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Preliminary Research Article

A Multicenter, Prospective, Randomized, Placebo-Controlled, Double-Blind Study of a Novel Pain Management Device, AT-02, in Patients with Fibromyalgia

Hiroshi Oka, MD, PhD,*,† Kenji Miki, MD, PhD,‡,§ Iwao Kishita,¶ David F. Kong, MD, AM, DMT,‖ and Takahiro Uchida, MD, MSc, PhD‖‖

*Tokyo Rheumatism Pain Clinic, Tokyo, Japan; †Department of Rheumatology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan; ‡Faculty of Health Science, Osaka Yukioka College of Health Science, Osaka, Japan; §Orthopaedic Surgery and Rheumatology, Hayaishi Hospital, Osaka, Japan; ¶PEACE OF MIND Co., Ltd., Kumamoto, Japan; ‖Duke Clinical Research Institute, Durham, North Carolina, USA; ‖‖Japanese Organization for Medical Device Development, Inc., Tokyo, Japan

Correspondence to: Hiroshi Oka, MD, PhD, Tokyo Rheumatism Pain Clinic, 2F Echizenya Building, 1-1-6 Kyobashi, Chuo-ku, Tokyo 104-0031, Japan. Tel: +81-3-6202-9080, ext. 9081; Fax: +81-3-6202-9082; E-mail: hoka@pain-clinic.tokyo

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Abstract

Objectives. Existing treatments for fibromyalgia have limited efficacy, and only a minority of individuals clinically respond to any single intervention. This study was a prospective, multicenter, randomized, double-blind, controlled clinical trial to evaluate the feasibility of alternating magnetic field therapy in fibromyalgia patients by comparing the Angel Touch device (AT-02) with a sham control (S-01). **Methods.** Two sites enrolled 44 subjects with diagnosed fibromyalgia. After informed consent, subjects taking prohibited concomitant drugs underwent a washout period of two or more weeks. All subjects then began a one-week run-in period. Numerical rating scale (NRS) pain scores were collected without device intervention for one day, followed by S-01 application to four or more painful sites for 10 minutes at each site, twice daily for six days. Subjects were then randomized to AT-02 or S-01, applied to four or more painful sites for 10 minutes at each site, twice daily for eight weeks. NRS scores were obtained twice daily during the entire treatment period. **Results.** The primary end point (change in NRS ± SD at week 8 vs baseline) was –0.94 ± 1.33 in the AT-02 group and –0.22 ± 1.38 in the S-01 group. A trend toward a between-group difference in eight-week NRS scores favored the AT-02 group (–0.73, 95% confidence interval = –1.56 to 0.11, $P = 0.086$). An adjusted repeated measure analysis detected a significant difference in NRS scores ($P = 0.039$). **Conclusions.** The reduction in NRS scores for AT-02 relative to sham was comparable to reductions observed in meta-analyses of fibromyalgia drug therapy. The unadjusted results and the persistence of the pain score reductions remain encouraging.

Key Words: Chronic Pain; Clinical Trial; Fibromyalgia; Magnetic Field Therapy; Myofascial Pain Syndrome; Randomized Controlled Trial

Introduction

Fibromyalgia is a common chronic pain disorder characterized by severe systemic pain and tenderness as the predominant symptom, often accompanied by neuropsychiatric symptoms, sleep disorder, depression, and dysautonomia [1,2]. The prevalence rates of fibromyalgia in Europe, Asia, and North America are comprable; fibromyalgia sufferers account for approximately 2% of the developed world's population [1,3].

Pharmacotherapy remains the principal treatment modality, although the efficacy of individual drugs is variable. Analgesics, antidepressants, and antiepileptics have been evaluated for fibromyalgia, with mixed results [2,3]. Pregabalin, an α2δ1 modulator, has analgesic, anticonvulsant, and anxiolytic-like properties and has been approved in the United States for peripheral neuropathic pain and fibromyalgia [4–7]. Other treatments include exercise therapy, cognitive behavior therapy, psychotherapy, and thermotherapy, but only a minority of individuals experience a clinically relevant response to any single intervention, leading to a multidisciplinary approach [2,3]. Existing treatments for fibromyalgia have limited efficacy and a high prevalence of adverse effects, leading to poor adherence. Thus, there is an unmet need for effective therapeutic modalities for fibromyalgia.

Device therapy for fibromyalgia has principally centered on transcutaneous electrical nerve stimulation (TENS) with delivery of pulsed electrical currents across the intact skin surface to stimulate peripheral nerves [1,8–10]. Portable, battery-powered TENS devices allow patients to self-administer electrical pulses with varying frequency, amplitude, and duration. Conventional TENS uses high-frequency, low-intensity currents to produce a strong, nonpainful sensation, and acupuncture-like TENS uses low-frequency, high-intensity currents to produce pulsate sensations, phasic muscle contractions, or both. A systematic overview of 19 randomized controlled trials with 1,346 participants provided tentative evidence that TENS reduces pain intensity over placebo (no current) TENS when administered as a standalone treatment for acute pain in adults [9]. Randomized clinical trials of TENS in fibromyalgia are ongoing [10].

An alternative approach to neuronal stimulation is induction of current using a magnetic field, rather than injection of current via electrodes. Exposure to alternating magnetic fields has been shown to relieve pain in animal models and human subjects [11–15]. Application of a dual magnetic field at 83.3 MHz/2 kHz increased intracellular calcium in cultured nerve cells, activated nerve growth factor (NGF) production in cultured glial cells, and increased neurotrophic mRNA expression levels in astrocytes [13,15]. In a rat sciatic nerve model of neuropathic pain, a seven-day course of magnetic stimulation created an analgesic effect that was attenuated by an anti-NGF antibody [15]. Analgesic effects have been suggested in human volunteers with shoulder stiffness [14], and an open-label series of 10 subjects with fibromyalgia exposed to magnetic stimulation demonstrated a reduction in numerical rating scale (NRS) pain scores.

This study was a prospective, multicenter, randomized, double-blind, controlled clinical trial to evaluate the feasibility of alternating magnetic field therapy in patients with fibromyalgia by comparing the efficacy and safety of the Angel Touch (AT-02) device with a sham control (S-01).

Methods

Study Device

Angel Touch (AT-02) is a minimally invasive device that consists of a controller and dual coil emitter assembly powered by a 3.7-volt battery. The dual emitter simultaneously generates alternating magnetic fields at 2 kHz and 83.3 MHz with field strengths of 20–24 μT and 400–500 nT, respectively. A magnetic field has both a magnitude and a direction; an alternating (oscillating) magnetic field exhibits a change in the magnitude and polarity of the field without a change in the direction. The overall energy approximates one-third of terrestrial magnetism. The controller has a timer function designed to discontinue power 10 minutes after the device is turned on.

The sham control device (S-01) has an identical resin case and controller unit but does not generate any alternating magnetic fields.

Study Population

Two sites in Japan (Tokyo Rheumatism Pain Clinic and Center for Pain Management, Hayaishi Hospital) enrolled subjects with newly diagnosed fibromyalgia and subjects with fibromyalgia treated with medical intervention. Subjects were between 20 and 80 years of age at the time of informed consent and met the American College of Rheumatology (ACR) 1990 diagnostic criteria for fibromyalgia [16]. All subjects had a pain numerical rating scale (NRS) of $\geq$4 and persistent pain for three months or longer. Although some patients were seeking additional treatment options other than pharmacotherapy, others were recruited from a group of patients who were satisfied with their existing treatment options. Written informed consent was obtained from all subjects. Investigators excluded subjects with major depression, schizophrenia, or dissociative disorder; poorly controlled thyroid dysfunction; previous pain-inducing disease (e.g., traumatic injury, arthritis, and autoimmune disease); implantable or life-sustaining electrical medical devices or ECG recorders; expected survival of less than three years; renal impairment with serum creatinine $\geq$2.5 mg/dL; previous drug or ethanol abuse; and dementia. Subjects with metal implants (e.g., artificial hips) were excluded unless the study device could be used 3 cm or more from the implant site. The study excluded subjects with intractable fibromyalgia, defined as an NRS of $\geq$4 despite coadministration of three or more of the following drugs: strong and weak opioid analgesic (such as tramadol, buprenorphine, fentanyl), pregabalin, duloxetine, and amitriptyline. Subjects could not be participating in another clinical drug or device trial. Pregnant women were excluded from the study, and all female subjects of childbearing potential underwent pregnancy testing.

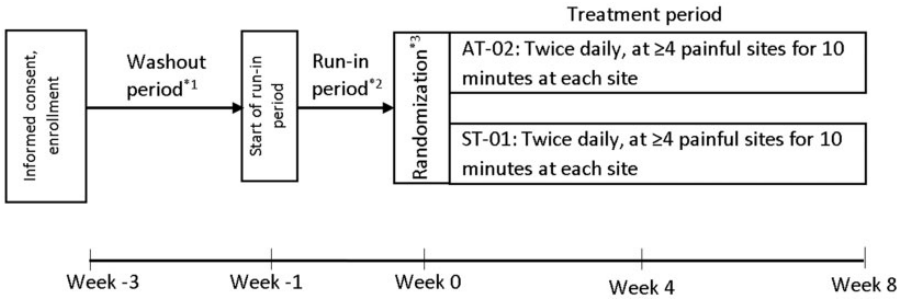

Figure 1. Study design. *1: Subjects taking a pain relief agent indicated for fibromyalgia or prohibited concomitant drugs (defined elsewhere) before enrollment underwent a washout period of two or more weeks immediately before the run-in period. A washout period was not required for subjects with newly diagnosed fibromyalgia and not taking prohibited drugs. *2: On day 1 of the run-in period, the sham device (S-01) was not used, and only numerical rating scale (NRS) measurement was performed. From day 2 of the run-in period, the sham device (S-01) was used twice daily at four or more painful sites for 10 minutes at each site. *3: Eligibility criteria at randomization: After the end of the run-in period, each subject was assessed for the placebo effect, and those with ≥30% improvement in mean NRS after the run-in period were excluded from randomization.

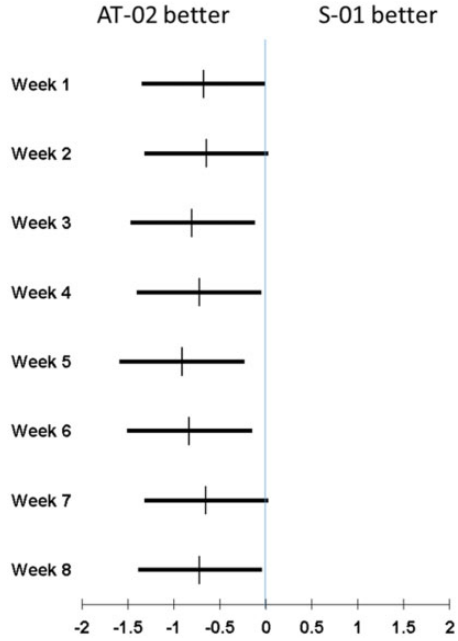

Figure 2. Between-group change in numerical rating scale (NRS) for each week in the treatment period, mixed effect model for repeated measures (MMRM) analysis with baseline NRS as the covariate. Vertical bars represent the point estimate of MMRM analysis; the extents of the horizontal bars represent 95% confidence limits.

Study Design

After screening and informed consent, subjects were enrolled in the study (Figure 1). Subjects taking a pain relief agent indicated for fibromyalgia or prohibited concomitant drugs before enrollment underwent a washout period of two or more weeks. Prohibited drugs included pregabalin; duloxetine hydrochloride; milnacipran hydrochloride; narcotic and non-narcotic analgesics (e.g., tramadol); local anesthetics used for pain relief; corticosteroids (except nasal drops, eye drops, ear drops, and inhalations); antidepressants (e.g., tricyclic antidepressants); serotonergic and adrenergic drugs, (e.g., 5-HT3 inhibitors, 5-HT4 inhibitors, 5-HTIB/ID receptor agonists, cyproheptadine hydrochloride, dimetotiazine mesilate, ifenprodil tartrate, adrenergic agonists, and MAO inhibitors); other drugs indicated for fibromyalgia in foreign countries; folk remedies; and all new pain relief drugs, except acetaminophen at a dose of up to 1,500 mg/d for the relief of fever or intolerable pain. A washout period was not required for subjects with newly diagnosed fibromyalgia and not taking prohibited drugs. All subjects then began a one-week run-in period. NRS scores were collected without device intervention for one day, followed by application of the S-01 control device to four or more painful sites for 10 minutes at each site, twice daily, for six days. At the conclusion of the run-in period, subjects without ≥30% improvement in mean NRS (measured once each in the morning and evening) observed at the last measurement in the run-in period compared with mean NRS measured on day 1 of the run-in period were randomized to either AT-02 or S-01. The assigned device was applied to four or more painful sites for 10 minutes at each site, twice daily for eight weeks. Baseline NRS scores were obtained twice daily during the six-day exposure to the S-01 device during the run-in period (days 2–7). NRS scores were also obtained twice daily during the entire eight-week treatment period. All subjects maintained diaries to record NRS values, sites of device application, adverse events, device status or malfunctions, and concomitant medications.

Patients with ischemic heart disease or ischemic cerebrovascular disease were allowed to use aspirin at a dose of ≤325 mg/d for antiplatelet therapy.

End Points and Analyses

The primary end point was the difference between the mean NRS at week 8 of the study period and the mean NRS during the six-day run-in period. Summary statistics of NRS during the run-in period (baseline) and at week 8 of the treatment period were calculated for each group.

A between-group comparison was performed using mixed effect model for repeated measures (MMRM) analysis with baseline NRS as the covariate. Secondary end points included the change over time in mean NRS for weeks 1 through 8 in the treatment period from the mean NRS during the run-in period. Summary statistics of pain intensity at baseline and at week 8 were calculated for each group. These summary statistics of the difference at week 8 from baseline were calculated and evaluated by *t* test. The two-sided significance level for the statistical tests was 0.05.

In addition to using NRS scores as a continuous measure, the number and percentage of patients with ≥30% and ≥50% response in NRS were calculated in each group and subjected to between-group analysis using the logistic regression model, with NRS during the run-in period as the covariate. Similarly, the number and percentage of patients with ≥30% and ≥50% response in pain intensity were calculated in each group and subjected to between-group analysis by the logistic regression model, with pain intensity at the start of treatment as the covariate. Exploratory subgroup analyses were performed by age, disease duration, and baseline patient characteristics.

As a sensitivity analysis, covariance analysis was prespecified with baseline pain intensity as the covariate, using missing values imputed by modified baseline-observation-carried forward (mBOCF) and last-observation-carried-forward (LOCF) approaches. In the mBOCF method, missing values were imputed by the baseline value in subjects who discontinued the study due to an adverse event and by the value at discontinuation (mean of nearest seven days for NRS) in subjects who discontinued the study for any other reason. In the LOCF method, missing values were imputed by the value at discontinuation (mean of nearest seven days for NRS) in subjects who discontinued the study. For the primary efficacy end point (NRS), missing NRS values during week 8 were imputed by a modified LOCF method. If one of the two NRS scores in a single day was missing, the nonmissing value was used as the NRS score for the day. If both NRS scores for a single day were missing, the day would be subtracted from the denominator used to calculate the mean NRS score for week 8.

The analysis population was established according to intention to treat. The sample size estimates assumed that the effect of AT-02 on NRS at week 8 compared with baseline would be similar to the effect observed in the previous single-arm study (mean = 3.39), and that the effect in the sham group would be similar to subjects taking placebo in a fibromyalgia drug study (mean = 1.58). Assuming a standard deviation of 1.93 and an alpha of 0.05, a study of 19 subjects per arm would have 80% statistical power to detect a difference in the mean NRS between the two groups. Enrollment was planned to be 20 subjects per arm, to allow for one dropout subject in each arm.

This study was conducted in compliance with the Declaration of Helsinki and applicable ethics guidelines. The study protocol and documentation were approved by the central ethics committee (institutional review board) of Adachi Kyosai Hospital, Medical Corporation Shinwakai. It is registered in the UMIN Clinical Trials registry (UMIN000024011).

Results

A total of 44 subjects were evaluated between September 2016 and January 2017, with 23 randomized to the AT-02 group and 21 randomized to the control S-01 group. One subject in the S-01 group withdrew consent during the study without using the study device. Basedline characteristics of the subjects are shown in Table 1. At baseline, 16 subjects (69.6%) in the At baseline, 16 subjects (69.6%) in the AT-02 group and 13 subjects (61.9%) in the S-01 group used medicinal therapies for fibromyalgia, predominantly acetaminophen (40.9%) (Table 2).

Nearly all subjects (95.4%) reported ≥70% compliance with their assigned study device at the beginning of the treatment period, and all subjects reported ≥70% compliance with their assigned study device during week 8 of the treatment period. During week 8, primary end point data collection was 96% complete, with 24 missing values among 602 NRS score entries. No subjects discontinued the study for any reason, so the sensitivity analyses using mBOCF and LOCF were not required.

The primary end point (change in NRS at week 8 vs baseline) was –0.94 ± 1.33 in the AT-02 group and –0.22 ± 1.38 in the S-01 group. There was a trend toward greater reduction in NRS scores for the AT-02 group (–0.73, 95% confidence interval [CI] = –1.56 to 0.11), but the adjusted difference between the two groups did not reach statistical significance in the ANCOVA analysis ($P = 0.0859$). In the AT-02 group, NRS scores decreased from the baseline value starting from week 1 of the device use (Table 3). In the S-01 group, NRS scores increased slightly for the first three weeks of the treatment period but tended to decrease after week 4. At every time point from week 1 to 8, the overall mean NRS was lower in the AT-02 group than in the S-01 group, with differences between –0.64 and –0.91 (Figure 2). At week 8 of the treatment period, seven subjects in the AT-02 group reported at least a 30% reduction in NRS scores from baseline, compared with four subjects in the S-01 group ($P = 0.37$). Two subjects in the AT-02 group reported at least a 50% reduction in NRS scores from baseline, compared with one subject in the S-01 group ($P = 0.61$).

In the between-group comparison using MMRM with baseline NRS as the covariate, which was evaluated as a secondary end point, the unadjusted between-group difference in the change in NRS at week 8 was –0.72 (95% CI = –1.39 to –0.04, $P = 0.0386$).

Table 1. Subject characteristics

		All Subjects	AT-02 Group	S-01 Group	*P* Value*
No. of subjects		44	23	21	
Female gender		39 (88.6)	22 (95.7)	17 (81.0)	0.18
Age, y	<60	30 (68.2)	13 (56.5)	17 (81.0)	0.11
	Mean ± SD	52.6 ± 14.1	57.0 ± 15.4	47.8 ± 10.8	0.03
Body height, cm					
	Mean ± SD	159.68 ± 7.01	158.45 ± 6.61	161.03 ± 7.35	0.23
Weight, kg					
	Mean ± SD	56.53 ± 10.51	54.78 ± 10.09	58.43 ± 10.87	0.25
BMI, kg/m^2					
	Mean ± SD	22.17 ± 3.86	21.88 ± 4.23	22.48 ± 3.49	0.61
Duration of fibromyalgia, y	Mean ± SD	9.19 ± 9.51	10.62 ± 11.54	7.62 ± 6.55	0.30
	<5 y	16 (36.4)	7 (30.4)	9 (42.9)	0.39
	5–<10 y	13 (29.5)	9 (39.1)	4 (19.0)	
	≥10 y	15 (34.1)	7 (30.4)	8 (38.1)	
Prior treatment for fibromyalgia		18 (40.9)	9 (39.1)	9 (42.9)	1.00

BMI = body mass index.
*Fisher exact test for discrete characteristics, Student *t* test for continuous characteristics.

Table 2. Prior fibromyalgia treatments

	All Subjects		AT-02 Group		S-01 Group	
No. of subjects with any prior treatment	18		9		9	
Tramadol-acetaminophen (Tramacet)	9	(20.5)	5	(21.7)	4	(19.0)
Duloxetine (Cymbalta)	6	(13.6)	3	(13.0)	3	(14.3)
Pregabalin (Lyrica)	4	(9.1)	1	(4.3)	3	(14.3)
Alprazolam (Constan)	2	(4.5)	1	(4.3)	1	(4.8)
Aripiprazole (Abilify)	1	(2.3)			1	(4.8)
Amitryptyline (Tryptanol)	1	(2.3)			1	(4.8)
Trazodone (Oleptro)	1	(2.3)			1	(4.8)
Prednisolone (Predonine)	1	(2.3)			1	(4.8)
Diclofenac (Voltaren)	1	(2.3)			1	(4.8)
Celecoxib (Celecox)	1	(2.3)			1	(4.8)
Loxoprofen (Loxonin)	1	(2.3)	1	(4.3)		

In exploratory subgroup analyses, among those <60 years of age, the change in NRS at eight weeks was –1.47 ± 1.31 in the AT-02 group and 0.21 ± 1.05 in the S-01 group, compared with an opposite effect observed in subjects aged 60 years and older (AT-02, –0.24 ± 1.04; S-01, –2.06 ± 1.12). There was a greater effect in subjects with fibromyalgia duration <10 years (AT-02, –1.19 ± 1.24; S-01, –0.22 ± 1.10) compared with subjects who reported fibromyalgia for 10 or more years (AT-02, –0.36 ± 1.44; S-01, –0.23 ± 1.83).

There were no adverse reactions reported in either group. One patient in the AT-02 group exchanged the index device for another AT-02 device when the patient inappropriately used a magnetic belt covering over the index device. Examination of the index device revealed no malfunction.

Discussion

Magnetic field devices have been developed and clinically accepted for transcranial stimulation in the treatment of depression [17,18] and migraine headache with aura [12]. This investigation is the first randomized, double-blinded, controlled study of an alternating magnetic field device for fibromyalgia. The results of the study are consistent with the previous single-arm first-in-human registry and lay the groundwork for future pivotal investigations. Although the adjusted difference between the two groups did not reach statistical significance in the primary end point analysis, the magnitude of the observed reduction in pain scores relative to sham (–0.73) was comparable to the magnitude of NRS pain score reductions observed in meta-analyses of pregabalin (600 mg daily, –0.72; 400 mg daily, –0.70; 300 mg daily, –0.51) and duloxetine (120 mg daily, 0.99; 60 mg daily, 0.89; 20 mg daily, 0.79) [2]. Similarly, Japanese fibromyalgia trials have shown similar effect sizes for pregabalin (–0.44, 95% CI = –0.78 to –0.11) [6] and mirtazapine (–0.44, 95% CI = –0.72 to –0.17) [19]. No adverse reactions occurred in either group, suggesting that magnetic stimulation is at least as safe as existing fibromyalgia treatment methods.

As with any evaluation of a novel technology, empirically estimating the anticipated treatment effect is challenging. For fibromyalgia, the effect sizes for existing drug and device therapies are particularly diverse. The potential effect of a sham or placebo device over no therapy may also vary [8]. Unlike TENS, which creates perceptible sensations, which are simulated to various degrees in placebo-controlled studies, magnetic stimulation does not create meaningful sensory perceptions [14]. The effect of the S-01 control arm was therefore expected to approximate a pharmacologic placebo arm. The effect size observed in the randomized study population was smaller than the sample size assumptions, decreasing the statistical power to detect a difference in the primary end point to 40%. The unadjusted results of the mixed effect model for repeated measures (MMRM), showing a change in NRS at week 8 of –0.72 (95% CI = –1.39 to

Table 3. Change in NRS (adjusted for duration of device use) for each week in the treatment period, MMRM analysis with baseline NRS as the covariate

	AT-02 Group (N = 23)		S-01 Group (N = 21)		Between-Group Comparison of Change (AT-02 vs S-01)	
Time Point	Observed Value	Change vs Baseline	Observed Value	Change vs Baseline	Estimate (95% CI)	(*P* Value)
Baseline						
Mean ± SD	5.82 ± 1.55	–	5.66 ± 1.82	–	–	–
Median	5.50		5.58			
Q1, Q3	4.67, 6.92		4.75, 7.10			
Min, max	3.3, 10.0		1.8, 9.0			
Week 1						
Mean ± SD	5.41 ± 1.87	–0.42 ± 0.88	5.92 ± 1.73	0.26 ± 0.82	–0.67 (–1.35 to 0.00)	0.052
Median	5.57	–0.12	5.86	0.13		
Q1, Q3	4.00, 6.79	–0.74, 0.25	4.79, 7.00	–0.21, 0.58		
Min, max	1.8, 10.0	–3.6, 0.7	3.2, 9.0	–0.8, 3.0		
Week 2						
Mean ± SD	5.25 ± 1.91	–0.57 ± 1.05	5.74 ± 1.63	0.07 ± 0.74	–0.64 (–1.32 to 0.03)	0.062
Median	5.50	–0.29	5.93	–0.20		
Q1, Q3	3.86, 6.50	–1.25, 0.00	4.57, 6.64	–0.45, 0.54		
Min, max	1.3, 10.0	–4.1, 0.8	3.2, 9.0	–0.8, 2.2		
Week 3						
Mean ± SD	5.08 ± 1.98	–0.74 ± 1.15	5.72 ± 1.69	0.06 ± 0.86	–0.80 (–1.47 to –0.12)	0.022
Median	5.50	–0.45	5.93	–0.03		
Q1, Q3	3.57, 6.43	–1.61, 0.00	4.14, 6.79	–0.40, 0.75		
Min, max	1.1, 10.0	–4.3, 1.0	2.8, 9.0	–1.3, 2.1		
Week 4						
Mean ± SD	5.02 ± 2.02	–0.80 ± 1.16	5.59 ± 1.79	–0.08 ± 0.87	–0.72 (–1.40 to –0.05)	0.037
Median	5.00	–0.65	6.00	–0.25		
Q1, Q3	3.43, 6.43	–1.64, 0.12	4.00, 7.00	–0.65, 0.19		
Min, max	1.1, 9.6	–4.3, 0.6	2.7, 9.0	–1.5, 2.2		
Week 5						
Mean ± SD	4.90 ± 2.07	–0.92 ± 1.10	5.65 ± 1.86	–0.01 ± 1.05	–0.91 (–1.59 to –0.23)	0.009
Median	5.00	–0.37	5.50	0.00		
Q1, Q3	3.06, 6.25	–1.82, 0.00	4.21, 7.00	–0.60, 0.54		
Min, max	1.6, 10.0	–3.8, 0.4	3.0, 9.0	–2.1, 2.4		
Week 6						
Mean ± SD	4.90 ± 2.02	–0.92 ± 1.02	5.57 ± 2.16	–0.09 ± 1.21	–0.83 (–1.51 to –0.15)	0.017
Median	4.71	–0.61	6.00	0.00		
Q1, Q3	3.00, 6.29	–1.46, –0.21	3.42, 7.00	–1.02, 0.75		
Min, max	1.6, 10.0	–3.8, 0.2	1.6, 9.7	–2.7, 1.5		
Week 7						
Mean ± SD	5.10 ± 2.17	–0.72 ± 1.43	5.59 ± 2.17	–0.07 ± 1.29	–0.65 (–1.32 to 0.03)	0.061
Median	5.07	–0.57	6.00	0.12		
Q1, Q3	3.14, 6.57	–1.61, 0.00	3.64, 7.00	–0.88, 1.01		
Min, max	1.6, 10.0	–3.8, 2.8	1.4, 9.1	–2.7, 1.7		
Week 8						
Mean ± SD	4.89 ± 2.15	–0.94 ± 1.33	5.44 ± 2.33	–0.22 ± 1.38	–0.72 (–1.39 to –0.04)	0.039
Median	4.57	–0.69	5.64	0.00		
Q1, Q3	3.00, 6.50	–1.89, 0.00	3.00, 7.00	–0.83, 0.73		
Min, max	1.1, 10.0	–4.3, 1.3	2.3, 10.0	–3.1, 1.6		

CI = confidence interval; MMRM = mixed effect model for repeated measures; NRS = numerical rating scale.

–0.04, $P = 0.0386$), remain encouraging, as is the persistence of the pain score reductions over the eight-week observation period. The treatment effect was observed to fully appear within the first week and was maintained over time.

This feasibility study was designed to assess the effectiveness and adverse effect profile of the AT-02 device on fibromyalgia, unconfounded by pharmacotherapy. Consequently, all subjects were weaned from prohibited analgesic drugs before the study interventions began. Although a device with minimal adverse effects might be a preferable substitute for medications, an important future question is whether magnetic stimulation has an additive effect on background therapy. In an open-label study (N = 10) conducted to evaluate AT-02 in patients with pharmacotherapy, the mean NRS pain score was ⊿ 3.39, while one patient had an NRS pain score of ⊿ 7.5 at week 8. At 72 weeks, two of 9 patients

reported being pain free, with a mean NRS pain score of 3.0 for the group. Existing fibromyalgia therapies have modest efficacy, rendering them less suitable as active controls due to limited assay sensitivity. At this point, we believe sham-control trials remain ethical in this space as long as informed consent is obtained and subjects and investigators maintain the right to withdraw at any time.

The exploratory subgroup results suggest that there may be heterogeneous response to magnetic stimulation in fibromyalgia syndromes. Future studies may further define the characteristics of responders and nonresponders.

The methods used in this study incorporated modern features for chronic pain trial conduct, with particular attention to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The single withdrawn subject and overall adherence to the trial protocol minimized the impact of imputation. Unlike TENS device studies, where blinding is difficult due to the sensations associated with injected electrical current, the absence of significant sensations with active magnetic stimulation therapy facilitated a blinded intervention.

In conclusion, subjects with fibromyalgia who received magnetic field therapy tended to have lower NRS pain scores over an eight-week time period compared with control subjects exposed to a sham device. The findings in this sample support the evaluation of magnetic stimulation in larger-scale studies to determine long-term effects.

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