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Spa Therapy for the Treatment of Fibromyalgia: An Open, Randomized Multicenter Trial

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Abstract: **Fibromyalgia is a common chronic pain pathology with an incidence of 4.3 per 1,000 person-years. An open, randomized clinical trial of patients with fibromyalgia comparing an immediate vs. delayed 18-day spa therapy in five spa therapy care facilities in France enrolled 220 patients. Randomization was in blocks of four, stratified by center, severity of fibromyalgia and previous spa therapy. Patients continued usual treatment. The main endpoint was the number of patients achieving minimal clinically important difference at 6 months, defined as 14% change in their baseline fibromyalgia impact questionnaire score. The intention-to-treat analysis included 100 and 106 patients in the intervention and control groups, respectively. At 6 months, 45/100 (45.0%) and 30/106 (28.3%) patients in the intervention and control groups, respectively, achieved a minimal clinically important difference (*P*= .013). There was also a significant improvement in pain, fatigue, and symptom severity (secondary outcomes) in the intervention group but not for generic quality of life (QOL), sleep or physical activity. None of the 33 serious adverse events reported by 25 patients were related to the spa therapy. Our results demonstrate the benefit of spa treatment in patients with fibromyalgia.**

Perspective: ***A 12-month, open, randomized clinical trial of 220 patients with fibromyalgia compared an immediate versus delayed (ie, after 6 months) 18-day spa therapy. The results showed a clinically significant improvement at 6 months for those who received immediate therapy which was maintained up to 12 months.***

Trial registration number: ***ClinicalTrials.gov: NCT02265029***

Key Words: *Fibromyalgia, spa treatment, pain measurement, patient satisfaction, treatment outcome.*

Fibromyalgia syndrome is a common chronic pain condition, which is usually diagnosed in patients aged 30 and 50 years.[10,39] The incidence of physician-diagnosed fibromyalgia in the general population is 4.3 per 1,000 person-years (range = 0.33-18.8) with about seven-times more women than men being affected. The physiopathology is not fully understood and there are no specific somatic signs. The

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International Association for the Study of Pain and American College of Rheumatology define fibromyalgia as chronic widespread pain, lasting for at least three months, without any apparent tissue damage or inflammation.[38] However, recent research suggest that fibromyalgia pain could be due to central nervous system sensitization, peripheral small fiber neuropathy or impaired cell-mediated immunity.[8,11,15,16,21,29,32,37]

The chronic pain is associated with fatigue, waking up without feeling rested, sleep disorders, cognitive disorders, other frequent general symptoms (eg, tension headaches, irritable bowel syndrome, pain in the temporo-mandibular joint), anxiety, and depression.[9] Diagnostic criteria include these symptoms, and pain assessment. Diagnosis involves determining a global score combining the number of painful sites (widespread pain index, WPI) and a symptom severity (SS) score.[38]

The fibromyalgia impact questionnaire (FIQ, score 0 to 100) is used to rate the severity of the fibromyalgia in the past week.[6] See the online supplementary for more details. A FIQ score <39 corresponds to a mild form, a score of 39 to 58 corresponds to a moderate form and a score of 59 to 100 corresponds to a severe form. Overall, 12% of patients have mild disease, 69% have a moderate disease and 19% have severe disease.[35]

The heterogeneous symptoms and poorly understood pathogenesis makes treatment for patients with fibromyalgia challenging.[2,12] The European League Against Rheumatism (EULAR) evidence-based guidelines recommend personalized management with a graduated approach adapted to the symptoms of fibromyalgia, shared decision-making, and non-drug therapies as first-line treatment.[26] Physical exercise was the only non-drug therapy with a 'strong' recommendation and other non-drug therapies, including spa therapy, had 'weak' recommendations. Since these guidelines were published results from randomized clinical trials assessing cognitive therapeutic approaches (mindfulness-based stress reduction and attention bias modification), in addition to usual treatment suggest that there is some short-term benefit for pain reduction with these approaches, although the long-term benefit is less certain.[7,31,34]

In Europe, spa therapy is frequently prescribed for patients with painful chronic diseases, such as osteoarthritis. Spa therapy, as practiced in France and other European countries, is a complex therapeutic intervention associating different hydrothermal treatments (such as hydromassage baths, hydro-mineral mud applications, body jet showers, and water affusion massages) with physiotherapy (such as supervised collective exercises in mineral water pools) and education (informal or organized in specific therapeutic programs). For example, the study Thermarthrose reported that a 3-week course of spa therapy together with home exercises and usual pharmacological treatments was beneficial at 6 months in patients with knee osteoarthritis compared with home exercises and usual pharmacological treatments, without spa therapy.[18] Several literature reviews have concluded that spa therapy could provide a small overall improvement in pain and health-related quality of life in patients with fibromyalgia, at least in the short-term, but the evidence is weak, particularly for long-term benefits.[1,5,14,19,20,24,27,30] Therefore, high-quality studies assessing long-term maintenance of the beneficial effects with larger sample sizes are needed to confirm the therapeutic benefit of spa therapy. Here we report results from a randomized clinical trial that aimed to assess the medium- and long-term benefits of spa therapy in patients with fibromyalgia syndrome, using recognized diagnostic criteria.

Methods

Study Design

The trial protocol was approved by the South-East II Ethics Committee (Lyon) on 16 April 2014 (ID: 2014-A00184-43). Patients with fibromyalgia were recruited between September 2014 and September 2017 and randomized to receive immediate or delayed spa therapy in an open randomized clinical trial. Patients were treated in one of the five participating spa therapy care facilities located in Aix-les-Bains, Allevard-les-Bains, Bourbon-Lancy, Lamalou-les-Bains and Uriage-les-Bains in France. Patients were recruited throughout France, either during a consultation with a participating pain or rheumatology specialist (n = 11) in private practice or hospital, through patient associations (pre-screening and transfer to a study physician by the coordination center) or selected by the coordination center via press advertisement or posters in the spa therapy care facilities.

Randomization, prepared by an external organization (ClinInfo, Lyon France), was centralized via an electronic case report form (eCRF) using a fixed block size of 4, stratified for the spa therapy care facility, FIQ score at inclusion <59 or ≥59, and first spa therapy or not.

Patients

Patients were eligible if they gave informed consent, had fibromyalgia for over a year, based on the American College of Rheumatology 2010 criteria,[38] had received stable medical treatment over the previous three months, had a FIQ score ≥ 39 (moderate to severe fibromyalgia), were aged >18 years, were available for the 3-week residential spa therapy within 6 weeks of inclusion (immediate group) or after the 6-month follow-up visit (delayed group), and were available for a 12-month follow-up visit. Exclusion criteria were contra-indication or intolerance to any aspect of the spa treatments (progressive cancer, behavioral disorders, immune deficiency, patient with psychosis on medication or not), rheumatology spa treatment in the current calendar year, changes in pain-related treatments in the previous three months, other known severe chronic diseases, such as severe asthma, severe cardiac, respiratory, hepatic or renal insufficiency, progressive inflammatory rheumatic disease and inflammatory colitis.

Intervention

Eleven investigator centers, located throughout France, not at the spa therapy care facilities, were responsible for recruiting and evaluating the patients. The patients were randomized to either the intervention group and received a 3-week spa therapy (6 d/wk, 18 days total) in one of the five participating spa therapy care facilities within 6 weeks of inclusion to the control group and received the same intervention after they had attended the 6-month study visit.

The spa therapy was standardized in the participating spa therapy care facilities. Each patient received 72 treatments during 2 hours in the morning for 18 days including the following:

1. Hydromassage baths
2. Hydro-mineral mud applications
3. Body jet showers with adjustment of the intensity of jets
4. Water affusion massages
5. Collective exercise in a mineral water pool under supervision of a state-registered physiotherapist

In addition, patients could attend a conference on their disease and weekly walking training sessions, but these activities were not mandatory. The walking training was given by a physical activity (APA) coach or a state-registered physiotherapist, with a progressive program over the 3 weeks. The content of both the conference and training was standardized at all centers. During the 3-week spa therapy the patients also had free access to on-site gym facilities.

The study patients were with other patients undergoing spa therapy. All patients continued to receive their usual treatments. The spa mineral water and treatments were approved and controlled by the French authorities. Attendance, tolerance, and correct use of the treatments was verified by a spa physician during consultations at the start, middle and end of the 3-week spa therapy.

The patients randomized to the delayed spa therapy group followed their usual treatment up to the 6-month follow-up visit when the primary outcome was evaluated. Then they received their 3-week spa therapy. This group was considered as the control group, since the primary outcome was evaluated at the 6-month follow-up visit before they had received the intervention.

Assessments

Efficacy

All patients were evaluated at baseline and followed-up at 3, 6, 9, and 12 months by the study physician who performed a clinical examination and competed the eCRF. At the same time as these visits, the coordinating center sent questionnaires (see below) directly to the patients, with a prepaid return envelope.

The primary endpoint was the percentage of patients with a minimal clinically important difference (MCID) defined as a decrease of more than 14% in their FIQ score at 6 months compared with inclusion.[3,23]

The secondary endpoints were: generic quality of life score measured by EQ-5D-3L[13], patient global assessment (PGA) and investigator global assessment (not the staff at the spa therapy care facilities) (IGA) scales, VAS (visual analogue scale) for pain (score between 0 and 100), pain catastrophizing scale (French version, PCS-CF scale), number of pain points (WPI score), symptom severity (SS) score, sleep (Pittsburgh Sleep Quality Index) and sleepiness (Epworth scale), fatigue (Pichot scale), Hospital Anxiety and Depression Scale (HAD scale), ability to manage a stressful situation (Coping questionnaire), physical activity (Baecke questionnaire), body mass index (BMI), and drug treatment for fibromyalgia. A brief description of the instruments used and their interpretation is given in Table 1.

All questionnaire scores were collected at baseline, and at 3-months, 6-months, 9-months, and 12-months, except for the EQ-5D-3L and Coping questionnaires, which were collected at baseline, and 6- and 12-months.

The VAS pain results were collected every three months up to 12 months from the patients' diaries. These diaries, which were paper-based, were used by the patients to record their physical activity, their treatments and any medical events, as well as the VAS during the 12-month follow-up.

Safety

All serious adverse events (SAEs) were recorded and notified to the French clinical trials pharmacovigilance system.

Sample Size Calculation

We assumed that the success rate in the intervention group would be 50%, ie, that 50% of the patients would achieve a decrease of more than 14% in their FIQ score at 6 months compared with inclusion and that the success rate in the control group would be 30%.[3] With an alpha risk of 5% and power of 80%, the number of patients needed was estimated to be 95 per group.[36] To allow for potential lost-to-follow-up, we included 220 patients, 110 per group.

Statistical Analysis

The statistician was not blinded to the treatment groups. Intention-to-treat analyses were performed. Categorical variables were expressed as frequencies and percentages and continuous variables as means and SDs, or medians and interquartile ranges (IQR; 25^{th} and 75^{th} percentiles). The primary endpoint was assessed using Chi^2 test. Risk ratios with 95% confidence intervals (CIs), odds ratios and 95% CIs, numbers needed to treat (NNT), and effect sizes were calculated. The Mantel-Haenszel test of homogeneity was used for subgroup analyses and results showing an interaction ($P < .20$) are presented here. Two-sided P values less than .05 were considered statistically significant. Analyses were

Table 1. Brief Description of Instruments Used for Primary and Secondary Endpoints

Instrument name (abbreviation)	*Aspect measured*	*Score(min – max)*	*Interpretation*
Fibromyalgia impact questionnaire (FIQ)	Impact of fibromyalgia on current overall health status	0 – 100	Higher scores indicate greater impact
Baecke physical activity questionnaire	Evaluation of level of physical activity	3 – 15	Higher scores indicate higher levels of physical actitivites
Coping questionnaire - stress	Patient's ability to manage a stressful situation	10 – 40	Higher scores indicate greater difficult to manage a stressful situation
Coping questionnaire - emotions	Patient's ability to manage their emotions in a stressful situation	9 – 36	Higher scores indicate greater difficult to manage emotions in a stressful situation
Coping questionnaire - social support	Patient's need for social support to manage a stressful situation	8 – 32	Higher scores indicate greater need for social support to manage a stressful situation
Epworth sleepiness score	Evaluation of patient's sleepiness	0 – 24	Higher scores indicate more sleepiness
EQ-5D-3L score	Generic quality of life	-0.53 – 1	Higher scores indicate better quality of life
EQ5D-3L perceived health	Generic quality of life	0 – 100	Higher scores indicate better perceived health status
Hospital anxiety and depression scale – anxiety (HADS– anxiety)	Evaluation of anxiety	0 – 21	Higher scores indicate higher anxiety
Hospital anxiety and depression scale – depression (HADS– depression)	Evaluation of depression	0 – 21	Higher scores indicate greater depression
Investigator global assessment (IGA)	Investigator-perceived overall health	0 – 10	Lower scores indicate good perception of overall health
Pain catastrophizing scale - French version (PCS-CF)	Quantification of an individual's pain experience	0 – 52	Higher scores indicate worse experience of pain
Pain visual analog scale (Pain VAS)	Overall evaluation of pain	0 – 100	Higher scores indicate worse pain
Patient global assessment (PGA)	Patient-perceived overall health	0 – 10	Lower scores indicate good perception of overall health
Pichot's fatigue scale	Evaluation of patient's fatigue	0 – 32	Higher scores indicate higher fatigue
Pittsburgh sleep quality index (PSQI):	Evaluation of sleep quality	0 – 21	Lower scores indicate better sleep quality
Symptom severity scale score	Evaluation of symptom severity	0 – 12	Higher scores indicate greater symptom severity
Widespread pain index (WPI)	Number of painful points	0 – 19	Higher scores indicate higher numbers of painful points

performed using Stata software (version 15.0). More details can be found in the online supplementary material.

We performed an *a posteriori* analysis to assess the impact of residential therapy versus day therapy (where the patients went home daily after therapy) on the primary endpoint.

Results

Patients

Between September 2014 and September 2017, more than 400 patients were preselected and 220 patients were randomized to the immediate spa therapy (intervention) or delayed spa therapy (control) groups (Fig 1). Follow up was completed in October 2018. Two patients were excluded from the control group after randomization because their therapeutic management had varied substantially in the three months prior to inclusion. In the intervention group, 19 of the 110 patients could not be analyzed, therefore 91 were included in the ITT analysis; 98 patients received immediate spa therapy. In the control group, 10 of the 108 patients could not be analyzed, therefore 98 patients were included in the ITT analysis; 100 patients received delayed spa therapy. The patients' characteristics at enrollment are summarized in Table 2. The overall baseline scores for EQ-5D-3L and HADs were similar between the intervention and control groups. However, we observed that the scores were worse as the severity increased (Supplementary Table 1).

Compliance

The spa therapies prescribed and carried out are summarized in Supplementary Table 2. Five patients discontinued spa treatment before completion due to pain (n = 2), sprained ankle during the weekend (n = 1) and unknown (n = 2).

Efficacy

Primary Endpoint

The success rate at 6 months, ie, the percentage of patients with more than a 14% decrease in their FIQ score at 6 months compared with their inclusion score, was statistically significantly higher in the intervention group with or without replacement of missing values (45/100 (45.0%) vs 30/106 (28.3%), $P = .013$ and 41/91 (45.1%) vs 29/98 (29.6%), $P = .028$, respectively) (Table 3). The risk ratio for success was 1.59 (95% CI: 1.10 − 2.31), the odds ratio was 2.07 (95% CI: 1.16 − 3.69) and the NNT was 6 patients (values calculated with replacement of missing values).

The FIQ score decrease was between 15% and 30% for 20.9% and 17.4% of the patients in the intervention and control groups, respectively, between, 31% and 45% for 9.9% and 9.2%, respectively and greater than 45% for 14.3% and 3.1%, respectively.

Secondary Endpoints

The change in the FIQ score over 6 months was statistically significantly different between the 2 groups ($P = .001$), with an effect size of 0.49 (Fig 2). The FIQ

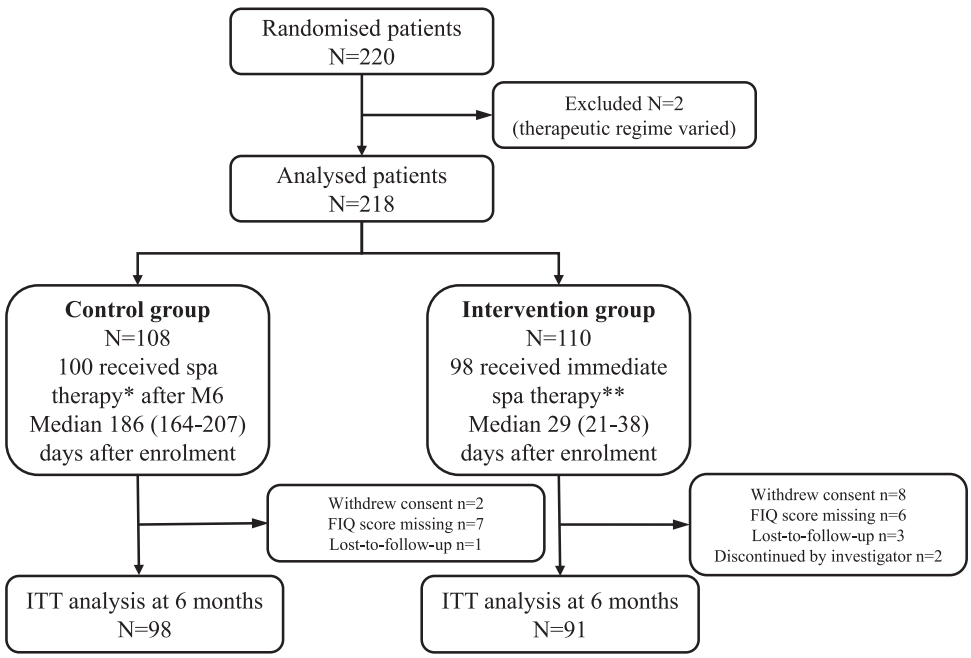


Figure 1. Study flow chart – Intention to treat (ITT) analysis.

Table 2. Baseline Characteristics of Participants

	Control group(N=108)	*Intervention group(N=110)*	*All(N=218)*
Female, n/N (%)	99 (91.7)	99 (90.0)	198 (90.8)
Age, mean ± SD	49.2 ± 8.8	50.4 ± 8.9	49.8 ± 8.8
Spa therapy care facility, n (%)			
Aix-les-Bains	30 (27.8)	31 (28.2)	61 (28.0)
Allevard-les-Bains	22 (20.4)	22 (20.0)	44 (20.2)
Bourbon-Lancy	12 (11.1)	10 (9.1)	22 (10.1)
Lamalou-les-Bains	24 (22.2)	26 (23.6)	50 (22.9)
Uriage-les-Bains	20 (18.5)	21 (19.1)	41 (18.8)
First time spa therapy, n (%)	70 (64.8)	73 (66.4)	143 (65.6)
Professional status, n (%)			
Employed	48 (44.4)	36 (32.7)	84 (38.5)
Sick leave	27 (25.0)	25 (22.7)	52 (23.9)
Disability	19 (17.6)	28 (25.5)	47 (21.6)
Retired	8 (7.4)	13 (11.8)	21 (9.6)
Other	6 (5.6)	8 (7.3)	14 (6.4)
Level of education, n (%)			
< Baccalaureate	34 (31.5)	35 (31.8)	69 (31.7)
High school diploma (baccalaureate)	33 (30.6)	28 (25.5)	61 (28.0)
University degree or higher*	41 (38.0)	47 (42.7)	88 (40.4)
BMI, mean ± SD	27.7 ± 5.8	26.6 ± 6.6	27.2 ± 6.2
	n=108	*n=107*	*n=215*
Clinical history and comorbidities, n (%) *(more than one answer possible)*	*n=108*	*n=108*	*n=216*
Psychological trauma or prolonged stress	71 (65.7)	64 (59.3)	135 (62.5)
Depression	58 (53.7)	64 (59.3)	122 (56.5)
Irritable bowel syndrome	54 (50.0)	63 (58.3)	117 (54.2)
Neurological disease			
Migraine	37 (34.3)	24 (22.2)	61 (28.2)
Neuropathic pain	15 (13.9)	20 (18.5)	35 (16.2)
Other neurological disease	22 (20.4)	21 (19.4)	43 (19.9)
Menopause	42 (38.9)	49 (45.4)	91 (42.1)
Rheumatic disease	29 (26.9)	33 (30.6)	62 (28.7)
Sleep apnea	15 (13.9)	18 (16.7)	33 (15.3)
Raynaud's disease	7 (6.5)	16 (14.8)	23 (10.6)
Cancer	2 (1.9)	6 (5.6)	8 (3.7)
Effort deconditioning	18 (16.7)	25 (23.1)	43 (19.9)
Current medication for fibromyalgia n (%) *(more than one answer possible)*	*n=107*	*n=108*	*n=215*
Weak opioids (Codeine, Tramadol, Lamaline)	59 (55.1)	61 (56.5)	120 (55.8)
Paracetamol	55 (51.4)	52 (48.1)	107 (49.8)
Antidepressants (tricyclic, SNRIs, SRIs)	47 (43.9)	48 (44.4)	95 (44.2)
NSAIDS	20 (18.7)	22 (20.4)	42 (19.5)
Pregabalin	12 (11.2)	13 (12.0)	25 (11.6)
Nefopam	9 (8.4)	6 (5.6)	15 (7.0)
Other fibromyalgia therapies in the last three months, n (%) *(more than one answer possible)*	*n=107*	*n=109*	*n=216*
Use of health care system	100 (93.5)	107 (98.2)	207 (95.8)
Physical exercise	81 (75.7)	76 (69.7)	157 (72.7)
Psycho-behavioral therapy sessions	54 (50.5)	48 (44.0)	102 (47.2)
Alternative and complementary medicine	47 (43.9)	54 (49.5)	101 (46.8)
Dietary supplements, herbal medicines, or homeopathy	47 (43.9)	48 (44.0)	95 (44.0)
FIQ, score, mean ± SD	70.5 ± 10.1	69.0 ± 12.5	69.7 ± 11.4
FIQ score < 59 (moderate), n (%)	14 (13.0)	23 (20.9)	37 (17.0)
FIQ score ≥ 59 (severe), n (%)	94 (87.0)	87 (79.1)	181 (83.0)
Widespread pain index score, mean ±SD	13.8 ± 2.8	14.3 ± 3.0	14.0 ± 2.9
Symptom severity scale score, mean ±SD	9.8 ± 1.6	10.0 ± 1.5	9.9 ± 1.6
Time since first fibromyalgia signs (years), median [IQR]	8 [5-14]	10 [6-20]	9 [5-16]

(*continued on next page*)

Table 2. Continued

	Control group(N=108)	*Intervention group(N=110)*	*All(N=218)*
Time since fibromyalgia diagnosis (years), median [IQR]	4 [2-7]	5 [3-8]	4 [3-8]
EQ-5D-3L score, mean ± SD	0.25 ± 0.24 *(n=93)*	0.26 ± 0.29 *(n=93)*	0.26 ± 0.27 *(n=186)*
EQ-5D-3L perceived health, mean ± SD	38.6 ± 15.9 *(n=96)*	42.8 ± 18.3 *(n=96)*	40.7 ± 17.2 *(n=192)*
Patient global assessment, mean ± SD	7.4 ± 1.6 *(n=103)*	6.9 ± 2.1 *(n=104)*	7.1 ± 1.9 *(n=207)*
Investigator global assessment, mean ± SD	6.0 ± 2.0 *(n=104)*	6.5 ± 1.6 *(n=103)*	6.3 ± 1.8 *(n=207)*
Pain VAS (patient diary), mean ± SD	59.6 ± 14.0 *(n=96)*	61.4 ± 17.1 *(n=93)*	60.5 ± 15.6 *(n=189)*
Pain Catastrophizing Scale (French) score, mean ± SD	30.8 ± 11.4 *(n=104)*	30.2 ± 12.0 *(n=106)*	30.5 ± 11.7 *(n=210)*
Pittsburgh Sleep Quality Index score, mean ± SD	12.3 ± 4.0 *(n=104)*	12.3 ± 4.1 *(n=105)*	12.3 ± 4.0 *(n=209)*
Epworth Sleepiness Scale score, mean ± SD	12.3 ± 6.2 *(n=103)*	12.7 ± 5.8 *(n=106)*	12.5 ± 6.0 *(n=209)*
Pichot's Fatigue Scale score, mean ± SD	26.2 ± 4.2 *(n=103)*	25.3 ± 4.7 *(n=105)*	25.7 ± 4.5 *(n=208)*
Hospital Anxiety and Depression Scale – Anxiety score, mean ± SD	12.2 ± 4.0 *(n=104)*	11.6 ± 4.3 *(n=105)*	11.9 ± 4.2 *(n=209)*
Hospital Anxiety and Depression Scale – Depression score, mean ± SD	10.3 ± 3.7 *(n=104)*	9.8 ± 4.1 *(n=105)*	10.0 ± 3.9 *(n=209)*
Coping Scale Score – Stress, mean ± SD	26.2 ± 6.4 *(n=96)*	26.7 ± 6.1 *(n=97)*	26.5 ± 6.2 *(n=193)*
Coping Scale Score – Emotion, mean ± SD	23.7 ± 5.7 *(n=96)*	24.4 ± 5.6 *(n=97)*	24.1 ± 5.7 *(n=193)*
Coping Scale Score – Social Support, mean ± SD	20.5 ± 5.5 *(n=97)*	21.8 ± 5.3 *(n=98)*	21.2 ± 5.4 *(n=195)*
Baecke physical activity questionnaire score, mean ± SD	7.2 ± 1.6 *(n=99)*	7.2 ±1.6 *(n=103)*	7.2 ± 1.6 *(n=202)*

*The number of women with a university degree or higher is slightly higher than the national average of 36.2% but was similar in both groups. BMI: body mass index; FIQ: fibromyalgia impact questionnaire; IQR: interquartile range; NSAIDs: nonsteroidal anti-inflammatory drugs; SNRIs: serotonin and norepinephrine reuptake inhibitors; SRIs: serotonin reuptake inhibitors; VAS: visual analogue scale

score at 6 months was <39 (mild impairment) for 6/98 (6.1%) and 17/91 (18.7%) patients in the control and intervention groups, respectively ($P = .008$).

The changes of the other scores over time are presented in Table 3. The evolution of the investigator's global impression of the disease activity was statistically different between the 2 groups ($P < .001$) with an improvement for the intervention group. No difference was seen for the patient's global impression ($P = .810$). The Pain VAS, PCS-CF, HADs (anxiety and depression), Pichot's Fatigue Scale and SS scores all showed a statistically significant improvement between inclusion and 6 months for the intervention group compared with the control group (Table 3).

The social support score in the Coping Scale was statistically significantly improved in the intervention group but not the stress and emotion scores. No statistically significant differences were observed for quality of life, sleep, physical activity, or BMI.

Paracetamol consumption at 6 months was lower in the intervention group (41.1% vs 57.3%, $P = .027$) and was the only drug or nondrug therapy that was statistically significantly different (Table 4).

The FIQ scores remained low at 9 and 12 months in the intervention group (Fig 3). Similar long-term persistence was observed for most of the other endpoints (Supplementary Table 3). In the control group, 90 of the 100 patients received their cure between month 6 and month 8. Their scores at month 9 and 12 were similar those in the intervention group; 61.4 and 60.7, respectively.

Safety

During the study 33 SAEs were reported by 25 patients. In the intervention group 11 patients reported 13 SAEs, and in the control group 14 patients reported 20 SAEs. In the intervention group, six were fibromyalgia-related, three related to another pathology, 2 were trauma-related, and 2 were surgery-related. In the control group, eight SAEs were fibromyalgia-related, 5 were surgery-related, 4 related to another pathology, and 3 were trauma-related.

Planned Subgroup Analyses and Unplanned post-hoc *Analyses*

No statistically significant differences for the primary endpoint were observed in the subgroup analysis by spa therapy care facility (Mantel-Haenszel test $P = .618$), or for first-time vs. previous spa therapy status (Mantel-Haenszel test $P = .256$).

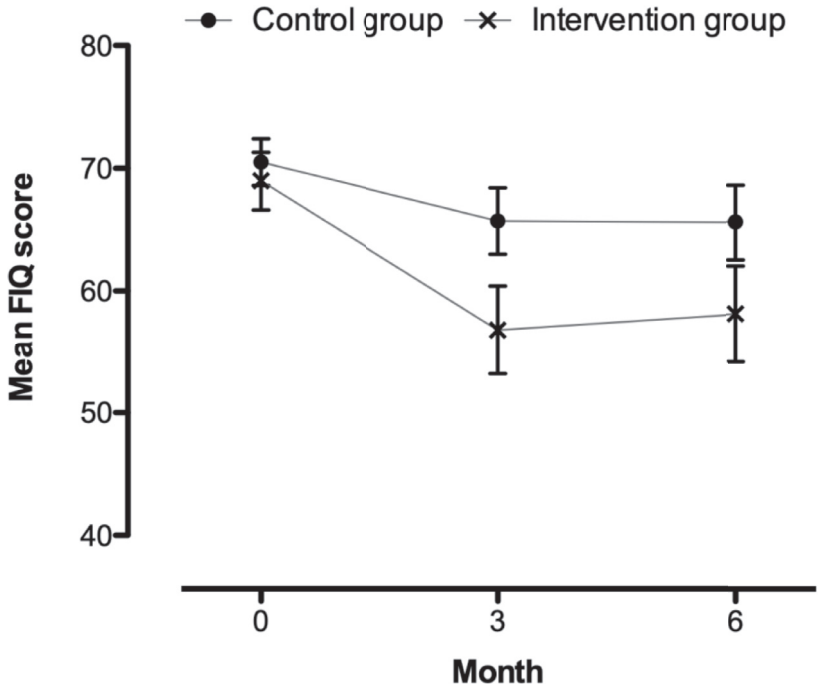
The baseline characteristics by severity at baseline are presented in Supplementary Table 1. The primary endpoint analyzed by the initial severity of the patient was not significantly different (Mantel-Haenszel test $P = .148$). The OR for success was 6.55 (95% CI: 1.19 – 36.0) for the 37 patients with moderately severe fibromyalgia

Table 3. Primary and Secondary Endpoints

		Control group	*Intervention group*	P *value**
Primary endpoint				
MCID at six-months, n/N (%)		30/106 (28.3)	45/100 (45.0)	**0.013**
Secondary endpoints				
Investigator Global Assessment, mean ± SD *n*	M0	6.0 ± 2.0 *n=104*	6.5 ± 1.6 *n=103*	**<0.001**
	M3	5.8 ± 1.9 *n=100*	5.5 ± 2.2 *n=88*	
	M6	6.2 ± 1.9 *n=92*	5.4 ± 2.0 n=87	
Patient Global Assessment, mean (± SD) *n*	M0	7.4 ± 1.6 *n=103*	6.9 ± 2.1 *n=104*	0.810
	M3	7.0 ± 1.7 *n=94*	6.3 ± 2.1 *n=90*	
	M6	7.0 ± 1.9 *n=96*	6.4 ± 2.1 n=89	
Pain VAS (diary), mean (± SD) *n*	M0	59.6 ± 14.0 *n=96*	61.4 ± 17.1 *n=93*	**0.013**
	M3	58.7 ± 20.1 *n=95*	54.4 ± 22.0 *n=91*	
	M6	58.9 ± 21.0 *n=78*	53.5 ± 22.3 *n=83*	
PCS-CF, mean ± SD *n*	M0	30.8 ± 11.4 *n=104*	30.2 ± 12.0 *n=106*	**0.031**
	M3	29.6 ± 10.5 *n=100*	25.3 ± 11.4 *n=91*	
	M6	29.4 ± 11.2 *n=97*	25.4 ± 12.4 *n=90*	
Widespread Pain Index Score, mean ± SD *n*	M0	13.8 ± 2.8 *n=108*	14.3 ± 3.0 *n=110*	**<0.001**
	M3	13.1 ± 3.7 *n=102*	11.4 ± 4.3 *n=93*	
	M6	13.2 ± 3.7 *n=96*	11.8 ± 4.5 *n=90*	
Pichot's Fatigue Scale Score, mean ± SD *n*	M0	26.2 ± 4.2 *n=103*	25.3 ± 4.7 *n=105*	**0.014**
	M3	25.2 ± 4.6 *n=100*	22.4 ± 5.8 *n=90*	
	M6	25.2 ± 4.8 *n=98*	22.9 ± 5.7 *n=91*	
Symptom Severity Scale Score, mean ± SD *n*	M0	9.8 ± 1.6 *n=108*	10.0 ± 1.5 *n=110*	**0.002**
	M3	9.4 ± 2.0 *n=102*	8.8 ± 2.1 *n=93*	
	M6	9.5 ± 1.8 *n=96*	9.0 ± 2.1 *n=90*	
HADs anxiety, mean ± SD *n*	M0	12.2 ± 4.0 *n=104*	11.6 ± 4.3 *n=105*	0.056
	M3	12.1 ± 4.4 *n=100*	10.3 ± 4.3 *n=90*	
	M6	11.7 ± 4.6 *n=98*	10.8 ± 4.6 *n=91*	
HADs depression, mean ± SD *n*	M0	10.3 ± 3.7 *n=104*	9.8 ± 4.1 *n=105*	**0.050**
	M3	10.6 ± 4.0 *n=100*	9.1 ± 4.0 *n=90*	
	M6	10.5 ± 4.1 *n=98*	9.4 ± 4.4 *n=91*	
EQ-5D-3L score, mean ± SD *n*	M0	0.25 ± 0.24 *n=93*	0.26 ± 0.29 *n=93*	0.801
	M6	0.30 ± 0.29 *n=94*	0.33 ± 0.32 *n=87*	
EQ-5D-3L Perceived Health Score, mean ± SD *n*	M0	38.6 ± 15.9 *n=96*	42.8 ± 18.3 *n=96*	0.910
	M6	43.0 ± 19.4 *n=96*	47.1 ± 21.5 *n=90*	
Pittsburgh Sleep Quality Index Score, mean ± SD *n*	M0	12.3 ± 4.0 *n=104*	12.3 ± 4.1 *n=105*	0.550
	M3	11.8 ± 4.3 *n=99*	11.5 ± 3.7 *n=91*	
	M6	11.7 ± 4.5 *n=98*	11.8 ± 3.8 *n=90*	
Epworth Sleepiness Scale Score, mean ± SD *n*	M0	12.3 ± 6.2 *n=103*	12.7 ± 5.8 *n=106*	0.432
	M3	12.2 ± 5.7 *n=100*	11.9 ± 5.7 *n=91*	
	M6	12.3 ± 5.5 *n=98*	12.0 ± 5.9 *n=91*	
Baecke Physical Activity Questionnaire, mean ± SD *n*	M0	7.2 ± 1.6 *n=99*	7.2 ± 1.6 *n=103*	0.796
	M3	7.3 ± 1.6 *n=100*	7.3 ± 1.2 *n=88*	
	M6	7.2 ± 1.6 *n=96*	7.2 ± 1.4 *n=87*	
BMI, mean ± SD *n*	M0	27.7 ± 5.8 *n=108*	26.6 ± 6.6 *n=107*	0.325
	M3	28.0 ± 5.9 *n=102*	26.9 ± 6.8 *n=92*	
	M6	28.1 ± 5.9 *n=96*	26.8 ± 6.9 *n=90*	
Coping Scale Score – Stress, mean ± SD *n*	M0	26.2 ± 6.4 *n=96*	26.7 ± 6.1 *n=97*	0.817
	M6	25.3 ± 6.4 *n=93*	26.2 ± 7.0 *n=82*	
Coping Scale Score – Emotion, mean ± SD *n*	M0	23.7 ± 5.7 *n=96*	24.4 ± 5.6 *n=97*	0.333
	M6	22.8 ± 5.5 *n=93*	22.6 ± 6.4 *n=82*	
Coping Scale Score – Social Support, mean ± SD *n*	M0	20.5 ± 5.5 *n=97*	21.8 ± 5.3 *n=98*	**0.045**
	M6	20.5 ± 5.1 *n=93*	19.9 ± 6.6 *n=82*	

*p-value for the comparison of the change over 6 months of the scores in the intervention and control groups. BMI: body mass index; IGA: investigator global assessment; FIQ: fibromyalgia impact questionnaire; HADs: Hospital Anxiety and Depression Scale; MCID: Minimal Clinically Important Difference on FIQ; PCS-CF: Pain Catastrophizing Scale (French); PGA: patient global assessment; IQR: interquartile range; VAS: visual analogue scale

(FIQ at inclusion <59) and 1.71 (95% CI: 0.91 − 3.23) for the 169 patients with severe fibromyalgia (FIQ at inclusion ≥59). In a *post-hoc* analysis, the difference for the success rate (primary endpoint) was not statistically significant between patients with severe fibromyalgia (FIQ at inclusion 59-71, n = 86) and very severe patients (FIQ at inclusion ≥ 72, n = 83) (Mantel-Haenszel test $P = .438$). In addition, no difference in the success rate was observed for patients who were resident during their therapy compared with those who were day patients



Immediate spa therapy X	n = 110	n = 92	n = 91
	69.0 (95% CI: 66.6 -71.3)	56.8 (95% CI: 53.2 -60.4)	58.1 (95% CI: 54.2 -62.0)
Deferred spa therapy ●	n = 108	n = 100	n = 98
	70.5 (95% CI: 68.6 -72.4)	65.7 (95% CI: 63.0 -68.4)	65.6 (95% CI: 62.5 -68.6)

Figure 2. Evolution of the FIQ score over time.

(Pearson chi^2 *P*= .20). Lastly, for the primary endpoint in the intervention group, we looked at the impact of the number of treatments patients received. The median number of treatments was 64 (25%, 75% quartiles: 50, 72). There were no differences in the success rates for patients into when analyzed in subgroups based on the number of treatments received: <50, 50-63; 64-71 and >72 (Pearson chi^2 *P* = .61).

Discussion

We conducted an open RCT in five spa therapy care facilities in France. Patients were randomized to receive spa therapy immediately (intervention group, N = 110) or after primary outcome evaluation at six months (control group, N = 108). The characteristics of the study population were consistent with those previously

Table 4. Drug and Other Fibromyalgia Therapies Use at 6 Months

	Control group(n=96)	*Intervention group(n=90)*	P *value*
Drug consumption, n (%)			
Paracetamol	55 (57.3)	37 (41.1)	**0.027**
NSAIDS	19 (19.8)	20 (22.2)	0.684
Nefopam	11 (11.5)	7 (7.8)	0.396
Weak opioids (Codeine, Tramadol, Lamaline)	55 (57.3)	46 (51.1)	0.398
Pregabalin*	8 (8.3)	13 (14.4)	0.188
Antidepressants (tricyclic, SNRIs, SRIs)	39 (40.6)	39 (43.3)	0.708
Other fibromyalgia therapies, n (%)			
Use of health care system	90 (95.7)	83 (95.4)	1.000
Psycho-behavioral therapy sessions	49 (52.1)	41 (47.1)	0.501
Alternative and complementary medicine	44 (46.8)	37 (42.5)	0.563
Dietary supplements, herbal medicines, or homeopathy	43 (45.7)	47 (54.0)	0.266

*Pregabalin was not indicated for fibromyalgia in France. NSAIDs: nonsteroidal anti-inflammatory drugs; SNRIs: serotonin and norepinephrine reuptake inhibitors; SRIs: serotonin reuptake inhibitors

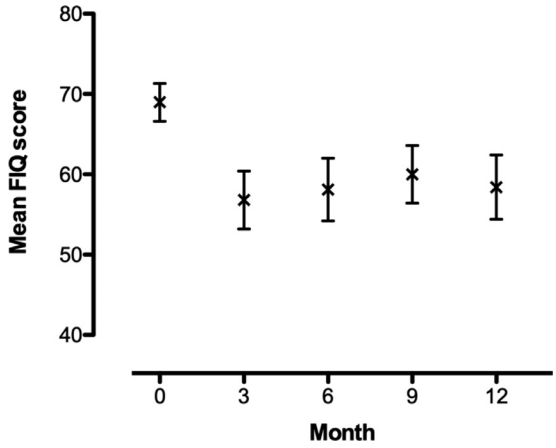


Figure 3. Long-term evolution of FIQ score for the intervention group.

reported in terms of age, gender, and symptoms and comorbidities.[25] All patients continued to receive their usual therapy. The spa therapy was standardized between the centers and the adherence was good with only four patients lost-to-follow-up. The success rate, ie, percentage of patients with a MCID, defined as >14% decrease in their FIQ score from baseline, was significant at 3 months, 6 months (primary outcome) and persisted up to 12 months. Improved scores were reported for most of the questionnaires and scales used showing the benefits for fibromyalgia symptoms. No significant center effect was observed. These results are consistent with those from a study that enrolled a total of 100 patients that provided evidence of effectiveness of spa therapy in controlling pain and improving functionality up to 6 months in patients with fibromyalgia.[17] The estimated NNT was 6 and the effect size was 0.49. This is comparable to the NNT of between 4 and 16 reported for aerobic exercise training for patients with fibromyalgia in a Cochrane systematic review for improved quality of life (self-reported FIQ).[4] The estimated NNT is also similar to that found for the spa therapy for patients with knee osteoarthritis in France.[18]

The longer-term benefit (up to 12 months) has rarely been reported.[3,23,30] For example, in a meta-analysis evaluating the benefit of hydrotherapy and balneotherapy for fibromyalgia, the median follow-up was 2.5 and 3.5 months, respectively.[30] In another meta-analysis evaluating complementary and alternative exercise for fibromyalgia; the longest follow-up was six months, and many trials had no follow-up.[28]

Our results showed a reduction in pain (EVA and WPI scores) and a decrease in paracetamol consumption (the only treatment self-managed by patients), while the consumption of other analgesics remained stable. We also observed significant benefits on severity and fatigue and borderline benefits for anxiety and depression. In contrast, spa therapy had no influence on the general quality of life, sleep, BMI, or physical activity. For physical activity, only 19% of patients participated in the weekly walking training, which is probably insufficient to have an impact after three weeks, and other physical activity was self-reported by the patients.

Although we observed a significant improvement in the IGA score for the intervention group, the PGA score was not significantly different between the groups. The lack of change in the PGA score may be because the patients suffer from a chronic illness. Our study failed to show an improvement in the general quality of life as measured using EQ-5D-3L. Spa therapy probably has, at most, only a very modest impact on the many psychosocial factors the influence the general quality of life. The EQ-5D-3L has been reported not to be very sensitive to changes in modest health states and to have a low sensitivity to detect clinical changes for some conditions.[22] It is recommended to also use a disease-specific instrument, which was the FIQ in our study. The newly developed EQ-5D-5L is more sensitive and should be used in future studies, but it had not been validated at the time of the design of our study.[22]

In addition, we demonstrated that spa therapy was safe for this population of patients with fibromyalgia. None of the SAEs were attributable to the spa therapy. It has been reported that there can be transient aggravation of pain when spa therapy starts but this is usually controlled by adapting the therapy. In a review of 33 randomized trials including 3,018 patients with chronic low back pain, knee osteoarthritis or fibromyalgia, only 1% of patients receiving spa therapy had to discontinue.[33]

The patients in our study were mainly recruited in university hospital pain clinics and therefore the fibromyalgia was likely to be more severe than in patients followed elsewhere. The *post-hoc* analysis showed that the benefit from the spa therapy was significant for the 83 patients with a FIQ score ≥72, although the benefit was lower than in patients with less severe fibromyalgia in our study.

One potential limitation of our study is the unblinded nature of the intervention. However, we compared immediate spa therapy (intervention group) with delayed spa therapy (control group) to enable all patients to receive spa therapy and therefore to limit the potential negative bias of patient disappointment. Although, the staff at the spa centers were not blinded, they were not involved in the evaluations, so it is unlikely that this introduced bias. Also, we cannot exclude that knowing they were going to go for a spa therapy, either immediately or after six months, had a positive effect on the patients or that the patients in the immediate spa therapy group felt stress because they had to organize their lives in a short time to able to be available for the3-week therapy. The data entry and analyses were not done under blind conditions as the dates of the therapy were available. However, the analyses were done independently of the data collection and after the database had been locked.

The primary endpoint was evaluated at six months, ie, before the control group had received the intervention, and long-term follow-up was assessed only for the intervention group. Although more patients withdrew in the intervention group than in the control group (8 vs 2), the reason was not related to the therapy but to difficulty to organize going away for the three-week spa therapy. Also, our pragmatic approach involved evaluating the

overall spa therapy and not the individual treatments. The treatments were standardized between the spa therapy care facilities and our aim was to evaluate the efficacy of the 3-week spa therapy with physiotherapy, since 19% of the patients also attended the weekly workshops for walking training. No structured therapeutic education program was included in the intervention. Compliance with the spa therapy was accurately recorded and was high. In addition, *a posteriori* analysis for resident verus day spa therapy showed no differences, suggesting that the de-stressing effect of being away from their normal environment was unlikely to have has an impact on the improvements observed.

Our results suggest that the indications for spa therapy could be extended to include prevention of progression to severe fibromyalgia in patients with moderate disease, ie, FIQ score between 39 and 58. In addition, the results from *post-hoc* analyses suggest that patients with severe fibromyalgia responded well. These results should be confirmed in randomized clinical trials.

In conclusion our results suggest that the assessed spa therapy provides a long-term beneficial clinical effect for patients suffering from moderate to severe fibromyalgia. Spa therapy can be considered as one of the potential non-drug therapies in a multidisciplinary approach to the management of fibromyalgia.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2021.02.010.

References

1. Ablin JN, Hauser W, Buskila D: Spa treatment (balneotherapy) for fibromyalgia-a qualitative-narrative review and a historical perspective. Evid Based Complement Alternat Med 2013:638050, 2013

2. Atzeni F, Talotta R, Masala IF, Giacomelli C, Conversano C, Nucera V, Lucchino B, Iannuccelli C, Di Franco M, Bazzichi L: One year in review 2019: Fibromyalgia. Clin. Exp. Rheumatol. 37(Suppl 116):3-10, 2019

3. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB: Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol 36:1304-1311, 2009

4. Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Goes SM, Boden C, Foulds HJ: Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 6: CD012700, 2017

5. Bidonde J, Busch AJ, Webber SC, Schachter CL, Danyliw A, Overend TJ, Richards RS, Rader T: Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev Cd011336, 2014

6. Burckhardt CS, Clark SR, Bennett RM: The fibromyalgia impact questionnaire: development and validation. J Rheumatol 18:728-733, 1991

7. Carleton RN, Asmundson GJG, Korol SL, LeBouthillier DM, Hozempa K, Katz JD, Vlaeyen JWS, Crombez G: Evaluating the efficacy of an attention modification program for patients with fibromyalgia: a randomized controlled trial. Pain 161:584-594, 2020

8. Caro XJ, Galbraith RG, Winter EF: Evidence of peripheral large nerve involvement in fibromyalgia: a retrospective review of EMG and nerve conduction findings in 55 FM subjects. Eur J Rheumatol 5:104-110, 2018

9. Chinn S, Caldwell W, Gritsenko K: Fibromyalgia pathogenesis and treatment options update. Curr Pain Headache Rep 20:25, 2016

10. Creed F: A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. Pain 161:1169-1176, 2020

11. de la Coba P, Bruehl S, Galvez-Sánchez CM, Reyes Del Paso GA: Slowly repeated evoked pain as a marker of central sensitization in fibromyalgia: Diagnostic accuracy and reliability in comparison with temporal summation of pain. Psychosom. Med. 80:573-580, 2018

12. Doebl S, Macfarlane GJ, Hollick RJ: ''No one wants to look after the fibro patient''. Understanding models, and patient perspectives, of care for fibromyalgia: Reviews of current evidence. Pain 161:1716-1725, 2020

13. EQ-5D Instruments. Available at: https://euroqol.org/eq-5d-instruments. Accessed May 20, 2020

14. Falagas ME, Zarkadoulia E, Rafailidis PI: The therapeutic effect of balneotherapy: Evaluation of the evidence from randomised controlled trials. Int. J. Clin. Pract. 63:1068-1084, 2009

15. Farhad K: Current diagnosis and treatment of painful small fiber neuropathy. Curr Neurol Neurosci Rep 19:103, 2019

16. Farhad K, Oaklander AL: Fibromyalgia and small-fiber polyneuropathy: What's in a name? Muscle Nerve 58:611-613, 2018

17. Fioravanti A, Manica P, Bortolotti R, Cevenini G, Tenti S, Paolazzi G: Is balneotherapy effective for fibromyalgia? Results from a 6-month double-blind randomized clinical trial. Clin. Rheumatol. 37:2203-2212, 2018

18. Forestier R, Desfour H, Tessier JM, Francon A, Foote AM, Genty C, Rolland C, Roques CF, Bosson JL: Spa

therapy in the treatment of knee osteoarthritis: A large randomised multicentre trial. Ann. Rheum. Dis. 69:660-665, 2010

19. Fraioli A, Grassi M, Mennuni G, Geraci A, Petraccia L, Fontana M, Conte S, Serio A: Clinical researches on the efficacy of spa therapy in fibromyalgia. A systematic review. Ann. Ist. Super. Sanita. 49:219-229, 2013

20. Giacomelli C, Sernissi F, Sarzi-Puttini P, Di Franco M, Atzeni F, Bazzichi L: Fibromyalgia: A critical digest of the recent literature. Clin. Exp. Rheumatol. 31:S153-S157, 2013

21. Han CL, Sheng YC, Wang SY, Chen YH, Kang JH: Serum proteome profiles revealed dysregulated proteins and mechanisms associated with fibromyalgia syndrome in women. Sci Rep 10:12347, 2020

22. Janssen MF, Bonsel GJ, Luo N: Is EQ-5D-5L better than EQ-5D-3L? A head-to-head comparison of descriptive systems and value sets from seven countries. Pharmacoeconomics 36:675-697, 2018

23. Kvien TK, Heiberg T, Hagen KB: Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): What do these concepts mean? Ann. Rheum. Dis. 66(Suppl 3):iii40-iii41, 2007

24. Langhorst J, Musial F, Klose P, Hauser W: Efficacy of hydrotherapy in fibromyalgia syndrome—A meta-analysis of randomized controlled clinical trials. Rheumatology (Oxford) 48:1155-1159, 2009

25. Laroche F, Guérin J, Azoulay D, Coste J, Perrot S: Fibromyalgia in France: Daily life, professional burden and care. National survey of 4516 patients. Rev Rhum 86:90-95, 2019

26. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Fluss E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT: EULAR revised recommendations for the management of fibromyalgia. Ann. Rheum. Dis. 76:318-328, 2017

27. McVeigh JG, McGaughey H, Hall M, Kane P: The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: A systematic review. Rheumatol. Int. 29:119-130, 2008

28. Mist SD, Firestone KA, Jones KD: Complementary and alternative exercise for fibromyalgia: A meta-analysis. J Pain Res 6:247-260, 2013

29. Montoro CI, Duschek S, de Guevara CM, Reyes Del Paso GA: Patterns of cerebral blood flow modulation during painful stimulation in fibromyalgia: A transcranial doppler sonography study. Pain Med 17:2256-2267, 2016

30. Naumann J, Sadaghiani C: Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: A qualitative systematic review and meta-analysis of randomized controlled trials. Arthritis Res Ther 16:R141, 2014

31. Pérez-Aranda A, Feliu-Soler A, Montero-Marín J, García-Campayo J, Andrés-Rodríguez L, Borràs X, Rozadilla-Sacanell A, Peñarrubia-Maria MT, Angarita-Osorio N, McCracken LM, Luciano JV: A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: The EUDAIMON study. Pain 160:2508-2523, 2019

32. Reyes Del Paso GA, de la Coba P: Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: An electrodermal study. PloS One 15: e0241154, 2020

33. Roques CF, Queneau P: Spa therapy for pain of patients with chronic low back pain, knee osteo-arthritis and fibromyalgia. Bull. Acad. Natl. Med. 200:575-586, 2016. discussion 586-577

34. Sanabria-Mazo JP, Montero-Marin J, Feliu-Soler A, Gasión V, Navarro-Gil M, Morillo-Sarto H, Colomer-Carbonell A, Borràs X, Tops M, Luciano JV, García-Campayo J: Mindfulness-Based Program Plus Amygdala and Insula Retraining (MAIR) for the treatment of women with fibromyalgia: A pilot randomized controlled trial. J Clin Med 9, 2020

35. Schaefer C, Chandran A, Hufstader M, Baik R, McNett M, Goldenberg D, Gerwin R, Zlateva G: The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. . *Health Qual Life Outcomes* 9:71, 2011

36. software N. Available at: https://www.statsols.com/. Accessed May 20, 2020

37. Wallace DJ, Gavin IM, Karpenko O, Barkhordar F, Gillis BS: Cytokine and chemokine profiles in fibromyalgia, rheumatoid arthritis and systemic lupus erythematosus: A potentially useful tool in differential diagnosis. Rheumatol. Int. 35:991-996, 2015

38. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 62:600-610, 2010

39. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L: The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19-28, 1995