Clinical Trial/Experimental Study

Medicine

OPEN

Millimetre wave-based neuromodulation combined with coaching improves quality of life in fibromyalgia patients

A 9-month prospective, multicenter, open, randomized, controlled trial

Caroline Maindet, MD[a,b], Laure Minier, PhD[c,*], Emilie Chipon, PhD[c], Mélanie Véloso, MSc[d], Anne Dumolard, MD[a], Mario Barmaki, MD[e], Alberta Lorenzi-Pernot, MD[f], Raphaël Gonon-Demoulian, MD, PharD[g], Patrick Ginies, MD[g], Frédéric Viseux, PhD[h,i], Antoine Lemaire, MD[h], Mireille Michel-Cherqui, MD[j,k], Rodrigue Deleens, MD[l], Alain Serrie, MD, PhD[m], Jean-Luc Bosson, MD, PhD[b,d,n], David Crouzier, PhD[c]

Abstract

Background: This study assessed the efficacy of a therapy combining a millimeter wave emitting wristband and coaching in improving the quality of life (QoL) of Fibromyalgia (FM) patients, compared to standard care.

Methods: An open, randomized clinical trial enrolled 170 patients with FM (2016 American College of Rheumatology criteria, Fibromyalgia Impact Questionnaire score ≥ 39) from 8 French pain centers, and compared Immediate versus Delayed therapy. Therapy was provided at inclusion (D0) and month three (M3) in the Immediate and Delayed groups respectively. Therapy in the Immediate group stopped from month six (M6) to month nine (M9). Randomization was stratified by center, and FM severity, allocation ratio was 1:1. The primary outcome compared the proportion of patients with a Fibromyalgia Impact Questionnaire reduction ≥ 14% (minimal clinically important difference), from D0 to M3 in both groups. Pain (Visual Analogic Scale), sleep (Pittsburg sleep quality index), anxiety and depression (Hospital Anxiety and Depression Scale), fatigue (Multidimensional Fatigue Inventory Questionnaire), patients' and clinicians' impression of change (patient global impression of change & clinician global impression of change), physical activity (Global Physical Activity Questionnaire), generic QoL (euroqol, 5 dimensions, 5 levels), pharmacological and complementary treatment intakes, and healthcare requirements were measured at M3, M6, and M9.

Results: At M3, 38/69 (55.1%) and 28/78 (35.9%) patients in the Immediate and Delayed groups respectively achieved the minimal clinically important difference ($P = .021$). There were also significant improvements in sleep quality, pain, anxiety, depression, general and physical fatigue in the Immediate versus the Delayed group at M3. These benefits persisted at M6.

Conclusion: Our results demonstrate that combined millimeter wave-based neuromodulation and coaching improve the QoL and other symptoms of patients with FM after 3 and 6 months.

Abbreviations: CI = confidence intervals, EULAR = European alliance of associations for rheumatology, FIQ = Fibromyalgia Impact Questionnaire, FM = fibromyalgia, MMW = millimeter waves, QoL = quality of life.

Keywords: fibromyalgia, millimeter-waves, non-pharmacological therapy, pain, quality of life

L. Minier, E. Chipon and D. Crouzier, are employed by Remedee Labs. A. Serrie and C. Maindet are members of Remedee Labs' scientific board. The remaining authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Remedee Labs, Montbonnot Saint-Martin, France, manufacturer of the Remedee Endorphin Band, conceptor of the coaching program and developer of the smartphone application provided for the study.

Supplemental Digital Content is available for this article.

[a] Pain Medicine Department, Grenoble Alpes University Hospital, Grenoble, France, [b] TIMC Laboratory CNRS-UMR 5525, Grenoble Alpes University, Grenoble, France, [c] Medical Research Department, Remedee Labs, Grenoble, France, [d] Data Engineering Cell, Grenoble Alpes University Hospital, Grenoble, France, [e] Pain and Support Care Department, Médipôle Lyon Villeurbanne, Lyon Villeurbanne, France, [f] Neurology Practice, Mornant, France, [g] Pain, Psychosomatics and Functional Disease Department, Montpellier University Hospital, Montpellier, France, [h] Pain Medicine Department, Valenciennes Hospital, Valenciennes, France, [i] Haut-de-France Polytechnical University, LAMIH, CNRS, UMR 8201, F-59313, Valenciennes, France, [j] Department of Anesthesiology and Pain Management Clinic, Foch Hospital, Suresnes, France, [k] Versailles-Saint-Quentin-en-Yvelines University, Versailles, France, [l] Pain Medicine Department, Rouen University Hospital, Rouen, France, [m] Department of Pain and Palliative Medicine, Lariboisière Hospital, Paris, France, [n] Public Health Department, Grenoble Alpes University Hospital, Grenoble, France.

** Correspondence: Laure Minier, Medical Research Department, Remedee Labs, 99 chemin de l'étoile, 38330 Montbonnot Saint-Martin, France (e-mail: laure.minier@remedee.com).*

How to cite this article: Maindet C, Minier L, Chipon E, Véloso M, Dumolard A, Barmaki M, Lorenzi-Pernot A, Gonon-Demoulian R, Ginies P, Viseux F, Lemaire A, Michel-Cherqui M, Deleens R, Serrie A, Bosson J-L, Crouzier D. Millimetre wave-based neuromodulation combined with coaching improves quality of life in fibromyalgia patients: A 9-month prospective, multicenter, open, randomized, controlled trial. Medicine 2025;104:10(e41706).

Received: 4 October 2024 / Received in final form: 10 February 2025 / Accepted: 11 February 2025

http://dx.doi.org/10.1097/MD.0000000000041706

1. Introduction

Fibromyalgia (FM) is a composite chronic pain disorder including widespread pain, fatigue, sleep disorders, stiffness, and mood disturbances. FM is considered as prototypical nociplastic pain, i.e., a chronic pain arising from altered nociception without clear evidence of tissue or somatosensory damage.[1] Central sensitization is the predominant explanation of FM's physiopathology, in interaction with psychosocial factors.[2] Based on the American College of Rheumatology 2016 criteria, prevalence has been estimated to 3.4% in the general population, with a female-to-male ratio of 2.[3]

In the United-States duloxetine, milnacipran and pregabalin are FDA-approved to specifically treat FM but the modest benefit and adverse effects associated with those treatments justify limiting their usage.[4] The European Alliance of Associations for Rheumatology (EULAR) advises that treatment should focus on symptom mitigation and quality of life (QoL) improvement. Non-pharmacological interventions are recommended as the first line of treatment and a combination of such therapies seems to be the most effective strategy for managing symptoms.[5] Interventions showing the most evidence of positive outcomes are aerobic exercise, hydrotherapy, relaxation, cognitive behavioral therapy and patient education.[5] More recent approaches include for example noninvasive neuromodulation and digital health interventions.[5]

Non-pharmacological interventions that rely on the body's endogenous opioid system are often offered to patients. The release of endorphins is believed to be regulated by peripheral nerve stimulation as suggested by numerous studies showing that painful and non-painful stimulations (physical exercise,[6] temperature variations,[7] cutaneous contact,[8] light[9]) lead to an increase in endorphin levels. Spa therapy,[10,11] acupuncture[12] and meditative movement therapies (taï chi, qiqong, yoga[13]) received a "weak for" recommendation by the EULAR work group for the management of FM. Such therapies rely on significant resources for their application; a dedicated treatment space, materials and on the presence of an expert to provide directions or care, since patients cannot use them alone, or in an ambulatory context.

Exposure of the peripheral nervous system to millimeter waves (MMW) has been shown to provide a neuromodulating effect, mediated by the release of various neurotransmitters, including endorphins.[14] When a MMW emitter is placed in contact with the skin, MMW stimulate nerve endings, and this activation leads to an increase of endorphin levels.[15] A hypoalgesic effect has been demonstrated in randomized, placebo-controlled, cross-over trials on acute pain.[16] In addition to their neuromodulation effects, endogenous opioids play a role in the balance of sympathetic/parasympathetic systems, causing inhibition of the sympathetic system and activation of the parasympathetic system.[17] This endorphin release facilitates parasympathetic activities such as sleep and stress regulation,[18] which are also disturbed in FM and more generally in nociplastic pain.[19] Benefits of exposure to MMW have been shown in postsurgical pain,[20] neuropathic pain,[21] and joint pain.[22]

The objective of this trial was to assess the efficacy of a therapy combining a self-managed MMW emitting device and a coaching program on FM patients' QoL, compared to standard care. The device was a wristband, which was portable and easy to use, and allowed patients to conduct their therapy autonomously after a period of coaching. Because compliance to treatment in chronic diseases is known to be poor (50% of patients take their treatment as prescribed[23]), a coaching program supported by human coaches and a smartphone application, was intended to enhance adherence to and benefits from the MMW therapy. The program involved behavioral change techniques such as education, training to use the device, virtual incentives, monitoring of therapy usage and benefits, etc cf.[24] The primary outcome was the proportion of patients whose score on the Fibromyalgia Impact Questionnaire (FIQ[25]) was reduced by 14% or more (threshold considered as clinically significant[26]), from inclusion (D0) to 3-month follow-up (M3) in a group of patients using the combined therapy in addition to standard care, compared to patients using standard care only. To investigate the efficacy of the device unaccompanied, coaching stopped after M3. Finally, to study the evolution of patient's QoL with no MMW device after having used it for 6 months, the wristband and application were removed from the patients during the 6-month (M6) follow-up visits. Outcome measures were taken again at M6 and 9-month (M9) follow-up visits.

2. Methods

2.1. Trial design & ethics

The protocol of this prospective, multicenter, randomized, open, controlled trial has been published in a peer-reviewed journal.[27] FM patients were randomized with a 1:1 allocation ratio into 2 parallel groups: a group receiving the therapy immediately after randomization (Immediate group) and a group receiving the therapy just after the measurement of the primary outcome at M3 (Delayed group). Such a design allowed both groups to have access to the therapy and thereby avoid (or limit) a disappointment bias in the control group. The inclusion of coaching in the therapy and the fact that the device produces heat when active made it difficult to use a placebo control. In the absence of a reference treatment for FM in France, the comparison was made with a group of patients following their individual treatment protocols as usual. The trial was designed and run following Ninot's recommendations for the evaluation of non-pharmacological intervention.[28]

The trial is registered under the national reference 2021-A01689-32/SI: 21.01127.000016 and registered as NCT05058092. It was approved by the French Ethics Committee "Comité de Protection des Personnes Sud-Méditerranée II" on October 1, 2021. All patients signed a consent form before being enrolled in the trial, in accordance with the Declaration of Helsinki II. A complimentary wristband was provided to participants who wished to keep one after the end of the study.

2.2. Participants

Participants were recruited in 8 French centers specialized in pain treatment. Participants were eligible for inclusion if they were aged ≥ 18 years old, had FM according to the American College of Rheumatology criteria 2016,[29] and had a score ≥ 39 (moderate and higher forms) on the French version of the FIQ on the day of inclusion (D0). They were excluded if they were experiencing or had previously experienced a depressive episode according to the French version of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,[30] if there had been substantial change in treatment in the 3 months prior to inclusion or planned following inclusion, they had a chronic inflammatory pathology, or if they had a dermatological condition or tattoos on the wrists.

2.3. Interventions

2.3.1. Immediate group. The Immediate group received the therapy right after randomization. From D0 to M3, they used the wristband and the smartphone application, and received human coaching. From M3 to M6, they used the wristband and mobile application. To assess any persisting effect of the therapy after desisting from wristband use, access to the wristband and application were removed from the patients from M6 to M9. From D0 to M9, patients carried on taking their regular treatment as usual.

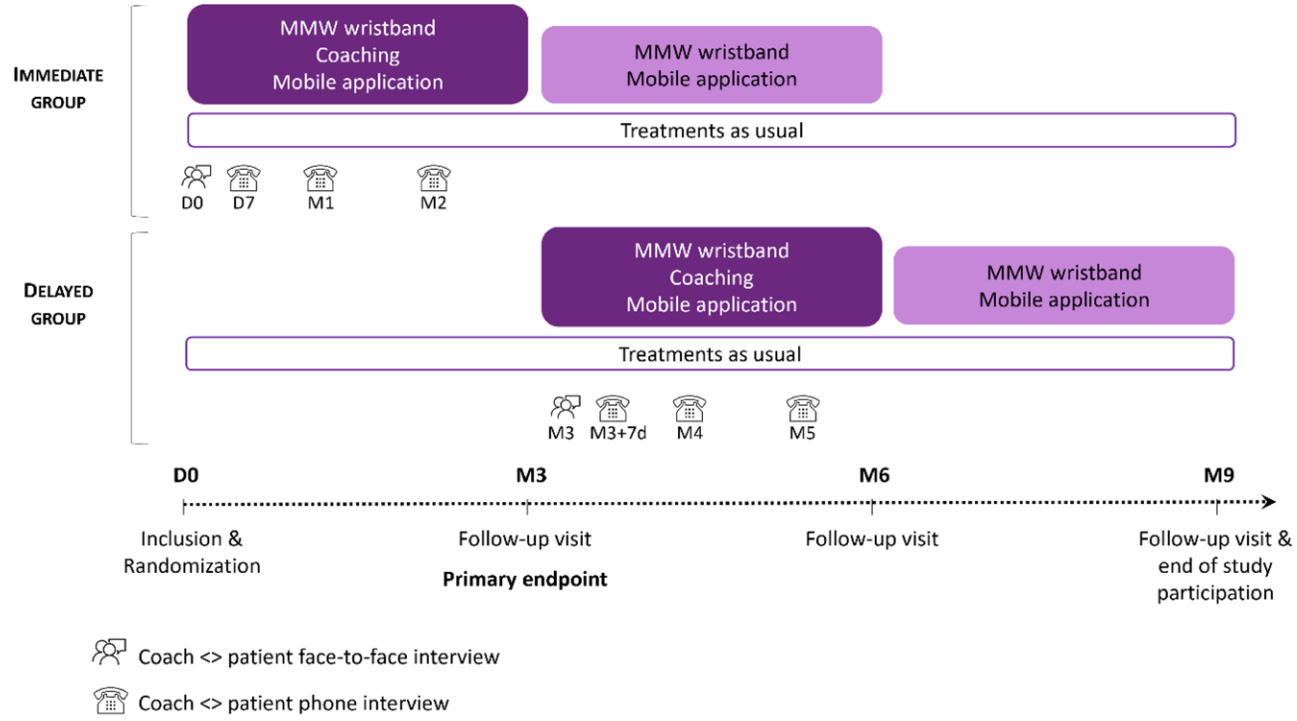


Figure 1. Study design.

2.3.2. Delayed group (control group). Between measurement of outcomes at M3 up until M6, patients used the wristband and the smartphone application, and received human coaching. From M6 to M9, they used the wristband and smartphone application. From D0 to M9, patients carried on taking their regular treatment as usual (see Fig. 1).

2.3.3. Combined therapy description. The therapy is composed of a millimeter emitting device (The Remedee Endorphin Band) and a coaching program. The coaching program is supported both by human coaches and a mobile application.

The wristband is designed to be a wearable, self-managed MMW emitting device. The technology used in the device has been tested for innocuity.[31] It contains 2 microelectronic components that can generate and amplify 61.2 GHz radiations when the band is active. During sessions that last 30 minutes, radiation is transmitted via the antennae towards the inner part of the patient's wrist. The waves penetrate the superficial layer of the skin and stimulate its nerve endings. Each session performed is recorded in the wristband's internal memory and can be transferred by Bluetooth to the smartphone application, and then to a server by internet connection. In this trial, patients were recommended to perform at least 3 sessions per day, every day, including 1 in the hour before bedtime to facilitate sleep onset and increase sleep quality. Additional sessions may be added if desired.

Coaching (i.e., behavior change techniques to improve adherence and efficacy) was provided through coaches and a smartphone application. Coaches were nurses, psychologists, or clinical research assistants from the participating centers. Prior to commencement of the study, coaches received 7 hours of specific training from a cognitive science researcher. The coaching program was a structured sequence of touch points (see Fig. 1) between coaches and patients based on Michie et al's recommendation[24] (see Data S1, Supplemental Digital Content, http://links.lww.com/MD/O455). A handbook was provided to coaches to ensure the standardization of protocols across investigating centers.

Coaching was intended to help patients be autonomous agents of their therapy, compliant and persistent in their adherence to usage recommendations. To assess patients' autonomy, human-supported coaching stopped after 3 months.

2.4. Outcomes

2.4.1. Primary outcome. The primary goal of this study was to compare the proportions of patients improving their health-related QoL, as measured by the FIQ.[32] The scores vary from 0 to 100, with higher scores indicating greater impact of FM on patients' QoL. The reduction in scores between 2 touch points means that the patient has improved their QoL. The primary goal of this study was to compare between the Immediate and Delayed groups the proportion of patients who experienced a clinically relevant reduction in their FIQ scores (i.e., ≥ 14%, Bennett, 2009) between D0 and M3. For each patient, the score reduction was computed as: FIQ score reduction = [(FIQ score$_{M3}$ – FIQ score$_{D0}$)/ FIQ score$_{D0}$] * 100. Patients were then split into 2 categories: reduction ≥ 14% versus reduction < 14%.

2.4.2. Secondary outcomes.

2.4.2.1. Group comparisons at M3. Secondary outcomes assessed the evolution of other health-related dimensions from D0 to M3:

1. Quality of sleep measured by the Pittsburg sleep quality index[33] questionnaire,
2. Pain score assessed on a Visual Analogic Scale during consultation with the physician and average pain score measured daily with a Visual Analogic Scale in a patient diary, for 7 consecutive days, 1 week per month, each month of the study,
3. Anxiety and depression measured by the Hospital and Anxiety Depression scale (HAD[34]),
4. Fatigue measured by the Multidimensional Fatigue Inventory Questionnaire[35],

5. Class, dose and number of analgesics, antidepressants and sleeping pills taken were weekly reported in a patient diary provided for the study,
6. Health care visits/consumptions related to FM symptoms were weekly reported in a patient diary provided for the study: care (procedures, medical consultations, hospitalizations); complementary care (acupuncture, osteopathy, naturopathy, etc); psycho-behavioral therapies; complementary treatments (phytotherapy, homeopathy, food supplements),
7. General QoL measured by the EQ-5D-5L questionnaire,[36]
8. Physical activity measured by the Global Physical Activity Questionnaire[37] and daily step counts measured by the patients' smartphones,
9. Patient's impression of change assessed by the patient global impression of change[38] scale at M3,
10. Caregiver's impression of change assessed by the clinician global impression of change[39] scale at M3.

2.4.2.2. Evolution at M3, M6, and M9. Primary outcome and secondary outcomes 1 to 10 were assessed again at M6 and M9.

2.4.2.3. Adherence. Wristband usage during the 6 months of possession was assessed based on wristbands' logs. Patients were considered compliant if they performed at least 2 sessions/day for at least 80% days of the 3 first months of wristband usage.

2.4.2.4. Safety. Number, description, and classification (serious/nonserious) of adverse events were reported.

2.4.2.5. Therapy usability and satisfaction. Usability of the wristband was measured by the modular evaluation of key components of user experience questionnaire at M6 for patients of Immediate group and at M9 for patients of Delayed group. Therapy satisfaction was measured with a questionnaire created by the sponsor and completed at M6 for patients of the Immediate group and at M9 for patients of the Delayed group.

Analyses were also run per-stratum (FIQ score categories: moderate vs severe) and per-protocol. Patients fulfilling the following criteria were included in the per-protocol analysis: (i) Patients with at least 80% days with at least 2 sessions/day during the 3 first months of wristband usage; (ii) Patients whose M3 follow-up consultation was conducted at theoretical date±2 weeks; and (iii) Patients whose M6/M9 follow-up consultations were conducted at theoretical date±3 weeks.

2.5. Sample size

We assumed that 50% of the patients in the Immediate group versus 25% in the Delayed group would achieve a decrease ≥ 14% of their FIQ score from baseline to M3. With an alpha risk of 5% and a beta risk of 10%, the number of patients needed was estimated to be 77 per group, 154 patients total. To allow for a potential participant drop-out rate of 10%, we included 85 patients per group, 170 patients total.

2.6. Randomization & blinding

Randomization lists were stratified by FIQ severity categories (moderate, i.e., 39 ≤ FIQ score < 59 vs severe, i.e., FIQ score ≥ 59) and centers (numbered from 1 to 8). Coaches and patients knew the patients' affiliation group, but physicians were blinded. Patients were instructed to not mention their affiliation group during the M3 consultation. For more details about randomization and blinding in the study, see Chipon et al.[27]

2.7. Statistical methods

The statistician was blind to group affiliation while running analyses on outcomes measured at M3. Fisher exact test was used to analyze the primary outcome. Logistic regression was used to test for center and FIQ severity categories effects. Multiple imputation was used to compensate for missing data. Linear regressions were used to analyze secondary outcomes. Repeated-measures ANOVA was used to analyze patients' daily pain scores recorded in diaries. The Mann-Whitney test was used to analyze the step count increase rate. Mixed-model regression including group and time were used to test secondary outcomes at different time points in the study (D0, M3, M6, and M9). Sensitivity analyses were run to check for normal distributions and extreme values. Cohen's kappa method was used to measure the clinician-patient agreement on their impression of change. Quantitative variables are represented by median and inter-quartile intervals, qualitative variables are represented both with effectives and percentages. Missing data are systematically mentioned and not included in descriptive analyses.

3. Results

Between the 15th of November 2021 and the 1st of April 2022, 170 patients were included in the study and randomized into the Immediate group (N = 84) or the Delayed group (N = 86). All study follow-ups were completed by the 28th of March 2023. Figure 2 displays the intention-to-treat flow chart and the per-protocol flow chart is available in Data S2, Supplemental Digital Content, http://links.lww.com/MD/O455. Patients who dropped out before the end of the study did not oppose the use of their data.

Table 1 presents the baseline demographic and clinical characteristics at inclusion for each group. Demographic and baseline characteristics were well balanced across the groups.

3.1. Primary outcome

The percentage of patients with more than a 14% decrease in their FIQ scores at M3 compared to D0, was significantly higher in the Immediate group than the Delayed group (38/69 (55.1%, 12 missing scores) vs 28/78 (35.9%, 6 missing scores), respectively, $P = .021$). The risk ratio for failure was 0.701 (95% confidence intervals (CI): [0.14; 0.955]), the risk difference was −0.192 (95% CI: [−0.350; −0.033]) and the number needed to treat was 6 patients (values were calculated without replacement of missing data). There was no center effect (centers 3 and 6 had too few patients to be included into the analysis) and no FIQ severity categories effect. Similar results were found in the FIQ severe category (30/55 (54.5% – Immediate group) vs 23/66 (34.8% – Delayed group), $P = .043$) and the per-protocol populations (33/53 (62.3% – Immediate group) vs 28/78 (35.9% – Delayed group), $P = .004$), but no statistical difference was found in the FIQ moderate category (8/14 (57.1% – Immediate) vs 5/12 (41.7% – Delayed), $P = .695$).

3.2. Secondary outcomes

3.2.1. Group comparisons at M3. The comparisons between groups at M3 on other health dimensions are presented in Table 2, together with the *P*-values of their statistical tests.

Pain measured every day for a week, at M1 ($m_{Immediate} = 5.9$ (1.7); $m_{Delayed} = 6.4$ (1.6)), M2 ($m_{Immediate} = 5.7$ (1.6); $m_{Delayed} = 6.3$ (1.7)) and M3($m_{Immediate} = 5.7$ (1.9); $m_{Delayed} = 6.2$ (1.6)) in patients' diaries did not show any group * time interaction effect ($P = .76$). There was also no statistical difference between groups at M3 regarding: step count, health care visits, pharmacological treatment and complementary treatment consumptions, complementary care and psycho-behavioral therapies.

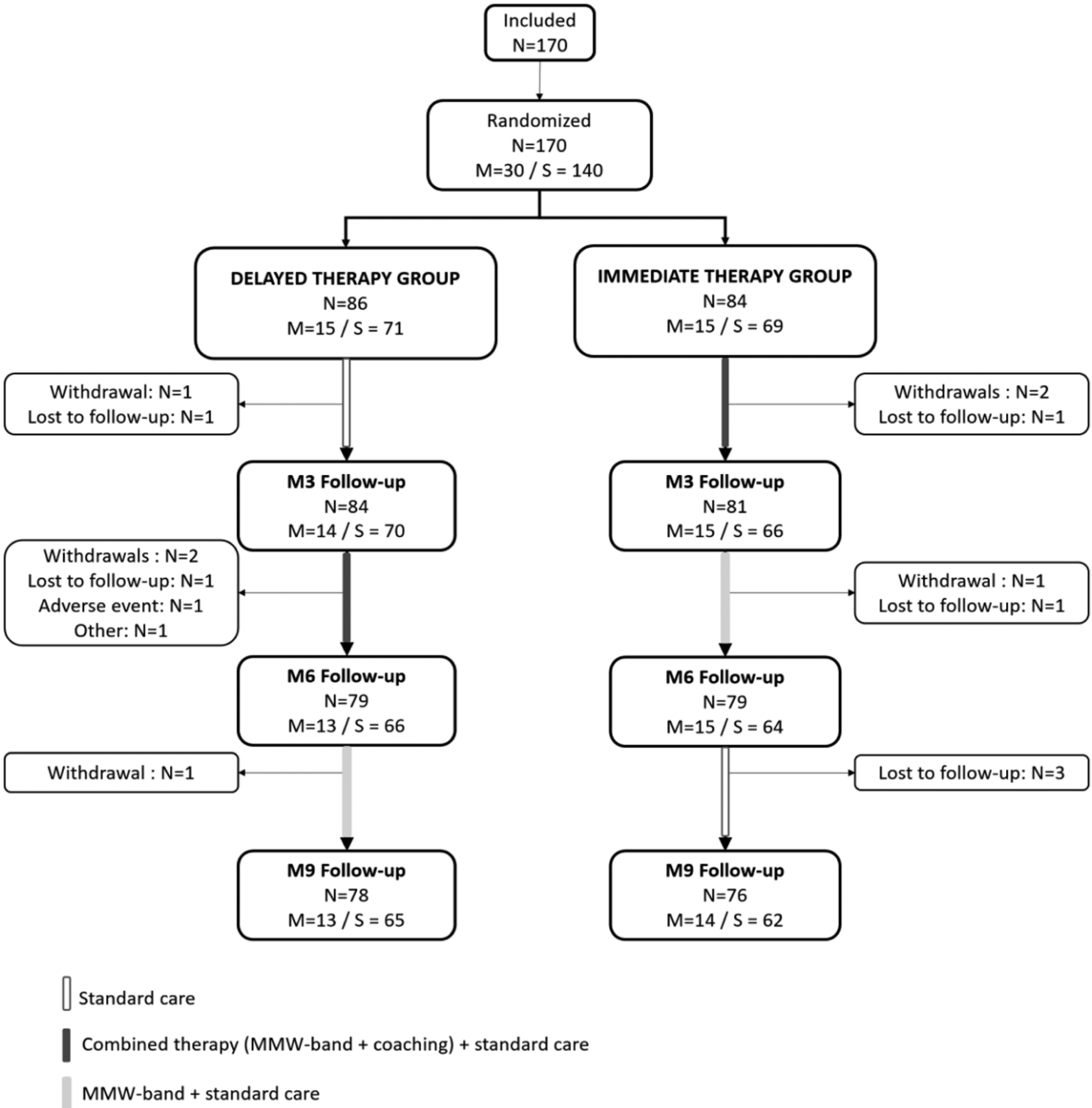


Figure 2. Flowchart. M: FIQ score moderate category; S: FIQ score severe category; M3: 3-month visit; M6: 6-month visit; M9: 9-month visit.

3.2.2. Evolution at M3, M6, and M9. There was a significant time (M3 vs M6 vs M9) *group (Delayed vs Immediate) interaction effect on the average FIQ scores ($P < .001$). Figure 3 displays the evolution of the mean FIQ scores along the time, in both groups. In the Immediate group, scores decreased from D0 (m = 69.3 (sd = 12.5)) to M3 (53.4 (sd = 16.9)) while patients received MMW wristband and coaching and remained stable from M3 to M6 (m = 53 (sd = 17.9)) while patients were using the wristband autonomously. After the wristband was removed from patients, scores increased again from M6 to M9 (m = 62 (sd = 19)), while keeping below their initial level. In the Delayed group, there was slight decrease in FIQ scores from D0 (m = 69.8 (sd = 11.1)) to M3 (m = 64 (sd = 15.5)) while patients were taking treatments as usual, followed by a larger decrease from M3 to M6 (m = 51.2 (sd = 17.7)), when they received wristband and coaching. The scores increased slightly again when this group used the wristband autonomously from M6 to M9 ((m = 55.2 (sd = 20)).

The interaction effect was also significant, with similar patterns, in the analyses by severity categories and in the per protocol populations.

Table 3 presents the values and the significance of the group (Immediate vs Delayed) * time (M3 vs M6 vs M9) interaction effects on the other health dimensions measured. We did not find any significant difference between groups on pain measured in patients' diaries. There was also no significant group effect for: step count, health care visits, pharmaceutical and complementary treatment consumptions, complementary care and psycho-behavioral therapies.

3.2.3. Adherence. Adherence in each group was analyzed from wristband logs. During the 6 months of usage, patients performed a mean of 2.8 sessions per day (sd = 0.9) in the Immediate group, and 2.6 sessions per day (sd = 1) in the Delayed group.

Table 1

Baseline demographic and clinical characteristics at inclusion.

	Delayed group (N = 86)	Immediate group (N = 84)	Total (N = 170)
Age, median [IQI]	49 [42; 54]	49.5 [43; 54]	49 [42; 54]
Gender, n (%)			
Females	83 (96.5%)	79 (94%)	162 (95.3%)
Males	3 (3.5%)	5 (6%)	8 (4.7%)
Height, median [IQI]	163 [158; 168]	165 [158; 170]	163.5 [158; 169]
Weight, median [IQI]	68 [59; 81]	69 [59.5; 83.5]	69 [59; 82]
Professional status, n (%)			
Unemployed	10 (11.8%)	16 (19%)	26 (15.4%)
Employed	36 (42.4%)	29 (34.5%)	65 (38.5%)
Sick leave related to FM	13 (15.3%)	11 (13.1%)	24 (14.2%)
Sick leave unrelated to FM	2 (2.4%)	1 (1.2%)	3 (1.8%)
Disability	16 (18.8%)	18 (21.4%)	34 (20.1%)
Retirement	8 (9.4%)	9 (10.7%)	17 (10.1%)
Missing	1	0	1
Pain score, median [IQI]	7 [5.3; 7.9]	7 [5.9; 8]	7 [5.8; 8]
Missing	1	0	1
FIQ score, mean (sd)	69.7 (11.4)	69.5 (12.3)	69.6 (11.8)
Missing*	2	3	5
FIQ category score, n (%)			
Moderate (39 ≤ FIQ score < 59)	15 (17.4%)	15 (17.9%)	30 (17.6%)
Severe (FIQ score ≥ 59)	71 (82.6%)	69 (82.1%)	140 (82.4%)
Comorbidities, n (%)			
Osteoarthritis	40 (46,5%)	32 (38.1%)	72 (42.4%)
Endometriosis (only for women)	12 (14.5%)	9 (11%)	21 (13%)
	n = 83	n = 79	n = 162
Hypothyroidism	9 (10.5%)	9 (10.7%)	18 (10.6%)
Hyperthyroidism	1 (1.2%)	1 (1.2%)	2 (1.2%)
Diabetes	2 (2.3%)	3 (3.6%)	5 (2.9%)
Gougerot-Sjögren syndrome	1 (1.2%)	4 (4.8%)	5 (2.9%)
Ankylosing spondylitis	1 (1.2%)	0 (0%)	1 (0.6%)
Others	34 (39.5%)	31 (36.9%)	65 (38.2%)
Upper-limbs paresthesia and/or allodynia at inclusion, n (%)	71 (82.6%)	73 (86.9%)	144 (84 .7%)
Of which:			
Tingling, n(%)	63 (88.7%)	68 (93.2%)	131 (91%)
Stinging, n(%)	50 (70.4%)	56 (76.7%)	106 (73.6%)
Numbness, n(%)	65 (91.5%)	66 (90.4%)	131 (91%)
Other, n(%)	25 (35.2%)	18 (24.7%)	43 (29.9%)

IQI = Inter-Quartile Interval; sd = standard-déviation.

*Note: FIQ severity categorization of the 5 patients with FIQ missing data has been estimated based on available data.

3.2.4. Safety. A total of 65 adverse events (AEs) with a causal relationship with therapy being either *possible*, *probable* or definite (i.e., *related*)) occurred on 51 different patients during this study (Table 4). Twenty-nine (44.6%) AEs were found to be *related*, all were nonserious and the most frequent were sensation of heat, local wrist pain or general pain, headaches, paresthesia, sleepiness/intense fatigue, hot flushes, and nausea. The sensation of heat is directly linked to the activation of the wristband, coupled with hypersensitivity/allodynia in FM patients. The other adverse effects reported, are commonly observed with noninvasive neuromodulation techniques such as TENS and tDCS.[40–42] 2 patients with a medical history of severe depression experienced a total of 3 serious AEs (severe depressive episodes), and a causal relationship with the treatment was found to be *possible*.

3.2.5. Therapy usability and satisfaction. Detailed results of the usability assessment of the wristband measured by the modular evaluation of key components of user experience questionnaire and therapy satisfaction are available in Data S3, Supplemental Digital Content, http://links.lww.com/MD/O455 and Data S4, Supplemental Digital Content, http://links.lww.com/MD/O455, respectively. Global judgment of wristband's user experience by patients was similar in both groups with a median assessment of 4 [3; 4.5] (where –5 is bad and 5 is good). The median assessments of satisfaction were: device: 80 [70; 95], application: 82.5 [70; 99] and coaching: 99 [90; 100] (with 0: very bad; 100: very good).

4. Discussion

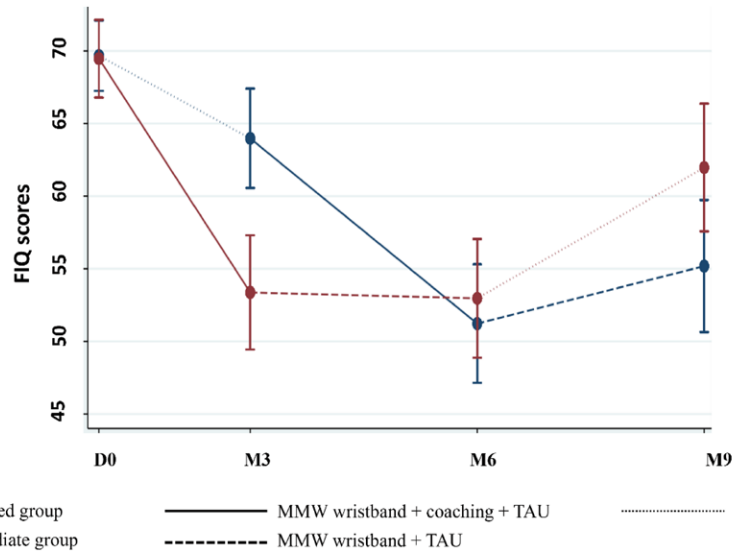
In this trial, FM patients were followed for 9 months. The first 3 months were intended to compare the efficacy of a therapy combining MMW-based neuromodulation and coaching in addition to standard care, as measured by patients' QoL at a clinically significant level, compared to standard care alone. We found that the proportion of patients improving their FIQ score beyond a clinically meaningful threshold after 3 months was significantly larger in the group using the therapy compared to the control group. Specifically, the proportions of patients with a FIQ improvement ≥ 14% and < 30% were 15.9% in the Immediate group and 24.4% in the Delayed group, a FIQ improvement ≥ 30% and < 45% were 24.6% in the Immediate group and 5.1% in the Delayed group, a FIQ improvement ≥ 45% were 14.5% in the Immediate group and 6.4% in the Delayed group. In addition, the group using the therapy also improved significantly on sleep quality, pain intensity, anxiety and depression, general and physical fatigue compared to the control group at M3. Corroborating these results, 75% of patients in the group using the therapy considered their condition improved (28.9% much and very much improved),

Table 2

Secondary outcomes—Group comparisons at M3.

	D0		M3		
	Delayed	**Immediate**	**Delayed**	**Immediate**	***P* value**
Sleep (PSQI)	n = 77 12.1 (4.3)	n = 67 12.6 (3.5)	n = 77 **12.2 (4.2)**	n = 67 **10.3 (3.5)**	**<10-3**
Pain (consultation VAS)	n = 82 6.5 (1.5)	n = 81 6.5 (1.8)	n = 82 **6.3 (1.8)**	n = 81 **5.7 (1.9)**	**.030**
Anxiety (HAD)	n = 79 11.4 (3.6)	n = 75 11.8 (4.5)	n = 79 **10.4 (3.7)**	n = 75 **9.6 (4.1)**	**.034**
Depression (HAD)	n = 80 9.8 (4)	n = 74 9.9 (3.9)	n = 80 **9.3 (4)**	n = 74 **8.3 (4.3)**	**.023**
General fatigue (MFI20)	n = 65 16.9 (2.9)	n = 52 17 (2.7)	n = 65 **16.6 (2.4)**	n = 52 **15.6 (2.8)**	**.015**
Physical fatigue (MFI20)	n = 62 15.8 (3.1)	n = 53 15.8 (2.8)	n = 62 **15.7 (3.1)**	n = 53 **14.4 (2.7)**	**.007**
Mental fatigue (MFI20)	n = 70 13.4 (3.5)	n = 58 14.2 (2.9)	n = 70 13.2 (3.7)	n = 58 12.6 (3.9)	.062
Activity reduction (MFI20)	n = 69 12.7 (3.9)	n = 58 13.1 (3.5)	n = 69 12.5 (3.7)	n = 58 11.7 (3.4)	.059
Motivation reduction (MFI20)	n = 68 12.3 (3.2)	n = 59 12.5 (3.1)	n = 68 11.9 (3.6)	n = 59 11.5 (3)	.375
QoL (EQ-5D-5L)	n = 81 0.5 (0.2)	n = 79 0.6 (0.2)	n = 81 0.6 (0.2)	n = 79 0.7 (0.2)	.325
Physical activity (GPAQ)	n = 80 2022.5 (2455.4)	n = 72 1586.9 (2001.9)	n = 80 2558.3 (3847.3)	n = 72 2253.9 (3882.5)	.791

Values are represented as means (standard-deviations). Bold values represent statistically significant differences between the Immediate and Delayed groups, for each of the health dimensions measured at M3 adjusted on D0.



Delayed group	69.8 (11.1) n = 84 missing = 2	64 (15.5) n = 84 missing = 5	51.2 (17.7) n = 79 missing = 7	55.2 (20) n = 78 missing = 4
Immediate group	69.3 (12.5) n =81 missing = 3	53.4 (16.9) n = 81 missing = 10	53 (17.9) n = 79 missing = 5	62 (19) n = 76 missing = 4

Figure 3. Evolution of the mean FIQ scores over time. Error bars represent 95% confidence intervals. Numerical values are means (SDs). Missing data refer to FIQ questionnaires for which FIQ total scores could not be computed. MMW: millimeter waves; TAU: treatments as usual.

Table 3

Secondary outcomes – evolution at M3, M6, and M9.

	D0		M3		M6		M9	
	Delayed N = 84	Immediate N = 81	Delayed N = 84	Immediate N = 81	Delayed N = 79	Immediate N = 79	Delayed N = 78	Immediate N = 76
Sleep (PSQI)***	12.2 (4.3)	12.5 (3.6)	12.1 (4.1)	10.5 (3.6)	10 (3.7)	10.4 (4.1)	10.3 (4.2)	12.4 (4.1)
missing values	5	6	5	11	1	4	4	4
Pain (consultation VAS)**	6.5 (1.6)	6.5 (1.8)	6.3 (1.8)	5.7 (1.9)	5.5 (2.2)	5.7 (2)	5.8 (2.2)	6.3 (2)
missing values	1	0	1	0	0	2	0	1
Anxiety (HAD)***	11.4 (3.6)	11.5 (4.4)	10.4 (3.7)	9.6 (4.1)	8.9 (4.1)	9.8 (3.9)	9.1 (4.1)	10.7 (4.3)
missing values	4	0	3	6	0	2	2	2
Depression (HAD)***	9.8 (4.1)	10.1 (3.9)	9.3 (4)	8.3 (4.3)	7.8 (4.4)	8.1 (4.4)	8 (4.6)	9.8 (4.6)
missing values	2	1	3	7	0	2	2	2
General fatigue (MFI)**	16.9 (2.8)	17 (2.7)	16.6 (2.3)	15.5 (3)	14.8 (3.3)	15.5 (2.7)	15.3 (3.2)	16.2 (2.8)
missing values	12	16	13	16	5	11	7	10
Physical fatigue (MFI)***	15.8 (3.1)	15.9 (2.7)	15.7 (3)	14 (2.7)	13.8 (3.1)	14.9 (2.8)	14.2 (3.4)	15.2 (2.9)
missing values	15	17	14	18	11	14	9	10
Mental fatigue (MFI)***	13.3 (3.4)	14 (3)	13.1 (3.6)	12.7 (3.8)	12.4 (3.5)	13.2 (3.3)	12.2 (3.9)	14.2 (2.9)
missing values	9	14	10	13	10	13	8	6
Activity reduction (MFI)**	12.5 (3.8)	13.2 (3.5)	12.6 (3.8)	11.7 (3.4)	11.7 (3.8)	12.1 (3)	11.5 (4)	13 (3.6)
missing values	8	10	12	18	12	11	7	8
Motivation reduction (MFI)**	12.3 (3.1)	12.7 (3.3)	12 (3.8)	11.4 (3.1)	11.2 (4.1)	11.6 (3.3)	11.5 (3.6)	13.2 (3.8)
missing values	8	11	12	16	9	10	5	8
Generic QoL (EQ-5D-5L)*	.5 (.2)	.6 (.2)	.6 (.2)	.7 (.2)	.7 (.2)	.7 (.2)	.7 (.2)	.6 (.2)
missing values	2	1	1	1	1	2	0	1
Physical activity (GPAQ)ns	2557.5 (5398.2)	1572 (1966.9)	2526.7 (3833.7)	2223 (3864.5)	2497.2 (2923.2)	1845.5 (2423.6)	2713.2 (5634.6)	1418.1 (2278.1)
missing values	3	1	3	8	0	3	2	2
Clinician's Global Impression of change (CGIC)								
Very much worse, n (%)	–	–	2 (2.4%)	1 (1.2%)	1 (1.3%)	0 (0%)	0 (0%)	4 (5.3%)
Much worse, n (%)	–	–	9 (10.8%)	2 (2.5%)	3 (3.8%)	6 (7.6%)	5 (6.4%)	18 (23.7%)
A little worse, n (%)	–	–	23 (27.7%)	4 (4.9%)	8 (10.1%)	8 (10.1%)	11 (14.1%)	23 (30.3%)
Unchanged, n (%)	–	–	35 (42.2%)	18 (22.2%)	11 (13.9%)	16 (20.3%)	21 (26.9%)	16 (21.1%)
Little improved, n (%)	–	–	10 (12%)	28 (34.6%)	31 (39.2%)	29 (36.7%)	26 (33.3%)	9 (11.8%)
Much improved, n (%)	–	–	4 (4.8%)	25 (30.9%)	20 (25.3%)	18 (22.8%)	11 (14.1%)	4 (5.3%)
Very much improved, n (%)	–	–	0 (0%)	3 (3.7%)	5 (6.3%)	1 (1.3%)	4 (5.1%)	1 (1.3%)
missing values	–	–	1	0	0	0	0	0
Patient's Global Impression of change (PGIC)								
Very much worse, n (%)	–	–	1 (1.2%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	1 (1.3%)	7 (9.3%)
Much worse, n (%)	–	–	8 (9.9%)	2 (2.6%)	2 (2.6%)	2 (2.6%)	3 (3.9%)	22 (29.3%)
A little worse, n (%)	–	–	23 (28.4%)	6 (7.9%)	2 (2.6%)	5 (6.6%)	5 (6.6%)	24 (32.0%)
Unchanged, n (%)	–	–	39 (48.1%)	10 (13.2%)	7 (9.0%)	10 (13.2%)	12 (15.8%)	14 (18.7%)
Little improved, n (%)	–	–	9 (11.1%)	35 (46.1%)	37 (47.4%)	35 (46.1%)	33 (43.4%)	2 (2.7%)
Much improved, n (%)	–	–	1 (1.2%)	20 (26.3%)	24 (30.8%)	22 (28.9%)	16 (21.1%)	6 (8.0%)
Very much improved, n (%)	–	–	0 (0%)	2 (2.6%)	5 (6.4%)	2 (2.6%)	6 (7.9%)	0 (0.0%)
missing values	–	–	3	5	1	3	2	1

Values are represented as means (sd), except for PGIC and CGIC represented as effectives and percentages. Regarding impression of change, there was 63.2% agreement between clinicians and patients in the Immediate group and 67.9% in the Delayed group at M3.

EQ-5D-5L = EuroQol group 5 Dimensions 5 Levels, GPAQ = Global Physical Activity Questionnaire, HAD = Hospital Anxiety Depression scale, MFI = Multidimensional Fatigue Inventory, ns = non-statistically significant, PSQI = Pittsburgh sleep quality index, VAS = Visual Analogical Scale.

*** The statistical significance of the interaction effects between time (M3 vs M6 vs M9) and groups (Immediate vs Delayed) with *P*-values < .001.

** The statistical significance of the interaction effects between time (M3 vs M6 vs M9) and groups (Immediate vs Delayed) with *P* values < .01.

* The statistical significance of the interaction effects between time (M3 vs M6 vs M9) and groups (Immediate vs Delayed) with *P* values < .05.

compared to 12.3% in the control group. From the blinded-clinician perspective, 69.2% versus 16.8% patients improved in the group using the therapy and the control group respectively. On the other hand, there were no significant differences between groups on generic QoL, mental fatigue, reduction of activities or motivation, pharmaceutical and complementary treatment intakes, nor healthcare consumption, or physical activity. These dimensions might require more than 3 months to evolve in a significant manner.

The longitudinal follow-up of this study was intended (i) to study the capacity of the patients to use the device autonomously, i.e., without coaching, and see the sustainability of the improvements in these conditions, and in a subsequent phase (ii) to study the persistence of benefits once the device was taken away from patients. Post hoc analyses investigating the number of adherent patients (i.e., performing ≥ 2 sessions/day on 80% of a 3-month period) showed that the proportion of adherent patients dropped from 72% in the phase with coaching to 37.6% in the phase without coaching (please note that this is an "intention-to-treat" analysis with a denominator counting all patients included in the trial, regardless of their status at the end of the wristband's period of use). However, FIQ scores were preserved together with patients' impression of change, with 77.6% of patients assessing their condition as improved at M6 in the Immediate group. Patients of the Delayed group received therapy with coaching at M3, and 84.6% assessed their health as improved at M6, while their FIQ scores reduced in a way similar to the Immediate group from D0 to M3. After using the therapy autonomously, 72.4% patients of the Delayed group assessed their health as improved at M9. These results show that usage without coaching indeed deviated from recommendations but was sufficient for patients to find benefits. On the

Table 4

Adverse events.

	Delayed n = 84	Immediate n = 81	All n = 165
Patients reporting 1 AEs or SAEs, n (%)	21 (25%)	17 (21%)	38 (23%)
Patients reporting 2 AEs or SAEs, n (%)	7 (8.3%)	5 (6.2%)	12 (7.3%)
Patients reporting 3 AEs or SAEs, n (%)	1 (1.2%)	0 (0%)	1 (0.6%)
Total	29 (34.5%)	22 (27.2%)	51 (30.9%)

Events depending on causality and severity

	AEs	SAEs	AEs	SAEs	AEs	SAEs
Related	19 (50%)	0 (0%)	10 (37%)	0 (0%)	29 (44.6%)	0 (0%)
Probable	8 (21.1%)	0 (0%)	7 (25.9%)	0 (0%)	15 (23.1%)	0 (0%)
Possible	9 (23.7%)	2 (5.3%)	9 (33.3%)	1 (3.7%)	18 (27.7%)	3 (4.6%)
	36 (94.7%)	**2 (5.3%)**	**26 (96.3%)**	**1 (3.7%)**	**62 (95.4%)**	**3 (4.6%)**

Causality: Possible: The relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible. Probable: The relationship with the use of the device seems relevant and/or the event cannot be reasonably explained by another cause. Related: the adverse event is associated with the device beyond reasonable doubt.
AEs = adverse events, SAEs = serious adverse events.

other hand, once the wristband had been removed from patients of the Immediate group, their condition declined (FIQ scores increased) and 70.6% patients assessed their QoL as worse at M9 than at M6. This may be related to the inter-individual variability of symptoms and their severity, as well as the presence of comorbidity. The management of nociplastic pain is a long-term process and, as recommended by EULAR, must be part of an individualized, multidisciplinary approach.[43]

Our choice to introduce coaching in combination with the MMW device was in anticipation of chronic patients' poor adherence to recommended treatment.[23,44] While digital interventions can be very effective in helping patients, a meta-analysis showed a 62% enhancement of effect size with the occasional assistance of a healthcare professional compared to an intervention without a healthcare professional.[45] With respect to adherence, our population was roughly split into 3 equal parts: those who failed to adhere even with coaching, those who were adherent with coaching but not without it, and finally those who remained adherent even without coaching. The program could be improved by identification of the patients who need sustained coaching, and reinforced support for those who could not adhere even with coaching.

The mean FIQ reduction in the Immediate group in comparison to the control group at M3 corresponds to a moderate effect size (Cohen's d = –0.62, favoring treatment). The estimated number needed to treat was 6 patients and the safety assessment reported only nonserious treatment-related AEs. These outcomes in terms of benefits and risks are in line with other non-pharmacological treatments available for the management of FM, as reported in a recent meta-analysis.[46] Kundacki et al (2022)[46] reviewed 163 trials assessing non-pharmacological treatments, spread across 20 categories (physical exercise, psychological therapies, balneotherapy, transcranial direct current stimulation, electrotherapy, multidisciplinary therapies, etc). Their focus was on studies assessing nonpharmacological interventions versus usual care, waiting list, no treatment, placebo/sham treatment and using the FIQ as quality-of-life outcome. They found an average effect size of –0.63 (95%CI: [–0.75; –0.51]. Only 8/20 categories of non-pharmacological interventions used placebo/sham controls.

In the Immediate group, 52.7% patients switched from the severe to the moderate FIQ severity category between D0 and M3, compared to 28.1% in the Delayed group. This is of relevance considering that Perrot et al (2012)[47] showed that as FM severity level worsened, patients had poorer overall health, perceived their prescription medications to be less effective and that the average cost/FM patient tended to increase.

One limitation of our study is the absence of a placebo-control group, made difficult to implement due to the introduction of coaching in the therapy. While the placebo effect cannot be ruled out from the factors promoting benefits in our trial, the sustainability of the benefits from M3 to M6 in the Immediate group is evidence in favor of the efficacy of MMW treatment. Indeed, a 6-month study assessing the durability of pregabalin's meaningful relief in FM patients showed that half the placebo group had loss of therapeutic response by Day 19, while half the pregabalin group still continued to respond by trial end.[48] In addition, our results have been obtained in comparison to standard care, and showed no effect of treatment center, which suggests good standardization of the procedure, including coaching.

In the Delayed group, patients received the therapy at M3, just after measurement of the primary outcome. We found a FIQ reduction ≥ 14% for 35.9% patients in this group at M3. It is possible that the anticipation of receiving a new therapy that day positively biased the results of patients from the Delayed group. Another explanation for this rather high proportion of clinically improved patients may lie in the Hawthorne effect, especially in a study design involving trained coaches.

The change in pain level in the Immediate group at M3, though statistically different from the control group, did not reach the minimal clinically important difference from D0 (12.3% decrease in pain for patients of the Immediate group from D0 to M3 vs a minimal clinically important difference of 30%–35%[49]). Patients' impression of improvement after using the therapy in the absence of a clinically significant decrease in their pain level might reflect their saying that "pain is still present but less overwhelming." Since endorphins play a role in mood regulation[50–52] and in the view that chronicity renders the pain less somatic and more affective in nature,[53,54] one might ask if the general impression of improvement in their condition could be due to reduced feelings of depression and anxiety.

5. Conclusion

The therapy assessed in this study is in line with recommendations of non-pharmacological treatments for the management of FM. It provides a device and training that allow patients to be autonomous and mobile in managing their condition. The efficacy in reducing the impact of FM on QoL after 3 months of

usage is comparable to non-pharmacological therapies and may be easier to implement in patients' lives.

Showing benefits on several dimensions, while presenting very limited side effects, it could be added to the therapeutic armamentarium, as a part of a multidisciplinary approach to the improvement of FM patients' QoL.

Acknowledgements

We are grateful to the following investigators and coaches who contributed to the Fibrepik study: G. Lalami, V. Paran, M. Proust, S. Uneisi (Grenoble), L. Habibeddine, Z. Halimi, J. Lebail, S. Magne, Paradisi-Prieur, S. Slimane, M. Thieux, (Villeurbane), K. Laval, P. Olive, (Montpellier), F. Taurel (Mornant), T. Leclerq, S. Velliet, M. Verhaeghe (Valenciennes), F. Krichen, S. Ma, A. Martin, K. Merlin (Suresnes-Foch), C. Bulté, U. Traore-Ouattara, (Rouen), M. Ghrissi, Meng Lang (Paris-Lariboisière).

Author contributions

Conceptualization: David Crouzier.
Formal analysis: Mélanie Véloso.
Investigation: Caroline Maindet, Anne Dumolard, Mario Barmaki, Alberta Lorenzi-Pernot, Raphaël Gonon-Demoulian, Patrick Ginies, Frédéric Viseux, Antoine Lemaire, Mireille Michel-Cherqui, Rodrigue Deleens, Alain Serrie.
Methodology: Anne Dumolard, Jean-Luc Bosson.
Project administration: Emilie Chipon, David Crouzier.
Resources: Laure Minier, Emilie Chipon.
Supervision: Caroline Maindet, Jean-Luc Bosson, David Crouzier.
Validation: Caroline Maindet, Jean-Luc Bosson.
Writing – original draft: Laure Minier.
Writing – review & editing: Caroline Maindet, Emilie Chipon, Mélanie Véloso, Anne Dumolard, Mario Barmaki, Alberta Lorenzi-Pernot, Raphaël Gonon-Demoulian, Patrick Ginies, Frédéric Viseux, Antoine Lemaire, Mireille Michel-Cherqui, Rodrigue Deleens, Alain Serrie, Jean-Luc Bosson, David Crouzier.

References

[1] Bidari A, Ghavidel-Parsa B. Nociplastic pain concept, a mechanistic basis for pragmatic approach to fibromyalgia. Clin Rheumatol. 2022;41:2939–47.
[2] Pinto AM, Luís M, Geenen R, et al. Neurophysiological and psychosocial mechanisms of fibromyalgia: a comprehensive review and call for an integrative model. Neurosci Biobehav Rev. 2023;151:105235.
[3] Häuser W, Brähler E, Ablin J, Wolfe F. Modified 2016 American College of Rheumatology fibromyalgia criteria, the analgesic, anesthetic, and addiction clinical trial translations innovations opportunities and Networks-American Pain Society Pain Taxonomy, and the Prevalence of Fibromyalgia. Arthritis Care Res (Hoboken). 2021;73:617–25.
[4] Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315:1624–45.
[5] Martinez JE, Guimarães I. Fibromyalgia – are there any new approaches?. Best Pract Res Clin Rheumatol. 2024;38:101933.
[6] Goldfarb AH, Jamurtas AZ. β-Endorphin response to exercise. Sports Med. 1997;24:8–16. https://doi.org//10.2165/00007256-199724010-00002
[7] Vescovi PP, Coiro V. Hyperthermia and endorphins. Biomed Pharmacother. 1993;47:301–4.
[8] Kaada B, Torsteinbø O. Increase of plasma beta-endorphins in connective tissue massage. Gen Pharmacol. 1989;20:487–9.
[9] Jussila A, Huotari-Orava R, Ylianttila L, Partonen T, Snellman E. Narrow-band ultraviolet B radiation induces the expression of β-endorphin in human skin *in vivo*. J Photochem Photobiol B. 2016;155:104–8.
[10] Langhorst J, Musial F, Klose P, Haüser W. Efficacy of hydrotherapy in fibromyalgia syndrome—a meta-analysis of randomized controlled clinical trials. Rheumatology. 2009;48:1155–9. https://doi.org//10.1093/rheumatology/kep182
[11] Maindet C, Maire A, Vermorel C, et al. Spa therapy for the treatment of fibromyalgia: an open, randomized multicenter trial. J Pain. 2021;22:940–51.
[12] Deare J, Zheng Z, Xue C, et al. Acupuncture for treating fibromyalgia. Cochrane Database Syst Rev. 2013;5:1–92.
[13] Langhorst J, Klose P, Dobos GJ, Bernardy K, Häuser W. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int. 2013;33:193–207.
[14] Radzievsky AA, Gordiienko OV, Alekseev S, Szabo I, Cowan A, Ziskin MC. Electromagnetic millimeter wave induced hypoalgesia: frequency dependence and involvement of endogenous opioids. Bioelectromagnetics. 2008;29:284–95.
[15] Radzievsky AA, Rojavin MA, Cowan A, Alekseev SI, Radzievsky AAJ, Ziskin MC. Peripheral neural system involvement in hypoalgesic effect of electromagnetic millimeter waves. Life Sci. 2001;68:1143–51.
[16] Partyla T, Hacker H, Edinger H, Leutzow B, Lange J, Usichenko T. Remote effects of electromagnetic millimeter waves on experimentally induced cold pain: a double-blinded crossover investigation in healthy volunteers. Anesth Analg. 2017;124:980–5.
[17] Holaday JW. Cardiovascular effects of endogenous opiate systems. Annu Rev Pharmacol Toxicol. 1983;23:541–94.
[18] Pilozzi A, Carro C, Huang X. Roles of β-endorphin in stress, behavior, neuroinflammation, and brain energy metabolism. Int J Mol Sci. 2021;22:338.
[19] Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet (London, England). 2021;397:2098–110.
[20] Korpan NN, Saradeth T. Clinical effects of continuous microwave for postoperative septic wound treatment: a double-blind controlled trial. Am J Surg. 1995;170:271–6.
[21] Moazezi Z, Hojjati SMM, Ayrapetyan S. Low intensity millimeter wave as a potential tool in treatment of diabetic sensorymotor polyneuropathy. Int Dental Med Disorders. 2008;1:50–5.
[22] Bakaliuk TG, Zoria LV, Pogorila MA. Microwave resonance therapy in primary osteoarthrosis: the pathogenetic validation of its clinical use. Patol Fiziol Eksp Ter. 1998;4:22–5.
[23] Sabaté E, Organization WH. Adherence to Long-Term Therapies: Evidence for Action. Geneva: World Health Organization; 2003.
[24] Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implementation Sci. 2011;6:42.
[25] Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol. 2005;23:S154–62.
[26] Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol. 2009;36:1304–11.
[27] Chipon E, Bosson JL, Minier L, et al. A drug free solution for improving the quality of life of fibromyalgia patients (Fibrepik): study protocol of a multicenter, randomized, controlled effectiveness trial. Trials. 2022;23:740.
[28] Ninot G. Non-Pharmacological Interventions: An Essential Answer to Current Demographic, Health, and Environmental Transitions. Montpellier, France: Springer International Publishing; 2021.
[29] Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46:319–29.
[30] Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: classification and criteria changes. World Psychiatry. 2013;12:92–8.
[31] Minier L, Debouzy JC, Foerster M, Pierre V, Maindet C, Crouzier D. Hypoalgesia and parasympathetic effects of millimeter waves on experimentally induced pain in healthy volunteers. Electromagn Biol Med. 2023;42:3–11.
[32] Perrot S, Dumont D, Guillemin F, Pouchot J, Coste J, French Group for Quality of Life Research. Quality of life in women with fibromyalgia syndrome: validation of the QIF, the French version of the fibromyalgia impact questionnaire. J Rheumatol. 2003;30:1054–9.
[33] Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.
[34] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
[35] Smets EMA, Garssen B, Bonke B, De Haes JCJM. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39:315–25.
[36] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–36.
[37] Armstrong T, Bull F. Development of the world health organization global physical activity questionnaire (GPAQ). J Public Health. 2006;14:66–70.

[38] Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther. 2004;27:26–35.
[39] Busner J, Targum SD. The clinical global impressions scale. Psychiatry (Edgmont). 2007;4:28–37.
[40] Dailey DL, Vance CGT, Rakel BA, et al. Transcutaneous electrical nerve stimulation reduces movement-evoked pain and fatigue: a randomized, controlled trial. Arthritis Rheumatol. 2020;72:824–36.
[41] Lloyd DM, Wittkopf PG, Arendsen LJ, Jones AKP. Is transcranial direct current stimulation (tDCS) effective for the treatment of pain in fibromyalgia? A systematic review and meta-analysis. J Pain. 2020;21:1085–100.
[42] Samartin-Veiga N, Pidal-Miranda M, González-Villar AJ, et al. Transcranial direct current stimulation of 3 cortical targets is no more effective than placebo as treatment for fibromyalgia: a double-blind sham-controlled clinical trial. Pain. 2022;163:e850–61.
[43] Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76:318–28.
[44] Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review. Acta Anaesthesiol Scand. 2016;60:416–31.
[45] Versluis A, Verkuil B, Spinhoven P, van der Ploeg MM, Brosschot JF. Changing mental health and positive psychological well-being using ecological momentary interventions: a systematic review and meta-analysis. J Med Internet Res. 2016;18:e152.
[46] Kundakci B, Kaur J, Goh SL, et al. Efficacy of nonpharmacological interventions for individual features of fibromyalgia: a systematic review and meta-analysis of randomised controlled trials. Pain. 2022;163:1432–45.
[47] Perrot S, Schaefer C, Knight T, Hufstader M, Chandran AB, Zlateva G. Societal and individual burden of illness among fibromyalgia patients in France: association between disease severity and OMERACT core domains. BMC Musculoskelet Disord. 2012; 13:22.
[48] Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain. 2008;136:419–31.
[49] Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. J Orthop Surg Res. 2015;10:24.
[50] Hegadoren KM, O'Donnell T, Lanius R, Coupland NJ, Lacaze-Masmonteil N. The role of β-endorphin in the pathophysiology of major depression. Neuropeptides. 2009;43:341–53.
[51] Rojas-Corrales MO, Berrocoso E, Gibert-Rahola J, Micó JA. Antidepressant-like effect of tramadol and its enantiomers in reserpinized mice: comparativestudy with desipramine, fluvoxamine, venlafaxine and opiates. J Psychopharmacol. 2004;18:404–11.
[52] Peter L, Tenore MDF. Psychotherapeutic benefits of opioid agonist therapy. J Addict Dis. 2008;27:49–65.
[53] Mansour AR, Farmer MA, Baliki MN, Apkarian AV. Chronic pain: the role of learning and brain plasticity. Restor Neurol Neurosci. 2014;32:129–39.
[54] McCarberg B, Peppin J. Pain pathways and nervous system plasticity: learning and memory in pain. Pain Med. 2019;20:2421–37.