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.

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Abstract

Methods. A randomised controlled trial was performed 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, compared to treatment as usual only in patients with fibromyalgia (FM). A total of 272 patients were randomly assigned to either the multicomponent treatment (*n*= 135) or treatment as usual (*n*= 137). The multicomponent treatment (2h weekly sessions) was delivered in groups of 20 participants. Treatment as usual was mainly based on pharmacological treatment according to the predominant symptoms. Data on functional impairment (the Revised Fibromyalgia Impact Questionnaire, FIQR as primary outcome) were collected, as well as for 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.

Results. At post-treatment, significant between-group differences ($p < .001$) with a large effect size (Cohen's $d > 0.80$) in favour of the multicomponent treatment were found in functional impairment, pain, kinesiophobia, and physical function, whilst differences with a moderate size effect (Cohen's $d > 0.50$ and < 0.80) were found in 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. Compared to usual care, there was evidence of short-term (up to three months) positive effects of the multicomponent treatment for FM. Nevertheless, some methodological shortcomings (absence of follow-up in the control group and monitoring of treatment

adherence, potential research allegiance, etc.) preclude robust conclusions regarding the proposed multicomponent program.

Impact statement

- This is to our knowledge the first randomised controlled trial 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. **Notwithstanding, further rigorous RCTs are needed to confirm the promising findings reported here.**

Introduction

Fibromyalgia (FM) is a syndrome characterized by chronic widespread musculoskeletal pain, fatigue, stiffness, sleep disturbances, 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 hypersensitisation of the Central Nervous System (CNS) that is characteristic of the Central Sensitisation Syndromes (CSSs), of which FM is the flagship.[4,5] CSSs are characterized by a malfunction in the balance between descending inhibitory and facilitatory 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]

Since the seminal meta-analysis performed by Häuser and collaborators,[13] multicomponent treatments involving physical exercise and **cognitive behavioral therapy (CBT)** 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[16] 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 pain neuroscience education (PNE) or mindfulness, whose recent empirical support for FM is promising as commented above.

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.[17-19] This therapeutic approach has been extensively investigated in various chronic pain conditions.[20-32] 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]

Psychological treatments that have shown promise in the management of FM include **CBT** and mindfulness. 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 high quality trials have demonstrated the efficacy and cost-utility of including mindfulness as an adjuvant therapy for the management of FM.[12,41]

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 differences between responders 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).[42] Those patients in the TAU group were given the opportunity to receive the multicomponent treatment once the study had finished.

Participants

A total of 272 patients who met the eligibility criteria were recruited from November 2018 to August 2019 by a 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.

The participants were recruited consecutively in different waves. The first wave was conducted from November to February (2 groups of 20 patients), the second wave from March to June (4 groups of 20 patients), and the third wave from August to October (1 group of 20 patients). 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 coded by the clinical trials unit to ensure concealment of randomisation. **Due to the characteristics of the study, participants and the therapist (MS) were not blind to the group allocations. Only the interviewer (MM) was blind to participants' random assignment in the RCT.**

Multicomponent treatment

The multicomponent treatment 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), the professional who delivered the treatments, 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.*[43] 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 treatment 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.[22] Individualised gradual programmes were implemented following the transtheoretical model of stages of change, developed by Prochaska and Diclemente.[44]

Taking the American College of Sports Medicine (ACSM) guidelines[45] as framework, all participants randomized to the "multicomponent treatment" group received the same exercise protocol. 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 and progression was monitored throughout the 12-week multicomponent treatment.

The program included multicomponent exercises such as stretching, balance training, posture correction and low-impact walking at a training load of 60-80% of maximum heart rate determined by 220-age (see an outline of the exercise program in Table 1 and supplementary appendix 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. **Patients who did not attend a session or did not practice the exercises were called or emailed to foster adherence.**

Insert Table 1 about here

Insert Table 2 about here

Treatment-as-usual (TAU) was mainly based on pharmacological treatment (duloxetine, amitriptyline, pregabalin, or tramadol) according to the predominant symptoms in monotherapy or combination therapy of two or more drugs. The rheumatologist from the UHVH (MA) monitored the pharmacological treatment.

The patients were instructed to continue their prescribed treatment with no change throughout the 3-month period. In Spain, some counselling about aerobic exercise adjusted to patients' physical limitations and education is usually provided by first-line clinicians and specialists, but pharmacological treatment **is** still the dominant treatment option. **For ethical reasons, control patients were offered the same treatment as the intervention group once the trial was concluded. Data of those control patients receiving the intervention once the trial had ended were not part of this study.**

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. (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 impairment during the last week. It 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 impairment. 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 was *α* = .85.

Statistical analyses

Data analyses were computed with 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 + multicomponent treatment 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 + multicomponent treatment (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 selection 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 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 between-group differences in terms of gender distribution, body mass index (BMI), and physical function. The mean age of all patients was 54

years (*SD* = 8.96), BMI of 27 (*SD* = 5.55), and the mean number of years diagnosed with FM was 17 (*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 impairment, 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)

A total of 70 patients (51.85%) receiving the multicomponent treatment reached the criterion of $\geq$ 20% FIQR reduction, and a total of 7 patients (5.2%) showed a reduction > 70% on their FIQR score. Only 1 patient in the TAU group was considered as a responder using the FIQR

improvement criterion of ≥ 20%. We analysed the baseline differences between responders and non-responders for all variables (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 to 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 instead with TAU alone for one of them to become a responder.

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 multicomponent treatment was an effective adjuvant for patients with FM, when compared with TAU alone. Specifically, significant differences with medium to large effect sizes were found in functional impairment, 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 treatments 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 [12,13,21,32-33,41]. Overall, they have demonstrated to be effective therapeutic options, leading to improvements in mental health, well-being, and physical function[11,13,19-27]. However, in most cases, the reported effect sizes ranged from small to moderate magnitudes.[18] 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[20-33] 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.[61] 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 multicomponent 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 treatment

could be effective for a long term or some type of periodic treatment 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 in this study. At least 20% of the sessions should be videotaped in future studies to assess treatment fidelity and therapist competence. Second, practising skills outside of the group is considered of crucial importance for improving outcomes in this type of therapies, **however treatment adherence to home practice was not specifically analyzed in this study. In our opinion, it may be worthwhile in the future to monitor daily home practice and adherence to drugs through a paper-and-pencil or digital log.** Third, as recently highlighted by Ollevier and colleagues,[62] there is a need for empirical evidence for the long-term efficacy of multicomponent therapies. In our case, it was not possible to follow up the control group beyond a period of 3 months due to ethical reasons. An assessment of the long-term effectiveness of our multicomponent treatment is necessary in the context of real-world clinical practise. **Fourth, using treatment as usual as control condition has a number of methodological drawbacks that were very well explained by Öst.[65] Future RCTs should assess the effectiveness of the proposed multicomponent program in comparison with other active non-pharmacological conditions equivalent to the multicomponent intervention in therapy time, therapist allegiance, or expectations.** Fifth, the multicomponent treatment tested here consisted of the combination of many therapeutic ingredients delivered by the same professional. Also 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's effect on the outcomes. Sixth, in this study we did not evaluate the acquisition of knowledge and skills in the PNE. It would be necessary that future RCTs include an evaluation of the patient's competencies and knowledge. **Regarding this issue, the revised Neurophysiology of Pain Questionnaire (rNPQ)[66] might be a good option for assessing neurophysiology of pain knowledge. The rNPQ is a psychometrically sound measure that evaluates how patients conceptualize biological mechanisms underpinning their pain.** Finally, 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.[67] 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.

Despite the limitations commented above, this is the first study to demonstrate the potential 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[11,13-15,19-28,68-73]. 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 as a result the adequate use of 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 could 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. Future studies should compare our multicomponent treatment with another equivalent in therapy time, therapist allegiance, or expectations to reach solid conclusions about the added value of this treatment package.

Author Contributions and Acknowledgements

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

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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 for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Table 1.
Outline of active group sessions in the multicomponent 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 **(marching/walking)** and muscle strengthening **(upper body and lower body)** 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 gradually increases.
- Cooling-down (10'): flexibility and relaxation exercises.

Homework (5') (moderate intensity walking: 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 tasks to do at home in order to increase 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).[45]

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 the 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 study following the CONSORT statement.

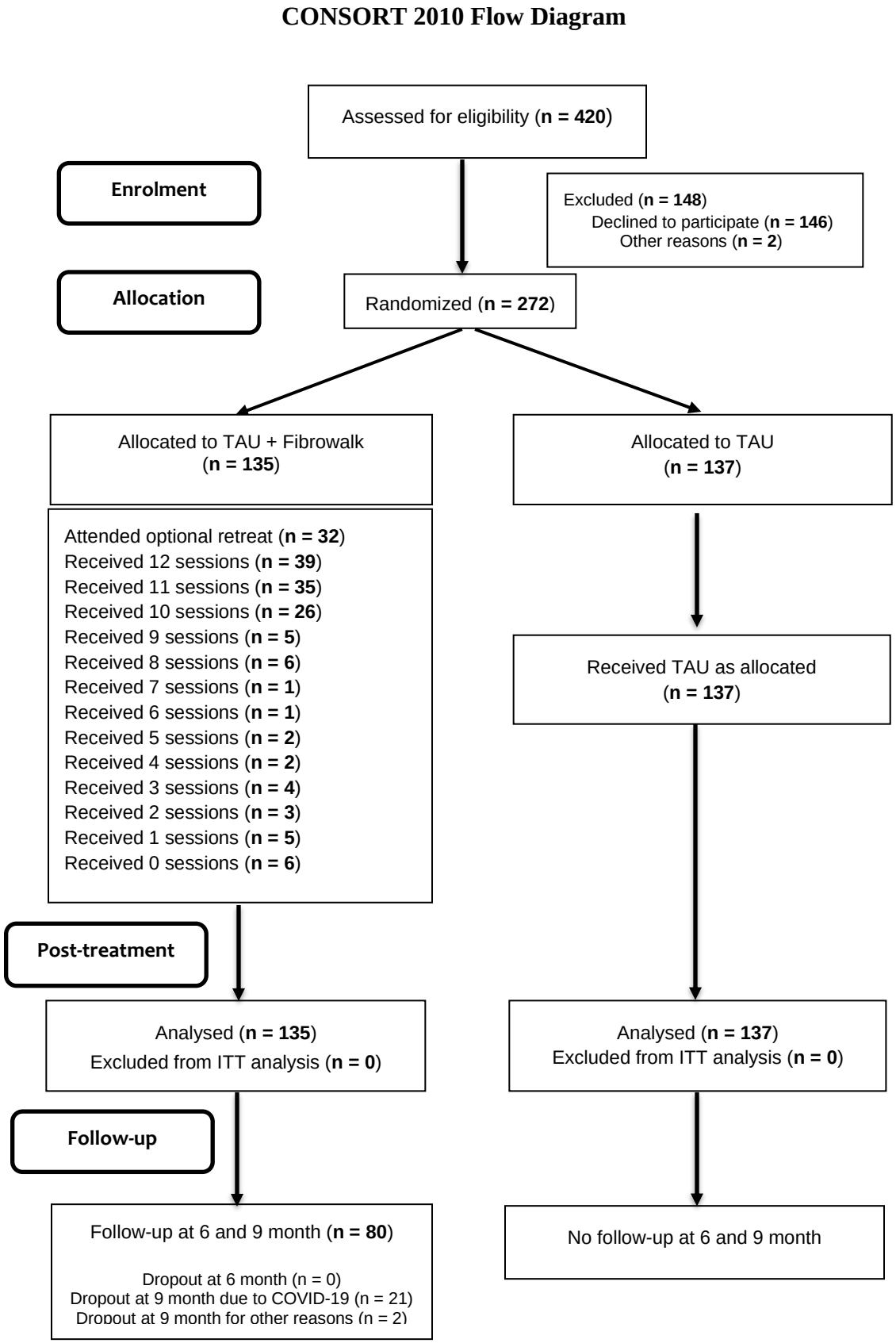

Table 3.

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

	TAU + Multicomponent treatment (*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				
Chronic fatigue, n (%)	113 (83.7)	118 (86.1)	.31	.58
Multiple chemical sensitivity, n (%)	47 (34.8)	37 (27.0)	1.94	.16
Irritable bowel syndrome, n (%)	63 (46.7)	76 (48.2)	.06	.80
Migraines, n (%)	77 (57.0)	80 (58.4)	.05	.82
Medication				
> 2 medications n (%)	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 + Multicomponent treatment (*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				
Chronic fatigue, n (%)	60 (85.7)	53 (81.5)	.43	.51
Multiple chemical sensitivity, n (%)	24 (34.3)	23 (35.4)	.02	.89
Irritable bowel syndrome, n (%)	32 (45.7)	31 (47.7)	.05	.82
Migraines, n (%)	38 (54.3)	39 (60.0)	.45	.50
Medication, n (%)				
> 2 medications, n (%)	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 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 + multicomponent treatment.[a]

	TAU + multicomponent treatment (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								
FIQR Functional impairment (0-100)	35.43	**.001**	.43	**.91**	45.32	**.001**	.49	**.85**
Secondary outcomes								
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 + multicomponent treatment (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).

Supplementary Appendix 1

PAIN NEUROSCIENCE EDUCATION (PNE)

PNE was not only an ingredient of the multicomponent therapy but also the core component that guided the approach taken by all the strategies involved. 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. In our study, the educational content was delivered in 11 sessions of 20' and one session (2h) as a summary of all content with their family. The main idea is that pain is not related to damage but to threat perception and requires an evaluation from brain. It was essential to dedicate enough time in each session, not only in the PNE part but also in the CBT and TE (in total between 15 and 20') to update their knowledge overthrowing the false belief that pain depends on the amount of damage that exists and that having pain without damage does not mean that you are making it up or have psychological problems that need to be treated. For that purpose, "expert patients" were recruited to help in next multicomponent groups. All the content of PNE had as reference the book entitled Explain Pain.[43] To communicate the information to the patients in the most comprehensive way, a presentation was used with images, examples, and metaphors [22]

Additional resources

- NOI Group: http://www.noigroup.com/
- Butler D, Moseley L, Sunyata A. Explain pain. Adelaide, Australia: Noigroup Publications; 2016.
- Pain in motion: http://www.paininmotion.be/
- Reconciling Biomechanics with pain science: http://www.greglehman.ca/
- Know pain, no pain: https://arturogoicoechea.com/
- Migraña. Una pesadilla cerebral (Migraine. A brain nightmare). A. Goicoechea. Ed. Desclée de Brouwer. 4ª ed. 2016

THERAPEUTIC EXERCISE (TE)

This ingredient is highly recommended in clinical practice guidelines for FM. TE reduces pain, fatigue, and depression, whilst producing improvements in mental health, psychological well-being, and physical functioning.[10,22-25] TE for FM should preferably be personalized to the individual clinical characteristics and integrated within other therapeutic approaches. [11] When there is central sensitization such as FM, the TE should be applied with cognitive targets (the application of CBT to TE under the principles of PNE [27,28]). The exercises that have shown to be most effective for FM are a combination of aerobic exercise and strength training [22]. How can you customize the exercise within a group that basically follows the same exercises and the same structure within each session? To perform the TE it was taken into account that the exercise:

1. It is an essential and necessary movement: It is necessary to explain and remind patients that, despite the pain, it is important to move and why, what we will do and to give them the confidence and motivation required to participate in the physical activities as well as to prevent injury or discouragement (health education and health risk appraisals). [47-48] Most people with FM have already found that spending a lot of time in bed or on the couch does not help reduce symptoms, on the contrary. Highlighting the importance of exercise and moving every day is a critical part of their treatment. This goal can be achieved with an emphasis on confrontation. It is very important for the patient to understand that fear of movement leads to avoidance behaviors that reduce their activity in daily life. So most of the strategies are directed to this end so that they can get back to the activities of daily life.
2. Set basal minimum: To begin the exercise, a minimum must be established from which the progression recommendation is established and made. This minimum is individualized according to the characteristics of each patient. **The basal intensity level of home exercises**

was self-selected. According to our experience, self-selected intensity is related to more positive affect than an intensity that is imposed by the instructor. It is not an issue of finding that exercise does not cause pain, since many of them have pain 24 hours a day, but rather to determine what minimum exercise they can perform without their symptoms being harmed. Tool 2 in Chapter 6 of the book *Explain Pain* [49] is extensively detailed.

3. Individualized gradual program: During the sessions, all the patients performed the same aerobic, muscular strength indoor exercises combined with balance and coordination exercises, but adapted in time and intensity to their own condition. Although all exercises are adapted to the capacities of each patient if, despite motivating them to do it, there is an exercise that someone considers very upsetting or unpleasant, they always have the option not to do it. There is a maximum time established within the program and within this time the duration is set individually as well as the intensity where each patient can perform the same exercise with different vigour. As homework, in general, walking is prescribed, although it also adapts to the patient's preferences and if they do not like it, they are invited to choose another aerobic exercise, such as swimming or cycling. Whatever aerobic exercises it is, the progression is established in the same way. The progression is agreed with the preferences and capacities of the patient. The minimum exercise that can be carried out is determined and how far it could go at the end of the three months, in duration and intensity.
4. Small increases, patterns: To establish the progression, two aspects were taken into account: (a) a more general one, in which the aerobic exercise prescribed at home (mainly walking) should be performed once a week the first month, twice a week the second month and three times a week the third month, and (b) one more individual to determine the time that should be carried out that exercise. From the minimum and maximum agreed exercise that each

patient can perform, the progression is established taking into account the phase of change in which they are. To progress through the stages of change, the cognitive, affective and evaluative processes involved have to be taken into account. There are ten change processes that result in strategies that help people make and maintain changes, although some processes are more relevant to a specific stage of change than other processes.[51-52] The closer to the precontemplation phase the patient is, the less demanding the progression can be considered.

PRECONTEMPLATION TO CONTEMPLATION
1. Consciousness Raising - Increasing awareness about the healthy behavior. 2. Dramatic Relief - Emotional arousal about the health behavior, whether positive or negative arousal. 3. Environmental Reevaluation - Social reappraisal to realize how their unhealthy behavior affects others.
CONTEMPLATION TO PREPARATION
4. Self-Reevaluation - Self reappraisal to realize the healthy behavior is part of who they want to be. 5. Counter-Conditioning - Substituting healthy behaviors and thoughts for unhealthy behaviors and thoughts. 6. Social Liberation - Environmental opportunities that exist to show society is supportive of the healthy behavior.
PREPARATION TO ACTION
7. Self-Liberation - Commitment to change behavior based on the belief that achievement of the healthy behavior is possible.
ACTION TO MAINTENANCE
8. Helping Relationships - Finding supportive relationships that encourage the desired change. 9. Reinforcement Management - Rewarding the positive behavior and reducing the rewards that come from negative behavior. 10. Stimulus Control - Re-engineering the environment to have reminders and cues that support and encourage the healthy behavior and remove those that encourage the unhealthy behavior.

5. Activities contingent on the task, not over time: All prescribed exercises were performed with progressive increases in intensity, duration and complexity. The instructions for the completion of the exercise were when the stipulated time ended and not because of the appearance of symptoms. The progression guide was also established throughout the 12 weeks of treatment contingent with the task and not with the symptom[28]. A time-contingent approach

(to establish a predetermined time of the duration of the exercise instead of to stop when the exercise hurts) applies to exercises and physical activity to motivate the deactivation of descending facilitating pathways orchestrated by the brain. Conversely, a symptom-contingent approach may imply that the brain produces more danger signals, increasing pain even though there is no real tissue damage.

6. Activities with cognitive and emotional targets: As the program progressed, the level of difficulty and complexity increased incorporating the performance of different cognitive or emotional tasks to the exercise. In this way, a physical exercise is proposed where a cognitive task must also be performed (for example, perform one exercise or another depending on a number that the physiotherapist says or saying two or three words per patient build a story among the whole group while doing the exercise) or an emotional task (while performing an exercise the person focuses their attention on looking for something in your environment or inside that gives you a positive feeling). The exercises were done in a playful way where the most important component is not the correct execution of it, but precisely encourage them to move without paying attention to their pain to reduce kinesiophobia, fear-avoidance behaviours and improve their functional capacity without increasing their perception of fatigue. The cohesion of the group plays an important role to achieve these goals. In this way, with gradual exposure and loss of fear of movement, the patient becomes more and more confident to perform any type of movement necessary for daily life.
7. Involvement in the tasks of daily life: Due to the fact that there is no specific injury or damage in FM, the exercises are performed taking into account the entire body and reproducing those movements that are necessary in daily life. It is intended to increase their physical capacity but above all their movement capacity, which allows them to be more and more autonomous

and have confidence in themselves to carry out those necessary movements of daily life. It is also important that, as far as possible, activities of daily living follow a gradual and progressive exposure and not just a specific exercise.

8. Lifestyle change: The ultimate purpose of the program is not so much pain reduction as that the patient can be incorporated into the activities of their daily life, family, work and recreation. For this, it is necessary to use all the available strategies to achieve a real change in their lifestyle. For this, it is essential that the patient acquires a fully active role focused on the recovery of his/her function and on those more psychosocial aspects that favour their disability. This more psychosocial part is the one that is also addressed with the reinforcement of CBT. Taking into account all the aspects described above, TE program was performed in two blocks:

(1) 40' in 11 sessions (less the family session) where the level of difficulty and dedication time gradually increased and following the recommendations of the ACSM[53] was done in three different parts:

- 5' of warm up: activation and mobility exercises using dynamic stretching of the main muscle groups (trapezius, bicep, deltoid, triceps, pectoralis, latissimus dorsi, abdominals, gluteals, quadriceps, hamstring and gastrocnemius).
- 25' of main exercises: distributed in approximately equal parts with moderate aerobic-cardiovascular, muscle strengthening exercises (exercises body-weight resistance), balance and coordination exercises performed in a ludic manner with cognitive and emotional targets (multitask works) where the level of difficulty and dedication time gradually increases in all types of exercise.

- 10’ of cool down: flexibility and relaxation exercises (as breathing) using static stretching to the main muscle group.

(2) As a homework: individualized walking guidelines (mainly). It was established the minimum baseline (walking time) and a general progression guide was established throughout the 12 weeks of treatment.

ADHERENCE TO THE EXERCISE AND TO THE PROGRAM

By explaining and taking into account throughout the entire program the following aspects we fostered the adherence to the TE [47-48], the fundamental part of this program:

1. The exercise is an essential and necessary movement (first point of the TE program), setting realistic, specific, measurable and short-term goals with the necessary steps to achieve their specific goal (individual goal setting increasing the intensity and duration gradually based on their own capacities) and documenting through the homework their activity behavior (self-monitoring sharing it to other patients).

2. To perform the TE following the ACSM [45] recommendations with an active warm up and cool down exercises to minimise injuries.

3. Reinforcement and incentives rewarding themselves and/or being rewarded from the researcher or from other participants such as simple recognition between patients or positive reinforcement both verbal and non-verbal that were not detrimental towards their goal.

4. Obstacles and barriers that have been encountered to perform homework are shared among patients and solutions are sought, sometimes applying the explained problem-solving tool together.

5. Social support to help motivation: Physical activity is encouraged as part of a group program, working toward a common goal. In addition, at the end of the program it is intended that the

person can make a change in their real lifestyle and can continue with that physical activity or group program. With the subsequent intervention, a group has been created expressly to carry out activities in nature.

6. 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.

COGNITIVE BEHAVIORAL THERAPY (CBT)

CBT is a form of psychological treatment that aims to change how we feel and act by learning ways to change our maladaptive thinking. CBT was applied following the principles of PNE in:

(a) TE to change pain-related cognitions and beliefs and influencing the confrontation to avoid kinesiophobia following the fear-avoidance model [48] As we said before, the main aim of the treatment is not to reduce pain but to be able to incorporated into the activities of their daily life, family, work and recreation. For this, the word confrontation regains special relevance. It is important for patients to understand that fear of movement leads to avoidance behaviors that reduce their activity of daily living. In this way, fear-avoidance is an important predictor of disability. If they avoid physical activity, their physical capacity (deconditioning) will decrease, their hypervigilance will increase, and disability will increase, thus fuelling the vicious cycle of increased fear and avoidance. The patient's beliefs that their pain is caused by injury or damage, what they will do is interpret it as threatening (catastrophic pain) and thus perpetuate their fear in relation to their pain. On the contrary, the confrontation with the activity opens a door to recovery.

It is important not only to explain this model but also to work on these erroneous pain cognitions, incorrect negative beliefs, catastrophic thoughts and negative affectivity from CBT, TE and PNE to achieve a behavioral change from the confrontation.

MINDFULNESS TRAINING (MT)

Finally, to cover some of the limitations of CBT we propose to combine CBT with MT. To facilitate understanding and to be able to provide support at home, mindfulness training (MT) was applied following the 8 weeks of Palouse Mindfulness, an online and free program created by a certified MBSR instructor, and inspired by the program founded by Jon Kabat-Zinn at the University of Massachusetts School of Medicine [40]. The contents of each week of the Palouse Mindfulness program were explained in the multicomponent treatment sessions and the tasks of each session were set as homework.

Palouse Mindfulness program: https://palousemindfulness.com/index.html

HOMEWORK

Homework is a fundamental part of the program since it allows a weekly monitoring of what has been understood allowing us to delve into concepts that have not been fully understood during the review phase at the beginning of each session. Homework is structured in two blocks:

(1) Cognitive tasks that are divided into:

(a) Written tasks: questions related to the explanations given in the PNE, CBT and MT programs are asked. They are open-ended, multiple-response or true/false questions about the main content given in each session.

(b) Instructions for putting into practice the techniques that have been explained in each session: patients need to carry a notebook and a pen to write down the fundamental

contents and they are provided with a photocopy of the powerpoint of the tools that are explained. In this way they can carry out homework and review the content at home with written support. The patient is encouraged by setting as homework the fact of having to apply the explained tools at least once a week.

(2) Physical task with a goal setting and self-monitoring that are divided into:

(a) It is facilitated with photography of the muscular strength exercises and the stretching that are carried out in the sessions

(b) The mindfulness techniques (such as the body scan).

(c) The personalized guideline of aerobic exercis