



## Effects of a 4-week AVACEN Treatment on Pain Perception in Fibromyalgia: An Open Label Study

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### Abstract

**Objectives:** To evaluate the efficacy of the AVACEN Treatment Method (ATM) at improving pain symptoms in fibromyalgia patients.

**Methods:** Twenty female and two male participants (26 to 76 years; M=48 years) diagnosed with fibromyalgia, were randomized into two groups. Group A (n=5) underwent one 10 min therapeutic warming session daily, and Group B (n=17 started, n=14 completed) underwent two 15 min warming sessions daily. The following endpoints were evaluated (a total of 10): widespread pain index (WPI), patient global impression of change, tender point counts (TPC), fibromyalgia impact questionnaire, Beck depression inventory, fatigue severity ratings, cognitive symptom severity, symptom severity score (SS) and weekly pain intensity ratings. Additional unconventional exploratory analysis of HRV and cytokines was performed to observe perception correlations of the participants.

**Results:** The daily 10 min warming sessions, resulted in a decrease in widespread pain and weekly pain intensity symptoms for the majority of participants in Group A. Increasing the treatment to two 15 min sessions daily demonstrated a pronounced reduction of pain symptoms for the participants in Group B. Data were analyzed with either a paired t-test, or the Wilcoxon signed rank test. The pre- and post-treatment data for Group B indicated a statistically significant reduction (p=0.05) in TPC, WPI, and SS scores. Inspections of HRV and Cytokines found no statistically significant data. No adverse events were reported.

**Discussion:** These results provide the first indications that the ATM has a statistically significant effect on the key scientifically recognized fibromyalgia diagnosis metrics of WPI, TPC and SS.

**Keywords:** Fibromyalgia; Widespread pain; Pain disorder; Therapeutic warming; AVACEN treatment method

### Studies

Patients with physician diagnosed FM were enrolled after IRB approval and trained in the use of the ATM device. Outcome measures included physician assessed FM diagnostic criteria including a tender point exam and self-assessed widespread pain ratings. A four-week pilot-study was conducted using ATM for 10 min once a day by 5 FM subjects (Group A). The study showed a reduction in FM related pain and related symptoms. A four-week follow-up study was conducted using ATM for 15 min twice a day by 17 subjects (2 male, 15 female) (Group B). All assessments were carried out before (n=17) and after (n=14) the treatment period. Data were analyzed with either a paired t-test, or the Wilcoxon signed rank test depending on parametric or non-parametric distribution. Comparing the data from before and after treatment for Group B indicated a statistically significant reduction (p=0.05) in Tender Point Counts (TPC), Widespread Pain Index (WPI) score and Symptom Severity (SS) score. These data suggest a positive effect of a one-month treatment with the AVACEN Treatment Method on Fibromyalgia pain and related symptoms.

### Introduction

Fibromyalgia (FM) is a common chronic pain disorder that also affects sleep and mood. The diagnosis of FM was classically made using a tender point exam system, but the new American College of Rheumatology Diagnostic Criteria recognizes the importance of quantitative measurement of widespread pain but still incorporates the key FM symptom of tender point count. The treatment of FM remains challenging, and the underlying pathology is poorly understood. Recent evidence implicates involvement of arteriovenous (AV) shunts of the extremities in FM pathology [1].

### The AVACEN Treatment Method

The AVACEN Treatment Method (ATM), previously known as the AVACEN Thermal Exchange System (TES) or the AVACEN Thermal Exchange Method (TEM), uses a therapeutic medical device and method that manipulates AV shunts in the palm of the hand. ATM noninvasively infuses heat into the circulatory system for whole body treatment.

### Fibromyalgia

Fibromyalgia (FM) is a complex chronic pain disorder that affects an estimated 10 million Americans [2,3]. FM is the second most

common rheumatologic disorder after osteoarthritis, and the most common diagnosis made by rheumatologists [2,3]. The estimated prevalence of FM in the general population is 2%, and 6-15% of outpatients suffer from FM. In both community and clinic settings, 85-90% of sufferers are women, and many are middle aged [2,3]. While it occurs most often in women, it has also been found to occur in men and children of all ethnic backgrounds [2,3]. The symptom presentations of FM vary widely and it can interfere with basic daily activities or become extremely debilitating for those with severe symptoms. The primary symptom of FM is widespread body pain [4], although many individuals with FM also complain of tenderness in specific areas of the body. Therefore, the development of pain when 4 kg of pressure is applied to 18 specific points along the body has been used to distinguish FM patients from non-FM patients [5,6]. Most people with FM also experience moderate to extreme fatigue, sleep disturbances; sensitivity to touch, light, and sound; and cognitive difficulties [7]. They may experience overlapping conditions such as irritable bowel syndrome, lupus and arthritis as well [8]. To date, the most consistently observed abnormalities in FM patients involve pain processing [9]. For instance, hyperalgesia and allodynia are often diagnosed in FM patients [10]. Hyperalgesia is an exaggerated and intensified experience of pain in response to a stimulus that ordinarily causes mild pain [11] Allodynia is a painful response to a stimulus that is not ordinarily painful. Hyperalgesia and allodynia result from sensitization, a process whereby the stimulus needed to generate a response decreases over time, while the amplitude of the response to any stimulus increases [12]. These nervous system alterations are considered fundamental features of chronic pain syndromes. Additionally, FM can be characterized by changes in the central nervous system (CNS) that result in altered pain perception [13]. Furthermore, heart rate variability (HRV) studies show that FM patients develop physiological changes that are consistent with ongoing sympathetic hyperactivity [14].

FM is also associated with considerable morbidity. As a result, the 2010 American College of Rheumatology diagnostic criteria for FM has shifted its focus to a diagnosis of exclusion in which assessments such as the Widespread Pain Index (WPI) and Symptoms Severity (SS) scale are used to rule out the possibility of other conditions. Additional standard diagnostic criteria include the presence of at least 11 out of 18 tender points on a physical examination and diffuse musculoskeletal pain (i.e., chronic widespread pain or CWP) for at least three months [15]. CWP is defined as pain that is present in the axial skeleton and at least two contralateral body quadrants [16].

The FDA has approved three prescription medications: pregabalin, duloxetine and milnacipran, for treating FM, and patients may also take analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) to help relieve the pain [17]. However, studies suggest that alternative noninvasive treatments can help alleviate pain in FM patients [18,19]. One such study found that participants with FM who received cortical electrostimulation, a noninvasive therapeutic approach that sends signals to the cortical tissue through electrodes placed on the scalp, reported symptom improvement that lasted for two or more years and reduced the need for medication [20]. This randomized placebo-controlled study also showed that FM patients reported modest improvements in pain, tender points, fatigue and sleep after electrostimulation [20].

Additional research suggests that anodal transcranial direct current stimulation, another noninvasive approach that uses low electrical currents to stimulate the brain *via* electrodes, can help improve pain

scores and quality of life for FM patients [21]. However, it is unclear whether these health benefits were due to the placebo effect. This was the case in one study where both the control group and FM participants who received low-frequency transcranial magnetic stimulation reported improved Fibro fatigue and Clinical Global Impression scores [22].

The AVACEN Treatment Method (ATM) is another alternative form of noninvasive, augmentative dry heat FM therapy. It uses active heat assisted by negative pressure that is applied to the palm of the hand of normothermic patients. Heat exchange occurs at the naturally occurring arteriovenous anastomoses (AVA) of the hand and the ATM utilizes these AVA to rapidly infuse heat into the circulatory system. Furthermore, as heat is applied to the surface of the palm, negative pressure is applied which enhances the continued exposure of blood to the warmed surface.

Previous studies have shown that blood vessels in the hand can be distended by exposing the hand to negative pressure and that the application of superficial heat to the mechanically-distended tissues increases blood flow through the hand [23]. When ATM is incorporated into a medical device for FM treatment, it is theorized that ATM distended tissues increases blood flow through the hand, thereby overriding potentially defective AV shunts, increasing microcirculation, and allowing muscle and skin tissue to acquire proper nutrition while promoting waste removal.

The current study is a broad open-label pilot study that was designed to understand the effects of ATM on FM patients, with endpoints including improvements in pain perception, depression, symptom severity, and quality of life. The ATM was applied in a minimal-therapeutic and therapeutic manner.

## Methods and Materials

The study was a 28-day (4-week) open-label trial that delivered a non-therapeutic ATM warming session to Group A (n=5) and a therapeutic ATM warming session to Group B (n=17). The research study design and the associated protocol were approved by the Institutional Review Boards of the University of California San Diego and the U.S. Department of Veteran Affairs. Pre- and post-treatment evaluations were conducted at the UCSD Pain Medicine Clinic in San Diego, CA. The participants completed the warming treatment sessions at home after being provided with an AVACEN Treatment Method device.

## Recruitment

The screening process was conducted through telephone interviews. Participants who were enrolled provided written consent and HIPAA approval was obtained prior to accessing their medical records. Patients who recently started, stopped, or changed pain or mood treatment were ineligible to enroll until three months had elapsed. Participants were advised to refrain from stopping, changing, or starting any new treatment programs other than the study intervention over the course of the study and to report any changes in their current treatment.

## Participants

Twenty female participants and 2 male participants, whose ages ranged from 21 to 76 years (M=48 years), that were diagnosed with FMS according to the 2010 ACR diagnostic criteria were enrolled in

the study. Three participants withdrew from the study for personal reasons and their post-therapy data were not obtained. Group A (n=5) underwent one ATM warming session for 10 min daily and Group B (n=14) underwent two 15 min ATM warming sessions daily.

### Study protocol

Following an initial telephone screening interview, the patients made two visits to the clinic: a pre-treatment visit (Experimental Day 1) and a post-treatment visit (Experimental Day 2) following the last day of the 28-day daily warming treatment regimen. On experimental day 1, additional screening was conducted, eligibility was confirmed, and the study procedures were explained to the participants. In addition, a physical examination and tender point assessment that focused on FMS symptoms was performed. Subjects then completed the Quality of Life assessment with the SF-36 Fibromyalgia Impact Questionnaire-Revised (FIQ-R) and the Beck Depression Inventory II. After a 5 min rest period, pain intensity and unpleasantness ratings were recorded using a numeric rating scale (NRS).

Additional assessments that were conducted included: baseline sensory thresholds (QST) testing, the Widespread Pain Index (WPI), the Patient Global Impression of Change (PGIC) Scale, the Fatigue Severity Ratings, Cognitive Symptom Severity Ratings, and Somatic Symptoms Severity Ratings.

On Experimental Day 1, participants were also trained on how to use the AVACEN Treatment Method (ATM) device. Participants underwent a brief warming treatment session. Each patient was then provided with an ATM device to take home. The first 5 patients (Group A) were instructed to do one 10 min warming session per day for 28 days. The next 17 patients (Group B) were instructed to do two 15 min warming sessions per day, for 28 days: once upon awakening and again in the evening before bed.

Each participant kept a diary to record their daily and weekly pain intensity, an unpleasantness rating, and their self-assessment of change on a 7 point Patient Global Impression of Change (PGIC) scale. Each participant was contacted by phone several times during the 4-week treatment period to ensure adherence to the protocol and to record adverse events.

After day 28, the participants reported to the clinic to return their ATM device and to complete the experimental day 2 post-treatment evaluation. Each of the assessments that were conducted on experimental day 1 was repeated on experimental day 2.

### Placebo condition

For the purposes of this study, the placebo effect has been defined as beneficial physiological or psychological changes associated with the application of a treatment known to be without any therapeutic effect for the specific condition being treated [24]. Therefore, the overall treatment results for Group B will need to be reduced by the placebo effects exhibited by non-therapeutic treated Group A to determine any net positive effect.

### Statistical methods

Descriptive statistics and correlation analyses were conducted by using either a paired t-test, or the Wilcoxon signed rank test depending on parametric or non-parametric distribution. A critical alpha level of 0.05 was used for all analyses.

## Results

The following common fibromyalgia endpoints were evaluated (a total of 10): widespread pain index, patient global impression of change, tender point count, fibromyalgia impact questionnaire, Beck depression inventory, fatigue severity ratings, cognitive symptom severity, symptom severity score (including somatic) and weekly pain intensity ratings.

No adverse events related to use of the ATM device or the ATM warming therapy were reported by any of the participants during the study.

Inspections of HRV and Cytokines found no statistically significant data. Although there appears to be a difference in these scores from pre- to post, these differences did not reach statistical significance (based on t-test analyses).

### Widespread pain index (Primary aim)

Widespread pain index scores for Group A and Group B at 4-weeks post ATM warming treatment were as follows (Table 1): For Group A (n=5): WPI scores improved by greater than 10% in 3 out of 5 (60%) participants, which reflected an average decrease of 24% from the pre-treatment scores; for Group B (n=14): WPI scores improved by greater than 10% in 13 out of 14 (93%) participants, which reflected an average decrease of 44% from the pre-treatment scores (Table 1). Comparing the data from before and after treatment for Group B indicated a statistically significant reduction ( $p=0.05$ ) in Widespread Pain Index (WPI).

### Tender point count (Primary aim)

Tender point count scores for Group A and Group B at 4-weeks post ATM warming treatment were as follows (See Table 1): For Group A, 2 out of 5 (40%) participants reported a lower tender point rating of by greater than 10%. For Group B, 8 out of 13 (62%) participants reported a lower tender point rating of by greater than 10%. The tender point data for participant 15 was lost. Comparing the data from before and after treatment for Group B indicated a statistically significant reduction ( $p=0.05$ ) in Tender Point Counts (TPC).

### Symptom severity score ratings (Primary aim)

Symptom severity score ratings for Group A and Group B at 4-weeks post ATM warming treatment were as follows (Table 1): For Group A, overall symptom severity ratings markedly improved by greater than 15% in 2 of 5 (40%) participants. For Group B, overall symptom severity ratings markedly improved by 20% or more in 8 of 14 (57%) participants. Comparing the data from before and after treatment for Group B indicated a statistically significant reduction ( $p=0.05$ ) in Symptom Severity (SS) score.

### Somatic symptoms severity ratings

Somatic symptoms severity ratings for Group A and Group B pre- and post- 4 weeks ATM warming treatment were as follows (Table 1): For Group A, ratings decreased (improved) in 1 out of 5 (20%) patients. For Group B, ratings decreased (improved) in 9 out of 14 (64%) patients. No further statistical analysis was conducted for this endpoint.

### Patient global impression of change (PGIC) scale

The PGIC scale ratings were as follows (Table 1): 1=no change or worse, 2=almost the same, 3=a little better, 4=somewhat better, 5=moderately better, 6=better, 7=a great deal better. For Group A, 2 out of 5 participants (40%) felt there was overall improvement due to the warming treatment. For Group B, nine out of 14 (64%) participants felt that there was overall improvement due to the warming treatment. No further statistical analysis was conducted for this endpoint.

### Fibromyalgia impact questionnaire

The FIQ ratings for Group A and Group B at 4-weeks post ATM warming treatment were as follows (Table 1): For Group A, a total of 3 out of 5 (60%) participants rated their Quality of Life as markedly improved by greater than 10%. For Group B, a total of 11 out of 14 (79%) patients rated their overall quality of life to be improved by greater than 10%. No further statistical analysis was conducted for this endpoint.

### Beck depression inventory

The BDI ratings for Group A and Group B at 4-weeks post ATM warming treatment were as follows (Table 1): For Group A, depression severity scores decreased in 2 out of 5 (40%) participants (indicating improvement). For Group B, depression severity scores decreased in 13 out of 14 (93%) participants (indicating improvement). No further statistical analysis was conducted for this endpoint.

### Fatigue severity ratings

Fatigue severity ratings for Group A and Group B at 4-weeks post ATM warming treatment were as follows (See Table 1): For Group A, post-treatment fatigue severity scores decreased in 1 out of 5 (20%) participants. For Group B, post-treatment fatigue severity scores decreased in 7 out of 14 (50%) participants. No further statistical analysis was conducted for this endpoint.

### Cognitive symptom severity ratings

Cognitive symptom severity ratings for Group A and Group B at 4-weeks post ATM warming treatment were as follows (Table 1): For Group A, cognitive symptom severity scores decreased in 2 out of 5 (40%) participants (indicating improvement). For Group B, cognitive symptom severity scores decreased in 6 out of 14 (43%) participants (indicating improvement). No further statistical analysis was conducted for this endpoint.

### Average weekly pain intensity

Individual patient ratings of the average weekly pain intensity over the 4-week ATM warming treatment period were as follows (Table 1): For Group A, 3 of 5 participants (60%) reported marked decreases in weekly pain intensity. For Group B, 8 of 14 participants (57%) reported marked decrease in weekly pain intensity. No further statistical analysis was conducted for this endpoint.

Outcome/Measure	Patients Reporting Marked Improvement (%)		Average Change in Score/Measure		Significant Difference (p value)
	Group A 10 min/day	Group B 30 min/day	Group A	Group B	
Widespread Pain Index scores	60	93	24%	44%	0.05
Tender point count	40	62			0.05
Symptom Severity Score ratings	40	57			0.05
Somatic Symptoms Severity ratings	20	64			
Patient Global Impression of Change (PGIC)	40	64			
Fibromyalgia Impact Questionnaire	60	79			
Beck Depression Inventory	40	93			
Fatigue Severity Ratings	20	50			
Cognitive Symptom Severity Ratings	40	43			
Average Weekly Pain Intensity	60	57			

**Table 1:** Summary of all results, including p values.

### Placebo effect

Participants in the daily 10 min non-therapeutic treatment session (Group A) reported improved conditions in all 10 endpoint studies with a mean improvement of 42% for all participants. This improvement may be attributed mostly to the placebo effect and should be studied further.

### Discussion

Pain is a pervasive symptom of FM. FM patients report heightened responses to painful stimuli, and they exhibit evidence of central nervous system (CNS) alterations compared to controls [25]. Such alterations are believed to reflect central sensitization that originates from hyperexcitability of dorsal horn neurons in the spinal cord [26]. CNS alterations can amplify and spread pain by increasing central neural connections and triggering sensory neurons to release

substances that result in peripheral sensitization (hyperexcitability) of adjoining sensory nerves [27]. Thus, both central and peripheral sensitization can alter pain perception and predict the chronicity of symptoms in patients.

Based on our literature review and prior research, we expected that ATM treatment would result in reduced widespread pain associated with FM. Our results appear to uphold this assumption, as the subjects that received a 15 min therapeutic treatment twice per day (total daily treatment time of 30 min) demonstrated an overall reduction of more than 40% in widespread pain index scores after 30 days. 93% of these subjects also reported a reduction of 29.4% or more in widespread pain index scores. 62% also reported a lower tender point count of two or more points, and 57% reported a reduction of 20% or more in overall symptom severity score rating. We also expect that the duration of effect is limited. Anecdotal reports suggest that once the patient ceases using the device on a regular basis, their fibromyalgia symptoms may return within 30 days.

Furthermore, results from this study indicate that ATM therapeutic warming sessions are effective at improving other FM symptoms in addition to pain. The majority of the Group B participants reported experiencing relief in terms of depression and fatigue severity. Furthermore, ATM also appeared to help diminish fibromyalgia impact on quality of life for most participants. Therefore, although based upon small sample sizes, we believe this study provides preliminary evidence of ATM device effectiveness in treating numerous and varied symptoms associated with FM.

As no adverse events were reported, the overall results indicate that the ATM warming sessions were delivered in a safe and convenient manner without causing the dangerous side effects that are associated with taking the current FDA approved drugs for FM pain such as duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica).

Other studies have demonstrated that similar dry heat therapies can have beneficial effects in managing conditions with associated chronic pain [28]. Studies suggest that Waon therapy (which involves heat from a far infrared ray dry sauna) improves cardiac function, neurohormonal factors and symptoms in patients with chronic heart failure, as well as decreased pain scores and blood flow in patients with severe peripheral arterial disease (PAD); [29]. In patients with FM, research suggests that Waon therapy can help reduce pain and improve quality of life scores [30]. FM patients also self-reported using cold and heat therapies to manage their pain [31]. Another study found that laser heat therapy improved upper body flexibility and pain in women with FM [32]. Our study supports these findings.

The current study is not without limitations. Although the primary aims of the study produced statistically significant results, we used a convenience sample and did not use a recognized control group model in the study design. Historically in pain management medical device research using heat therapy, it has been difficult to design a valid control due to the subjects being physically aware of the local application of heat. However, we feel that the non-therapeutic treatment administered to Group A merits serious consideration as a control apparatus.

Due to budgetary restrictions, analyses were limited to repeated measurements of ANOVA for Group B. Nonetheless, these results are promising indicators of the positive effect of the AVACEN Treatment Method device on the primary FM diagnosis symptoms of widespread pain, tender point count and symptom severity score.

## Investigators

### Initial study

**Primary:** Tobias Moeller-Bertram, M.D., Dr. Med, MAS (Clinical Research) (UCSD, VA)<sup>1,2,3,4</sup>.

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### Follow-on study

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