Effectiveness of a Multicomponent Treatment based on Pain Neuroscience Education, Therapeutic Exercise, Cognitive Behavioural Therapy, and Mindfulness in Patients with Fibromyalgia (FIBROWALK study): A Randomized Controlled Trial.

Authors

Mayte Serrat*, Juan P. Sanabria-Mazo*, Míriam Almirall, Marta Musté, Albert Feliu-Soler, Jorge L. Méndez-Ulrich**, Antoni Sanz**, Juan V. Luciano**

Author affiliations

- M. Serrat, PT, MSc, PhD Student, Unitat d'Expertesa en Síndromes de Sensibilització Central, Hospital de la Vall d'Hebron**;** Research Group on Stress and Health, Faculty of Psychology, Universitat Autònoma de Barcelona, Spain; Escoles Universitàries Gimbernat, Universitat Autònoma de Barcelona, Sant Cugat del Vallès, Barcelona, Spain. ORCID: 0000-0002-5591-9407
- J.P. Sanabria-Mazo, MSc, PhD Student, International University of Catalonia, Spain; Faculty of Psychology, Universitat Autònoma de Barcelona, Spain; Teaching, Research, & Innovation Unit - Parc Sanitari Sant Joan de Déu, St. Boi de Llobregat, Spain. ORCID: 0000-0003-1688-435X
- M. Musté, BD, Unitat d'Expertesa en Síndromes de Sensibilització Central, Hospital de la Vall d'Hebron, Barcelona, Spain. ORCID: 0000-0002-0748-1121
- Feliu-Soler, PhD, Faculty of Psychology, Universitat Autònoma de Barcelona, Spain; Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain;

Teaching, Research, & Innovation Unit - Parc Sanitari Sant Joan de Déu, St. Boi de Llobregat. ORCID: 0000-0003-2810-7670

- J.L. Méndez-Ulrich, PhD, Research Group on Stress and Health, Faculty of Psychology, Universitat Autònoma de Barcelona, Spain. ORCID: 0000-0001-9718-0607
- Sanz, PhD, Research Group on Stress and Health, Faculty of Psychology, Universitat Autònoma de Barcelona, Spain. ORCID: 0000-0002-7952-4477
- J.V. Luciano, PhD, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat; Teaching, Research, & Innovation Unit - Parc Sanitari Sant Joan de Déu, St. Boi de Llobregat, Spain. ORCID: 0000-0003-0750-1599
- M. Almirall, MSc, PhD Student, Unitat d'Expertesa en Síndromes de Sensibilització Central. Hospital de la Vall d'Hebron, Barcelona, Spain. ORCID: 0000-0002-4874-8013

* Mayte Serrat and Juan P. Sanabria-Mazo contributed equally to this article and should be considered co-first authors.

** Address the correspondence either to: Dr Méndez-Ulrich, Dr Sanz, or Dr Luciano at: jorgeluis.mendez@uab.cat, antonio.sanz@uab.cat, or jvluciano@pssjd.org, respectively.

Keywords. Fibromyalgia, multicomponent treatment, pain neuroscience education, therapeutic exercise, cognitive behavioural therapy, mindfulness, randomized controlled trial.

Abstract

Methods. A randomised controlled trial (RCT) was carried out to evaluate the effectiveness of a 12-week multicomponent treatment based on pain neuroscience education, therapeutic exercise, cognitive behavioural therapy and mindfulness, in addition to treatment as usual (TAU), compared to TAU only in patients with fibromyalgia (FM). The multicomponent treatment (2h weekly sessions) was delivered in groups of 20 participants. TAU was mainly based on pharmacotherapy. We collected data on functional impairment (the Revised Fibromyalgia Impact Questionnaire [FIQR], as primary outcome), pain, fatigue, kinesiophobia, physical function, anxiety, and depressive symptoms (secondary outcomes) at baseline, at 12 weeks and, for the multicomponent group only, at 6 and 9 months. An intention to treat approach was used to analyse between-group differences. We also analysed baseline differences between responders ($\geq$ 20% FIQR reduction) and non-responders and computed the number needed to treat (NNT).

Results. A total of 272 patients with FM were randomly assigned to either the multicomponent treatment (n = 135) or TAU (n = 137). Significant between-group differences ($p < .001$) with a large effect size (Cohen's $d > .80$) were found for functional impairment, pain, kinesiophobia, and physical function, whilst differences with a moderate size effect (Cohen's $d > 0.50$ and < 0.80) were found for fatigue, anxiety, and depressive symptoms. Non-responders scored higher on depressive symptoms than responders at baseline. The number needed to treat was 2 (95% CI 1.7 - 2.3).

Conclusions. Our results indicate that, when compared to TAU, the multicomponent treatment was effective for improving FM-related symptoms. Nevertheless, we must temper our findings in light of some methodological limitations in the study design.

Impact statement

- This is the first RCT showing positive effects on a wide range of clinical outcomes of a multicomponent treatment that integrates pain neuroscience education for patients with fibromyalgia.
- This work reports promising results and it might be the first step towards a paradigm shift in the management of fibromyalgia.

Introduction

Fibromyalgia (FM) is a complex syndrome characterized by chronic widespread musculoskeletal pain, fatigue, stiffness, sleep problems, and distress.[1,2] The estimated prevalence of FM is around 2% in the general population worldwide and 2.45% in Spain.[3] Regarding aetiology, it is posited that FM involves hypersensitization of the Central Nervous System (CNS) that is characteristic of the Central Sensitization Syndromes (CSSs), of which FM is the flagship.[4,5] CSSs are characterized by a malfunction in the balance between descending inhibitory and facilitation pathways, which cause hyperalgesia and allodynia.

The altered function of the descending nociceptive inhibitory pathway[5,6] is a biological mechanism moderated by cognitive biases, such as negative and maladaptive thoughts, as well as emotional and behavioural factors that lead to dysfunctional beliefs, which, in turn, can distort perception and facilitate the experience of pain.[7,8] Due to the involvement of all the above factors and the complexity of FM therapeutic management, there is a need to develop interdisciplinary and multicomponent approaches.[9-12] In this regard, multicomponent treatments including various empirically-validated therapeutic ingredients are currently considered the gold standard.[11,13-15]

Pain neuroscience education (PNE) is based on the reconceptualization of an individual's understanding of pain, emphasizing that any credible evidence of danger or safety in body tissues can increase or decrease pain perception, respectively.[16-18] This therapeutic approach has been extensively investigated in various chronic pain conditions.[19-32] A recent systematic review[33] has supported the efficacy of PNE in the improvement of pain-related disability, pain catastrophizing, avoidance behaviour, and inactivity. It is important to point out that PNE seems even more effective when it is combined with

therapeutic exercise, gradual exposure techniques, or cognitive behavioural therapy (CBT).[34-36]

Concerning therapeutic exercise, recent meta-analyses have supported its effectiveness for improving a wide range of FM symptoms. For instance, Sosa-Reina and colleagues conducted a meta-analysis of 14 RCTs and found that therapeutic exercise reduces pain, depressive symptoms, and increases global well-being and both components of health-related quality of life.[37] Therefore, personalized therapeutic exercise should be integrated into the multicomponent packages used for treating FM.[15] CBT-based treatments strengthen self-efficacy and promote adaptive coping strategies in patients suffering from chronic pain.[38,39] A meta-analysis of 29 RCTs testing the effectiveness of CBT-based interventions for FM observed significant and small to medium mean effect sizes in pain relief, improvement of quality of life, reduction of negative mood, disability and fatigue.[38]

Mindfulness-based interventions are a form of structured training aimed at helping people to relate to their physical and psychological conditions in more accepting and non-judgmental ways.[40] It has significant effects on pain intensity, anxiety, depression, and quality of life[12]. Recent well-executed trials have demonstrated the efficacy and cost-utility of including mindfulness as an adjuvant therapy for the management of FM.[12,41]

Since the seminal meta-analysis performed by Häuser and collaborators,[13] multicomponent treatments involving physical exercise and CBT-based strategies are increasingly being recommended to manage the wide range of FM symptoms and tackle the multifactorial causes of the syndrome. However, although the literature suggests that multicomponent treatments are the gold standard for FM management, there is still no consensus about which combination of therapeutic ingredients to be used. García and

colleagues[42] performed a systematic review of interventions for FM and concluded that multimodal and multidisciplinary approaches should be implemented in daily practice. Specifically, the following ingredients were recommended: aerobic exercise, muscle strength, CBT-based interventions and some forms of relaxation after exercise. As far as we know, there is no evidence about these techniques together nor in combination with PNE or mindfulness, whose recent empirical support for FM is promising as commented above.

Therefore, the main objective of this RCT was two-fold: (a) To analyse the effectiveness of a 12-week multicomponent treatment (Fibrowalk protocol), based on PNE, therapeutic exercise, CBT, and mindfulness training, as an add-on to Treatment as Usual (TAU) to improve functional impact (primary outcome), as well as pain, fatigue, kinesiophobia, physical function, anxiety, and depressive symptoms (secondary outcomes) compared to TAU; and (b) to explore the baseline differences between responders ($\geq$ 20% FIQR reduction after the 12-week intervention) and non-responders in terms sociodemographic and clinical characteristics.

METHODS

Design

A randomised controlled trial (RCT) was conducted in the context of real-life clinical practice with data collected at baseline (pre), at the end of the 12-week intervention (post) and, for the multicomponent treatment only, at 6 and 9 months (follow-up). This RCT received approval from the Ethics Committee of Clinical Investigation (PR(AG)120/2018) of the University Hospital Vall d'Hebron in Barcelona (UHVH) and was registered at ClinicalTrials.gov (NCT04284566). This study is reported according to the guidelines issued by the Consolidated Standards of Reporting Trials (CONSORT).[43] Those patients in the TAU

group were given the opportunity to participate in the intervention immediately after the 3-month intervention period instead to wait the additional 6-9 months.

Participants

A total of 272 patients who met the eligibility criteria were recruited from November 2018 to August 2019 by the physical therapist (MS) of the Central Sensitivity Syndromes Specialized Unit (CSSSU) at the UHVH. The inclusion criteria were: (a) fulfil the 2010/2011 American College of Rheumatology (ACR) FM diagnostic criteria. The diagnosis was verified by a rheumatologist (MA) of the CSSSU; (b) adults > 18 years old, and (c) provide written informed consent. The exclusion criteria were having terminal illnesses or programmed interventions that might interrupt the study. No stringent eligibility criteria were established due to the naturalistic nature of the RCT. Excluding patients with lower education or comorbidities might have turned away many patients from our RCT who would otherwise be eligible, that is we put emphasis on external validity.

All recruited patients were considered capable of following the multicomponent therapy if they were allocated to it. Lack of adherence to drugs or home activities was not an exclusion criterion given the nature of our trial and we analysed data from all participants who underwent random allocation. Treatment allocation was performed by the clinical trials unit in accordance with computer-generated randomisation sequences.

Procedure

The main researcher (MS), through an initial interview, after verifying the inclusion and exclusion criteria, provided an overview of the study to all the participants. All participants gave written informed consent before randomisation. They were also informed of their right

to withdraw from the study at any time, with the guarantee that they could continue to receive their usual treatment.

Each participant who voluntarily agreed to take part in the study was assigned to an alphanumeric code list and was randomized using the SPSS v26.0 to either the multicomponent treatment or TAU. This process was carried out using numbered envelopes containing sheets with information regarding participant allocation. The envelopes were prepared by the nurse (MM). Neither the participants nor the therapist (MS) could be blinded but the main researcher (MS) who carried out the intervention did not participate in the patient assessment process and the staff responsible for the assessment (MM) was blinded to the treatment allocation. For the entire treatment period (3 months) a total of 5-10 min per week was spent on e-mail or phone contact with some patients from hospital staff (MS) to foster treatment adherence.

Intervention

The intervention was carried out in groups of 20 patients per session, with a frequency of one 2h weekly session for 12 weeks. The first author (MS), who delivered the multicomponent intervention, is both a physical therapist (> 15 years of experience) and a health psychologist (>6 years of experience). In addition, she has also been trained in CBT and mindfulness.

The multicomponent treatment included PNE, therapeutic exercise, CBT, and mindfulness training. PNE was not only a part of multicomponent therapy but was also the fundamental component that guided the approach taken by all the strategies involved. In short, PNE involves a profound change in the way in which pain is conceptualized, of everything that we transmit to the patient, and how we explain it to them. All the aspects of PNE were reinforced point by point in each session with the Spanish version of the book

entitled *Explain Pain.*[44] Most patients had primary or secondary studies and they had no specific learning, behavioural or intellectual difficulty. Theoretical concepts included in both CBT and PNE components of the intervention were adapted to an informal language to ensure they were understood by patients without great effort. To communicate the information to the patients in the most comprehensive way, a presentation was used with images, examples, and metaphors.[21] Individualised gradual programmes were implemented following the transtheoretical model of stages of change, developed by Prochaska and Diclemente.[45.]

Taking the American College of Sports Medicine (ACSM) guidelines as framework, all participants randomized to the "multicomponent treatment" group received the same exercise intervention, performed under the supervision of the first author (MS). In order to increase the level of difficulty and commitment, each session had a three part structure: warm up, main exercise and cool down; and as a homework: individualized walking guidelines were given establishing the minimum baseline and guiding progression throughout the 12-week multicomponent treatment to increase the resistance of each participant. At the beginning of each session an approximate interval of 15 minutes was reserved to comment on the most important aspects of the homework between sessions, as well as to review the concepts already explained. The feedback obtained from the participants was used to clarify the concepts in which doubts and misinterpretations had arisen.

The program included multi-component exercises such as stretching, balance training, posture correction, limbs extension, and low-impact walking at a training load of 60-80% of maximum heart rate (see an outline of the exercise program in Table 1). It is well known that exercise intensity is a crucial element of an exercise program. If minimal

threshold values are not met, it can result in lack of exercise effect, whereas excessive intensity causes overtraining and low exercise adherence. In that sense, to increase the adherence to treatment the intervention was carried out in a playful way with the support of role-playing techniques, by fostering social interactions, goal setting, self-monitoring and reinforcement.

The guidelines of the motivational interview[46,47] and the cognitive-behavioural fear-avoidance model[48] were part of the theoretical framework used for the present study. The intervention was carried out by fostering social interactions, with the support of role-playing techniques to better understand the information and to emphasize adherence to treatment. All sessions had the same predefined structure, which is detailed in Table 1.

Insert Table 1 about here

Insert Table 2 about here

Treatment-as-usual (TAU) consisted of prescribing drugs adapted to the symptomatic profile of each patient. The patients were instructed to continue their baseline medical treatment with no change throughout the 3-month period. In Spain, some counselling about aerobic exercise adjusted to patients' physical limitations is usually provided by first-line clinicians and specialists, but pharmacotherapy it's still the dominant treatment option. Patients were offered the opportunity to participate in the next wave of group intervention at the end of the study (3 months).

Study measures

All patients were evaluated before ("pre") and after ("post") treatment using an online battery of measures. Only patients receiving the multicomponent treatment were evaluated at 6- and 9-months follow-up. Most of the patients on TAU group accepted to participate

that's why it was not possible to follow-up the TAU group up to 3-month intervention period (see figure 1).

Socio-demographic and clinical characteristics.

A socio-demographic and clinical *ad-hoc questionnaire* was used to obtain the following general and clinical patient data: age, educational level, socioeconomic status, marital status, and comorbid medical conditions.

Primary outcome.

The *Revised Fibromyalgia Impact Questionnaire* (FIQR)[49] was used to measure the functional impairments in FM during the last week, and is divided into three dimensions: *physical dysfunction* (scores from 0 to 30), *overall impact* (scores from 0 to 20), and *intensity of symptoms* (scores from 0 to 50). It consists of 21 items that are answered on a 0-10 numerical scale where higher scores indicate greater functional impact. This is currently considered the *"gold standard"* for evaluating the functional status of patients with FM. The Spanish version shows adequate internal consistency (Cronbach's α = .93),[50-52] which, in our study was α = .94.

Secondary outcomes.

Visual Analog Scale (VAS) of the FIQR[49] was used to measure fatigue and pain, with scores ranging from 0 to 10. Higher scores indicate greater perceived fatigue and pain, respectively.

Tampa Scale for Kinesiophobia (TSK)[53] was used to measure kinesiophobia. This scale is composed of 11 items, which are answered on a 4-point Likert scale (from 0 to 11). Total scores of the TSK can range from 11 to 44, where higher scores indicate a greater fear of pain and movement. The Spanish version shows adequate internal consistency (α = .79);[54] and in our sample was α = .87.

Hospital Anxiety and Depression Scale (HADS)[55] was used to measure depressive and anxiety symptoms. It consists of two dimensions (anxiety and depression) of 7 items each, with a 4-point Likert scale response format. A total score measuring general distress can also be computed. Total scores of each scale (HADS-A and HADS-D) range from 0 to 21, where higher scores indicate higher symptom severity. The Spanish version shows adequate internal consistency for HADS-A *(*α = .83) and for HADS-D (α = .87);[56] and in our sample was α = .83 and .85, respectively.

Physical Functioning component of the 36-Item Short Form Survey (SF-36)[57] was used to measure physical functioning. This subscale comprises a total of 10 items, with a 3-point Likert scale response format. Total scores are transformed in order to range from 0 to 100, with higher scores indicating better physical functioning. The Spanish version shows adequate internal consistency *(*α = .94);[58] and in our sample, α = .85.

Statistical analyses

Data analyses were conducted using SPSS v26.0. Descriptive statistics were calculated for all measures of the study and were presented as means and standard deviations for the continuous variables, and frequencies and percentages (%) for the categorical variables. Continuous variables were analysed using the Levene test for testing equal variances and the Kolmogorov-Smirnov test to evaluate normality. For the continuous variables, Student's *t-test* was used to examine the between-group differences in sociodemographic and clinical characteristics. For the categorical variables, the χ^2-test was used.

The between-group differences were analysed following an intention to treat (ITT) approach. Specifically, we conducted a 2 x 2 mixed ANCOVA with group (TAU+Fibrowalk vs. TAU) as between-subjects factor and study period as the within-subjects factor (pre vs.

post), introducing baseline scores in the SF-36 (physical function) as a covariate. The partial eta-square (ηp^2) was estimated for the two complete models (main effects of group and phase, and group x phase interaction). We also conducted an intragroup analysis for the multicomponent treatment group (pre, post, follow up + 6, follow up + 9), with the baseline values as reference for comparison. The effect size (Cohen's *d*) for each pairwise comparison was reported, using the grouped reference *SD* to weigh the differences in the previous and subsequent means and to correct the population estimate.[59,60] Separate models were estimated for each of the secondary outcomes using the same analytical strategy. All outcomes were analysed using the last observation carried forward (LOCF) method for imputing missing values.

To assess the clinical relevance of the improvement in the primary outcome (FIQR), patients who, within 12 weeks of the multicomponent treatment, presented a reduction in the FIQR score ≥ 20% in the total score with respect to the baseline (pre-post) were considered as responders. Reductions of 20% or greater in the FIQR total score are considered to be clinically relevant.[61] Differences in baseline variables between responders and non-responders to the multicomponent treatment were compared using the Student's *t-test* for quantitative variables and χ^2-test for categorical variables. This classification (responders vs. non-responders) was used to calculate the number needed to treat (NNT) in the multicomponent treatment group compared to TAU. NNT refers to the estimated number of participants who need to be treated in the TAU+Fibrowalk (i.e., rather than the TAU alone) for one additional patient to benefit.

Role of the Funding Source

The funding source played no role in the design, execution, or reporting of this study.

RESULTS

From August to November 2019, 420 patients met the inclusion and exclusion criteria and were asked to participate in the study. Of these, 272 accepted and were randomly allocated to the multicomponent treatment (n = 135) or TAU (n = 137). All participants were included in the ITT analysis. The distribution of included patients according to the recommendations outlined by the consolidated standards of reporting trials (CONSORT) is described in Figure 1.

Insert Figure 1 about here

Baseline differences between multicomponent treatment vs TAU

As shown in Table 3, there were significant differences between groups in terms of gender distribution, Body mass index (BMI), and physical function. The mean age of all patients was 53.61 years (SD = 8.96), BMI of 27.01 (SD = 5.55), and the mean number of years diagnosed with FM was 16.65 (SD = 16.66). Of the sample, 22.4% were actively employed, 45.6% reported having a secondary education level, and for 84.5% their condition was comorbid with chronic fatigue.

Insert Table 3 about here

Between-group differences in the primary and secondary outcome measures.

In the multicomponent treatment, there were 23% dropouts, whilst in the control group there were none. When comparing baseline differences between dropouts and non-dropouts in terms of sociodemographic and clinical variables, we found that dropouts were older (58.35 ± 8.52 vs. 52.62 ± 8.27, p = .001, d = 0.68) and had higher physical function scores (28.44 ± 20.49 vs. 20.34 ± 12.03, p = .04, d = 0.48).

An ITT and a completers approach were used to compare the post-treatment effects of the different conditions on the primary and secondary outcomes. Means and SD of the differences between the pre-test and post-test values in both approaches are shown in Table 4 (ITT) and Supplementary Table 1 (completers). The effect size was somewhat smaller with the ITT approach, but significant large and moderate differences were found in both approaches. Significant improvements (p = .001) with a large effect size (Cohen's d > 0.80) between groups were found for functional impact, pain, kinesiophobia, and physical function; and with a moderate effect size (Cohen's d > .50 and < 0.80) for fatigue, anxiety, and depressive symptoms.

Insert Table 4 about here

Number needed to treat (NNT)

The multicomponent treatment group not only showed an improvement in symptomatology but also a total of 70 patients (51.85%) in this group reached the criterion of $\geq$ 20% FIQR reduction, and a total of 7 patients (5.2%) showed a reduction of more than 70% on their FIQR score. Only 1 patient (.73%) in the TAU group was considered as a responder using the FIQR improvement criterion of $\geq$ 20%. We analysed the differences between responders and non-responders for all variables at baseline (Table 5). The non-responder group scored significantly higher than responders on depressive symptoms at baseline (p = .01; d = 0.45). There were no significant differences between groups in terms of any other socio demographic or clinical variables.

The absolute risk reduction (ARR) in the multicomponent treatment group compared with TAU was 51.85% (95% CI 42.57% - 59.67%) with NNT 2 (95% CI 1.7 - 2.3), meaning that 2 patients would need to be treated in the multicomponent treatment group for one of

them to become a responder, which would not otherwise have been possible in the TAU group.

Insert Table 5 about here

Within-group differences in the intervention group at follow-up.

Data for all the studied variables showed a similar trend throughout the 6 and 9-month follow-up (Table 6). Despite showing a slight worsening of symptoms at 6 months, which increased at 9 months, the improvements at the 6 and 9-months follow-up remained statistically significant ($p = .01$ for all variables studied, with a large effect size, (Cohen's $d > 0.80$).

Insert Table 6 about here

Discussion

Our results indicated that the Fibrowalk treatment was an effective adjuvant therapy for patients with FM, when compared with TAU alone. Specifically, significant differences with medium to large effect sizes were found in functional impact, pain, kinesiophobia, and physical function. Despite showing a slight worsening of symptoms at 6 months, which increased at 9 months in the multicomponent treatment group, improvements at 6 and 9-months follow-up remained statistically significant for all study outcomes. Our results are in line with previous literature on multicomponent interventions for FM[11,13-15], showing that an approach based on the aforementioned ingredients seems to be effective for improving a wide range of FM symptoms.

However, the use of TAU as a comparison condition is a clear limitation of this study because TAU-treated patients obviously received "less treatment hours" than those in the multicomponent treatment condition. This issue poses threats to the internal validity of our RCT and, therefore, we strongly recommend using *bona-fide* active treatments as comparison

in future research on our multicomponent treatment program. In addition, due to the nature of the study, we do not know which exact ingredients of the therapy made it effective, so further research is needed in this regard.

To our knowledge, different multicomponent programs have been tested (e.g. physical activity plus CBT) as an add-on of usual care for the management of FM [12,13,20,31-33,41]. Overall, they have demonstrated to be effective therapeutic options, leading to improvements in mental health, well-being, and physical function[11,13,18-26]. However, in most cases, the reported effect sizes ranged from small to moderate magnitudes.[17] There are many recent examples of trials sustaining the efficacy of these treatments for improving a wide range of outcomes in FM. For instance, a recent uncontrolled pilot study[62] examining the efficacy of a multicomponent therapy (exercise therapy *plus* CBT) for FM that was similar in duration (12 weeks) delivered a multidisciplinary team (an occupational therapist, a physiotherapist, and a psychologist) yielded significant improvements mainly at 12-weeks follow-up in functional status, depressive symptoms, perceived pain, grip strength, and in the 6 min walking test. Notwithstanding, a next step in this field is to know what treatment works for whom and under what circumstances. Frequently, only a fourth to a third of patients receiving group therapy show clinically relevant improvement.[9] There are some interesting initiatives highlighting the need for a paradigm shift which propose tailoring treatments to individual characteristics, measurement-based care, and focus on specific therapeutic processes in order to improve overall effectiveness.[9,11,16,63.64]

We want to highlight that this is the first study to demonstrate the effectiveness of a multicomponent treatment that specifically integrates PNE in patients with FM. PNE has been extensively investigated in different chronic pain conditions[19-33] but its effectiveness

has not been shown before in combination with other non-pharmacological therapies in FM patients.

Another major finding of our study was the significantly higher baseline score in the depression scale in the group of non-responders. A recent study on multicomponent therapy in FM, dropouts were associated with moderate to severe depression.[62] Although our findings require further replication, they warn of the importance of assessing depression levels in FM patients, since mood alterations might buffer treatment effects. Patients with high depression levels may require more individualized treatment by mental health professionals before implementing group multi-component therapy.

At present, there are no highly effective treatments for FM. However, using the approach presented in this paper, 5.4% of the participants showed ≥ 70% improvement in their FIQR score, and 51.85% reached the criterion of ≥ 20% FIQR reduction. These data open up the possibility of achieving better symptom outcomes in this syndrome with a paradigm shift in treatment. Future research on this type of multicomponent approach should also focus on long-term clinical outcomes (1- and 2-year follow-ups) compared to an active control group, as well as the underlying mechanisms involved in the improved outcomes.

There are some potential reasons for the slight loss of effectiveness of the multicomponent treatment at follow-up, such as the fact that patients were no longer attending weekly group sessions or may have reduced home practice. It is an important point to explore if this intervention could be effective for a long term or some type of periodic intervention is needed to maintain its beneficial effects. Thus, future studies should focus on how to increase the frequency and quality of home practice, not only along the 12 weeks of

group treatment but also once it is over. In our opinion, the inclusion of booster sessions seems a recommendable option.

Limitations and strengths

First, therapy sessions were not audio- or videotaped. Future studies replicating our treatment should randomly select at least 20% of the sessions in order to be reviewed by independent experts with the aim of assessing fidelity to the treatment as reported in the study protocol and therapist competence. Related to this, practicing skills outside of the group is considered of crucial importance for improving outcomes in this kind of therapies, but adherence to home practice was not systematically measured in our RCT. Second, as recently highlighted by Ollevier and colleagues,[62] there is a need for empirical evidence for the efficacy of multicomponent, long-term therapies. In our case it was not possible to follow up the control group beyond a period of 3 months post-intervention, due to ethical reasons. An assessment of the long-term effectiveness of Fibrowalk is necessary in the context of real-world clinical practice using an active treatment as comparator. Third, there was an absence of blinding in the group assignment, due to the characteristics of the therapy.

Fourth, Fibrowalk consisted of the combination of many therapeutic ingredients delivered by the same professional (MS), a physiotherapist that is also a psychologist. As recommended by Öst,[65] at least three trained therapists should be implicated in RCTs of non-pharmacological therapies and patients have to be randomized to therapists to examine a potential therapist effect on the outcomes. Fifth, there was an excessive number of patients per group (n = 20), due to the pressures of care in daily clinical practice. Future research might be conducted with smaller patient/therapists ratios, to facilitate the understanding and assimilation of all concepts and to better manage the therapeutic groups. Notwithstanding,

although our results are very promising, it should be interpreted with caution because our multicomponent therapy needs replication in other contexts (primary care) and other cultures. An aspect that merits attention in future studies is the assessment of patients' stages of change, because we think that this aspect might account for variability in treatment adherence and moderate the impact of the intervention on treatment outcomes.

Despite these hopeful results future "dismantling" studies should identify which of the therapeutic elements (or combination of them) make the most significant contribution to the effects of our treatment before solid conclusions can be drawn. Recently, methodologists have recommended "factorial designs" to test the active components of complex therapies.[64] These factorial designs permit to explore main effects of components and interactions among components. In short, using our multicomponent treatment as example, patients would be randomized in the RCT with a factorial design across four factors [presence or absence of PNE (PNE+ vs PNE-); presence or absence of CBT (CBT+ vs CBT-); presence or absence of PT (PT+ vs PT-); and presence or absence of MT (MT+ vs MT-)]. This means that patients would be randomized to all of the possible combinations: all four components (PNE+; CBT+; PT+; MT+), 3 of the 4 components, 2 of the 4 components, 1 of the 4 components; or none of these components (PNE-; CBT-; PT-; MT-). This design would allow not only us to test the main effect of each component but also their interactions.

As stated above, this is the first study to demonstrate the effectiveness of a multicomponent treatment that specifically integrates PNE in patients with FM. There are many studies that support the individual effectiveness of each of the treatment components that constitute this multicomponent therapy[11,13-15,18-27,63-72]. In spite of the complexity of integrating different ingredients, the present RCT was designed on the basis of a clear and

replicable methodology. The greatest strengths of this RCT include the fact that it is based on an empirically-validated framework, involving a large sample size. We also observed a relatively low dropout rate, possibly due to the use of the adherence strategies (phone and email contacts) established with some participants to avoid treatment attrition as much as possible.

CONCLUSION

Our results suggest that the tested multicomponent treatment is not only a promising intervention that can significantly improve the core symptoms of FM in comparison with usual treatment, but also it provides new and useful information that could be used to inform the planning of a future paradigm shift in the management of this prevalent and costly syndrome. This study also highlights the need for further research aimed at evaluating this multicomponent treatment in other contexts to verify its cross-cultural validity.

Author Contributions and Acknowledgements

All authors have read and agreed to the published version of the manuscript.

Concept/idea/research design: M. Serrat, M. Almirall, A. Sanz

Writing: M. Serrat, J.P. Sanabria-Mazo, M. Almirall

Data collection: M. Serrat, M. Musté

Data analysis: M. Serrat, J.P. Sanabria-Mazo, J.L. Méndez-Ulrich, J.V. Luciano

Project management: M. Serrat, A. Feliu-Soler, J.L. Méndez-Ulrich, A. Sanz, J.V. Luciano, M. Almirall

Fund procurement: M. Serrat, M. Almirall

Providing facilities/equipment: M. Serrat, M. Almirall

Providing institutional liaisons: M. Serrat, A. Feliu-Soler, J.L. Méndez-Ulrich, A. Sanz, J.V. Luciano, M. Almirall

Consultation (including review of manuscript before submitting): M. Serrat, J.P. Sanabria-Mazo, M. Musté, A. Feliu-Soler, J.L. Méndez-Ulrich, A. Sanz, J.V. Luciano, M. Almirall

Ethics Approval

This research was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and was approved by the hospital's Ethics Committee (PR(AG)120/2018). All participants gave written informed consent before randomization.

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Clinical Trial Registration

This study is registered at ClinicalTrials.gov (NCT04284566).

Disclosures

The authors completed the ICJME Form fot Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Table 1.
Outline of active group sessions in Fibrowalk treatment.[a]

Review Phase (15'): To reassure acquisition of PNE-related concepts and skills of the previous session:

- Clarification of doubts and revision of homework.
- Brief review of contents of the previous session.

Conceptual Phase (1h).

- 20' Pain Neuroscience Education (PNE).
- 20' Cognitive Behavioural Therapy (CBT).
- 20' Mindfulness.

Sessions:

1. PNE (1,2) + CBT (1) + MT (1)
2. PNE (3,4) + CBT (2) + MT (2)
3. PNE (5,6) + CBT (3) + MT (3)
4. PNE (7,8) + CBT (4) + MT (4)
5. PNE (9,10) + CBT (5) + MT (5)
6. PNE (11) + CBT (6) + MT (6)
7. PNE (12) + CBT (7,8) + MT (7,8)
8. PNE (13) + CBT (9) + MT (9)
9. PNE (14) + CBT (10) + MT (10)
10. Family Session (PNE 1-16)
11. PNE (15) + CBT (11) + MT (11)
12. PNE (16) + CBT (12) + MT (12)

Physical Phase (40')[b]. The same steps (1-8) for the 12 sessions:

- Warm-up (5') activation and mobility exercises.
- Therapeutic exercise (25'): moderate aerobic-cardiovascular and muscle strengthening exercises combined with some balance and coordination exercises performed in a playful manner with cognitive and emotional targets (multitask works) where the level of difficulty and dedication time gradually increases.
- Cooling-down (10'): flexibility and relaxation exercises.

Homework (5') (first month once per week, second month twice per week, and third month three times per week):

- Cognitive (related to CBT and MT) and physical task to do at home to increases the patient's resistance involving a constant challenge for them.

[a] The numbers in parentheses (from 1 to 12) of the Conceptual Phase of PNE, CBT and MT and the numbers (from 1 to 8) on Physical Phase are explained on Table 2.

[b] The Physical Phase was designed following the recommendations of the American College of Sports Medicine (ACSM).[61]

Table 2.
Steps of the multicomponent treatment: PNE, therapeutic exercise, CBT, and mindfulness.

Pain Neuroscience Education (PNE)
1. Disassembling beliefs. 2. Danger signals: modulation and modification. 3. Concept of pain, fatigue, and pain system. 4. Concept of central nervous system and central sensitization. The role of the brain. 5. Acute vs. Chronic Pain: The purpose of acute pain and how it originates in the nervous central system (CNS). 6. Pain vs. damage. 7. Pain neuromatrix theory and representation of the virtual body. 8. Nociception, nociceptors, action potential, peripheral sensitization, and synapses. 9. Ascending and descending inhibitory pathways, spinal cord. 10. Relationship with attention, perception, pain cognitions, and pain behaviours. 11. Allodynia and hyperalgesia, hypersensitivity of nervous central system. 12. Pain memory, pain perception, and autoimmune evaluation error. 13. Relationship with stress. Etiology. 14. Neuroplasticity and how the pain becomes chronic. 15. Relationship with emotions. 16. Re-education, gradual activity, and therapeutic exercise.
Therapeutic Exercise (TE)
1. Essential and necessary movement. 2. Set basal minimum. 3. Individualised gradual program. 4. Small increases, patterns. 5. Activities contingent on the task, not over time. 6. Activities with cognitive and emotional targets. 7. Involvement in the tasks of daily life. 8. Lifestyle change.
Cognitive Behavioural Therapy (CBT)
1. Relaxation and breathing. 2. Modulating factors of pain. 3. Catastrophizing and fear of movement (fear avoidance model)[54] 4. Painful experiences: confrontation (fear avoidance model)[54] 5. Vital values and setting goals. 6. Organization of time. 7. Sleep patterns. 8. Sexual issues. 9. Handling of attention. 10. Cognitive restructuring. 11. Emotional regulation and assertiveness. 12. Troubleshooting.
Mindfulness Training (MT)

1. An Introduction to Body Scanning.
2. Elementary Awareness.
3. Sitting Practice and introduction to Yoga.
4. Mindfulness and the Brain.
5. Mindfulness and communication: guilt, empathy, and conflict management.
6. Responding vs. reacting.
7. Dig deeper into personal practice.
8. Mindfulness and Compassion: Strength vs. Cooperation.
9. Stress Management.
10. Thoughts Management.
11. Management of difficult emotions or feelings.
12. Dig deeper into personal practice.

Figure 1.
Flowchart of participants in the Fibrowalk study following the CONSORT statement.

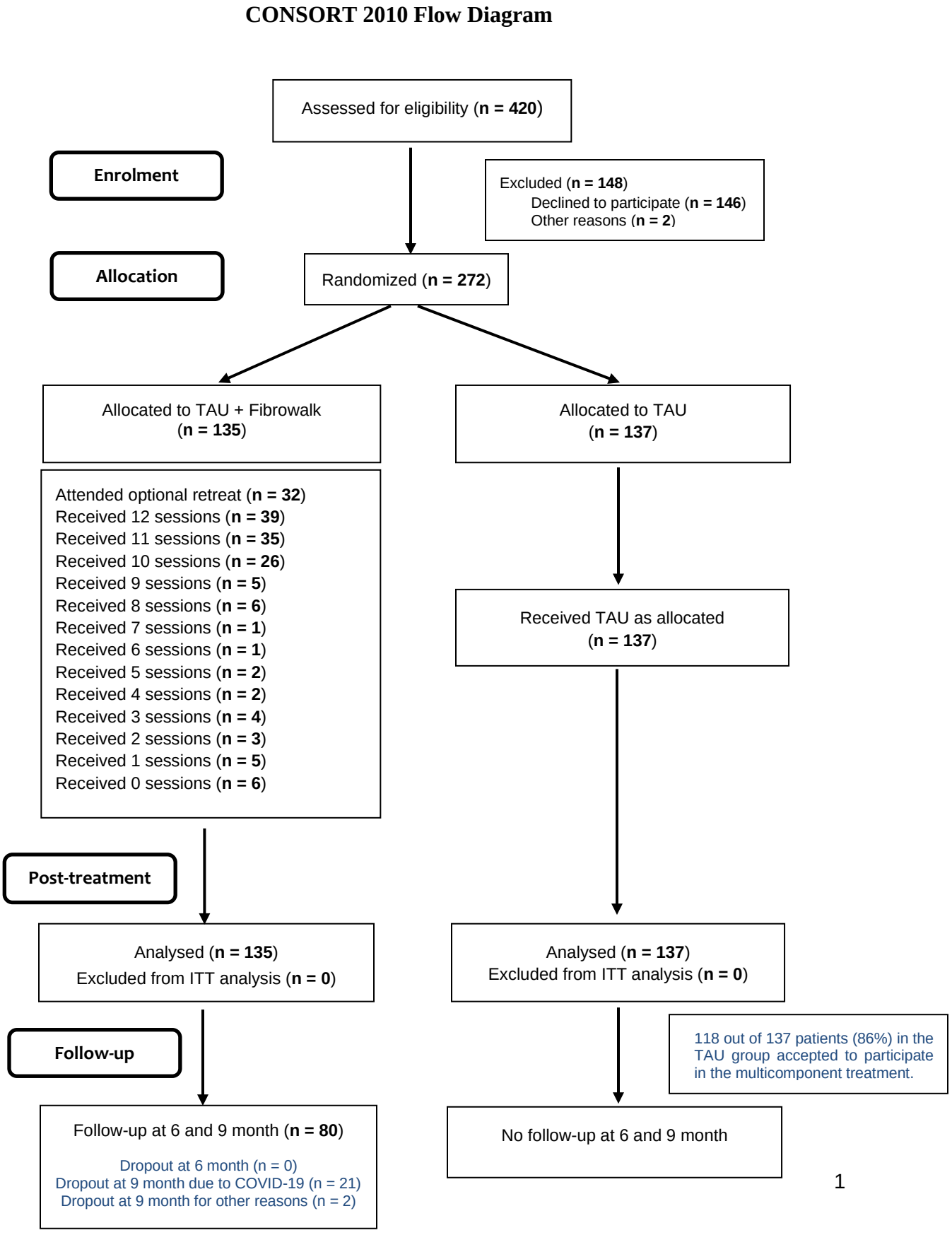

Table 3.

Baseline differences between participants allocated to TAU+Fibrowalk and TAU.[a]

	TAU + Fibrowalk (*n* = 135)	**TAU (*n* = 137)**	***t/x2***	***p*[b]**
General measures				
Women, n (%)	131 (97)	137 (100)	4.12	**.05**
Age, M (SD)	53.98 (8.65)	53.24 (9.26)	.68	.50
BMI (kg/m2), M (SD)	27.95 (5.92)	26.08 (4.99)	2.82	**.01**
Years of illness, M (SD)	17.47 (11.79)	15.84 (9.37)	1.26	.21
Married or in couple, n (%)	92 (68.1)	82 (59.9)	5.94	.11
Cohabitating, n (%)	119 (88.1)	119 (86.9)	.10	.75
Secondary studies, n (%)	59 (43.7)	65 (47.4)	9.53	.09
Labour assets, n (%)	21 (15.6)	40 (29.2)	13.69	.09
Disability in process, n (%)	39 (28.9)	42 (30.7)	.10	.75
Comorbidity, n (%)				
Chronic fatigue	113 (83.7)	118 (86.1)	.31	.58
Multiple chemical sensitivity	47 (34.8)	37 (27.0)	1.94	.16
Irritable bowel syndrome	63 (46.7)	76 (48.2)	.06	.80
Migraines	77 (57.0)	80 (58.4)	.05	.82
Medication, n (%)				
> 2 medications	23 (32.9)	31 (47.7)	4.81	.31
Primary outcome, M (SD)				
FIQR_Functional impairment (0-100)	75.43 (12.37)	73.9 (9.76)	1.13	.26
Secondary outcomes, M (SD)				
VAS Pain (0-10)	8.03 (1.04)	7.79 (1.12)	1.84	.07
VAS_Fatigue (0-10)	7.90 (1.44)	7.80 (1.41)	.58	.56
TSK-11 Kinesiophobia (11-44)	31.43 (7.07)	30.42 (6.85)	1.20	.23
HADS Anxiety (0-21)	14.14 (4.37)	13.35 (3.93)	1.57	.12
HADS_Depression (0-21)	12.64 (4.58)	11.94 (4.11)	1.33	.18
SF-36 Physical function (0-100)	22.26 (14.81)	26.61 (14.02)	2.49	**.01**

[a] The values represent means (M) and standard deviation (SD) or frequency (f) and percentages (%), in their respective order of presentation. BMI = Body mass index. FIQR: Revised Fibromyalgia Impact Questionnaire; VAS: Visual Analogue Scale; TSK-11: Tampa Scale for Kinesiophobia; HADS: Hospital Anxiety and Depression Scale; SF-36: SF-36 Health Survey.

[b] Bold type indicates statistically significant group differences.

Table 4.

Between-group differences from an ITT approach.[a]

	TAU + Fibrowalk (*n* = 135)		TAU (*n* = 137)		Phase x Group interaction			
	Pre	**Post**	**Pre**	**Post**	***f***	***p*** [b]	η_p^2	***d*** [c]
Primary outcome, M (SD)								
FIQR Functional impairment (0-100)	75.43 (12.37)	58.58 (19.91)	73.9 (9.76)	79.77 (9.72)	190.93	**.01**	.42	**1.36**
Secondary outcomes, M (SD)								
VAS Pain (0-10)	8.03 (1.04)	6.33 (1.98)	7.79 (1.12)	8.09 (.98)	128.73	**.01**	.32	**1.13**
VAS Fatigue (0-10)	7.90 (1.44)	6.75 (1.86)	7.80 (1.41)	7.69 (1.68)	20.79	**.01**	.07	.56
TSK-11 Kinesiophobia (11-44)	31.43 (7.07)	20.08 (9.43)	30.42 (6.85)	31.76 (6.25)	172.01	**.01**	.39	**1.47**
HADS Anxiety (0-21)	14.14 (4.37)	11.09 (4.72)	13.35 (3.93)	14.23 (3.83)	77.19	**.01**	.22	.73
HADS Depression (0-21)	12.64 (4.58)	9.70 (4.96)	11.94 (4.11)	13.01 (3.62)	85.14	**.01**	.24	.77
SF-36 Physical function (0-100)	22.26 (14.81)	41.19(20.54)	26.61 (14.02)	19.56 (13.69)	190.35	**.01**	.42	**1.25**

[a] Effect considering covariate SF-36 baseline scores. η_p^2 = partial η_p^2 as effect size. *d* = Cohen's *d*.

[b] Bold type indicates statistically significant group differences.

[c] Bold type indicates large size effect (Cohen's $d > .80$).

Table 5.

Baseline differences between responders and non-responders.[a]

	Responders (*n* = 70)	**Non-responders (*n* = 65)**	***t*/χ^2**	***p*[b]**
General measures				
Women, n (%)	69 (98.6)	62 (95.4)	1.19	.27
Age, M (SD)	53.19 (8.86)	54.82 (8.40)	1.10	.27
BMI (kg/m2), M (SD)	27.15 (5.46)	28.81 (6.32)	1.63	.11
Years of illness, M (SD)	17.97 (12.64)	16.94 (10.89)	-.51	.61
Married or in couple, n (%)	52 (74.3)	40 (61.5)	6.11	.11
They live accompanied, n (%)	64 (91.4)	55 (84.6)	1.50	.22
Secondary studies, n (%)	31 (44.3)	28 (43.1)	3.53	.47
Labour assets, n (%)	15 (21.4)	15 (23.1)	5.51	.70
Disability in process, n (%)	17 (24.3)	22 (33.8)	1.50	.22
Comorbidity, n (%)				
Chronic fatigue	60 (85.7)	53 (81.5)	.43	.51
Multiple chemical sensitivity	24 (34.3)	23 (35.4)	.02	.89
Irritable bowel syndrome	32 (45.7)	31 (47.7)	.05	.82
Migraines	38 (54.3)	39 (60.0)	.45	.50
Medication, n (%)				
> 2 medications	23 (32.9)	31 (47.7)	4.81	.31
Secondary outcome, M (SD)				
VAS Pain (0-10)	7.87 (.98)	8.20 (1.09)	1.85	.07
VAS Fatigue (0-10)	7.69 (1.53)	8.14 (1.31)	1.84	.07
TSK-11 Kinesiophobia (11-44)	30.57 (7.26)	32.35 (6.80)	1.47	.14
HADS Anxiety (0-21)	13.79 (4.11)	14.52 (4.64)	.98	.33
HADS Depression (0-21)	11.67 (4.08)	13.69 (4.88)	2.61	**.01**
SF-36 Physical function (0-100)	20.00 (10.60)	24.69 (18.07)	1.82	.07

[a] The values represent means (M) and standard deviation (SD) or frequency (f) and percentages (%), in their respective order of presentation. The ranges of measurements corresponding to each instrument are presented in parentheses. BMI = Body mass index. FIQR: Revised Fibromyalgia Impact Questionnaire; VAS: Visual Analogue Scale; TSK-11: Tampa Scale for Kinesiophobia; HADS: Hospital Anxiety and Depression Scale; SF-36: SF-36 Health Survey.

[b] Bold type indicates statistically significant group differences.

Table 6.

Comparison between primary and secondary outcomes at pre-, post-, follow-up + 6, and follow-up + 9 in TAU + Fibrowalk.[a]

	TAU + Fibrowalk (*n* = 48)				Comparison Post vs. Pre			
	Pre	**Post**	**Follow-Up +6**	**Follow-Up +9**	***F***	***p*[b]**	**η_p^2**	***d*[c]**
Primary outcome, M (SD)								
FIQR Functional impairment (0-100)	74.58 (13.84)	51.35 (19.21)	58.76 (20.51)	61.01 (18.19)	84.66	**.001**	.64	**1.4**
Secondary outcomes, M (SD)								
VAS Pain (0-10)	8.04 (.94)	5.75 (2.13)	6.29 (2.05)	6.65 (1.86)	65.13	**.001**	.58	**1.41**
VAS Fatigue (0-10)	8.06 (1.16)	6.56 (1.86)	6.48 (2.10)	6.81 (1.78)	33.40	**.001**	.42	**1.15**
TSK-11 Kinesiophobia (11-44)	31.04 (6.86)	17.27 (6.80)	20.85 (7.24)	20.98 (6.15)	155.32	**.001**	.77	**2.04**
HADS Anxiety (0-21)	14.38 (4.46)	10.38 (4.60)	11.23 (4.04)	11.79 (3.89)	31.49	**.001**	.40	**.89**
HADS Depression (0-21)	13.02 (4.56)	8.85 (4.89)	10.31 (4.42)	10.50 (4.31)	40.77	**.001**	.47	**.89**
SF-36 Physical function (0-100)	20.73 (13.01)	45.31 (18.11)	41.46 (20.49)	39.06 (18.81)	100.31	**.001**	.68	**1.58**

[a] Due to ethical reasons was not possible to follow-up the control group. η_p^2 = partial η_p^2 as effect size. *d* = Cohen's *d*.

[b] Bold type indicates statistically significant group differences.

[c] Bold type indicates large size effect (Cohen's *d* > .80).

	Comparison Follow-Up+6 vs. Pre				Comparison Follow-Up+9 vs. Pre			
	F	***p*[b]**	**η_p^2**	***d*[c]**	***F***	***p*[b]**	**η_p^2**	***d*[c]**
Primary outcome, M (SD)								
FIQR Functional impairment (0-100)	35.43	**.001**	.43	**.91**	45.32	**.001**	.49	**.85**
Secondary outcomes, M (SD)								
VAS Pain (0-10)	35.80	**.001**	.43	**1.11**	27.22	**.001**	.37	**.95**
VAS Fatigue (0-10)	20.67	**.001**	.31	**1.07**	21.36	**.001**	.31	**1**
TSK-11 Kinesiophobia (11-44)	88.31	**.001**	.65	**1.46**	132.28	**.001**	.74	**1.56**
HAD Anxiety (0-21)	23.80	**.001**	.34	**.75**	29.08	**.001**	.38	.63
HAD Depression (0-21)	23.78	**.001**	.34	.61	28.33	**.001**	.38	.57
SF-36 Physical function (0-100)	63.99	**.001**	.58	**1.22**	79.26	**.001**	.63	**1.15**

[a] Due to ethical reasons was not possible to follow-up the control group. η_p^2 = partial η_p^2 as effect size. *d* = Cohen's *d*.

[b] Bold type indicates statistically significant group differences.

[c] Bold type indicates large size effect (Cohen's $d > .80$)

Supplementary Table 1.

Between-group differences from a completers approach.[a]

	TAU + Fibrowalk (*n* = 103)		TAU (*n* = 137)		Phase x Group interaction			
	Pre	**Post**	**Pre**	**Post**	***F***	***p*[b]**	**η_p^2**	***d*[c]**
Primary outcomes, M (SD)								
FIQR functional impairment (0-100)	75.24 (11.79)	53.13 (18.24)	73.9 (9.76)	79.77 (9.72)	285.39	**.01**	.55	**1.44**
Secondary outcome, M (SD)								
VAS Pain (0-10)	8.0 (1.0)	5.78 (1.85)	7.79 (1.12)	8.09 (.98)	198.65	**.01**	.46	**1.49**
VAS Fatigue (0-10)	7.9 (1.40)	6.39 (1.81)	7.80 (1.41)	7.69 (1.68)	29.42	**.01**	.11	**.93**
TSK-11 Kinesiophobia (11-44)	31.05 (7.12)	16.17 (6.12)	30.42 (6.85)	31.76 (6.26)	316.32	**.01**	.57	**2.24**
HADS Anxiety (0-21)	14.14 (4.28)	10.14 (4.32)	13.35 (3.93)	14.23 (3.83)	99.23	**.01**	.29	**.93**
HADS Depression (0-21)	12.61 (4.41)	8.76 (4.52)	11.94 (4.11)	13.01 (3.62)	106.75	**.01**	.31	**.86**
SF-36 Physical function (0-100)	20.34 (12.03)	45.15 (18.97)	26.61 (14.02)	19.56 (13.69)	283.76	**.01**	.54	**1.56**

[a] Effect considering covariate SF-36 baseline scores. η_p^2 = partial η_p^2 as effect size. *d* = Cohen's *d*.

[b] Bold type indicates statistically significant group differences.

[c] Bold type indicates large size effect (Cohen's *d* > .80).