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Sustained Acoustic Medicine: A Novel Long Duration Approach to Biomodulation Utilizing Low Intensity Therapeutic Ultrasound

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Abstract

Therapeutic ultrasound is an established technique for biomodulation used by physical therapists. Typically it is used to deliver energy locally for the purpose of altering tissue plasticity and increasing local circulation. Access to ultrasound therapy has been limited by equipment and logistic requirements, which has reduced the overall efficacy of the therapy. Ultrasound miniaturization allows for development of portable, wearable, self-applied ultrasound devices that sidestep these limitations. Additionally, research has shown that the timescale of acoustic stimulation matters, and directly affects the quality of result. This paper describes a novel, long duration approach to therapeutic ultrasound and reviews the current data available for a variety of musculoskeletal conditions.

Keywords

Therapeutic ultrasound; regeneration; biomodulation; SAM

1. INTRODUCTION

Ultrasound, or mechanical pressure waves with frequencies above 20 kHz, has been studied for over 70 years. Ultrasound waves are used for a diverse range of biomedical applications including imaging, tissue ablation, and exerting forces on objects in the body such as kidney stones[1, 2]. In each case, the energy transferred by the wave is utilized in the body to mediate some beneficial medical effect. Another technique is the use of ultrasound as a direct therapy, so the acoustic waves transfer energy into tissue to mediate beneficial effects[3, 4]. This is similar to therapies utilizing light, however, the longer wavelength associated with acoustic waves means they are attenuated to a lesser degree, enabling the waves to penetrate much deeper into the body than optical frequency electromagnetic waves of similar intensity. This therapy is used clinically to apply heat to deep tissue, in order to modulate cellular metabolism and tissue properties, and to apply mechanical stimulation, which causes increased nutrient transfer out of the blood stream and to the surrounding tissue[5, 6].

Therapeutic ultrasound is used in the treatment of muscle spasms, joint contractures, and to accelerate healing. Typical application of ultrasound therapy is performed in a clinical setting[6]. This is primarily due to the potential for thermal injury if traditional ultrasound

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therapy is provided improperly[1]. Ultrasound causes heating of tissue, and improper treatment can cause tissue damage. As a secondary cause, ultrasound equipment costs thousands of dollars, and typically is large enough to require dedicated space for treatment. An ultrasound transducer, typically engineered into a hand-held wand, is applied to the body by a trained medical practitioner and activated for 5–20 minutes.

In studies designed to elucidate the mechanism of action exploited by the clinical applications of therapeutic ultrasound, the direct biological effects of the mechanical wave have been studied. There are a number of different means for mechanical energy to influence biological systems. On the molecular level, ultrasound provides mechanical agitation, which is converted to heat as it is absorbed[5, 6]. Heat increases the Brownian motion of molecules in the blood stream, interstitial fluid, and cytosol[7]. The elevated temperature increases the rate of biochemical reactions[8]. The mechanical waves of ultrasound directionally accelerate transport kinetics, providing a force that drives convective mass transport, which occurs significantly faster than diffusion[9]. On the cellular level, ultrasound causes cells and tissue structures to experience a cycle of compression and rarefaction. This phenomenon increases the exchange rate on the interfaces between the cytosol, interstitial fluid, and bloodstream[10]. Cellular processes can be activated through mechanosensing proteins on the cell membrane, which modulate cell behavior[11]. These changes in cell behavior can lead to increased cellular migration, proliferation, or protein synthesis, depending on the cell type and the signaling proteins expressed on the cell surface[11, 12]. The cellular level is also modulated by the changes on the molecular level, because the increased transport kinetics will modulate the concentration and gradient of soluble cell signaling factors[13]. On the tissue level, ultrasound provides mechanical cues that can align collagen fibers or other extracellular matrix structures[14, 15]. The heat deposited in the area and the mechanical waves lead to increased local circulation, enhancing the nutrient supply to an area that is primed to distribute those nutrients from the blood stream to the cells[16]. The rate of waste removal is also increased, further improving the local cellular environment. Ultrasound also increases the elasticity of the overall tissue and increases the lubricity of the synovial fluid in the joint space[17].

2. CLINICAL BENEFITS AND LIMITATIONS OF ULTRASOUND

The biological effects of ultrasound have been successfully evaluated in both human trials of clinical benefit and animal studies of mechanisms of action. A profile of randomized clinical trials for shoulder ailments found that the most benefits were seen with ultrasound when at least 4,000 J, on average, of acoustic energy was applied per treatment[18–20]. Ultrasound was also typically applied multiple times per week (3–5 in these studies). When used to treat tendinitis in the elbow and the knee, daily therapeutic ultrasound over 12 weeks resulted in significant reduction in pain and improvement in strength[21, 22]. In addition to these standard musculoskeletal ailments, therapeutic ultrasound has also been used to treat osteoarthritis. A pilot test of daily ultrasound for pain therapy found a clinically significant 2 point decrease in pain on a 10 point visual-analog scale[23]. The scientific community has built a clinical consensus on the benefit of daily treatment with more than 4,000 J of acoustic energy depositived per treatment. Multiple animal models have demonstrated that daily ultrasound therapy on models of osteoarthritis has resulted in improved gross appearance of the joint,

delayed the progression of the disease, and improved histology scores in terms of cellular morphology at the bone interface[24–28]. Tendons treated with daily or multiple daily sessions of ultrasound therapy for 5–20 minutes possessed greater tensile strength and demonstrated increased collagen synthesis when compared with untreated tendons.

Therapeutic ultrasound is a widespread technique, with over 80% of physiotherapists using it in their practice[29–31]. However, ultrasound is often not applied the same way or with the same protocol in practice as it is during clinical research. Therapeutic ultrasound has been limited in its application by the requirement that a trained clinician administers the treatment. Due to the logistical difficulties associated with the therapy, the majority of patients who receive therapeutic ultrasound get therapy once or twice a week. The problem with this treatment paradigm is that the dosing provided is sub-optimal compared to what clinical research has shown is possible with optimal dosing.

3. SUSTAINED ACOUSTIC MEDICINE: A NOVEL TREATMENT CONCEPT TO IMPROVE CLINICAL PRACTICE

In order to facilitate the translation of clinical research to clinical practice, it is clear that the therapy must be adapted for self-administration. It is not reasonable to expect patients to access their healthcare practitioners on a daily basis. As mentioned in the introduction, therapeutic ultrasound is applied by practitioners because it can pose a safety risk if it is not applied properly or when effective acoustic coupling is not maintained for the entire treatment. Reducing the power output of the device mitigates some of the risk associated with thermal injury. Research has shown that ultrasound intensity under 150 mW/cm^2 can be applied to the body for multiple hours without damaging tissue[32–34]. This type of therapy, called Low Intensity Therapeutic Ultrasound, or LITUS, has been studied for its ability to mediate significant results in recovery. The second obstacle to self-application requires innovative device engineering to overcome the challenges associated with proper treatment placement and protocol. Finally, in order to optimize the acoustic dose given the reduced intensity and to make sure sufficient energy is delivered to trigger a robust biological response, the treatment time could be extended to guarantee maximum delivery of acoustic energy.

Combining those features into a low intensity ultrasound device that can be safely applied by a user for multiple hours would enable a new type of ultrasound therapy, designed around the premise of prolonging the mechanical stimulus of the tissue to provide a robust biological response, and matching the time scale of the therapy to the timescale of the cell and tissue processes which it is accelerating during healing and recovery. This represents a new paradigm in therapeutic ultrasound, where duration is considered to be as important as frequency and intensity. Because this concept provides sustained mechanical stimulation of tissue, this treatment regimen is called sustained acoustic medicine (SAM). SAM conveys that the prolonged ultrasound therapy is having distinct, duration dependent effects, exponentially increasing the biological benefits of traditional Low Intensity Therapeutic Ultrasound (LITUS). SAM simultaneously increases the total dose of acoustic energy and the effectiveness of that dose, optimizing the strength of the therapy.

4. TECHNOLOGY FACILITATING THE SAM APPROACH TO ULTRASOUND THERAPY

4.1 Ultrasound Circuit Miniaturization

Novel circuit design and construction has dramatically increased the achievable efficiency with ultrasound, facilitating a transformation in equipment size from the bench scale to the handheld scale. This ultrasound device is a diverging-wave system that operates near 3 MHz with 0.132 W/cm^2 ultrasound intensity for 4 hrs of treatment. The high efficiency RF ultrasound driver[35–38] employs a parallel pin-driver configuration of MOSFET(s) to obtain a non-reactive output impedance of approximately 0.5 Ohm and a frequency bandwidth from DC-40 MHz. The voltage and frequency operating range of the ultrasound driver made it particularly well suited for portable and low-voltage battery powered ultrasound applications. The element is a silver-plated piezocrystal of lead-zirconate-titanate (PZT-4), that is air backed to uniformly channel the ultrasound towards the body.

4.2 Portable, Wearable Device Design

Inspired by low impedance design principles, a system can be effectively designed to be entirely portable and wearable. The first FDA cleared device using the principles of SAM (conveniently named sam®) to enhance ultrasound therapy is currently available for characterization and study. The circuit and the transducer were housed in a custom built plastic shell, sealed to prevent access and tampering, with the air-backed crystal positioned in a 5° divergent lens. The battery, along with timer and control circuitry are located in a separate housing, connected to the transducer driver assembly by a cable and a custom interlock. There is a split-cable adaptor that facilitates the connection of two transducers to one battery pack (Figure 1).

SAM devices have been designed with efficiencies upward of 90% in battery to acoustic energy conversion. The corresponding transducer efficiency was measured to be 96%. When operated continuously from the battery at an acoustic output power of 1.3 W, or 0.132 W/cm^2, the system can operate for up to 4 hours, which provides an acoustic dose in excess of 18,000 J. In comparison to the average clinical therapeutic ultrasound systems, the wearable ultrasound device is less than 1/20th of the size, does not require wall power, and provides an increased acoustic dose.

4.3 Long Duration Coupling Reservoir

The bandage is the first FDA-cleared ultrasound coupling system designed for four hours of use (Figure 2). During traditional ultrasound therapy, patients expose the area to be treated, and the area has a small amount of coupling medium applied to the skin, to prevent air from interrupting the wave path. Because of the dramatically different speed of sound through aqueous media and air, air reflects and scatters the acoustic wave, preventing it from arriving at its intended destination. The practitioner will regularly add more coupling medium throughout the treatment as it evaporates. For a self-administered treatment, the coupling reservoir would need to function for up to four hours without any intervention. This was achieved using a bandage which maintains attachment to the body during treatment, firmly

secures the transducer in place, and maintains the coupling medium between the lens and the body for four hours. The coupling medium used is a novel, hydrogel based coupling medium that is over 90% water content, giving it the acoustic properties necessary for quality coupling[39]. The bandage was tested to maintain effective coupling of over 93% of the treatment area between the applicator lens and the body. Throughout the testing, the human factors performance was assessed to guarantee the bandage would perform in a variety of locations on different body types, and a patient could successfully apply it with minimal training and effort.

4.4 Closed Loop Temperature Monitoring

Despite the low intensity of the acoustic energy, there were concerns that the SAM therapy approach could unknowingly generate hazardous transfer of thermal energy to the body. To prevent this, a temperature monitor was added to the piezocrystal, and connected to a switch. This final precaution guaranteed that the system would operate within the validated realm of mechanical and thermal therapy.

5. SUSTAINED ACOUSTIC MEDICINE ENABLES RAPID TRANSLATION OF THERAPEUTIC ULTRASOUND'S BENEFITS TO CLINICAL PRACTICE

With an effective SAM device, there was the need to put the concept of the therapy into practice, to test if a prescription-strength therapy could be successfully applied by a layperson and if the therapy would have the expected beneficial effects. To test the potential power of SAM therapy, pilot clinical trials were run on conditions where ultrasound is either currently used, or where ultrasound therapy is of interest to the research community.

5.1 Condition #1: Trapezius muscle spasm[38]

Subjects (N=30) diagnosed with chronic trapezius muscle spasm whose pain was not managed with opioid pain medication alone were prescribed a system to be used in conjunction with pain medication. Subjects applied the device at the onset of a muscle spasm for one hour. Subjects successfully recorded their pain and overall therapeutic benefit scores using the (VAS) and global rate of change (GROC) scales, respectively.

On average, placebo users had an 8% pain reduction, while active users experienced a significant 16% reduction in pain ($p < 0.05$). Figure 3 shows the temporal percent change in VAS over a 60-min treatment and 60-min post treatment as recorded in the patients diary averaged across the 10 treatment sessions. Active male and female users respond faster than placebo treatment as shown by the greater slope in the percent pain reduction graphs.

5.2 Condition #2: Rotator Cuff Pilot Data[40]

This pilot study evaluated SAM therapy in the management of shoulder pain from rotator cuff tendinopathy. Four subjects were enrolled and instructed to wear the device for 3–4 hours per day for 12 consecutive treatment sessions. Subjects recorded their daily pain score on the visual analog scale (1 to 10) and global rate of health improvement scale (−7 to 7). Across the 12 treatments, subjects reported a 30% reduction in pain and 52% improvement in health compared to baseline scores ($p<0.05$). This pilot study demonstrated the ability of

patients to self-apply the SAM device and to utilize it to improve pain related to a widespread medical condition.

5.3 Condition #3: Osteoarthritis of the Knee[23]

Subjects with radiographic mild to moderate clinical knee osteoarthritis (Grade 1–2 on the OARSI scale) in one or both knees, average pain score >4 on a 10 point VAS scale during the week prior to enrollment were accepted into a clinical evaluation of SAM therapy for the relief of osteoarthritis pain. Participants were asked to report their medications but were not asked to modify them. Participants in the sample were taking a median of four prescription medications including Opiod/Narcotic, NSAID, Neurocognitive and Muscle Relaxers. Subjects were trained on the use of a device delivering SAM therapy, and asked to self-treat their affected knee at least four times per week for six weeks, recording their pain before and after treatment. Participants attended bi-weekly visits to the clinical study site to assess compliance.

Forty seven (N=47) subjects completed the study (n=28 active, n=19 placebo). For subjects with moderate to severe starting pain (VAS score ≥5, n=20 active, n=8 placebo), patients with active devices reported a 2.5 point decrease in pain over the six week study which was statistically different from the 1.23 point decrease of the placebo group ($p<0.03$) (Figure 4). The Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) suggests that a decrease of 2/10 points on a VAS scale is clinically meaningful[41], and the active device met that threshold.

5.4 Tendon Pain Relief and Recovery[42]

This study evaluated the ability of SAM therapy to relieve pain for patients suffering from tendon problems in the elbow, knee, or ankle. Subjects (N=25) were recruited into this study if they had a tendon issue that had been persistent for at least six weeks, and had been treated previously by a physical therapist without successful resolution. Subjects treated themselves daily with the device for a six week period. All subjects experienced reduced tendon pain with ultrasound therapy. VAS measurements decreased significantly throughout the 6-week study (Figure 5 top). The largest reduction in pain was observed at week 6, with a 4.28 VAS point decrease from baseline, $p < 0.001$. An overwhelming majority of patients who completed the trial, 93.75%, experienced at least a 50% decrease in pain. Pain also decreased significantly each day from start to end of treatment (0.60 VAS points, $p < 0.001$, Figure 5 bottom). VAS progressively decreased from pre-treatment ($M = 2.67 \pm 1.32$), 30 minutes ($M = 2.44 \pm 1.31$), 2 hours ($M = 2.21 \pm 1.29$), and 4 hours into treatment ($M = 2.06 \pm 1.30$), $F(3,19) = 7.89$, $p = 0.001$. There was a similar reduction in pain of 0.64 VAS points during the first 2 weeks of treatment when pain scores were higher, with a change from 3.35 pre-treatment to 2.71 post 4-hour treatment, $F(3,19) = 13.84$, $p < 0.001$.

6. DISCUSSION OF THERAPY, TECHNOLOGY, AND OPPORTUNITIES

SAM therapy is an innovative treatment approach method to promote more rapid ultrasound-mediated biomodulation using long duration exposures to acoustic waves. By prolonging the time in which the cells and tissue are stimulated with mechanical oscillations, SAM therapy

seeks to trigger a more robust mechanotransduction response, leading to a greater activation of cells in the form of protein synthesis, cell proliferation, and integration between the cells and the extracellular matrix. The clinical application of SAM is as innovative as its therapeutic benefit. A self-applied treatment, SAM therapy engages patients directly, empowering them to take a direct role in administering their treatment and involving them with care. Patients who are actively involved with their care generally have better outcomes to their treatment, and data from the trials discussed above has suggested that there are patients who began exercise regimens or taking other active steps to ensure their health in addition to applying SAM on a daily basis.

In addition to the therapeutic innovation of the device, it is technically innovative. There were substantial engineering challenges to incorporating prescription strength, non-pharmaceutical therapy into a wearable device that can be easily used by the majority of patients without issue. Additionally, this wearable product actually provides treatment to a patient during normal daily activities. Most wearable wellness technology currently functions to obtain and report data only. This system moves a step beyond that, by providing a medically proven therapy that can accelerate healing and recovery, and gathering local information on temperature to regulate the rate at which that therapy is delivered. To successfully administer this therapy, innovative materials were required to successful couple and transfer the acoustic energy into the body efficiently. As this technology is advanced, further miniaturization may allow for the development of a system that is easily wearable with the entire therapeutic unit in a single shell. The technology will also need to be developed to allow for multiple different frequencies, intensities, and treatment profiles. As SAM is studied more in the field, researchers will begin to describe specific effects of ultrasound for conditions, and begin to optimize acoustic dose, duty cycle, frequency, intensity to maximize the beneficial biological response for individual conditions. As wearable technology and sensors develop further, additional technical features may also for direct observation of the body’s response to therapeutic ultrasound, both physically and biochemically. Additionally, the user interface for the device can be made more accessible to the average user. Particularly, by developing secure algorithms that can work with existing portable technology, software will allow patients to observe and monitor their treatment, and may interact with other wearable technology to assess things like strength, range of motion, or daily activity for the purpose of evaluating the body’s performance and recovery.

SAM has successfully mediated biomodulation in a large number of pre-clinical and clinical trials. SAM therapy has stimulated the deposition of collagen and increased the tensile strength of healing tendons in animal models. This compliments its pain relieving benefits that have been seen in the clinical trials. SAM therapy provides a long duration, robust mechanotransduction signal that is processed repeatedly as cells experience a continuous, oscillating pressure wave. Further research is required to identify the exact mechanisms of action and the basis for the sustained effect. The promise of SAM is a therapeutic technology that could be used by anyone, anywhere to treat soft tissue injuries. SAM may represent the next step in ultrasound therapies, and is the first available technology to bring a prescription strength biomodulation treatment to a wearable form factor.

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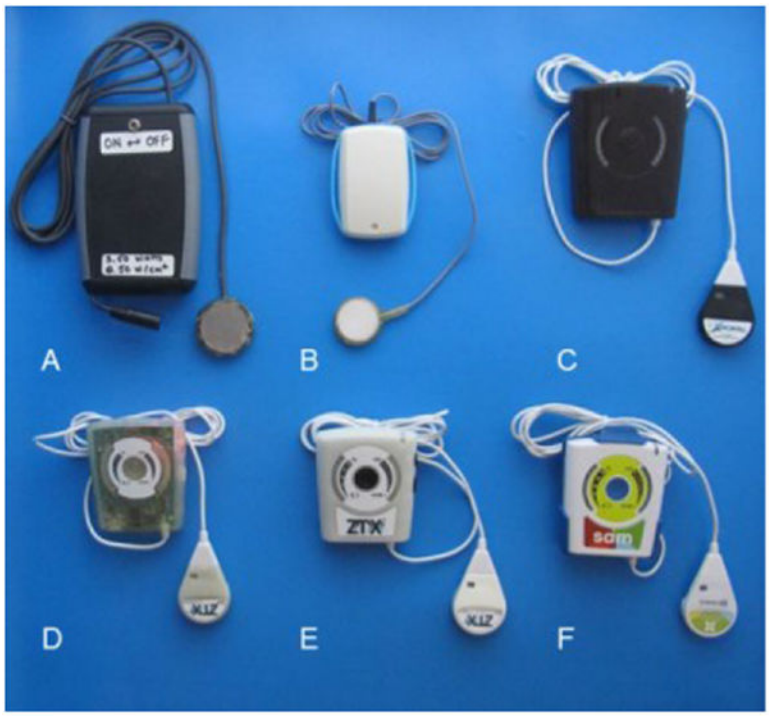

Figure 1:
(a-f) Depictions of design iterations of portable, wearable device design, progressing from initial prototype towards final design.

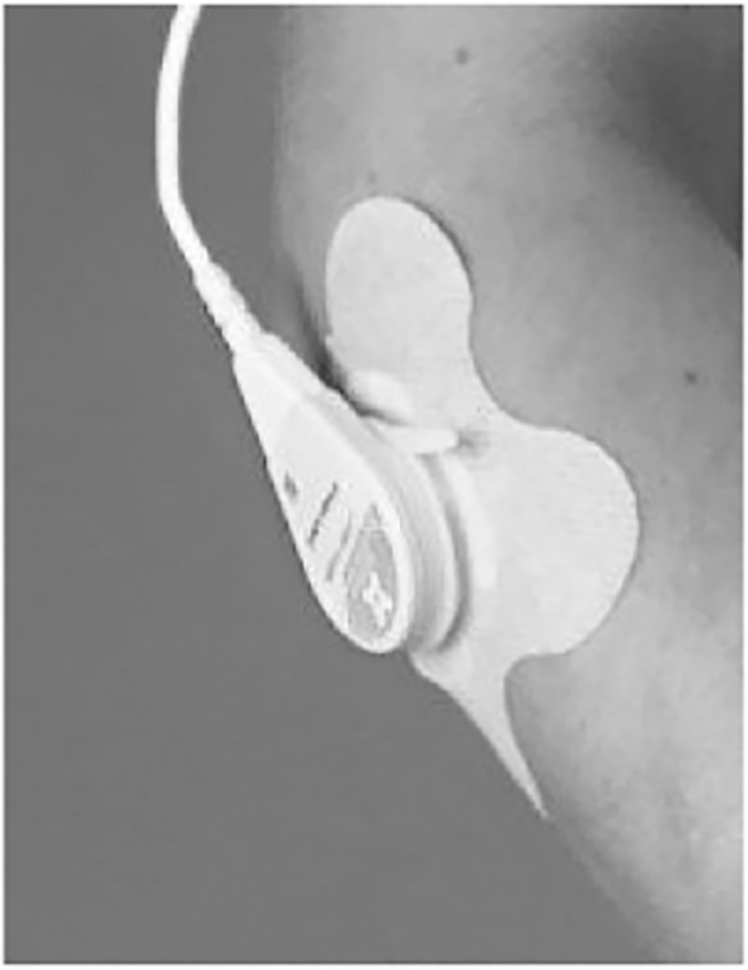

Figure 2:
Bandage containing long-duration coupling medium attached to the body.

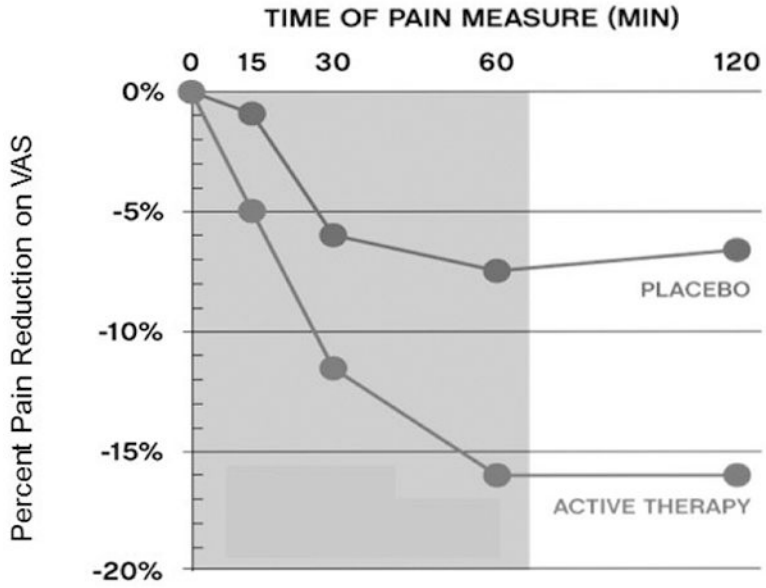

Figure 3:
Placebo controlled pain relief for trapezius muscle spasms in a patient population where opioids were not providing adequate pain relief.

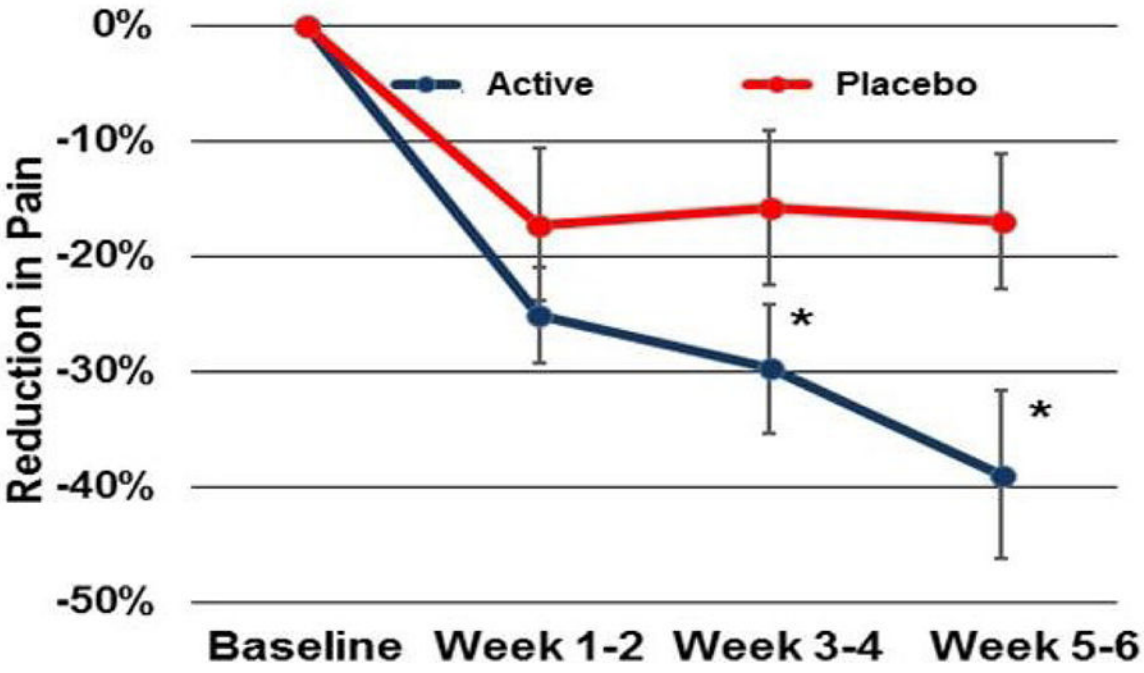

Figure 4:
Placebo controlled pain relief for osteoarthritis over six weeks of SAM therapy.

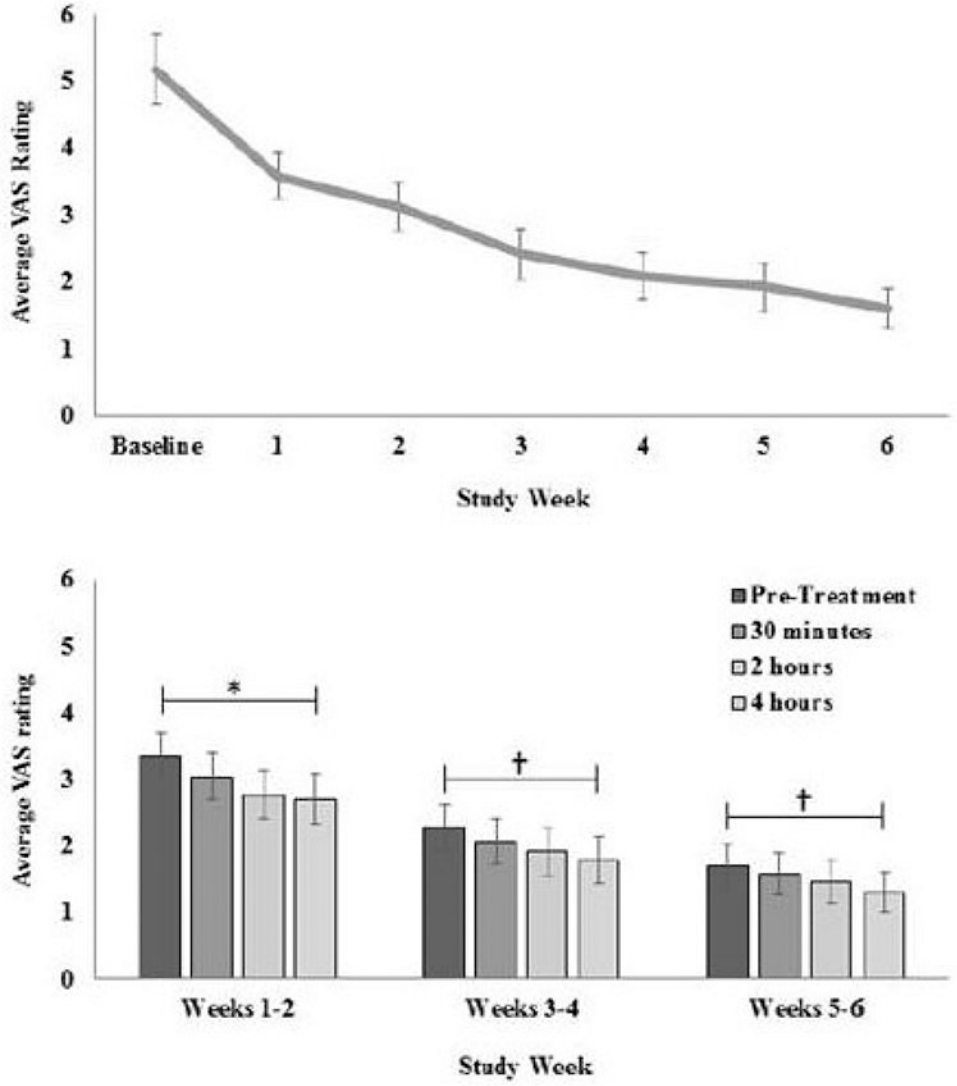

Figure 5:

(top) Subject pain over six weeks of SAM therapy. The average pain decrease was 4.28 points on a 10 pt VAS scale ($p < 0.001$). (bottom) Subject pain decrease across single treatments (averaged over two week data periods). *($p < 0.001$), †($p = 0.08$)