Significant values ($p < 0.05$) are shown in bold.

* The baseline level of the variable is a significant covariate in the model.

† Current episode of depression is a significant covariate in the model.

B, regression coefficients; CI, confidence interval; *d*, Cohen's d as an effect size measure; ITT, intention-to-treat; MBSR, mindfulness-based stress reduction; TAU, treatment-as-usual

receiving MBSR achieved a significant increase post-treatment on the mindfulness (FFMQ) facets of observing ($B = 4.16$, 95% CI 1.97-6.35, $d = 0.79$), acting with awareness ($B = 3.83$, 95% CI 1.37-6.28, $d = 0.66$), and nonjudge ($B = 5.50$ 95% CI −2.89 to 8.12, $d = 0.89$), on psychological flexibility (PIPS, $B = -8.17$ 95% CI −12.93 to −3.42, $d = 0.67$) and on self-compassion (SCS-12), although this last effect became a marginal tendency after computing the Benjamini–Hochberg correction ($P = 0.054$). At 12-month follow-up, differences between MBSR and TAU were observed on the FFMQ facets of observing ($B = 4.42$, 95% CI 1.93-6.91, $d = 0.84$), describing ($B = 4.28$, 95% CI 1.39-7.17, $d = 0.66$), acting with awareness ($B = 3.14$, 95% CI −0.37 to 5.90, $d = 0.53$), and nonjudging of inner experience ($B = 4.21$, 95% CI 1.24-7.17, $d = 0.66$), and also on the PIPS ($B = 10.38$, 95% CI −15.78 to −4.98, $d = 0.88$).

In terms of the comparison MBSR vs FibroQoL, MBSR achieved significantly greater improvements post-treatment on the FFMQ facets of observing ($B = 3.33$, 95% CI 1.20-5.47, $d = 0.66$) and nonjudging of inner experience ($B = 3.42$, 95% CI 0.88-5.96; $d = 0.57$), for the PIPS ($B = -5.83$ 95% CI −10.43 to −1.23, $d = 0.49$) and for the SCS-12, although this latter effect was lost after computing the correction for multiple comparisons ($P = 0.15$). At follow-up, significant differences between MBSR and FibroQoL were only found in the FFMQ facets of describing and for the PIPS, but both became marginal tendencies once Benjamini–Hochberg correction was computed ($P = 0.09$ for describing and $P = 0.06$ for the PIPS).

Finally, the comparison FibroQoL vs TAU reflected only 1 significant difference post-treatment in the FFMQ facets of acting with awareness ($B = 2.76$, 95% CI 0.33-5.19, $d = 0.46$). At follow-up, scores on this facet remained significantly higher for the FibroQoL group than the MBSR group ($B = 3.64$, 95% CI 0.89-6.39, $d = 0.62$), as did the facets of observing ($B = 3.41$, 95% CI 0.93-5.88, $d = 0.63$) and nonjudging of inner experience, but this last effect became a marginal tendency after computing the Benjamini–Hochberg correction ($P = 0.07$).

We recomputed all data analyses of the primary, secondary, and process measures using a *per-protocol* approach (by excluding participants who had not attended at least 6 treatment sessions of MBSR/FibroQoL; Supplementary Tables 1 and 2, available at http://links.lww.com/PAIN/A846). In the comparison between MBSR and TAU, the results paralleled the findings obtained with the conservative ITT approach. However, in those comparisons including the FibroQoL group, some significant differences were observed; under the *per-protocol* approach, FibroQoL achieved a significant improvement compared with TAU in the HADS post-treatment ($B = -3.39$, 95% CI −6.31 to −0.46, $d = 0.51$) and in the FIQR ($B = -9.45$, 95% CI −16.23 to −2.67, $d = 0.28$) and the PSS-10 ($B = -3.88$, 95% CI −7.69 to −0.07, $d = 0.55$) at 12-month follow-up. Also, using this approach, 2 significant differences between MBSR and FibroQoL at the post-treatment assessment that had been observed using the ITT approach were lost: HADS ($B = -2.49$, 95% CI −5.72 to 0.74, $d = 0.51$) and PCS ($B = -4.36$, 95% CI −8.96 to 0.24, $d = 0.48$).

3.7. Number needed to treat

A total of 29 patients (50%) in MBSR, 18 (30%) in FibroQoL, and 10 (18%) in TAU reached the criterion of ≥20% FIQR reduction post-treatment (ie, "responders"). The absolute risk reduction (ARR) in MBSR vs TAU was 31.8% (95% CI = 15.4%-48.2%) with NNT = 4 (95% CI = 2.1-6.5), meaning that 4 patients would need to be treated with MBSR for one of them to become a responder, who would not have done so in the TAU group. The ARR in MBSR vs FibroQoL was 20% (95% CI = 2.7%-37.3%) with NNT = 5 (95% CI = 2.7-37.3); in this case, despite being significant, it is noteworthy that the CI is very wide, which means that caution is required in interpreting the practical value of this result. The ARR obtained with FibroQoL vs TAU was 11.8% (95% CI −3.6% to 27.3%) with NNT = 9. Because in this latter case the 95% CI for the ARR extends from a negative number (FibroQoL may harm) to a positive number (FibroQoL may benefit), the NNT result is unreliable. In other words, we cannot say with 95% certainty whether FibroQoL is harmful, has no effect, or is helpful compared with TAU. At follow-up, a total of 18 patients (37%) in MBSR, 15 (29%) in FibroQoL, and 3 (6%) in TAU reached the criterion of ≥ 20% FIQR reduction. A significant ARR was found for MBSR vs TAU (AAR = 30.5%, 95% CI = 15.4%-45.6%) with NNT = 4 (95% CI = 2.2-6.5) and FibroQoL vs TAU (AAR = 23.3%, 95% CI = 9.1%-37.5%) with NNT = 5 (95% CI = 2.7-11). The NNT was also calculated considering "responder" as any participant who changed to a less severe cluster after treatment compared with the one that he/she had been allocated at baseline. A significant ARR was found post-treatment in the comparison MBSR vs TAU: ARR = 23.1% (95% CI = 5.5%-40.7%) with NNT = 5 (95% CI = 2.5-18.3). The comparison MBSR vs FibroQoL also yielded significant results: ARR = 22.1% (95% CI = 4.7%-39.4%) with NNT = 5 (95% CI = 2.5-21.3; note the very wide IC range again). The other comparisons did not yield significant differences (the ARRs extended from a negative number to a positive number).

3.8. Other clinical results

3.8.1. Impression of change (post-treatment)

Focusing on MBSR, the answers given to the PGIC showed that 7 participants (15.9%) felt "very much improved," 18 participants (40.9%) felt "much improved," 11 participants (25%) reported that had "minimally improved," and 8 participants (18.2%) reported "no changes." No participant reported feeling worse. Regarding FibroQoL, only 1 patient (3.4%) felt "much improved," 8 participants (27.6%) experienced "minimal improvement," 16 participants (55.2%) reported feeling "no changes," and 4 patients felt "minimally worse" or "much worse" (6.9% in both cases). The statistical analysis revealed that the between-group differences in the PGIC were statistically significant ($\chi^2 = 27.43$, $P < 0.001$). A similar pattern of results was found for all PSIC items in favor of MBSR (P ranging from 0.009 to <0.001). Most participants attending MBSR groups felt improvement to some degree (minimal, much, or very much) in mood (88.6%), physical activities (75%), social activities (65.9%), work-related activities (65.9%), and pain (65.9%). FibroQoL achieved lower percentages in all the areas, including mood (55.2%), social activities (37.9%), physical activities (27.5%), work-related activities (17.8%), and pain (10.3%) (see Supplementary Table 3, available at http://links.lww.com/PAIN/A846).

3.8.2. Opinion about the intervention

Both MBSR and FibroQoL were considered highly recommendable (M = 9.16, SD = 1.62 for MBSR, and M = 7.94, SD = 1.95 for FibroQoL). Again, MBSR obtained significantly more positive ratings for all the recommendation ($P < 0.05$ in all cases).

3.8.3. Adverse effects

Relatively few adverse effects were reported. In the MBSR group, 3 participants reported having experienced notable

Table 4

Descriptive statistics and between-group analyses for process variables (ITT approach).

	TAU, Mean (SD)	FibroQoL, Mean (SD)	MBSR, Mean (SD)	TAU vs FibroQoL			TAU vs MBSR			FibroQoL vs MBSR		
				d	*t* (*P*)	*B* (95% CI)	*d*	*t* (*P*)	*B* (95% CI)	*d*	*t* (*P*)	*B* (95% CI)
FFMQ												
Observe (8-40)*												
Baseline	23.99 (6.94)	23.13 (6.24)	24.03 (6.96)									
Post-treatment	24.11 (7.49)	24.07 (6.98)	28.34 (7.06)	0.13	0.75 (0.454)	0.83 (−1.34 to 2.99)	0.79	**3.74 (<0.001)**	4.16 (1.97 to 6.35)	0.66	**3.07 (0.002)**	3.33 (1.20 to 5.47)
Follow-up	23.09 (8.03)	26.00 (7.71)	28.56 (7.48)	0.63	**2.71 (0.007)**	3.41 (0.93 to 5.88)	0.84	**3.49 (<0.001)**	4.42 (1.93 to 6.91)	0.22	0.82 (0.413)	1.02 (−1.42 to 3.45)
Describe (8-40)*												
Baseline	26.04 (7.89)	25.57 (8.87)	25.43 (7.39)									
Post-treatment	27.09 (8.38)	25.33 (8.29)	27.03 (7.42)	0.23	−1.03 (0.302)	−1.31 (−3.80 to 1.18)	0.09	0.59 (0.554)	0.76 (−1.76 to 3.27)	0.32	1.65 (0.099)	2.06 (−0.39 to 4.52)
Follow-up	24.00 (8.64)	25.43 (9.93)	27.96 (8.08)	0.17	0.78 (0.436)	1.14 (−1.73 to 3.99)	0.66	**2.91 (0.004)**	4.28 (1.39 to 7.17)	0.50	**2.18 (0.029)**	3.15 (0.32 to 5.97)
Act with awareness (8-40)*												
Baseline	26.34 (8.68)	25.16 (7.98)	25.70 (8.13)									
Post-treatment	23.20 (9.09)	24.37 (7.81)	26.84 (8.37)	0.46	**2.23 (0.026)**	2.76 (0.33 to 5.19)	0.66	**3.06 (0.002)**	3.83 (1.37 to 6.28)	0.20	0.87 (0.383)	1.07 (−1.34 to 3.47)
Follow-up	21.36 (7.73)	22.94 (7.88)	24.12 (9.31)	0.62	**2.60 (0.010)**	3.64 (0.89 to 6.39)	0.53	**2.23 (0.026)**	3.14 (0.37 to 5.90)	0.09	0.37 (0.714)	0.50 (−2.20 to 3.21)
Nonjudge (8-40)*												
Baseline	25.35 (9.03)	24.52 (8.88)	24.64 (8.02)									
Post-treatment	23.67 (9.35)	25.63 (8.17)	29.10 (7.18)	0.32	1.58 (0.114)	2.08 (−0.50 to 4.67)	0.89	**4.14 (<0.001)**	5.50 (2.89 to 8.12)	0.57	**2.65 (0.009)**	3.42 (0.88 to 5.96)
Follow-up	21.62 (9.71)	23.84 (10.13)	25.06 (8.63)	0.47	**1.98 (0.048)**	2.96 (0.02 to 5.91)	0.66	**2.79 (0.005)**	4.21 (1.24 to 7.17)	0.19	0.85 (0.398)	1.24 (−1.64 to 4.13)
Nonreact (7-35)*†												
Baseline	19.11 (6.46)	19.12 (5.49)	20.85 (5.58)									
Post-treatment	19.76 (5.19)	20.72 (5.66)	23.62 (5.49)	0.22	0.98 (0.328)	1.02 (−1.03 to 3.06)	0.50	1.84 (0.066)	1.93 (−0.13 to 3.99)	0.28	0.89 (0.372)	0.92 (−1.10 to 2.93)
Follow-up	19.11 (6.68)	20.76 (6.97)	21.84 (6.85)	0.32	1.26 (0.207)	1.50 (−0.83 to 3.84)	0.29	0.77 (0.440)	0.93 (−1.43 to 3.28)	0.03	0.49 (0.623)	0.58 (−2.88 to 1.72)
PIPS (12-84)*†												
Baseline	52.71 (16.16)	53.93 (14.93)	54.84 (16.48)									
Post-treatment	50.94 (16.55)	49.88 (15.08)	45.66 (13.69)	0.19	−0.97 (0.335)	−2.35 (−7.13 to 2.43)	0.67	**−3.38 (0.001)**	−8.17 (−12.93 to −3.42)	0.49	**−2.49 (0.013)**	−5.83 (−10.43 to −1.23)
Follow-up	54.63 (15.10)	50.56 (16.69)	46.15 (11.44)	0.41	−1.73 (0.085)	−4.76 (−10.18 to 0.66)	0.88	**−3.78 (<0.001)**	−10.38 (−15.78 to −4.98)	0.47	**−2.09 (0.037)**	−5.62 (−10.91 to −0.33)
SCS-12 (1-5)*												
Baseline	2.85 (0.97)	2.90 (0.99)	3.01 (0.83)									
Post-treatment	2.67 (0.86)	2.89 (0.88)	3.22 (0.76)	0.18	0.72 (0.470)	0.10 (−0.17 to 0.36)	0.66	**2.63 (0.009)**	0.36 (0.09 to 0.62)	0.47	**1.96 (0.050)**	0.26 (0.00 to 0.52)
Follow-up	3.01 (1.05)	3.32 (1.07)	3.56 (0.86)	0.16	0.53 (0.596)	0.08 (−0.22 to 0.37)	0.49	1.72 (0.086)	0.26 (−0.04 to 0.53)	0.34	1.21 (0.227)	0.18 (−0.11 to 0.48)

We controlled for current episode of depression and baseline level of the variable. Mean and SD are not adjusted. When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, the following effects were no longer significant: MBSR vs FibroQoL in "describe" (follow-up $P = 0.09$), in the PIPS (follow-up $P = 0.06$), and in the SCS-12 (post-treatment $P = 0.15$); TAU vs FibroQoL in "nonjudge" (follow-up $P = 0.07$); MBSR vs TAU in the SCS-12 (post-treatment $P = 0.05$). The number of participants varied across assessment periods due to dropouts (see flow chart).

* The baseline level of the variable is a significant covariate in the model.

† Current episode of depression is a significant covariate in the model.

B, regression coefficients; CI, confidence interval; *d*, Cohen's *d* as an effect size measure; ITT, intention-to-treat; MBSR, mindfulness-based stress reduction; TAU, treatment-as-usual.

Table 5

Direct and bootstrap indirect effects in the multiple mediational models of MBSR vs TAU (effects of pre-to-post changes in process variables on pre-to-follow-up changes in primary and secondary outcomes).

Outcome and mediators (R^2)	Direct effects				Indirect effects			
	Path	Coeff.	SE	*P*	Path	Boot.	SE	95% CI
FIQR (0.19)								
M1 = act with awareness (0.07)	a_1	3.78	1.50	**0.012**				
M2 = psychological inflexibility (0.09)	a_2	−9.68	3.28	**0.003**	$a_1 \times b_1$	−1.88	1.12	−5.15 to −0.36
	b_1	−0.50	0.23	**0.031**				
	b_2	0.36	0.13	**0.004**	$a_2 \times b_2$	−3.48	1.80	−8.12 to −0.79
	c'	−4.41	3.77	0.242				
PCS (0.15)								
M1 = psychological inflexibility (0.11)	a_1	−10.48	3.26	**0.001**				
	b_1	0.25	0.11	**0.002**	$a_1 \times b_1$	−2.66	1.56	−6.55 to −0.37
	c'	−4.55	3.09	0.140				
PSS-10 (0.12)								
M1 = act with awareness (0.07)	a_1	3.72	1.51	**0.014**				
M2 = psychological inflexibility (0.09)	a_2	−9.55	3.28	**0.004**	$a_1 \times b_1$	−1.18	0.69	−3.05 to −0.18
	b_1	−0.32	0.15	**0.033**				
	b_2	0.14	0.07	**0.039**	$a_2 \times b_2$	−1.30	−0.72	−3.17 to −0.24
	c'	−1.67	2.38	0.485				

A generic example of a multiple mediational model (with 2 mediators) is displayed in Figure 2. Significant values ($p < 0.05$) are shown in bold.
CI, confidence interval; FIQR, Revised Fibromyalgia Impact Questionnaire; MBSR, mindfulness-based stress reduction; PCS, Pain Catastrophizing Scale; PSS-10, Perceived Stress Scale; TAU, treatment-as-usual.

adverse effects during and/or after the intervention with significant frequency: one experienced fatigue (mild), and another experienced palpitations (intense). A third participant said that she had experienced a variety of adverse effects (fatigue, tension, headaches, dizziness, somnolence, gain of weight, and loss of sexual desire) at a moderate intensity and frequency, although they possibly did not understand that the effects had to be related to the intervention, or they could have been associated with medications they were taking (Lyrica and Zolpidem)—it was not possible to verify. Five participants reported experiencing adverse symptoms after the MBSR intervention but at a very low frequency and intensity. In the case of the FibroQoL groups, only 1 participant reported notable adverse effects with significant frequency: severe tension and slight headaches. Seven other FibroQoL participants reported experiencing adverse symptoms (headaches, tension, and fatigue), but these were transient, infrequent, and/or low intensity.

3.8.4. Mindfulness practice during mindfulness-based stress reduction

The self-report practice logs showed that the mean days of practice per week was 2.5 (SD = 2.17), with a mean duration of 53 minutes (SD = 49) per day of practice. Twenty-three participants (30.7%) reported no practice any day during the intervention, and 41 (54.7%) reported practicing at least 2 days per week. To find possible effects of the frequency of practice, the participants were divided in 2 subgroups taking the median as the dividing line: those who had practiced 2 days or more per week during the intervention and those who had practiced less than 2 days. These 2 subgroups did not present any significant difference regarding their sociodemographic characteristics. Those who practiced ≥2 days per week had lower baseline levels on the PCS ($P = 0.01$) but showed no other pretreatment differences on outcome measures. When controlling for baseline levels on the PCS, significant differences were observed between participants in the 2 MBSR practice subgroups (ie, those who practiced 2 or more days per week vs those who practiced less than 2 days per week) in the HADS-Depression ($P = 0.03$) and HADS-Total score ($P = 0.04$) at post-treatment; marginal tendencies towards between-group differences were found in then PSS-10 at post-treatment ($P = 0.06$), and in the HADS-Depression ($P = 0.05$) and FSDC ($P = 0.05$) at 12-month follow-up. In each case, those who had practiced 2 days or more per week achieved better or marginally better results.

3.9. Longitudinal mediation analyses: the role of mindfulness facets, psychological inflexibility, and self-compassion

We computed bivariate correlational analyses between baseline-follow-up differences in the primary and secondary outcomes and pre–post treatment differences in the process variables within the MBSR group (Supplementary Table 5, available at http://links.lww.com/PAIN/A846). Only path analysis models for clinical outcomes with significant correlations with any process variable were computed. The path analysis results are detailed in **Table 5** and illustrated in **Figure 2**.

Three of the 6 tested path models did not show a partial or total mediation effect. As shown in **Figure 2**, none of the 3 models with significant mediational effects yielded significant direct paths between the treatment arm and clinical outcomes. In the mediational model for the FIQR, the treatment arm predicted the change in FFMQ-facet acting with awareness and the change in the PIPS, which in turn predicted the change in FIQR scores at follow-up. Regarding the mediational model for the PCS, the treatment arm significantly predicted changes in the PIPS, which in turn predicted changes in pain catastrophising. Finally, in the model for the PSS-10, the treatment arm significantly predicted the change in FFMQ-acting with awareness and the change in the PIPS, which in turn predicted the change in perceived stress.

4. Discussion

This RCT aimed to assess the efficacy of MBSR compared with FibroQoL and usual care for the management of FM, and to analyze the role of different process variables as mediators of long-term clinical improvement. Compared with usual care, MBSR achieved significant effects on the primary and secondary

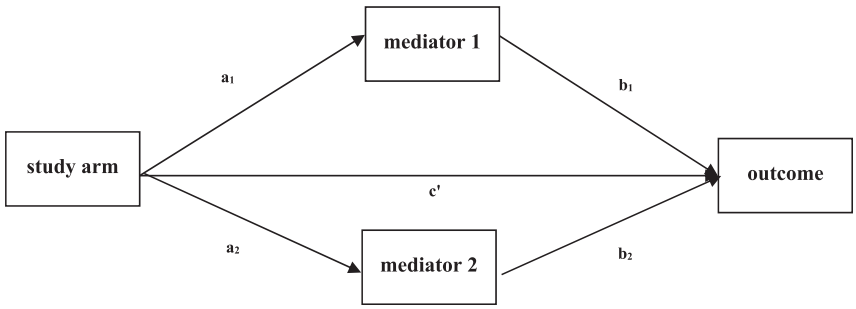

Figure 2. Generic example of a multiple mediational model (with 2 mediators). When the intervening mediator/s (M1 and M2) explain the relationship between study arm and outcome, we have a full mediational model. If study arm still has an effect on outcome after including the mediator/s in the model, the model is consistent with partial mediation.

outcomes both at post-treatment and at follow-up. Although some of them might need to be interpreted with care due to certain imprecise effect estimates (wide CIs), these results are particularly relevant, as they indicate that functional impact and symptoms in FM are moderately or largely improved by MBSR added to usual care in comparison to usual care alone. This is consistent with previous preliminary evidence.[12,28,74,77] The superiority of MBSR over usual care was corroborated by the low NNT values, even considering strict criteria such as changing to a lower FM severity cluster. The secondary outcomes reflected large improvement at the post-treatment assessment but only moderate amelioration improvement at 12-month follow-up, except for fibromyalginess (FSDC) and cognitive impairment (MISCI), where effects were larger. In the case of MISCI scores, this was mainly due to the trend towards increasing cognitive impairment apparent in the TAU group over time. This latter trend potentially underlines the clinical importance of addressing "fibrofog," a symptom which is associated with an accelerated aging and loss of brain gray matter.[45]

Both MBSR and FibroQoL achieved a similar level of adherence in terms of attendance at sessions (about 65%) and were rated positively by participants, although perceived clinical improvement was larger for MBSR. The efficacy of MBSR compared with FibroQoL was significant greater immediately at post-treatment evaluation on both the FIQR and all the secondary outcomes, with the sole exception of fibromyalginess, although some of these effects were presented along with wide CIs. At follow-up, MBSR showed superior efficacy in reducing pain catastrophising and fibromyalginess, but the differences between the 2 active treatments were no longer significant for the remaining outcomes. Again, the NNTs reflect these results: 1 of 5 patients treated with MBSR would become a responder at post-treatment assessment (although the wide CI range around this NNT is an important caveat), but in the long term, this number increased to a nonsignificant value. This echoes previous evidence for the robust short-term utility of MBSR for FM.[17,32]

There are a number of potential reasons for the relative loss of efficacy of MBSR at long term, such as the fact that participants were no longer attending weekly group treatment sessions or may have reduced home practice with mindfulness. In this study, patients completed self-reported practice logs during the MBSR intervention, but in the follow-up phase, this was not required. Participants generally admitted having practiced meditation intermittently and not very often, although this was not formally analyzed. Previous studies[10,55,69] have found that frequency of practice of mindfulness during the intervention is related to or even mediates significant effects in different symptoms (eg, depressive symptoms and distress) in patients with chronic pain or depression. Similarly, a recent meta-analysis[64] has found a significant association, albeit small, between participants' self-reported home practice and the mindfulness-based intervention outcomes across 28 studies. Considering all this evidence, it seems reasonable to believe that some outcomes are particularly practice-dependent. Hence, if the frequency of practice decreased once the intervention was over, the improvements achieved throughout the 2-month intervention could be partially lost. A main focus for future research should be how to enhance the frequency and quality of mindfulness practice, not only during the intervention but especially once it is over—ideas such as smartphone's apps or booster sessions, which have been tested in some previous research,[13,31,60,68] could be worthy of examination.

Notably, FibroQoL obtained larger effects when the per-protocol analysis was performed, indicating that attending at least 6 sessions was a relevant factor in relation to outcome. This was clearly observed when it was compared with usual care, as some significant differences which were not appreciated under the ITT analysis emerged, including one in the FIQR at follow-up. Treatment adherence, both in terms of attendance to the sessions and home practice (which was not formally assessed in the FibroQoL groups, yet encouraged in every self-hypnosis training session), is a continuing key issue for clinicians when implementing psychotherapies. Although the attendance ratio was relatively good for both interventions in this study, the results support a need for continuing refinements.

Our results indicated that acting with awareness and psychological inflexibility were both significant mediators of MBSR effects compared with TAU in relation to the FIQR and in the PSS-10, while in the case of the PCS, the only mediator was the psychological inflexibility. Psychological inflexibility is defined as the inability to act effectively in accordance with a valued life in the presence of unpleasant thoughts, emotions, or bodily symptoms[35] and has been found as a general mediator of the effects of forms of CBT such as ACT or ABCT.[14,58,83] These therapies emphasize processes of change such as mindfulness, acceptance, values, goals, and meta-cognition, and it seems appropriate that psychological flexibility acts as a generic important mediator of this type of interventions.[34] Relatedly, acting with awareness refers to the ability to focus on one's activities in the here and now. It is worth mentioning that acting with awareness is a key component of psychological flexibility[57] and has been found to be strongly associated with positive psychological outcomes.[8]

Some limitations of this study are notable. First, the randomization was not stratified with respect to the presence of comorbid

major depression, which resulted in MBSR having significantly fewer participants with a current episode of major depression compared with FibroQoL. However, all the analyses were performed after adjusting for this variable, and the only significant effect of doing so was found for the PCS. Furthermore, a difference that should be taken in consideration between the FibroQoL program that was implemented in a previous study[53] and the one that was implemented in the present one is that, in the previous study, the professionals who conducted the FibroQoL program were previously known to the participants in the primary care setting. This additional contact could have enhanced the therapeutic alliance, a relevant factor in any treatment context and particularly in a syndrome such as FM that is often associated with the experience of feeling stigmatized.[36] Low follow-up rates (around 65%) should be considered when interpreting our results. They could have the effect of biasing results in favor of one treatment or another; this is grounded in the idea that those participants who drop out of a study might be different than those who remain in it. In fact, we found that those participants who remained until follow-up assessment had higher level of education. This variable, however, did not have any effect on the primary outcome at any timepoint, and the attrition rates at post-treatment and follow-up were very similar across the conditions. We did not find attrition bias attributable to the variables considered in this study. However, other unknown variables, other differences not assessed here between dropouts and those assessed at follow-up, could have affected outcomes, as the differences between ITT and per-protocol analyses suggest.

Future studies should specifically focus on who drops out and why to improve adherence to protocols and avoid possible bias. Another limitation is that MBSR and FibroQoL were not fully equivalent in therapy time and expectations; there was not a comparable 6-hour optional retreat in FibroQoL and treatment expectations were slightly higher in patients assigned to MBSR, although this difference was not found to be related to treatment outcomes. An important aspect that deserves attention is that those patients who were randomly assigned to MBSR or FibroQoL seldom complied with optimal attendance rates (≥6 treatment sessions). Also, mindfulness practices at home were probably inadequate in the MBSR program, as the frequency was much lower than what it is recommended (ie, 6 or 7 days per week), and practices at home were not systematically recorded in the FibroQoL groups, so it was not possible to assess the potential effects of frequency of practice in these participants. Finally, the format of the MBSR program, although it was modified to some degree, may remain a challenge in this population. It requires formal practice over 45 minutes per day over the course of 8 weeks, continuing during follow-up, to maintain the health benefits. Such a schedule may be difficult for anyone to maintain. Alternative formats may be explored in the future, such as shorter daily practices (20 minutes) or establishing online groups or prompts to enhance adherence to mindfulness training. These modifications in the format might augment the possibility of incorporating mindfulness into the daily lives of participants. At the same time, studies of relations between changes in format and relative impact on process or therapeutic change would be welcomed.

The aforementioned limitations call for a discussion about effects sizes at the group level. MBSR achieved statistically significant results even with suboptimal retention and treatment adherence. We should reflect about what is more recommendable, an intervention that shows small effect sizes at group level but with very good adherence or an intervention that shows moderate-large effect sizes at group level in a relatively small subgroup of treated individuals. One of the main problems of mindfulness-based interventions is that they are based on high-dose training, and some treated participants are reluctant to invest so much time on mindfulness practices at home. Less intense interventions that impact a larger percentage of the target population might be preferable for policy makers. We think that cost-effectiveness analyses can help us to resolve this dilemma. To address the efficiency of mindfulness-based interventions as stand-alone or concomitant treatments is an issue of crucial importance for the implementation of these therapies in real-world clinical practice. In fact, there has been a recent call for more well-designed health economic analyses of psychological treatments.[19,22]

To sum up, this study has demonstrated the clinical utility of including treatment methods such as those included in MBSR as coadjuvants to usual care for managing FM. However, the reported attrition rates emphasize the importance of finding strategies to increase retention and treatment adherence.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

Trial number: NCT02561416. The study has been funded in part by the Instituto de Salud Carlos III (ISCIII) of the Ministry of Economy and Competitiveness (Spain) through the Network for Prevention and Health Promotion in Primary Care (RD16/0007/0005; RD16/0007/0012), by a grant for research projects on health from ISCIII (PI15/00383) cofinanced with European Union ERDF funds. The first listed author (A.P.-A.) has a FI predoctoral contract awarded by the Agency for Management of University and Research Grants (AGAUR; FI_B00754). The second listed author (A.F.-S.) has a "Sara Borrell" research contract from the ISCIII (CD16/00147). The fourth listed author (L.A.-R.) has an FI predoctoral contract awarded by the Agency for Management of University and Research Grants (AGAUR; FI_B00783). The last listed author (J.V.L.) has a "Miguel Servet" research contract from the ISCIII (CP14/00087).

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A846.

Article history:
Received 28 January 2019
Received in revised form 22 June 2019
Accepted 3 July 2019
Available online 13 August 2019

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