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Clinical researches on the efficacy of spa therapy in fibromyalgia. A systematic review

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Abstract

Background. Fibromyalgia is characterized by chronic widespread pain, tenderness at muscle and tendon insertions point when digital pressure is applied, sleep disorders, chronic fatigue, depressive episodes, anxiety, and other functional somatic syndromes. ***Objective***. The aim of this study was to determine whether balneotherapy with mineral waters and mineral-water containing mud is effective in the management of fibromyalgia. ***Methods.*** We conducted a systematic review of the literature regarding spa therapy in the treatment of the fibromyalgia. We searched many databases for articles published between 2000 and 2012 and we selected 7 studies among 65 articles retrieved. A total of 142 patients received balneotherapy and 129 were controls.
Conclusion. Study data confirms that spa therapy could improve the symptoms of fibromyalgia including pain, depression and minor symptoms.

Key words
- review
- baths
- mud therapy
- fibromyalgia

INTRODUCTION

Fibromyalgia is a chronic syndrome of unknown etiology. The criteria for diagnosing the syndrome recommended by the American College of Rheumatology (ACR) include a history of "widespread pain for at least 3 months" and "pain on compression at 11 or more of the 18 tender points" (muscle and tendon insertion points) associated with the disease, but it is also frequently associated with sleep disturbances, chronic fatigue, depressive episodes, anxiety, stiffness, irritable bowel syndrome, irritable bladder syndrome, temporomandibular disorders, and functional disability [1-3]. Consequently, the fibromyalgia syndrome (FMS) can have a substantial impact on patients' work capacity, family life, social commitments, and quality of life [4].

Fibromyalgia is the second most common rheumatic disease and accounts for 20% of all rheumatological diagnoses [5]. Its estimated prevalence in the general population ranges from 0.5% to 5.0%, and rates in the United States (2.0%) are similar to those reported in Italy (2.2%) [6-8]. In general, the prevalence is three times higher in females than in males [9, 10].

Many factors are thought to play pathogenetic roles in fibromyalgia, including genetic and familiar factors, altered nociception and/or serotonergic neurotransmission, dysfunction of the hypothalamic-hypophyseal-adrenal axis, immune changes involving cytokine and autoantibody production, autonomic nervous system dysfunction, environmental factors, and stress [11-21]. Particular importance has been ascribed to altered pain perception. Patients with FMS display increased sensitivity to tactile pressure and lower thresholds for pressure-induced pain [22]. Altered neurotransmitter levels have been observed along the nociceptive pathways (reduced levels of serotonin and norepinephrine, increases in substance P level), and the altered processing and abnormal levels of serotonin and norepinephrine have relevant implications for the therapy of fibromyalgia [23-26]. Increased plasma levels of prostaglandin E2 (PGE_2) have also been documented in patients with FMS, and one third of these individuals also had detectable skin levels of interleukins 1 (IL-1) and 6 (IL-6) and tumor necrosis factor alpha (TNF-α) [26].

Various drugs are used to treat fibromyalgia, including non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, anxiolytics, corticosteroids, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors, but the best results seem to be obtained with inhibitors of serotonin and norepinephrine reuptake, tricyclic antidepressants, or the alpha 2 delta ligands gabapentin and pregabalin [27-35].

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Non pharmacological approaches are also used [36-45]. There is a substantial body of evidence supporting the therapeutic efficacy of cardiovascular exercise, cognitive behavioral therapy, and patient education in general, whereas the benefits of strength training, hypnotherapy, biofeedback, acupuncture, chiropractic, electrotherapy, and ultrasound are less clear [27].

METHODS

We conducted a systematic review of the literature regarding spa therapy in the treatment of the fibromyalgia syndrome in order to research the evidence of the efficacy of this treatment. We searched the PubMed, Medline, Cochrane Library, Embase, Web of Science databases for articles published between 2000 and 2012 with any of the following key words: fibromyalgia, spa therapy, balneology, mud-pack therapy, mineral waters, randomized clinical trial. On the whole, we examined data from 65 scientific studies on balneotherapy for fibromyalgia and limited our review to studies of balneotherapy consisting specifically of baths/mud-baths containing mineral waters from thermal springs including those that combined this type of balneotherapy with physiotherapy (*e.g.* massage, exercises, etc.).

For the quality assessment of the studies that were included in the review after the preliminary selection we considered the scientific value of the international journals that published these researches, the number of patients included in the studies, the methods used to study the patients and the possibility of exclusion of more frequent studies bias. Moreover, we cannot exclude the existence of publication bias that can occur for any scientific research especially if related to topics concerning therapeutic methods.

The final selection comprised 6 randomized controlled trials [46-51] and 1 retrospective analysis of patients' medical records [52]. The studies had been conducted in 10 different spas (4 in Italy, 6 in Turkey). It is important to note that the limited number of studies conducted on this issues is in stark contrast with the high prevalence of fibromyalgia, especially among women (3.6%), and with the high number of health spas operating in European and non-European countries [9]. *Table 1* shows the authors, the location of spa and the chemical characteristics of the mineral waters used in the different studies.

A total of 303 subjects were initially enrolled in the 7 studies, but only 271 (258 females, 13 males) completed the treatment protocols. One hundred forty two of these participants were assigned to the experimental groups of the various studies, which were treated with thermal spring water baths and/or mud-baths (with or without other forms of treatment). The other 129 were allocated to the control groups, which did not usually receive any type of spa therapy. However, in the study conducted by Altan, *et al.* [50], the experimental group was treated with a combination of thermal balneotherapy and physical exercise, while the control patients received balneotherapy alone; in the study of Cimbiz *et al.* there was not a control group and all patients received thermal balneotherapy and physiotherapy [52].

Each report was reviewed to identify the criteria used for study enrolment and for assignment to experimental *vs* control groups, the characteristics of the balneotherapies themselves, the methods used to assess treatment efficacy, the tests used for statistical analysis of the results, and the conclusions reached by the investigators. Because the methods used differed markedly from study to study, we were unable to conduct a quantitative analysis of pooled data from the 7 studies (meta-analysis). Instead, data from each study were critically analyzed and the main findings compared with those of the other studies.

Furthermore for the purpose of this review we re-evaluated the resultsf of the different studies using the same statistical methods (Student's t test for unpaired data) but it was not possible for three studies because in the first and in the second [50, 51] the results were presented as median and in the other there was not a control group [52].

Criteria used for study enrolment and treatment-group allocation

In 6 of the 7 studies we reviewed [46-51], enrolment was based on the ACR criteria for diagnosis of fibromyalgia [1], and treatment-group assignment was randomized. The seventh article described the results of a retrospective study conducted in Turkey by Cimbiz *et al.* [52]. Inclusion in this study population was based on data found in the medical record archives of the University of Dumlupiran's Department of Physical Therapy and Rehabilitation, and all of the patients included in the analysis had received balneotherapy (*i.e.*, there was no control group).

Treatment characteristics

Patients in the experimental groups of three studies [47, 48, 51] and those in the control group investigated by Altan *et al.* [50] were treated with hot mineral water baths, while the experimental group studied by Fioravanti *et al.* received hot mineral water baths plus mud-pack therapy [46]. In the studies by Dönmez *et al.* [49], Cimbiz *et al.* [52], and in the experimental group investigated by Altan *et al.* [50] patients were treated with hot mineral water baths combined with different types of physiotherapy (massages, exercise, electrotherapy).

The experimental group studied by Fioravanti *et al.* received hot mineral water baths and mud packs 12 times in the space of 2 weeks [46]. Those studied by Dönmez *et al*. received the same number of treatments, but they consisted of hot mineral water baths alone [49]. As for the studies by Ardiç *et al.* [47], Evcik *et al.* [48], and Cimbiz *et al.* [52], the study treatment consisted of hot mineral water baths 5 times a week for 3 weeks (total: 15 treatments); in the latter of the three studies, the baths were combined with massage and physical therapy [52]. Özkurt *et al.* treated the patients by two hot mineral water baths every day for two weeks [51]. Altan *et al.* treated all patients with hot mineral water baths 3 times a week for 12 weeks (total: 36 treatments), and those in the experimental group also received physiotherapy (exercises) [50].

Table 1
Studies on spa therapy for fibromyalgia syndrome (FMS) included in the review

Authors	Location of spa	Mineral water content
Fioravanti *et al*. [46]	Sardara (Italy) Rapolano (Italy) Montegrotto (Italy) Agnano (Italy)	Sulfate-bicarbonate Sulfate-bicarbonate Sodium bromide/sodium iodide Sodium bromide/sodium iodide
Ardiç *et al*. [47]	Denizli (Turkey)	Sulfate-bicarbonate-calcium-magnesium
Evcik *et al*. [48]	Afyon (Turkey)	Sodium bicarbonate
Dönmez *et al*. [49]	Balçova (Turkey)	Sodium chloride/sodium bicarbonate
Altan *et al*. [50]	Bursa (Turkey)	Sodium, sulfate
Özkurt *et al*. [51]	Tuzla (Turkey)	Sodium chloride, calcium
Cimbiz *et al*. [52]	Tutav (Turkey)	Sodium, sulfate, calcium, magnesium

The studies also differed in the ways they handled treatments already being used by patients at the time of enrolment. In one study, all such treatment was suspended [47]. In 3 others, "drug therapy" (type not specified) was continued [46, 49, 52]. In the study of Özkurt *et al.* the patients of control group continued to have their medical care and so study group [51]. In the sixth study patients were allowed to continue NSAID therapy, but antidepressants were discontinued [48], and the seventh study adopted the opposite strategy, interrupting NSAID treatment and continuing antidepressants, provided they had been started at least 1 month before enrolment in the study [50].

Timing of assessments of treatment efficacy

In all of the studies we reviewed, clinical assessments and laboratory tests were naturally performed before treatment began and after it had been completed. The duration of treatment varied from 2 weeks in three studies [46, 49, 51] and 3 weeks in three others [47, 48, 52] to 12 weeks (3 sessions a week) in the study by Altan *et al.* [50]. In 5 studies, patients were also reassessed weeks or even months after completion of therapy (16 weeks [46], 24 weeks [48, 50], at the end of the 2nd week, the 1st month and the 3rd month [51] and in an other study, 1, 3, 6, and 9 months after treatment [49].

Clinical variables assessed as indexes of treatment efficacy

In 5 of the studies we reviewed [47-49, 51, 52] pain was rated by the patients themselves using the complete (0-10 cm) visual analogue scale [53] but in the study of Özkurt *et al.* [51] these values were expressed in mm (from 0 to 100 mm). In contrast, Fioravanti *et al.* used the VAS for "minor symptoms" which includes FMS symptoms other than pain (headache, asthenia, sleep disturbances, gastrointestinal disturbances) [46]. Ratings range from 0 (absence of the symptom) to 100 (maximum severity). As for Altan *et al.*, they used the quantitative VAS with pain intensity ratings ranging from 0 to 10, as well as a qualitative rating with 5 grades (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain, 4 = unbearable pain) [50].

Another clinical tool frequently used in these studies is the Fibromyalgia Impact Questionnaire (FIQ). Patients are asked to respond to a series of questions on their physical and psychological well-being and on the disease's repercussions on their daily life [54, 55]. Fioravanti *et al.* [46] used the Italian version of the FIQ [56]. Ardiç *et al.* [47], Dönmez *et al.* [49], and Özkurt *et al.* [51] used the Turkish version [57], and Evcik *et al.* [48] used the international FIQ [54]. The FIQ was not used at all in the other two studies [50, 52].

Another instrument long been recommended by the ACR is the tender points count (TPC), which is a measure of the pain elicited by digital compression at 18 specific points indicated on a map of the human body [1]. This type of assessment was used in all of the studies we reviewed with the exception of that conducted by Cimbiz *et al.* [52].

The Beck Depression Inventory (BDI) is used to rate the severity of the illness in terms of depression, which is frequently associated with FMS. It was used in 5 of the studies we reviewed: in 4 cases [47-49, 51], the authors used the original version of the BDI, which is widely used in different areas of psychology and psychiatry [58], whereas the fourth study [50] used a version that had been modified on the basis of previous experience with this tool in patients with FMS [59].

Statistical analysis

The methods used to analyze the results of treatment varied widely in the 7 studies, and global analysis of all the data was really not possible. Generally speaking, treatment efficacy was assessed in two ways: a) intragroup comparison of data collected before and after the treatments; b) comparison of experimental group vs. control group data collected at the same points in time. In the study conducted by Cimbiz *et al.*, which did not include a control group, the analysis was limited to comparison of base-line (pretreatment) and post-treatment data [52]. In the study of Altan *et al.* [50], the experimental group was treated with hot mineral water baths and exercise/physiotherapy, whereas the controls received only balneotherapy. In this case, the efficacy of the spa therapy, with or without physiotherapy, can be assessed with pre *vs* post-treatment comparisons within each of the two groups.

In 5 of the studies we examined, quantitative findings were expressed as means ± standard deviation, and comparison of the results obtained in these trials was therefore possible. In contrast, Dönmez *et al.* and

Özkurt *et al.* reported medians and ranges, which limits the demonstrative power of their comparative analyses and precludes comparison of their findings with those of others [49, 51, 60]. Özkurt *et al.* use means and standard deviation only for the comparison between experimental and control groups at the baseline to demonstrate that there where not significant differences between the two groups before the beginning of the study [51] *(Table 2)*.

The 7 studies also differed widely in the methods of the statistical analyses used. Four of the studies used the Mann-Whitney U test (in some cases for both intra-group and inter-group comparisons; in others only for the latter) [46-49]. In the study of Özkurt *et al.* was used Student's t test and Mann-Whitney test for the comparison at the baseline between the two groups and the Friedman test for the comparison between the different times of the study in the single groups [51]. The other 2 studies relied on Student's t test for unpaired and paired data (inter and intra-group comparisons, respectively) [50, 52], and other types of analysis were used occasionally in all of the studies (*e.g.*, analysis of variance, Spearman test, Friedman test) *(Table 2)*.

RESULTS

The main results reported by the authors of each study are summarized below. Findings are expressed as mean with standard deviation, as well as in terms of their statistical significance based on the different tests used. In an attempt to provide a unified view of the data generated by these studies, we also report the results of our own statistical analyses of the results conducted with a same test but it was not possible for three studies [50-52] because of the different methods used by the Authors *(Table 2)*.

Visual analogue scale measurements of symptom severity

Six of the studies reported conventional VAS pain scores, and in all these studies values recorded in the experimental group at the end of treatment were significantly different from those recorded at baseline (with P values ranging from 0.01 to 0.000) [47-52]. The same applies to scores recorded during longer-term follow-up (24 weeks after completion of treatment in the studies by Evcik *et al.* [48] and Altan *et al.* [50]; 9 months post-treatment in that conducted by Dönmez *et al.* [49]; 1 month and 3 months post-treatment in the study by Özkurt *et al.* [51]. In the study by Fioravanti *et al.*, where the VAS for minor symptoms was used, highly significant improvement was noted at the end of 2-week treatment and 16 weeks after treatment completion ($P < 0.001$) [46]. In the 5 studies with control groups that did not receive any type of spa therapy, scores recorded for these patients at the end of therapy and during long-term follow-up were not significantly different from those at baseline [46-49, 51]. As noted above, the controls studied by Altan *et al.* received balneotherapy alone, without the physical therapy that was also used in the experimental group [50]. In this case, the results observed at the end of therapy and 24 weeks after treatment were significantly better than those seen at baseline in both groups, which indicates that balneotherapy is effective for the treatment of fibromyalgia, regardless of whether or not it is associated with physiotherapy. Finally, in the study by Cimbiz *et al.*, where all patients received balneotherapy plus physiotherapy, significant differences were observed between median values recorded at baseline, at the end of treatment, and at discharge from the spa [52].

For the purposes of the present review, we re-evaluated the results of the different studies using the same statistical method, the Student's t test, which is used to compare the means of two frequency distributions. This was not possible for VAS data from 3 of the studies because in 2, the results were expressed as median values (rather than means) [49, 51], and in the other there was no control group [52]. Our analysis showed that in 3 of the studies reviewed, there were no significant differences between the baseline scores of the two groups, but very significant intergroup differences emerged in the values recorded at various points after treatment [46-48]. In contrast, in the study by Altan *et al.*, where balneotherapy was used in both the experimental (with physiotherapy) and control groups (without physiotherapy), there were no significant intergroups differences at any of the assessment time points [50] *(Table 3)*.

In the study of Özkurt *et al.* [51] the values of the pain were assessed using 100-mm Visual Analog Scale and expressed as median and min-max values. The comparison of the results was evaluated before and after the treatment, at the end of the 1st month and at the end of 3 months; all the differences were significant ($P = 0.000$)

Tender points count

In 6 studies, tenderness was evaluated at 18 specific sites, as recommended by the ACR for diagnosis of fibromyalgia [1] (although in Dönmez *et al.* and in Özkurt *et al.* [49, 51] the results are reported as medians rather than means). Tender points count (TPC) were not performed in the study by Cimbiz *et al.* [52].

Comparison of baseline and post-treatment findings in the experimental groups revealed significant differences. Some of these were particularly large, as for example, in the study by Evcik *et al.*, where the mean post-therapy TPCs was half that recorded at baseline [48]. In contrast, no significant differences were noted in the control groups except for the one studied by Altan *et al.*, which was treated with balneotherapy without physical exercises [50].

For the purposes of the present review, we also analyzed the TPCs in control and experimental groups with the Student's t test. Although there were no significant differences between the two groups' baseline values, those recorded after completion of therapy were markedly different. It is important to note that in the study by Ardiç *et al.* significant differences between the experimental and control groups were present at baseline, but the worse scores were actually found in the experimental group (15.25 *vs* 12.78 in controls) [47]. In the study by Altan *et al.*, where controls and experimental group patients alike received

Table 2
Statistical analysis used in the studies included in the review

Authors	Quantitative findings	Methods to analyze the results A	Methods to analyze the results B
Fioravanti *et al*. [46]	means ± standard deviation	intragroup comparison of base-line and post-treatment data	intergroup comparison of data pre and post-treatment
Ardiç *et al*. [47]	means ± standard deviation	intragroup comparison of base-line and post-treatment data	intergroup comparison of data pre and post-treatment
Evcik *et al*. [48]	means ± standard deviation	intragroup comparison of base-line and post-treatment data	intergroup comparison of data pre and post-treatment
Dönmez *et al*. 49]	medians and ranges (1)	intragroup comparison of base-line and post-treatment data	intergroup comparison of data pre and post-treatment
Altan *et al*. [50]	means ± standard deviation	intragroup comparison of base-line and post-treatment data	intergroup comparison of data pre and post-treatment
Özkurt *et al*. [51]	medians and ranges (1) means ± standard deviation (2)	intragroup comparison of base-line and post-treatment data	intergroup comparison before the beginning of the treatment
Cimbiz *et al*. [52]	means ± standard deviation	intragroup comparison of base-line and post-treatment data	_____

(1)Intervals between minimum and maximum values; (2)only for the comparison between experimental and control group before the beginning of the treatment.

balneotherapy, the improvement in TPCs was not significantly affected by the addition of physiotherapy in the experimental group [50] *(Table 4)*.

Fibromyalgia Impact Questionnaire

FIQ scores from the different studies also confirm the efficacy of balneotherapy on symptoms of the disease. The questionnaire was not used in the study by Cimbiz *et al.* [52], but in all the other studies highly significant differences were observed between baseline and post-treatment scores in the experimental groups. In contrast, no significant differences were noted after therapy in the control group, and in some studies longer-term follow-up assessments revealed scores that were actually worse than those found at baseline. In the study by Altan *et al.*, where all patients received balneotherapy, significantly improved scores were seen at the 12-week assessment in both the experimental and control groups, but by week 24 the difference was no longer significant in the control group (where balneotherapy was administered without physiotherapy) [50]. In the study of Özkurt *et al.* where the values are expressed as median and min/max in the experimental group were 57.6 (23-92.1) before the treatment and 41.9 (11.4-77.2) after the treatment but in the control group were respectively 52.5 (10.3-86.1) and 49.5 (19.7-87).

For the purposes of this review, we also used the Student's t test to compare FIQ scores recorded at different time points in the experimental and control groups only for the four studies that used the same methodology to evaluate the results (means ± SD scores).

Baseline scores for the 2 groups were not significantly different in any of the studies, but post-treatment assessments generally revealed significant intergroup differences in favor of the experimental subjects. In the study by Ardiç *et al.*, the baseline scores for the experimental group were actually worse than those of controls (although, as noted above, this difference was not significant because in the control group was used thermal balneotherapy without physical therapy with exercises) [47]. Three weeks later, the scores of the controls had actually increased slightly, whereas those of the experimental group were appreciably improved, with a decrease of approximately 10 points, although this change, too, failed to achieve statistical significance. As for the study by Altan *et al.*, post-treatment scores in the 2 groups were (not surprisingly) similar, even at 24 weeks [50] *(Table 5)*.

Beck Depression Inventory

The Beck Depression Inventory (BDI) was used to assess efficacy in 4 of the studies we reviewed but in the study of Özkurt *et al.* the results were expressed as median (min-max) values [51]. Ardiç *et al.* [47] and Evcik *et al.* [48] found significant improvement at 3 weeks in the experimental group ($P < 0.001$) but not in the controls. The latter study also included an assessment 24 weeks after completion of treatment, which showed no significant differences (*vs* baseline) in either group of patients. Similar findings were reported by Altan *et al.*, who found significant BDI improvement at 12 and 24 weeks only in the experimental group [50].

Our own analysis, based on the Student's t test, of intergroup BDI differences documented in these studies is summarized in *Table 5*. In the first of these studies, our analysis revealed a significant difference between the baseline values for the two groups ($P = 0.003$) (a situation that is generally unacceptable in an RCT) [47]. Compared

Table 3
Results observed in the 4 studies that assessed efficacy with visual analogue scores of symptom severity

Study	Assessment point	Mean ± SD scores		P *
		Experimental group	Control group	
Fioravanti *et al*. [46][(a)]	Baseline	65.64 ± 1.51	69.12 ± 17.94	NS
	2 wks	53.17 ± 9.23	68.66 ± 16.98	< 0.000
	16 wks	53.44 ± 7.99	70.88 ± 6.13	< 0.000
Ardiç *et al*. [47]	Baseline	8.17 ± 0.84	8.00 ± 0.76	NS
	3 wks	4.00 ± 2.17	8.25 ± 0.89	< 0.000
Evcik *et al*. [48]	Baseline	7.2 ± 1.6	7.3 ± 1.3	NS
	3 wks	2.7 ± 1.3	6.1 ± 1.2	< 0.000
	24 wks	3.5 ± 1.0	6.1 ± 1.2	< 0.000
Altan *et al*. [50][(b)]	Baseline	7.91 ± 1.81	7.5 ± 1.82	NS
	12 wks	5.81 ± 2.7	5.63 ± 1.62	NS
	24 wks	5.39 ± 2.84	6.36 ± 2.33	NS

*Intergroup comparison, Student's t test; [(a)]visual analogue scale (VAS) for minor symptoms (score range 0-100); [(b)]experimental group and control group received hot mineral water baths experimental group also received physical therapy with exercises.

Table 4
Results observed in the 4 studies that assessed efficacy in terms of pain at tender points

Study	Assessment point	Mean ± SD scores		P*
		Experimental group	Control group	
Fioravanti *et al*. [46]	Baseline	13.83 ± 2.74	14.00 ± 2.32	NS
	2 wks	9.67 ± 5.31	14.24 ± 2.72	< 0.000
	16 wks	9.17 ± 4.16	14.53 ± 2.67	< 0.000
Ardiç *et al*. [47]	Baseline	15.25 ± 1.77	12.78 ± 1.48	< 0.000
	3 wks	11.42 ± 3.12	13.89 ± 2.32	< 0.003
Evcik *et al*. [48]	Baseline	13.5 ± 2.0	13.8 ± 2.6	NS
	3 wks	5.9 ± 2.7	12.7 ± 2.3	< 0.000
	24 wks	6.2 ± 2.2	12.9 ± 2.3	< 0.000
Altan *et al*. [50][(a)]	Baseline	15.29 ± 2.21	15.95 ± 1.59	NS
	12 wks	8.46 ± 3.71	10.04 ± 3.18	NS
	24 wks	8.79 ± 3.80	10.77 ± 4.96	NS

*Intergroup comparison, Student's t test; [(a)]experimental group and control group received hot mineral water baths; experimental group also received physiotherapy (exercises).

with the experimental group, the controls displayed a markedly lower BDI at baseline. However, at the 3-week assessment, the indexes for the two groups were no longer significantly different. In other words, the experimental group entered the study with more severe depression than the controls, but after completion of the spa therapy protocol, their depression had improved to the extent that it was similar to that seen in controls, thereby confirming the efficacy of spa therapy. In the study by Evcik *et al.* the two groups were not significantly different from one another at baseline, but significant differences emerged at the 3-week and 24-week assessments, with lower mean BDIs in the experimental group at both time points [48]. The groups studied by Altan *et al.* had similar BDI profiles at baseline, but by week 12 the index for the experimental group was significantly lower than that of the controls [50]. Twenty-four weeks later, however, this improvement was no longer significant *(Table 6)*. Finally in the study of Özkurt *et al.* [51] the values measured before and after the treatment expressed as median (min-max) were respectively 14 (5-26) and 10 (0-32) and the differences were significant at the Friedman test, but in the control group the values were 11.5 (3-30) and 11.5 (2-31) and the differences were not significant.

Other parameters used to assess efficacy

In some of the studies, other parameters were also used to clinically assess the patients' conditions. Fioravanti *et al.* [46], for example, used the Health Assessment Questionnaire [61, 62] and the Arthritis Impact Measurement Scales, which are used to evaluate rheumatic diseases in general but are not specific for the FMS [63, 64]. As for Dönmez *et al.* [49] they used VAS not only to evaluate pain but also to assess other FMS symptoms (sleep, fatigue, anxiety, etc.); similar considerations apply to the study by Altan

Table 5
Results observed in the 4 studies that assessed efficacy in terms of Fibromyalgia Impact Questionnaire scores

Study	Assessment point	Mean ± SD scores		P*
		Experimental group	Control group	
Fioravanti *et al*. [46]	Baseline	61.00 ± 16.71	66.84 ± 18.60	NS
	2 wks	46.83 ± 20.82	68.18 ± 17.26	< 0.000
	16 wks	43.64 ± 19.82	66.41 ± 18.40	< 0.000
Ardiç *et al*. [47]	Baseline	62.58 ± 9.72	59.24 ± 11.32	NS
	3 wks	52.81 ± 11.47	61.49 ± 8.09	NS
Evcik *et al*. [48]	Baseline	48.5 ± 8.8	48.4 ± 8.9	NS
	3 wks	12.8 ± 5.6	46.6 ± 9.4	< 0.000
	24 wks	29.5 ± 4.8	48.1 ± 8.8	< 0.000
Altan *et al*. [50][(a)]	Baseline	62.58 ± 13.14	57.47 ± 11.67	NS
	12 wks	48.29 ± 19.4	50.17 ± 11.95	NS
	24 wks	49.37 ± 20.35	52.96 ± 16.92	NS

*Intergroup comparison, Student's t test; [(a)]experimental group and control group received hot mineral water baths; experimental group also received physical therapy with exercises.

Table 6
Results observed in the 3 studies that assessed efficacy in terms of Beck Depression Inventory scores

Study	Assessment point	Mean ± SD scores		P*
		Experimental group	Control group	
Ardiç *et al*. [47]	Baseline	24.25 ± 7.34	14.44 ± 5.39	< 0.003
	3 wks	16.08 ± 6.02	17.78 ± 6.87	NS
Evcik *et al*. [48]	Baseline	13.9 ± 3.8	14.3 ± 3.8	NS
	3 wks	7.0 ± 1.9	13.1 ± 3.3	< 0.000
	24 wks	11.3 ± 2.5	13.3 ± 3.4	< 0.05
Altan *et al*. [50][(a)]	Baseline	14.08 ± 5.20	14.59 ± 5.86	NS
	12 wks	9.21 ± 6.97	19.95 ± 5.79	< 0.05
	24 wks	10.00 ± 7.57	14.86 ± 9.45	NS

*Intergroup comparison, Student's t test; [(a)]experimental group and control group received hot mineral water baths; experimental group also received physical therapy with exercises.

L. *et al.*, which included patients' overall assessments of their ability to carry out daily activities and physicians' assessments of the patients' general level of health [50]. Özkurt *et al.* adopted Turkish version of Short Form 36 (SF-36) which is a 36-item questionnaire providing informations about health status [51, 65, 66].

These were not considered in the present review since they could not be compared with corresponding data from the other studies. The study by Ardiç *et al.* deserves special mention [47]. These investigators also assessed serum levels of inflammation markers and found a significant post-treatment decrease in PGE_2 levels, which was seen solely in the experimental group.

DISCUSSION

Spa therapy is a time-honored therapeutic practice, which has been used throughout the world and was especially popular in the cultures of ancient Greece and Rome. For centuries, its efficacy was supported by empirical data alone, but in today's world of evidence-based medicine, claims of therapeutic efficacy must be based on data generated by RCTs. In the case of spa therapy, however, this type of research is associated with some obstacles, because a double-blind placebo control is difficult to design, when the test therapy consists of mud-packs or mineral water baths, and it is not easy to form a control group that will receive "placebo" therapy. Nonetheless, in our opinion, the studies considered in our systematic review (6 of which were RCTs) furnish acceptable evidence of the efficacy of balneotherapy for long-standing, symptomatic management of the FMS. This conclusion is also supported by findings from other recent RCTs, which have focused on the efficacy of spa therapy in other rheumatological diseases and in pain management in general [67-70], and hot mineral water baths and mud-pack therapy are also known to be associated with other effects that can also reasonably be expected to improve the symptoms of FMS, such as increases in plasma endorphin and cortisol levels, activation of the diencephalic-pituitary-adrenal axis, and decreases in plasma levels of several inflammatory mediators (IL-1, IL-6, PGE_2, LTB_4, TNF-α) [47, 71-82].

Spa therapy can be useful, as alternation, to break during some time drug therapy, that is based on

antiinflammatory agents and analgesics. These drugs have a stronger activity on pain and phlogosis, but they have also adverse side effects. Spa therapy generally is almost lacking of collateral effects.

CONCLUSION

As noted earlier, a number of drugs are used to treat fibromyalgia, and our systematic review shows that balneotherapy and mud-packs with mineral waters from thermal springs could serve as a safe and effective adjunct to these approaches, providing long-lasting attenuation of the major symptoms of this syndrome. The data we reviewed indicate that sulfate-bicarbonate waters and those containing iodine and bromine salts could be effective for this purpose, but future studies might add other types of mineral water to this list. The most common form of therapy involved hot mineral-water baths at least 12 times over a 2-week period, with or without hot mud-pack therapy or physical therapy.

The studies we reviewed differed markedly from one another in terms of the methods used. Consequently, meta-analysis of the data was not possible. However, comparison of experimental and control group data with the Student's t test (or the Friedman test in the study of Özkurt *et al.*) showed highly significant improvement in the clinical parameters assessed by the investigators that was generally limited to the test group alone. The only exception was the study by Altan *et al.*, who compared balneotherapy alone (controls) and balneotherapy associated with physiotherapy. In this case, similar improvement was seen in both groups at all assessment points [50].

Therefore, on the basis of our review, mineral-water balneotherapy appears to offer proven efficacy for the treatment of fibromyalgia. Naturally, these findings might receive additional confirmation in the future from more in-depth studies conducted in multiple spas. For patients with a disease like FMS, which has clear psychological components, spa therapy offer additional benefits that could be therapeutic, such as a pleasant climate, relaxing natural scenery, and clean air.

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Conflict of interest statement

There are no potential conflict of interest of any financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of this study.

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