BioElectronics

Changing the Way People Heal & Stop Pain

ActiPatch®

Mechanism of Action & Clinical Evidence

BioElectronics Corporation 4539 Metropolitan Court, Frederick, Maryland 21704 USA
Phone: 1-866-757-2284 | Fax: 301-874-6935 | E-mail: info@bielcorp.com | Web: www.bielcorp.com

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Mechanism of Action & Physiologic Evidence

Treating Pain by Mitigating Central Sensitization

Background:

The ActiPatch is a pulsed shortwave therapy (PSWT) product. Although historically there was a lack of understanding regarding the mechanism of action through which PSWT provides therapeutic effects, over the last two decades, advances in understanding of pain mechanisms and strides made in neurobiological research have prompted a re-investigation into the mechanism of action behind PSWT. There is growing evidence of the therapeutic effects of PSWT technology based on both clinical studies (Bagnato, G.L. et.al. 2015, Rawe, I. et.al. 2012, Brook, J. et.al. 2012) and real world evidence (Rawe, I. et.al. 2015).

This paper examines how PSWT products such as the ActiPatch work. While traditional theories of electrophysiology conclude that at power levels which the ActiPatch operates at, direct nerve stimulation is not possible, we show how low power PSWT can be sufficient to incoherently modulate the activity of afferent nerves, through a well-established and understood mechanism known as stochastic resonance. Clinical research conducted at the Clinical Science & Engineering Research Laboratory at Binghamton University, New York provides physiologic evidence that PSWT technologies operating at power levels similar to the ActiPatch indeed modulate the activity of afferent nerves.

It is well documented that the modulation of nerves ("neuromodulation"), specifically that of afferent nerves, provides relief from chronic pain. Chronic pain can be extremely difficult to diagnose and treat, but there is growing evidence that a large number of chronic pain etiologies, including low back pain, knee pain and neck pain, can be linked to changes in signal processing at the level of the central nervous system (Reynolds, Stuart W. et. al 2016). This process, termed central sensitization, is well accepted in the pain community and is responsible for temporal, spatial, and threshold changes in pain sensitivity that lead to the perception of pain even after an injury has healed. In other words, with central sensitization, pain thresholds are lowered, leading to a heightened perception of pain. The strategy for central sensitization pain relief is to reset the pain thresholds in the cells of the central nervous system through providing new sources of repetitive, afferent information (Nijs, Jo et.al. 2011). Neuromodulation has already shown promise in helping manage many conditions linked to central sensitization, such as overactive bladder and incontinence. (Bartley, J. et.al. 2013)

In light of the ability of PSWT technology to neuromodulate afferent nerves, the data shows ActiPatch provides pain relief, as demonstrated by clinical and real world evidence, through mitigation of central sensitization. This paper explains how low power PSWT technology such as the ActiPatch can interact with biological tissue' provides physiologic evidence of its interaction with tissue; discusses central sensitization; and discusses why and how the ActiPatch is capable of mitigating chronic pain through mitigation of central sensitization.

Stochastic Resonance

PSWT devices such as the ActiPatch provide pain relief through prolonged stimulation of incoherent (stochastic) stimuli that the brain cannot interpret. Simply put, a repeated application of a signal at intensity levels too low to consistently trigger a pain response can still initiate a system response because the system is not only exposed to the applied signal, but also to electrical noise in the physiologic environment. This noise in physiological systems, such as neural systems, while ubiquitous, is widely considered to be essential in facilitating information processing in the body (McDonnell, MD et.al. 2011). The phenomenon whereby the presence of "noise" in non-linear systems can be used to enhance the detection of sub-threshold stimuli is referred to as "stochastic resonance (SR). As stated above, in a situation where there is a detection threshold, such as exists for nerves, a sub-threshold "signal" in the presence of noise may randomly become sufficiently large to exceed the necessary threshold to activate the nerve. A characteristic feature of SR in a system is that the system output, when plotted against system noise power, will produce a peak response at a non-zero value (figure 1) (McDonnell and Abott 2009). Since sensory nerves have a lower threshold of activation when compared to motor nerves and muscles, (Mogyoros, I et.al. 1996), it indicates that the low incident power of PSWT modalities (inherently sub-threshold) can be sufficient to non-deterministically modulate the activity of sensory nerves.

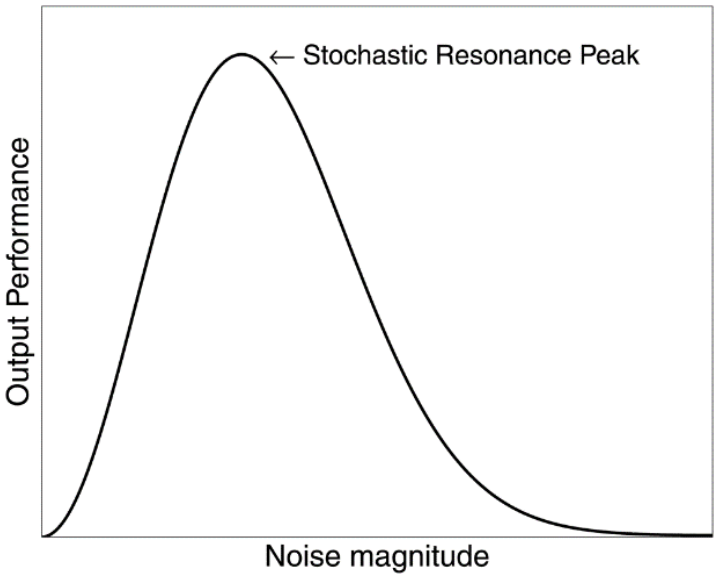


Fig 1: A classic stochastic resonance phenomenon curve. System response parameters can be enhanced by the 'right' amount of input noise and has a single maximum resonant point. (McDonnell and Abott 2009)

Clinical Assessment Using PSWT Stimuli

Research efforts at the Clinical Science and Engineering Research Center in Binghamton University, Binghamton, NY indicate that the mechanism of action for ActiPatch (and PSWT stimuli) are neuromodulation based. Because sensory nerves have the lowest amplitude threshold for stimulation, sensory nerve modulation provides an excellent option to assess nerve

modulation. A protocol was developed to demonstrate physiologic effects that are indicative of neuromodulation when sensory nerves are exposed to PSWT stimulation. Early results from a series of physiologic experiments indicated the possibility of identifying sensory nerve modulation using a reflex arc response, specifically a skeletal muscle reflex arc pathway. Reflex arcs are the involuntary pathways involved in maintaining body status, for example, moving one's hand away from painful stimuli. Reflex arcs are found throughout the body, originating at various sensory organs whose axons travel up to the spine and after passing through one or more synapses, trigger a motor nerve which results in muscle contraction (figure 2).

While sensory nerves are easily stimulated, determining whether a sensory nerve has been stimulated is quite difficult. As a result, the end effect, *i.e.*, the muscle contraction resulting from the reflex response, is typically a far more convenient output to measure. While stimulating the motor nerve or muscle appears more straightforward, these require a much higher signal strength than sensory nerves to be stimulated. Moreover, stimulation of the motor nerve or muscle results in muscle fatigue and can lead to a decay in the response during the experiment. As a result, it is more efficient to target the sensory nerves when using PSWT technology.

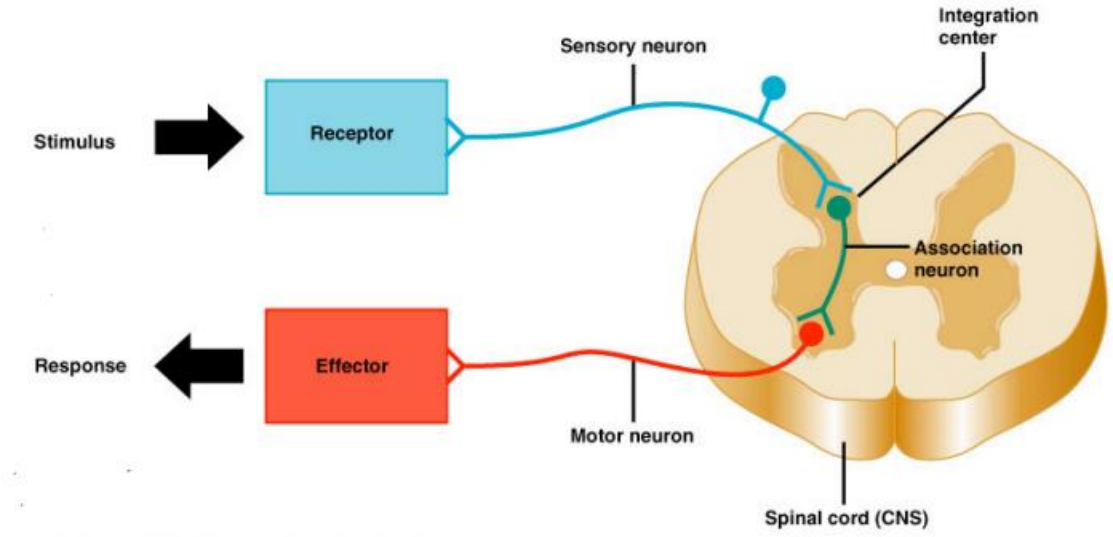


Fig. 2: Typical reflex arc pathway. A sensory stimulus travels along the sensory neuron to the dorsal root of the central nervous system at the spinal cord. This synapses on to the motor neuron through an association neuron,

Model System: Soleus Reflex Arc

While there are many reflex arcs in the body, we decided to use a particular reflex arc system that would allow us evaluate the effects of PSWT stimuli over an extended period of time. The autogenic inhibitor reflex arc, a.k.a. soleus reflex arc, is the mechanism through which postural balance is achieved, where afferent feedback from mechanoreceptors located on the sole of the

foot (plantar surface) results in an efferent response through the gastrocnemius and soleus muscles (figure 3). The soleus muscle, apart from helping to maintain posture and balance, also plays an important role in returning blood and interstitial fluid from the lower limbs back to the heart (Rowell 1993).

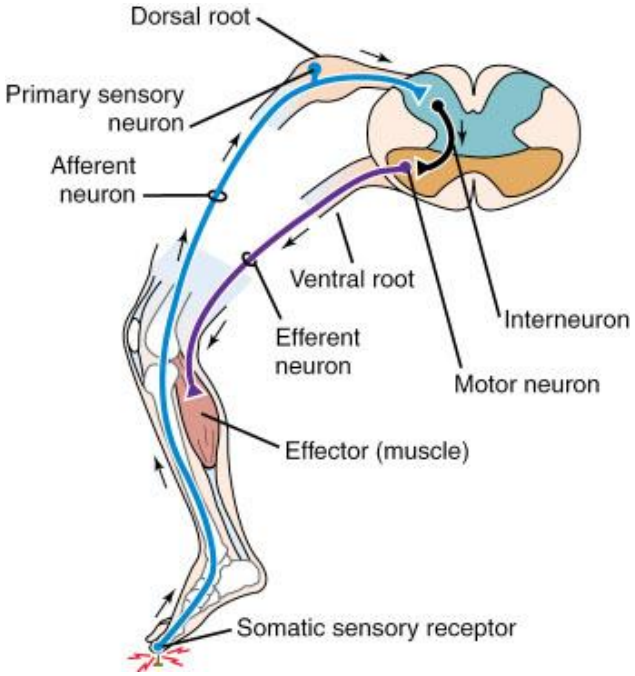
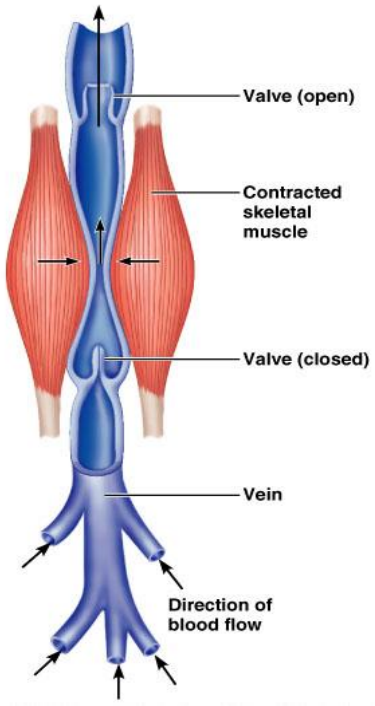


Fig 3: Autogenic inhibitor reflex arc of the soleus muscle. Sensory information is picked up by mechanoreceptors in the plantar surface of the forefoot, which travels to the dorsal root and stimulates the motor nerve permeating the soleus muscle (gastrocnemius shown here). (Dictionary 2011)

Approximately half of the total muscle mass in our body, to which blood is supplied by the cardiovascular system, is in the lower extremities. This means that, in humans, about 70% of the blood rests below the heart level (Rowell 1993). The action of muscles in the lower body enhances flow in the deep veins serving to return venous blood to the heart for re-circulation, with unidirectional valves preventing back flow of blood. In addition, this muscle activity returns lymphatic fluid (fluid which has "leaked" from the capillary system) back to the vascular system. The soleus muscles in the lower legs play a particularly critical role in this process of returning fluid to the heart (figure 4). The Frank-Starling law of the heart states that increased fluid return to the heart results in greater stroke volume (defined as the volume of blood pumped by the left ventricle of the heart, per beat) and correspondingly increases cardiac output (Moss 2002). Conversely, without lower limb muscle pumping on the venous side of circulation, humans would not be able to return enough blood back to the heart to maintain adequate cardiac output when sitting or standing upright (Rowell 1993). During voluntary muscle contraction, for example during walking, the gastrocnemius is the primary muscle involved in lower limb

skeletal muscle pumping. However, during quiet sitting or standing, adequate blood and lymphatic fluid return to the heart must be maintained, and this is accomplished through involuntary soleus muscle contraction. In individuals with inadequate soleus muscle activity when standing or sitting, inadequate fluid return to the heart will result in the heart trying to 'compensate' by pumping either harder or faster, but in the absence of adequate venous return, cardiac output will drop. At the same time, the fluid pooled into the lower limbs can lead to venous insufficiency, deep vein thrombosis, venous ulcers, etc., that is, a number of serious health conditions.

Fig. 4: Skeletal muscle pump and its function in promoting blood flow. Blood moves from superficial to deep veins. During contraction, skeletal muscle pumping serves to propel this blood to the heart. During relaxation, deep veins allow blood from superficial veins to move in flow. The soleus muscle is a specialized deep postural muscle which contains large venous sinuses into which blood pools until a soleus muscle contraction occurs. The soleus involuntarily contracts every one to two minutes while sitting quietly. (Cummings 2004)



Since plantar mechanoreceptors respond to electrical stimulation, as well as mechanical stimulation, to regulate postural balance, (Maurer, et al. 2001) this presents a scenario where PSWT stimulation could also be used to test for activation of these receptors. As such, it follows that electrically stimulating the mechanoreceptors on the plantar surface should result in enhanced cardiovascular function, a response which is relatively straightforward to ascertain. Mechanical plantar stimulation as a means of activating the soleus muscle pump to influence cardiac function has been documented in numerous studies out of the Clinical Science and Engineering Research Center at Binghamton University. Baniak et.al (Baniak, et al. 2014) used this approach to improve fluid return to the heart and reduce fibromyalgia symptoms; Goddard, et al. (2007) used it to show lower limb edema in otherwise healthy adult women; Pierce (Pierce and McLeod 2009) used it to reduce edema in chronic heart failure patients; and, Madhavan et.al (Madhavan, Stewart and McLeod 2006) have used this approach to reduce tachycardia during orthostasis. While the above studies utilized mechanically based stimulation methods, this model

system was used to investigate the effects of electromagnetic stimuli resulting from PSWT stimuli.

Methodology

Design Overview: This study was a single-blind, randomized, IRB-approved pilot trial that included 5 young adult women who met the inclusion criteria indicative of poor soleus muscle function, such as coldness in extremities, sleepiness when seated, or dizziness when standing up. The subjects were blinded from the nature of the signal chosen for any given experiment.

The testing protocol involved two phases: 1) Having the subject sit quietly for 90 minutes to allow for interstitial pooling; and 2) Following this, initiating PSWT modulation of the plantar surface receptors for 60 minutes to observe the extent to which the soleus reflex was activated. Cardiovascular hemodynamics were monitored at 30 second intervals throughout the 150-minute experimental session.

Hemodynamic Assessment:
A number of methods are available to measure hemodynamic parameters, but we chose bio-reactance given the relative accuracy and portability of the technology. Bio-reactance relies on high frequency AC currents injected into the thorax via a pair of surface electrodes and then measures the corresponding phase shifts via another electrode pair (figure 5) (CheetahMedical 2014). To ensure accuracy of measurements, two sets of this four electrode recording arrangement are utilized, and the results compared. By measuring these phase shifts over time, stroke volume can be assessed over (every 30 seconds) for up to several hours. Importantly, this assessment can be undertaken with the subject upright, which serves our purpose of obtaining measurements for seated subjects (i.e. under orthostatic stress). We utilize an FDA approved bio-reactance monitoring device (NICOM®, Boston, MA; figure 6), which incorporates a blood pressure monitoring cuff.

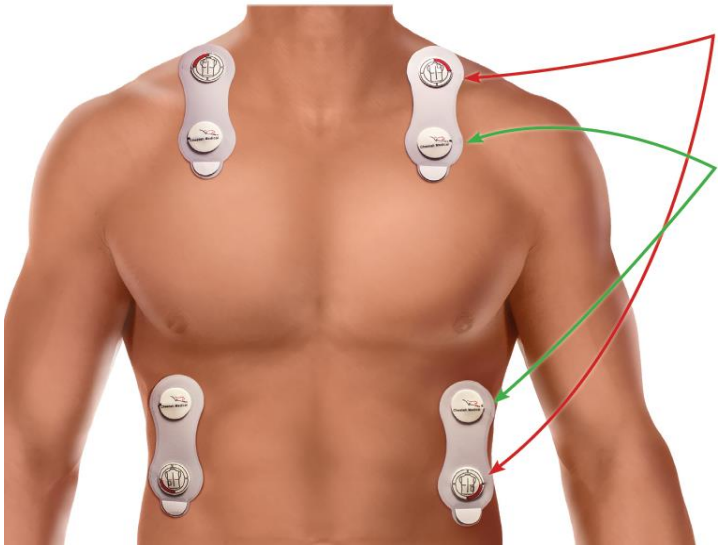


Fig. 5: Cardiac output monitoring using the bio-reactance method. Four sets of electrodes are placed around the heart. An electric current of known frequency is applied between the outer sensors (red arrows) and is recorded by the inner pair (green arrows). A phase shift proportional to the volume of blood flow can be observed, allowing calculation of stroke volume.

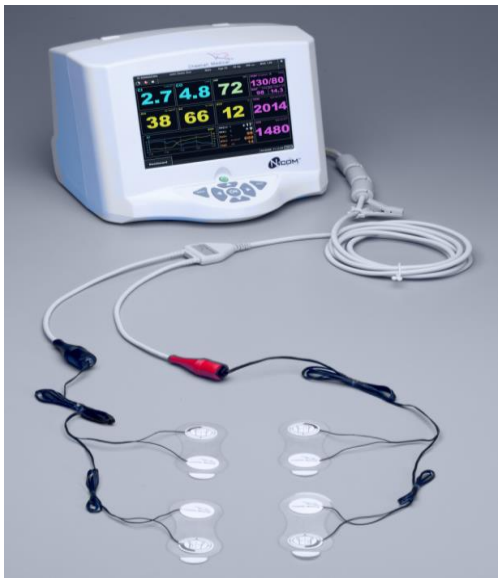


Fig. 6: FDA-approved NICOM® cardiac monitoring device. Parameters such as SV, CO, HR can be measured using this device. Measurements were updated every 30-60 seconds. (CheetahMedical 2014)

Electromagnetic Stimulation

Plantar nerve modulation is accomplished using an PSWTPSWT stimulus, operating at a carrier frequency of 27 MHz and using a peak incident power of 70 uW/cm^2.

Outcome Measurement: The primary outcome assessments were changes in the temporal slopes of various hemodynamic parameters, for quiet sitting without PSWT activation versus quiet sitting with PSWT activation. To allow for quantitative comparisons, the data was separated into two segments (quiet sitting and PSWT stimulation) and a linear regression (least squares method) was fitted to estimate the slopes for both these segments. The output for each experiment was the difference in these slopes between the stimulation period and quiet sitting period (control period).

Differences in slope values between the stimulation and quiet sitting period were indicative of cardiovascular changes resulting from neuromodulation. Preliminary experiments have shown that Cardiac Index (CI) (L/min/m^2) is a useful hemodynamic measure, as it combines the effects on heart rate and stroke volume (that is, cardiac output = stroke volume x heart rate), moreover, by normalizing an individual's cardiac output to their body surface area (i.e. cardiac index) allows pooling of data sets across multiple subjects. As such, CI was used as the base hemodynamic measure for quantifying the results from the study. Additionally, total peripheral resistance index (TPRI), which normalizes an individual's mean arterial pressure to their cardiac index, was also used as a hemodynamic measure.

Results:

Figures 7 and 8 depict the temporal trends of CI and TPRI for experiments using the PSWT stimulus. This data represents the mean of temporal trends from 5 subjects. Each subject acts as their own control during the quiet sitting phase of the first 90 minutes, following which the PSWT stimulus is applied.

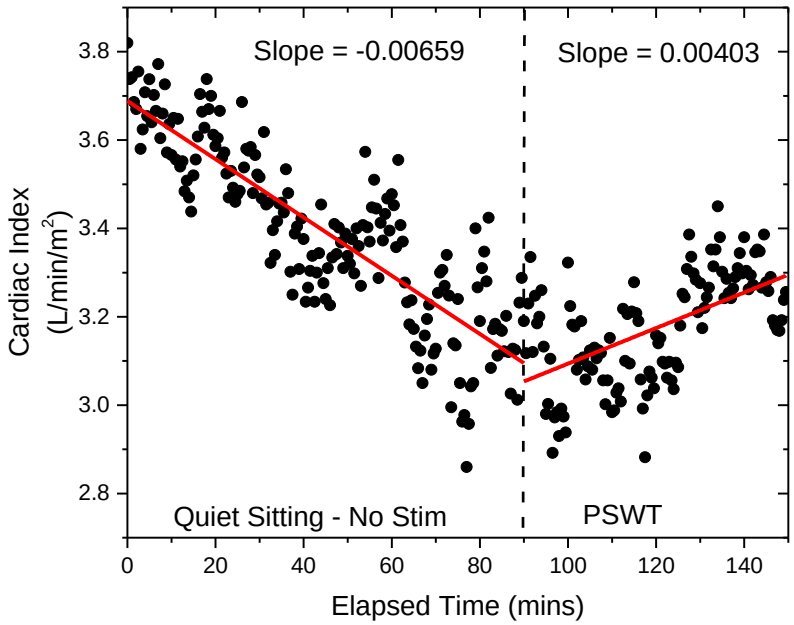


Fig. 7: Temporal trend of mean CI for 5 individuals over 150 minutes. CI declines continuously for the first 90 minutes, indicative of lower leg pooling during quiet sitting. Upon applying the PSWT stimulus, the trend is reversed and CI continues to increase till the end of the experiment. Analysis using the slope difference method indicated an increasing trend, with a slope difference of 0.01 (± 0.01).

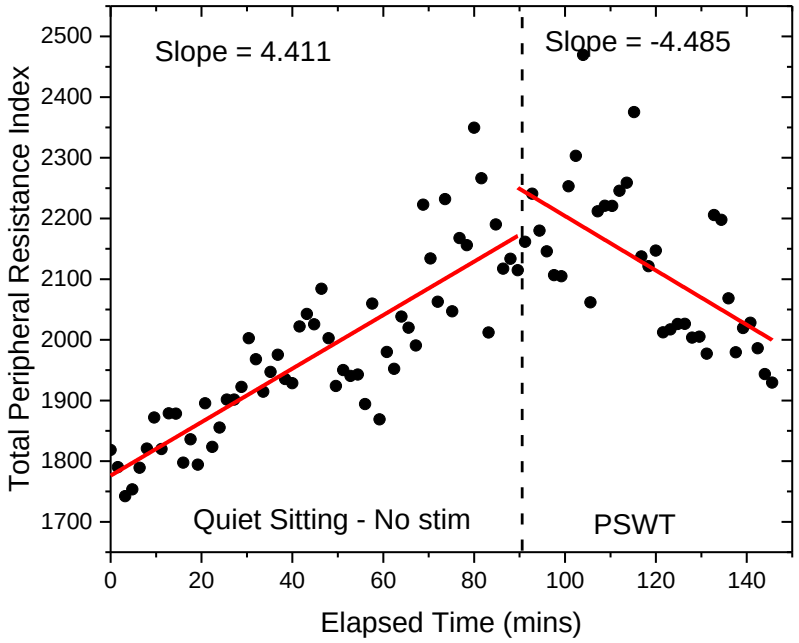


Fig. 8: Temporal trend of mean TPRI for 5 individuals over 150 minutes. TPRI continuously increases for the first 90 minutes, indicative of lower leg pooling during quiet sitting. Upon applying the PSWT stimulus, the trend is reversed and TPRI continues to decline till the end of the experiment. To mitigate subject discomfort, blood pressure was taken only every 2 minutes. Analysis using the slope method indicated a reversal in trend with a slope difference of -8.89 (± 8.78)

The magnitude of change in both hemodynamic parameters shown in the above figures indicate that after 90 minutes of quiet sitting, using the PSWT stimulus consistently increased activity of the soleus muscle pump via the reflex arc. The slope values obtained for the experiments indicate that afferent nerves can be modulated to evoke efferent responses (as measured by changes in hemodynamic performance) using the ActiPatch.

Central Sensitization & Chronic Pain

Pain is the normal physiologic signal by which brain communicates to an individual that one or more tissues in the body are in danger, or have already been damaged. Typically, when the tissue damaging agent is removed, or the tissue heals, the pain subsides. Sometimes, however, even long after the tissues have healed, the brain continues to sense pain – this is referred to as chronic pain. Chronic pain results from the process of sensitization, which most often occurs when high levels of acute pain are sustained for an extended time period. When sustained tissue insult or injury sensitizes the central nervous system even non-painful stimuli can produce painful responses. This process occurs in the spine of the individual, which is considered part of the central nervous system, and so is referred to as "central sensitization." Central sensitization is associated with a wide variety of pain conditions, including osteoarthritis of the knee pain, neck pain, low back pain, dysmenorrhea, fibromyalgia, myofascial pain, migraines and painful bladder, among many others (Reynolds, Stuart W. et. al 2016). In the case of chronic pain resulting from central sensitization, stimuli that are normally painless can produce pain (allodynia) while stimuli that produce pain will produce pain at much higher levels (hyperalgesia) (figure 9) (Reynolds, Stuart W. et. al 2016).

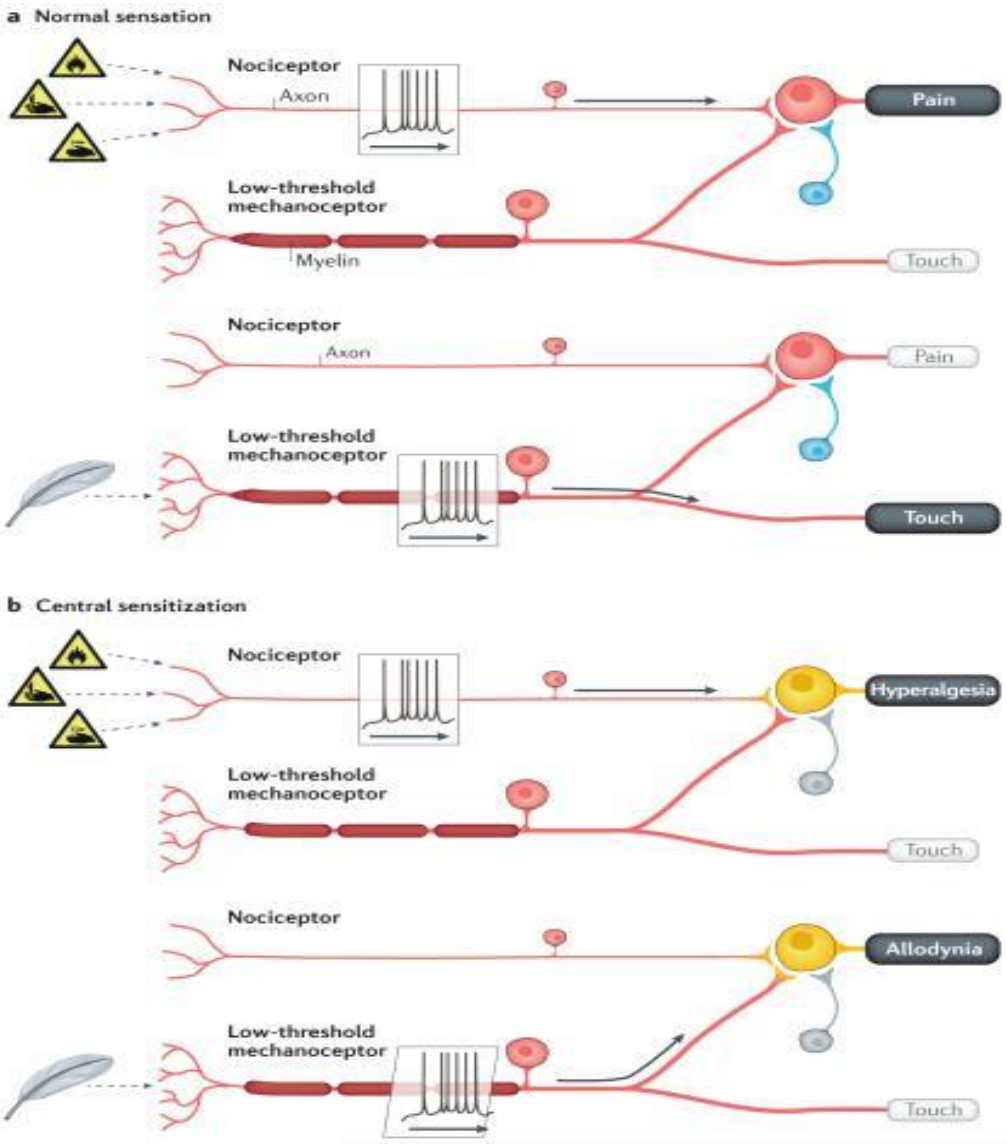


Fig. 9: Mechanism of central sensitization. a) In normal sensations, non-painful stimuli activate pathways that lead to a sensation of touch, while high-threshold stimuli activate noxious pathways that lead to a sensation of pain. b) In central sensitization, non-painful stimuli activate pain sensations, while high-threshold stimuli lead to an amplified pain response. (Reynolds, Stuart W. et. al 2016)

Central sensitization results from lowered pain thresholds that are due to a disruption of the normal habituation/sensitization process. Specifically, the central nervous system continuously receives large amounts of information from the periphery of the body and internal organs, including noxious, mechanical, chemical and motor/sensory stimuli. The background level of this activity is referred to as "afferent noise" (Gillespie, James I. et.al. 2009). In order to appropriately process critical afferent inputs, the system must constantly adapt to the background levels of these inputs. In this way, differences from the background are easily detected and sent to the brain for processing. Habituation is the process by which sensation thresholds are raised, while the process of sensitization results in a lowering of sensation thresholds. Habituation and sensitization are normal physiologic processes that allow our nervous system to operate optimally. In the case of "central sensitization" the normal habituation/sensitization process has been disrupted such that even normal background "noise" can be sensed as painful. Nonetheless, "central sensitization" does not appear to be a pathology, rather, the system has become "stuck" in a pain state. Since peripheral information plays a crucial role in central sensitization the key to mitigating central sensitization, and moving the system out of the pain state, lies in providing new peripheral information (Nijs, Jo et.al. 2011).

Central sensitization pain is addressed by raising the pain threshold levels back towards normal levels. The challenge in reestablishing normal background pain threshold levels is that the most common means for stimulating musculoskeletal sensation is through movement or touch (e.g. manual therapy or exercise). Though there is evidence that exercise therapy benefits patients with chronic pain (Mjor 2001), it can be painful, and people are hesitant to undertake the necessary activity, let alone undertake them for the prolonged time period required to exit the pain state. When using PSWT devices such as the ActiPatch to increase background noise levels the stimulation is below the sensory level (sub-sensory) due to the low power level and the incoherent[1] (random) nature of the stimulation. In other words, the strategy for mitigating central sensitization pain is to modulate the activity of afferent nerves through incoherent, sub-sensory stimuli. As a result, there is no sensation, but the central nervous system still "sees" an increase in "afferent noise" and, over time, raises the pain tolerance thresholds through the habituation process. Importantly, this could mean that neuromodulation based therapies such as the ActiPatch are not simply masking the underlying pain, but may in fact over time be treating the pain by "moving" an individual out a "centrally sensitized pain state". This interesting possibility needs to be explored further in prospective clinical studies investigating long-term relief from chronic pain. There is growing evidence that neuromodulation has therapeutic benefits for other centrally sensitized conditions like overactive bladder, incontinence and other pelvic conditions (Reynolds, Stuart W. et. al 2016).

[1] *Incoherent stimulation is a process where sub-threshold levels of input combine with resting "afferent noise" to non-deterministically activate nerves.*

Evidence for Mitigating Central Sensitization

There are currently no methods to directly assess the mechanisms responsible for central sensitization. However, there are some techniques, known as quantitative sensory testing (QST) that can test the manifestation of central sensitization in clinical conditions such as chronic pain (Reynolds, Stuart W. et. al 2016). QST has been established as a reliable way of quantifying changes in central sensitization conditions, and its reproducibility has been tested in a multi-center study (Geber C, et.al. 2011). Some of the most commonly used QST methods with respect to chronic pain are pain threshold and pain tolerance testing. In the osteoarthritis of the knee study (Bagnato, G.L. et.al. 2015), QST was conducted in the form of pain pressure threshold testing, which revealed that individuals in the ActiPatch-treatment group demonstrated a significantly higher pain tolerance than individuals in the placebo group, both locally and peripherally. Moreover, data collected in the registry study (Rawe, Ian et.al. 2015) indicate that many of the subjects reported pain relief only after a few days of use. The QST results, in combination with the time delay in experiencing pain relief indicate that the ActiPatch does not mask the underlying pain, but mitigates the underlying condition. Evidence from the 6-month observational study provided in **Attachment A,** indicates that individuals using the ActiPatch over a period of 6-months consistently report improved sleep quality, more physical activity and an overall improvement in quality of life. We believe these pieces of evidence, especially data indicating a restoration of pain pressure thresholds, present the best case yet that the ActiPatch provides chronic pain relief by mitigating the underlying cause: central sensitization.

Conclusion

The ActiPatch is a wearable PSWT technology that utilizes low power, PSWT technology to provide relief from chronic, musculoskeletal pain. The technology modulates afferent nerve activity in an incoherent manner by adding to the ambient physiologic “noise”, a phenomenon understood as stochastic resonance. The evidence for modulating afferent nerve activity with PSWT technology was provided in a reflex arc model system, specifically the soleus muscle reflex arc. When PSWT technology such as the ActiPatch was used to stimulate plantar nerves, it led to changes in cardiac parameters such as cardiac index and total peripheral resistance index, indicating activation of plantar, afferent nerves.

There is increasing evidence that many complex, chronic conditions such as pain of the knee, low back & neck, fibromyalgia and overactive bladder are manifestations of a hypersensitive central nervous system; this phenomenon is referred to as central sensitization. There is growing evidence that neuromodulation is beneficial in managing some of the clinical conditions that are due to central sensitization. Because central sensitization can be mitigated through the provision of new, repetitive information, it is likely that PSWT reduces chronic pain by mitigating central sensitization. QST evidence indicates that pain tolerances were increased in ActiPatch users, which is one of the best ways to quantify changes in central sensitization. Improvements in sleep quality, physical activity and an overall quality of life are supportive of our conclusion that the

ActiPatch provides relief from chronic musculoskeletal pain through mitigation of central sensitization, a task accomplished through neuromodulation of afferent nerves.

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Central sensitization: Implications for the diagnosis and treatment of pain

Clifford J Woolf
Program in Neurobiology and FM Kirby Neurobiology Center, Children's Hospital Boston, and Department of Neurobiology, Harvard Medical School, Boston, Ma

Clifford J Woolf: clifford.woolf@childrens.harvard.edu

Abstract

Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, the phenomenon of central sensitization. Central sensitization manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. It can be readily and rapidly elicited in human volunteers by diverse experimental noxious conditioning stimuli to skin, muscles or viscera, and in addition to producing pain hypersensitivity, results in secondary changes in brain activity that can be detected by electrophysiological or imaging techniques. Studies in clinical cohorts reveal changes in pain sensitivity that have been interpreted as revealing an important contribution of central sensitization to the pain phenotype in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and postsurgical pain. The comorbidity of those pain hypersensitivity syndromes that present in the absence of inflammation or a neural lesion, their similar pattern of clinical presentation and response to centrally acting analgesics, may reflect a commonality of central sensitization to their pathophysiology. An important question that still needs to be determined is whether there are individuals with a higher inherited propensity for developing central sensitization than others, and if so, whether this conveys an increased risk both of developing conditions with pain hypersensitivity, and their chronification. Diagnostic criteria to establish the presence of central sensitization in patients will greatly assist the phenotyping of patients for choosing treatments that produce analgesia by normalizing hyperexcitable central neural activity. We have certainly come a long way since the first discovery of activity-dependent synaptic plasticity in the spinal cord and the revelation that it occurs and produces pain hypersensitivity in patients. Nevertheless, discovering the genetic and environmental contributors to and objective biomarkers of central sensitization will be highly beneficial, as will additional treatment options to prevent or reduce this prevalent and promiscuous form of pain plasticity.

Introduction

In 1983 I published a study indicating that many features of the pain hypersensitivity accompanying peripheral tissue injury or inflammation were the direct result of an

There is no conflict of interest.

augmentation of sensory signaling in the central nervous system [255]. A central amplification during angina pectoris had been postulated exactly 100 years before by W Allen Sturge MD, who in an 1883 paper in Brain envisaged a possible central nervous system "commotion …… passed up from below" that somehow contributed to the clinical features of ischemic cardiac pain. However, the importance of this clinical insight lay largely dormant for a century, except for one human volunteer study on secondary hyperalgesia that was recognized by the authors as suggestive of a possible central contribution to the spread of pain sensitivity [101]. What I found in a preclinical study on stimulus-response relations in the spinal cord was that the afferent activity induced by peripheral injury triggered a long-lasting increase in the excitability of spinal cord neurons, profoundly changing the gain of the somatosensory system [255]. This central facilitation manifested as a reduction in threshold (allodynia), an increase in responsiveness and prolonged aftereffects to noxious stimuli (hyperalgesia), and a receptive field expansion that enabled input from non-injured tissue to produce pain (secondary hyperalgesia) [255–256;273;51;268].

I have recently reviewed the circumstances surrounding the discovery of the activity-dependent synaptic plasticity in the spinal cord that generates post-injury pain hypersensitivity [259], and that became termed "central sensitization" [272], as well as the current state of understanding of the cellular and molecular mechanisms responsible for this form of neuronal plasticity [147]. What I would like to specifically address in this review are the clinical implications of the phenomenon. What has central sensitization taught us about the nature and mechanisms of pain in patients, and what are the implications of central sensitization for pain diagnosis and therapy? Before doing this though, it is important first to understand exactly what central sensitization represents, how it has changed our general understanding of pain mechanisms, as well as reviewing the substantial data on central sensitization derived from studies on experimental pain in human volunteers.

What is central sensitization?

Prior to the discovery of central sensitization, the prevailing view on pain processing in the central nervous system was of a largely passive neural relay that conveyed by encoded action potentials, information on the onset, duration, intensity, location and quality of peripheral noxious stimuli, much like a telephone wire, from one site to another. More specifically, the CNS pathway was seen to constitute particular anatomical connections in the spinal cord, brain stem, thalamus and cortex (the "pain pathway"), linking the sensory inflow generated in high threshold primary afferents with those parts of the cortex that lead to the conscious awareness of painful sensations. The spinal gate control theory by Melzack and Wall in 1965 had highlighted that this sensory relay system could be modulated in the spinal cord by inhibitory controls [163], and considerable progress had been made by the early 1980's in identifying such inhibitory circuits [18]. Indeed this, together the discovery of enkephalins and endorphins [109;98], diffuse noxious inhibitory controls [150], transcutaneous nerve stimulation [224], and the rediscovery of acupuncture [25], generated a much greater emphasis at that time on endogenous inhibitory controls than on those factors that might increase excitation, and thereby produce pain hypersensitivity. However, there was one exception, that which related to the discovery of peripheral sensitization in the 1970's [178]. Work by Iggo [112;28] and Perl [33;177;20] had identified specific high threshold sensory neurons tuned to respond only to noxious stimuli, hence their name nociceptors [265], a term first coined by Sherrington based on his studies on noxious stimulus evoked flexion reflexes. Furthermore, first Perl then others showed that nociceptor peripheral terminals could become "sensitized" after injury, reducing their threshold, mainly to heat stimuli, and only within the site of injury where the terminal was exposed to inflammatory modulators, the zone of primary hyperalgesia [178;146;138;41;23]. While this

phenomenon clearly is a very important contributor to inflammatory pain hypersensitivity [22], it cannot account for dynamic tactile allodynia, the temporal summation of pain, or secondary hyperalgesia. Some other explanation was needed as the neurobiological basis for these symptoms, which turned out to be increased synaptic function triggered within the CNS by nociceptive inputs [257;237;268].

The realization that synapses were subject to a form of use-dependent plasticity that could increase their strength or efficacy had steadily gained ground by the early 1980's. The phenomenon had first been described in the CNS as short lasting a post-tetanic potentiation of mono synaptic IA synaptic input to motor neurons by Lloyd in 1949 [155], one that could spread to other synapses on motor neurons [21]. This was followed by the discovery of windup in dorsal horn neurons by Mendell and Wall in 1965 [164], where repeated low frequency stimulation of a nerve at constant C-fiber strength were found to elicit a progressive increase in action potential firing over the course of the stimulus. A transformative breakthrough was the first description of long term potentiation (LTP) in the hippocampus by Bliss and Lomo in 1973, where a brief high frequency coincident input produced a persistent increase in synaptic efficacy, opening the door for an extensive and still ongoing study into the molecular mechanisms of synaptic plasticity. LTP was first recorded in the spinal cord in 1993 [182], where it represents a particular component of the general phenomenon of central sensitization [113;122;114]. In 1976 Kandel and colleagues described a sensitization of the gill withdrawal reflex in the sea snail Aplysia, which was associated with a facilitation of the synapse between sensory and motor neurons [29]. However, this data was interpreted as reflecting memory and learning rather than an invertebrate model of pain hypersensitivity, although of course the two phenomena converge in this, and other model systems, although there are differences too [274;122].

What I found in my original 1983 and subsequent pre-clinical studies with colleagues at University College London, was that a brief (~10–20 second), low frequency (1–10Hz) burst of action potentials into the CNS generated by electrical stimulation or natural activation of nociceptors increased synaptic efficacy in nociceptive neurons in the dorsal horn of the spinal cord and this lasted for tens of minutes after the end of the conditioning stimulus [255;244;256;267;50;245;273;51;272;263;230;264]. This phenomenon differed from windup, which represented a progressively increasing output **during** the course of a train of identical stimuli (technically called homosynaptic potentiation); central sensitization was concerned instead with the facilitation that manifested **after** the end of the conditioning stimuli, and that once triggered remained autonomous for some time, or only required a very low level of nociceptor input to sustain it. Furthermore, central sensitization represented a condition where input in one set of nociceptor sensory fibers (the conditioning input) amplified subsequent responses to other non stimulated non-nociceptor or nociceptor fibers (the test input; this form of facilitation is termed heterosynaptic potentiation to distinguish it from homosynaptic potentiation where the test and conditioning input are the same) [231]. The classic form of LTP in the hippocampus is homosynaptic with changes in efficacy restricted to activated synapses, a convergent plasticity, and while this is a feature of some aspects of central sensitization [190], most of its clinically relevant attributes relate to its divergent heterosynaptic components [147]. The underlying neurobiological basis for central sensitization is that for most central circuits, the receptive field properties of neurons defined by the firing of action potentials is only the "tip of the iceberg". Most of the synaptic input to neurons is subthreshold [262–263], acting subliminally either because synaptic input is too weak or membrane excitability is restrained by inhibitory inputs. Increasing synaptic strength by a presynaptic increase in an excitatory transmitter release or in the post synaptic response to the transmitter [264;271;231;129;247;130;133;154;46;100;151–152;227] or by reducing inhibition [208;168;12;103;180;165;226] or increasing membrane excitability can recruit these normally subthreshold inputs to suprathreshold action potentials, producing

profound changes in functional properties [270]. More recently it has become appreciated that in addition to activity-dependent synaptic plasticity, changes in microglia, astrocytes, gap junctions, membrane excitability and gene transcription all can contribute to the maintenance of central sensitization [234;189;43;48;88;104;205;44;47;186]. Figures 1 and 2 summarize sensory processing under normal circumstances and the changes that result from induction of central sensitization.

An important implication of these early basic science studies was the possibility that the pain we experience might not necessarily reflect the presence of a peripheral noxious stimulus. We learn from our everyday experience interfacing with the external environment to interpret pain as reflecting the presence of a peripheral damaging stimulus, and indeed this is critical to its protective function. Central sensitization introduces another dimension, one where the CNS can change, distort or amplify pain, increasing its degree, duration, and spatial extent in a manner that no longer directly reflects the specific qualities of peripheral noxious stimuli, but rather the particular functional states of circuits in the CNS. With the discovery of central sensitization, pain conceptually at least had become “centralized” instead of being exclusively peripherally driven. In this sense central sensitization represents an uncoupling of the clear stimulus response relationship that defines nociceptive pain. Nociceptive pain reflects the perception of noxious stimuli. In the absence of such potentially damaging stimuli there is no nociceptive pain. However, after the discovery of central sensitization it became clear that a noxious stimulus while sufficient was not necessary to produce pain. If the gain of neurons in the “pain pathway” in the CNS was increased, they could now begin to be activated by low threshold, innocuous inputs. In consequence pain, could in these circumstances become the equivalent of an illusory perception, a sensation that has the exact quality of that evoked by a real noxious stimulus but which occurs in the absence of such an injurious stimulus. This does not mean the pain is not real, just that it is not activated by noxious stimuli. Such pain can no longer be termed nociceptive, but rather reflects a state of induced pain hypersensitivity, with almost precisely the same “symptom” profile to that found in many clinical conditions. This raised the immediate obvious question, was central sensitization a contributor to clinical pain hypersensitivity?

These notions were generally not very well received initially, particularly by physicians who believed that pain in the absence of pathology was simply due to individuals seeking work or insurance-related compensation, opioid drug seekers, and patients with psychiatric disturbances; i.e. malingerers, liars and hysterics. That a central amplification of pain might be a “real” neurobiological phenomenon, one that contributes to diverse clinical pain conditions, seemed to them to be unlikely, and most clinicians preferred to use loose diagnostic labels like psychosomatic or somatoform disorder to define pain conditions they did not understand. We can now 30 years later, based on data from many studies in human volunteers and patients, address whether central sensitization, defined operationally as ***an amplification of neural signaling within the CNS that elicits pain hypersensitivity***, is a real phenomenon or not, and can assess its relative contribution to inflammatory, neuropathic and dysfunctional pain disorders in patients [258;53].

Central sensitization in human volunteers

The first clear demonstration of central sensitization in human volunteers came from a psychophysical study by LaMotte and colleagues on the secondary cutaneous hyperalgesia that is elicited by intradermal capsaicin injection (which activates the TRPV1 receptor). They found intense localized pain lasting minutes at the injection site, followed immediately by three zones of hyperalgesia; a small zone of heat hyperalgesia close to the injection site lasting 1–2 hours, an intermediate zone of dynamic tactile allodynia spreading beyond the

area of heat hyperalgesia and lasting several hours, and the largest zone to pinprick, way outside of the injection site, which remained present for up to 24 hours [145]. The investigators then showed that the secondary mechanical hyperalgesia required sensory inflow to the CNS because local anesthesia prior to the capsaicin injection blocked it. In addition because the pain sensitivity crossed a tight band that prevented circulation in the skin, they concluded that it was not due to a local spread of the capsaicin or any peripheral inflammatory mediator. An even more direct demonstration that activity dependent central sensitization was responsible for tactile allodynia and secondary hyperalgesia in humans came from a second study by La Motte, this time with Torebjork in 1992 [233]. They again used intradermal injection of capsaicin to induce an area of tactile allodynia that lasted for 2 hours. Nerve block experiments revealed that while the capsaicin and heat pain was carried by C fibers, the mechanical allodynia was transferred to the CNS by low threshold myelinated fibers. The most elegant part of the study was their finding that electrical intraneural stimulation of single Aβ mechanoreceptive fibers that elicited a non painful tactile sensation before the capsaicin injection, began to produce pain if the fibers' receptive field fell within the zone of secondary mechanical hyperalgesia. Lidocaine anesthesia of the cutaneous innervation territory of the stimulated fiber did not reverse the pain, showing this was not peripheral in origin. They concluded that the pain evoked by stroking the skin area surrounding a painful intradermal injection of capsaicin "is due to reversible changes in the central processing of mechanoreceptive input from myelinated fibres which normally evoke non-painful tactile sensations".

Another early study, this time by Koltzenburg and Torebjork, using mustard oil (which activates TRPA1) as the pain conditioning stimulus, together again with differential nerve blocks, confirmed that brush-evoked mechanical allodynia was mediated by low threshold Aβ fibers that normally encode non-painful tactile sensations [140]. Unlike after capsaicin, however, the mustard oil evoked tactile allodynia required an ongoing low level input from C-nociceptors to sustain it, indicating that different sensory fibers may have different central actions, some short and others long lasting, and indeed further studies have shown differences in the duration of tactile allodynia after capsaicin and mustard oil [139], the significance of which was not appreciated a the time because it was not clear then that these irritants acted on quite different TRP receptors.

That central sensitization could cause a spread of pain sensitivity across peripheral nerve territories, the neurological dogma for diagnosing a disease of the central rather than peripheral nervous system, was shown by Max and colleagues using the intradermal capsaicin model in volunteers together with radial or ulnar nerve blocks to clearly identify individual nerve territory [192]. Complementing this, a study comparing skin hyperaemia induced by a skin burn injury found that the skin blood flow changes induced by the injury had disappeared by the time secondary mechanical hyperalgesia peaked, and the two were not correlated in time or space, supporting the conclusion that peripheral mechanisms do not contribute to secondary hyperalgesia [198]. Even more dramatic perhaps, was the relatively recent demonstration that intradermal capsaicin induces contralateral hyperalgesia and allodynia that is delayed in its manifestation and reduced in extent compared to the ipsilateral secondary hyperalgesia, but present in a majority of subjects [206], a form perhaps of "tertiary hyperalgesia" that cannot be peripheral in origin. What pain sensitivity we feel then, can be determined by the state of excitability of neurons in the CNS.

Central amplification of Aδ nociceptor fiber test input following a C-fiber conditioning input was shown to contribute to pinprick/punctate secondary hyperalgesia, again using the intradermal capsaicin model [279], underscoring the different identity of the afferent signals that elicit central sensitization as a conditioning stimulus (C-fibers) from those that elicit allodynia (Aβ) or hyperalgesia (Aδ), a further clear manifestation of heterosynaptic

facilitation. In a similar vein, another study found that pin prick hyperalgesia induced in response to intradermal capsaicin was actually mediated by capsaicin-insensitive afferents, showing that the test and conditioning inputs in this setting are quite different [87], while the secondary hyperalgesia elicited by intradermal capsaicin was shown by yet other investigators, to be restricted to mechanical stimuli, with no correlation between the magnitude of capsaicin evoked pain and the extent of punctate or tactile secondary hyperalgesia [237]. Furthermore, temporal summation to pin prick in the zone of capsaicin injection (as model of homosynaptic facilitation/windup) was mechanistically independent of the development of secondary hyperalgesia, because while the gain of the stimulus-response relationship in the zone of secondary was increased, that of the windup was not changed, even though the actual pain was enhanced [158]. A similar conclusion was made after a study where repeated intradermal capsaicin injections were reported to produce a progressively diminishing pain, presumably due to desensitization, while the allodynia and punctate hyperalgesia continued to increase [254]. Two more recent studies using high frequency stimulation as the conditioning input to mimic conditions that elicit LTP, found that while changes in the conditioned site (homotopic site) do occur, they are accompanied by a development of pain hypersensitivity in the adjacent non-stimulated heterotopic site (reduction in threshold, pain evoked by light tactile stimuli, and exaggerated response to suprathreshold pinprick stimuli [136;240], and both sets of investigators concluded that heterosynaptic facilitation predominates in this model of central sensitization, exactly as it does for the low frequency conditioning inputs that mimic the natural firing range of nociceptors. Generalizing, it seems clear that heterosynaptic changes are a major feature of the presentation of central sensitization.

Apart from changes in subjective pain measures, the consequences of central sensitization can also be detected using objective biomarkers. These include long-term changes in nociceptive withdrawal reflexes [24] and increases in cortical event related potential amplitudes [240]. Magnetic source imaging reveals an increase in the excitability of neurons in the somatosensory cortex evoked by low threshold Aβ stimulation within the capsaicin-induced zone of secondary hyperalgesia [17], while magnetoencephalography detects changes in the patterns of cerebral processing [159] and functional MRI, changes in BOLD signals in the cortex, both during secondary hyperalgesia [16]. Another MRI study found changes in the brainstem that are apparently specific to central sensitization, in addition to the changes in the primary somatosensory cortex that are related to the intensity of pain [153].

While most studies have looked at the effects of skin conditioning stimuli on skin pain sensitivity, experimental muscle pain produced by hypertonic saline injections produces long lasting changes in thermal sensitivity in the area of referred pain [203], while sustained nociceptive stimulation of myofascial trigger points induces a wide spread central sensitization [273;275]. Interestingly, in preclinical models, muscle and joint conditioning afferents have a longer lasting action in producing central sensitization than those from skin [244]. A reverse approach has shown that cutaneous capsaicin increases myofascial trigger point pressure sensitivity in segmentally related muscles [211]. Conditioning nociceptive stimuli originating in viscera, such as exposure of the lower esophagus to acid, also induces central sensitization, leading to viscerovisceral (pain hypersensitivity in the upper esophagus) and viscerosomatic hypersensitivity (allodynia on the chest wall) [193] that can be captured by esophageal evoked potentials [194], and is associated with increased temporal summation [196]. A recent study has replicated this esophageal model of central sensitization using acid and capsaicin infusions, showing also thermal and mechanical pain hypersensitivity in the rectum after the esophageal stimulation [27], indicating how widespread the effects of central sensitization are in the gastro intestinal tract. These changes may be mechanistically related to widespread clinical pain syndromes [95].

One emerging area of considerable interest is the utility of experimental central sensitization in human volunteers to test efficacy in centrally acting drugs. Drugs with efficacy in preclinical models, such as NMDA receptor antagonists [271] can be tested in Phase 1b human proof of principle studies [212]. Ketamine inhibits central temporal summation [8] and secondary mechanical hyperalgesia [142] evoked by repetitive nociceptive electrical stimulation in humans as well as primary and secondary hyperalgesia after an experimental burn injury [116], visceral conditioning inputs [253;251] and topical [6] or intradermal [204] capsaicin, but not A delta mediated nociceptive pain [181]. Ketamine's action on experimental pain can be detected by fMRI [210]. Similar activity is found for i.v. dextromethophan [115]. Collectively these data strongly support a role for the NMDA receptor in acute activity-dependent central sensitization [147]. However, the trials also indicate the lack of therapeutic index between reducing central sensitization and inducing psychotomimetic side effects. Another class of drugs that has been extensively studied in human experimental models of central sensitization is the gabapentanoids. Oral gabapentin at doses similar to that used for chronic neuropathic pain when given to human volunteers reduced tactile allodynia and decreased mechanical secondary hyperalgesia elicited by intradermal capsaicin [92]. Even single administration of gabapentin had an antihyperalgesic effect on capsaicin-induced secondary hyperalgesia and reduced fMRI signatures of central sensitization [110]. In another study gabapentin, interestingly reduced cutaneous evoked central sensitization but not muscle pain [201]. Two studies have looked at pregabalin's efficacy in experimental human central sensitization, one evoked by electrical stimuli [49] and the other by intradermal capsaicin [246]. Both of these double blind studies demonstrated efficacy for pregabalin in terms of experimental tactile allodynia and secondary hyperalgesia. These data suggest that a major component of gabapentin or pregabalin's mechanism of action is a reduction of central sensitization [238]. Many other centrally acting drugs with analgesic efficacy in patients reduce central sensitization preclinically, including duloxetine, milnacipran and lamotrigene [118;170;15] but have not been tested for this action in humans. Drugs that have failed to show efficacy in human studies of activity-dependent central sensitization are NK1 receptor antagonists [252] [49] and COX-2 inhibitors [35;250;49]. A COX-2 inhibitor does have efficacy though if the central sensitization is triggered by peripheral inflammation [225], as predicted by preclinical models [189].

Interestingly, while gender has been described as important for differences in nociceptive pain sensitivity, a study on the secondary hyperalgesia induced by heat and capsaicin did not reveal a gender difference [119]. Nevertheless, recent data show that pain sensitivity including secondary hyperalgesia and brush evoked allodynia is heritable, with an estimated 50% genetic contribution to the pain variance [172]. The genetic polymorphisms involved in the differential susceptibility to secondary hyperalgesia have not been comprehensively investigated, although some candidates are beginning to be identified in studies of experimental central sensitization [228]. This is an area that requires major research.

The following conclusions can be made from this survey of the published studies of experimental pain hypersensitivity in human volunteers. Central sensitization is a robust phenomenon, readily induced in human volunteers in response to diverse ways of activating nociceptors (electrical stimulation, capsaicin, mustard oil, acid, heat burn, UV burn, hypertonic saline). Generally this activity-dependent plasticity manifests immediately, but its effects persist for many hours beyond the inducing conditioning stimulus, eventually returning, however, back to baseline, indicating its usual full reversibility. The phenomenon can be elicited by conditioning skin, muscle or visceral organs, and typically presents as dynamic tactile allodynia and punctate hyperalgesia but also enhanced pressure, and in some cases, thermal sensitivity, spreading from the conditioning site to neighboring non stimulated sites, and even to very remote regions. Although there is a homosynaptic

(homotopic) aspect to the phenomenon, its major manifestation is heterosynaptic (heterotopic), and for this reason and its reversibility, it is perhaps inaccurate to equate central sensitization with the LTP like phenomena in the cortex that are specifically associated with long term memory. Because central sensitization can be induced in almost all subjects and detected using subjective and objective outcome measures and is sensitive to pharmacological interventions, it is a useful tool for determining the activity of drugs on centrally driven pain hypersensitivity.

Globally, the data obtained in human volunteer studies demonstrate that induction of use-dependent central facilitation in nociceptive central pathways increases pain sensitivity and may, therefore, contribute to clinical pain syndromes. Experimental studies in human volunteers are necessarily restricted to using non-injurious conditioning inputs, and therefore are limited to studying only the activity-dependent components of pain hypersensitivity elicited by sensory inputs, and not those transcription-dependent and structural changes that manifest after inflammation or nerve injury, which may have different mechanisms, time courses and presentations [269;171;121;160;261;189;123;229;97;53;242]. The limited experience with more severe human experimental injury indicates that central sensitization also contributes to the late hyperalgesia present in this model [58;176].

Central sensitization and the clinical pain phenotype

What features of the clinical phenotype may be contributed to, or generated exclusively by central sensitization? While the human experimental studies reviewed above indicate that if a patient has dynamic tactile allodynia, secondary punctuate/pressure hyperalgesia, temporal summation and sensory aftereffects, central sensitization may well be involved. Any sensory experience greater in amplitude, duration and spatial extent than that would be expected from a defined peripheral input under normal circumstances, qualifies as potentially reflecting a central amplification due to increased excitation or reduced inhibition. These changes could include a reduction in threshold, exaggerated response to a noxious stimulus, pain after the end of a stimulus, and a spread of sensitivity to normal tissue. However, because we cannot directly measure sensory inflow, and because peripheral changes can contribute to sensory amplification, as with peripheral sensitization, pain hypersensitivity by itself is not enough to make an irrefutable diagnosis of central sensitization. A further complication is that because peripheral input commonly is the trigger of central sensitization, a reduction in pain sensitivity produced by targeting a peripheral trigger with a local anesthetic does not exclude central amplification, but may rather indicate a role of peripheral input in maintaining it [140]. Nevertheless, there are some features of patient's symptoms which are more likely to indicate central rather than peripheral contribution to pain hypersensitivity. These include pain mediated by low threshold Aβ fibers (determined by nerve block or electrical stimulation), a spread of pain sensitivity to areas with no demonstrable pathology, aftersensations, enhances temporal summation, and the maintenance of pain by low frequency stimuli that normally do not evoke any ongoing pain. To assess how central sensitization may present in patients, we need a detailed phenotyping of different patient cohorts to capture exactly what changes in sensitivity occur, where and when [93;188;86;9;11;197;55]. Ideally this should be combined with objective measures of central activity, such as fMRI, so that clear diagnostic criteria for determining the presence of central sensitization in patients can be established. The utility of diagnostic criteria for the presence of central sensitization would not only be insight into the pathophysiological mechanisms responsible for producing pain, but more so in defining potential treatment strategies. If a particular patient's pain is primarily the result of abnormal activity in nociceptors, as in patients with primary erythromelalgia [74], the optimal therapy required is likely to be different from a patient whose tactile allodynia and secondary hyperalgesia are entirely maintained by central sensitization due to changes in synaptic efficacy in the spinal

cord. This is the rationale for a mechanism-based approach to the diagnosis and treatment of pain [266;258]. Indeed response to a trial treatment, such as to the NMDA receptor antagonist ketamine, can itself be a potential diagnostic for the presence central sensitization.

To which clinical syndromes does central sensitization contribute?

Given the caveats about the lack of absolute diagnostic criteria for identifying the presence of central sensitization in patients, a fairly large number of studies have nevertheless putatively identified this phenomenon as contributing to patients' pain phenotype. I will briefly review these, based on disease.

Rheumatoid arthritis (RA)

Patients with RA, the prototypic inflammatory joint disease, have extra-articular tenderness which is correlated with the extent of joint disease [141] but whether this is the result of peripheral or central sensitization has not been studied. A study on juvenile chronic arthritis reported enhanced sensitivity to noxious stimuli both at joints and in remote areas in patients with and without active disease, suggesting the possibility that the disease when active sets up a state of autonomous central sensitization [107]

Osteoarthritis (OA)

This degenerative joint disease with characteristic destruction of cartilage and alteration in bone is a very common cause of chronic pain, particularly in the elderly. The degree of pain does not always correlate with the extent of joint damage or presence of active inflammation raising the possibility that there may be a central component to the pain [26]. Supporting this is the enhanced degree and duration of pain and secondary hyperalgesia evoked by intramuscular injection of hypertonic saline in patients with OA compared to controls [13]. Patients with high pre-operative pain and a low pain threshold have a higher risk of persistent pain after total knee replacement for OA, which was interpreted as reflecting central sensitization [157]. Another study on 62 patients showed that pain of central neural origin (widespread reduced pressure pain thresholds) negatively impacted on knee functional capacity [117]. OA patients have a lower pain threshold and have punctate hyperalgesia in areas of referred pain, which is associated with greater activation in the brainstem as detected by fMRI, representing a possible biomarker for central changes [99]. The centrally acting amine uptake inhibitor duloxetine which reduces central sensitization in preclinical models [124;15], significantly reduced pain more than placebo in an RCT in 231 patients with knee OA pain [45], indicating that drigs that target central sensitization are efficacious in this patient population. In a recent phenotyping study in 48 patients with painful knee OA and 24 age matched controls, the patients had reduced pressure pain thresholds both at the joint and in remote areas, and increased temporal summation. While the degree of sensitization correlated with the pain, it did not correlate with radiological findings, leading to the conclusion that central sensitization is an important contributor to knee OA pain [7]. Collectively, these data intriguingly suggest that the pain of OA, a peripheral pathology, has an important central component, and this is clearly deserving of more study to understand its extent, mechanism and therapeutic implications.

Temporomandibular disorders (TMD)

Unlike OA, the pathophysiology of this syndrome is much less well understood. However, TMD has been found to be associated with an increase in generalized pain sensitivity after isometric contraction of the orofacial muscles [166], and widespread bilateral mechanical [78] and thermal [175] pain sensitivity is reported in women with myofascial TMD compared to age matched controls, which was interpreted as suggesting widespread central

sensitization. In addition, a greater referred pain is elicited from the more frequent trigger points that are found in these patients, than in controls [77].

As for other types of facial pain, mechanical allodynia is a major feature of periradicular inflammation (periradicular periodontitis) with reduced threshold also in contalateral non inflamed teeth, reflecting central sensitization [132]. After a third molar extraction evidence for central sensitization could be detected for at least a week (enhanced response to repetitive intraoral pinprick and electrical stimulation, aftersensations and extraoral hyperalgesia) [126].

Fibromyalgia (FM)

One of the first suggestions that fibromyalgia patients may have generalized central sensitization came from a psychophysical study that identified widespread reduction in thermal and mechanical pain thresholds, as well as greater cerebral laser evoked potentials [90], a finding replicated soon after [156]. Another early small study using ketamine, showed an NMDA-dependent component to fibromyalgia and suggested that tender points may represent secondary hyperalgesia due to central sensitization [209]. Supporting this, Arendt-Nielson and colleagues found in small study that fibromyalgia patients had lower pressure thresholds and increased temporal summation to muscle stimulation, and that intramuscular hypertonic saline injections provoked a longer lasting and more widespread pain. In a related study, they found that the referred pain, temporal summation, muscular hyperalgesia and muscle pain in fibromyalgia patients were all attenuated by ketamine [96]. In 2001 Staud and Price begun a series of studies on fibromyalgia, first showing temporal summation and after sensations of the pain elicited by repetitive cutaneous thermal stimuli and repetitive mechanical stimuli to muscles [221]. In a second study they found that temporal summation occurred at substantially lower forces and at a lower frequency of stimulation in fibromyalgia patients than in control subjects, and that painful after sensations were greater in amplitude and more prolonged [215]. The enhanced experimental pain in fibromyalgia patients was shown to contribute to the variance of the clinical pain [220]. These investigators then showed that the maintenance of experimentally induced pain in fibromyalgia patients requires significantly less frequent stimulation than in normal controls, and concluded that this heightened sensitivity to very low frequency inputs contributes to the persistent pain in these patients [218]. A later study showed that the temporal summation of pain and its maintenance were widespread, and could be equally elicited from hands or feet, leading to the conclusion that central sensitization in these patients was generalized across the neuraxis [219]. In an fMRI study they then found a stimulus and frequency dependent activation in several brain regions in fibromyalgia patients and controls, including ipsilateral and contralateral thalamus, medial thalamus, S1, bilateral S2, mid- and posterior insula, rostral and mid-anterior cingulate cortex. The stimulus temperatures necessary to evoke equivalent levels of brain activity were, however, significantly less in fibromyalgia patients, suggesting that the enhanced neural mechanisms in fibromyalgia are not the result of selective enhancement at cortical levels [216]. The Staud and Price group then designed experiments to see if peripheral sensitization may contribute to the enhanced temporal summation of thermal pain in fibromyalgia patients and concluded that it does not, based on thermal thresholds [214]. Recently they have found using local anesthetic injections though, that peripheral input from muscle appears to be important in maintaining central sensitization in FM patients [217]. This would mean that fibromyalgia may have both peripheral and central contributions, whose extent may vary from patient to patient. Certainly muscle afferents seem to have a potent capacity in preclinical [244] and experimental human studies [275] to induce central sensitization.

A quantitative sensory testing study in 85 fibromyalgia patients and 40 matched controls found that the patients had altered heat and cold thresholds and a reduced tolerance for pain,

as well as a reduced nociceptive reflex threshold, a measure of central excitability [65]. The latter finding was sufficiently different from controls that the authors suggest it could be used as a diagnostic measure of central sensitization, identifying patients for whom centrally acting drugs may be particularly beneficial. Other studies have confirmed the increased generalized sensitivity in FM patients to pressure and thermal stimuli [179]; [94;173] and to electrical stimulation of skin and muscle, with enhanced cortical evoked potentials [66]. The data overall seem to support a major role for central sensitization in the generation of the symptoms of FM, and the success of centrally acting treatments, such as pregabalin or duloxetine in treating these conditions, may reflect a reduction in central sensitization in these patients.

Miscellaneous Musculoskeletal Disorders

Chronic neck pain resulting from whiplash is associated with lowered pain thresholds in uninjured tissue [57;222]. Injection of local anesthetic into myofascial trigger points in these patients results in an immediate increase in range of motion and elevation in pressure pain thresholds, which was felt to reflect dynamic maintenance of central sensitization by afferent triggers [85]. Patients with shoulder impingement syndrome also show widespread muscle sensitivity and an increased number of trigger points [105]. A widespread (bilateral) mechanical pain hypersensitivity is observed in patients with unilateral epicondylalgia (tennis elbow) interpreted as indicating central sensitization, possible induced by a peripheral trigger [75]. Similar generalized deep tissue hyperalgesia can also be demonstrated in patients with chronic radiating low back pain with intervertebral disc herniation [173]. Collectively these data indicate that diverse musculoskeletal disorders are characterized by a spread of pain sensitivity to deep uninjured tissue and that low level peripheral inputs may maintain this.

Headache

The first intimation that headaches have an important component mediated by central sensitization came from a study of spontaneous tension-type headaches which found that even in the absence of headache pericranial muscle tenderness was increased in patients compared to control subjects. During headache, muscle tenderness increased and thermal pain threshold decreased in the temporal region, but remained normal in the hand which was interpreted as indicating that segmental central sensitization contributed to pain in frequent sufferers of tension-type headache [120]. This was then followed by the observation by Bernstein and colleagues that cutaneous allodynia developed in 79% of patients during migraine attacks in, and sometimes beyond the area of referred pain [36–37]. This finding has been repeated in several studies since then [161;135;207;52]. While cephalic and extracephalic allodynia are well described, spontaneous body pain and allodynia has also been reported as preceding migraine attacks [56]. Laser evoked cutaneous pain thresholds are reduced during migraine attacks and cortical evoked potentials increased [62]. No change in heat pain thresholds are found in chronic tension-type headache, but there is pericranial tenderness [63;80] and hyperalgesia of neck shoulder muscles [81]. Nociceptive input from muscles has been suggested to contribute to the induction central sensitization in tension-type headache [79], much as has been suggested for FM. In patients with cluster headaches the nociceptive flexion reflex threshold is reduced on the symptomatic side [191]. In a population study on primary headaches in 523 patients, evidence for pain hypersensitivity was found in those with tension type pain, with a greater disturbance in individuals with chronic or more frequent headaches, implying that central sensitization may contribute to the chronification of headache [30], something that is supported by epidemiological data [31]. In a longitudinal prospective study on whether increased pain sensitivity is a cause or an effect, a study in 100 individuals found that subjects had normal thresholds prior to the development of headache, but this decreased in those who then

developed chronic tension-type headache, suggesting that the pain hypersensitivity is a consequence of frequent tension-type headaches, and not a predictor or risk factor [32], a finding interpreted as showing that central sensitization plays a role in the chronification of tension-type headaches. Interestingly, a study in patients with either chronic migraine and chronic tension-type headache, found in both cohorts reduced threshold for pressure, pinprick, blink, and the nociceptive flexion reflex, as well as higher windup ratios [83], possibly reflecting a common role for central sensitization in the chronification of different types of headache.

Neuropathic pain

The first demonstration of a likely contribution of central sensitization to neuropathic pain came from a study by Campbell and colleagues, who showed that an ischemic conduction block of large myelinated fibers specifically reduced dynamic tactile allodynia [42], a finding that was soon replicated [140]. Since then careful phenotyping studies of conditions like carpal tunnel syndrome have revealed enhanced bilateral sensitivity and an extraterritorial spread of symptoms in patients with unilateral or single nerve entrapment, supporting a contribution of central sensitization [61;76;82;278]. Furthermore, ketamine reduces established peripheral neuropathic pain [125] and chronic phantom limb pain [73] indicating that ongoing activity- and NMDA receptor-dependent synaptic plasticity may contribute to maintaining neuropathic pain. That tricyclic antidepressants, dual uptake inhibitors and calcium channel alpha(2)-delta ligands, all centrally acting drugs that normalize enhanced neural activity, are the current first line treatments for neuropathic pain [72], reinforces the importance of the central component of the pain and its suitability as a target for treatment.

Complex regional pain syndrome (CRPS)

A prominent feature of chronic CRPS1 is tactile hyperesthesia and pressure hyperalgesia [241], which can be registered as enhanced S1 activation by a neuromagnetometer [243]. There is also thermal hyperalgesia in acute CRPS1 patients, which on the side ipsilateral to the diseased limb, may have a peripheral component due to ongoing aseptic inflammation, but the presence of contralateral hypersensitivity in the absence of any inflammatory changes points to an involvement of the CNS [108]. In a small randomized placebo controlled trial intravenous ketamine reduced CRPS pain [200].

Post-surgical pain

This is a very heterogenous group comprising acute postoperative pain and persistent pain of multiple causes, including surgical induced neuropathic pain [131;1]. In the acute phase, incisional pain is associated with a secondary punctate hyperalgesia that is ketamine sensitive [223], with no spread in thermal sensitivity [143] indicating induction of central sensitization. Considerable controversy exists over whether pre-emptive treatment targeting central sensitization is superior to postoperative treatment in treating either the acute postoperative pain or its transition to chronic pain [260;68;128;60;149;70–71;102;4–5;54;236]. Surprisingly, because of numerous technical problems related to the design, conduct and interpretation of such studies, this turns out to be a difficult issue to resolve [167;134]. This is not the place to review the full literature on pre-emptive analgesia, however my personal take on the available data is that there appears to be a small signal for pre- vs. postoperative analgesic treatment in some settings, but it is likely not generally clinically relevant. It seems clearly important though, that patients have full analgesia established on recovery from a general anesthetic or adequate regional anesthesia during surgery, and that this be maintained until surgical healing is well advanced [19;277;14]. The treatment plan for controlling postoperative pain can potentially include drugs with action on central sensitization such as ketamine [184], pregabalin [162;34], gabapentin [202] and

duloxetine [106], which in the limited number of trials currently available show some efficacy, but more RCT are required to assess their utility in treating acute postoperative pain or in reducing the risk of developing chronic pain [59].

Visceral Pain Hypersensitivity Syndromes

Pain hypersensitivity is a feature of several common disorders of the gastro-intestinal tract including irritable bowel syndrome, non-cardiac chest pain and chronic pancreatitis, that all appear to have a central sensitization component. A majority of IBS patients have both rectal and somatic hypersensitivity [249]. Repetitive sigmoid stimulation in patients with IBS induces rectal hyperalgesia and viscerosomatic referral [169]. Local rectal anesthesia reduces rectal and somatic pain in irritable bowel syndrome patients, supporting the possibility that visceral hyperalgesia and secondary cutaneous hyperalgesia in irritable bowel syndrome is the result of central sensitization dynamically maintained by input from the GIT. Patients with non cardiac chest pain have esophageal hypersensitivity [195], with a reduced tolerance to repeated distension, increased size of referred pain and a greater propensity to show secondary hyperalgesia after acid infusion in their lower esophagus [69], all interpreted as reflecting the consequence of central sensitization. Chronic pancreatitis is associated with generalized deep pressure hyperalgesia [39;174] and patients display greater degree and spatial extent secondary hyperalgesia elicited by repetitive experimental stimulation, suggesting enhanced central sensitization [67], that is reduced by a thorascopic splanchnic denervation [38], which may reflect that visceral input from the pancreas maintains the central sensitization.

In the urological tract, pain hypersensitivity is a feature of interstitial cystitis, chronic prostatitis, endometriosis, and vulvodynia, conditions whose pathophysiology and etiology is however, poorly understood. Although central sensitization has been hypothesized to contribute [137], not much data is available and few studies have been performed. Men with chronic prostatitis have though heightened pain sensitivity in the perineum [276;239], while women with vulvodynia have an enhanced post capsaicin allodynia and secondary hyperalgesia compared to controls [84].

Co-morbidity of pain conditions characterized by pain hypersensitivity

Pain can be defined as **nociceptive** when it is generated by noxious stimuli, **inflammatory** when produced by tissue injury and/or immune cell activation, and **neuropathic**, when it is due to a lesion of the nervous system. What about pain conditions though, where there is no noxious stimulus, inflammation or damage to the nervous system? There are several common syndromes that present with pain hypersensitivity but no clear etiological factor, i.e. are considered “unexplained” and which might actually reflect not peripheral pathology but a primary dysfunction of the nervous system. These include fibromyalgia, tension-type headache, temporomandibular joint disease and irritable bowel syndrome, all of which may have a specific contribution to their phenotype by central sensitization, as detailed above. If a heightened sensitivity of the CNS or an increased propensity to develop central sensitization is a common feature of these syndromes, one would expect that there may be increased co-occurrence or comorbidity of the different conditions. It is also possible that an enhanced capacity to produce or maintain central sensitization is the primary defect in some of these syndromes.

In a study on almost 4,000 twins for comorbidity of chronic fatigue, low back pain, irritable bowel syndrome, chronic tension type headache, temporomandibular joint disease, major depression, panic attacks and post-traumatic stress disorder, associations were found that far exceeded those expected by chance, and the conclusion was that these conditions share a common etiology [199]. Another large epidemiological study on 44,000 individuals

including twins for comorbidity with chronic widespread pain, found co-occurrence with chronic fatigue, joint pain, depressive symptoms, and irritable bowel syndrome, leading to the conclusion that associations between chronic widespread pain and its comorbidities may include genetic factors [127]. Yet another study on 2299 subjects for four unexplained syndromes; chronic wide spread pain, chronic orofacial pain, irritable bowel and chronic fatigue, again found that the occurrence of multiple syndromes was greater than expected by chance [2]. These epidemiological findings strongly suggest that there may be a common mechanistic basis for these diverse conditions, and that it may have a hereditary component.

Smaller studies have found comorbidity between fibromyalgia and the following conditions: migraine in females but not males [111], primary headache [64], chronic fatigue symptom [89], systemic lupus erythematosus [213], irritable bowel syndrome [144], rheumatoid arthritis [183], the premenstrual syndrome [3], chronic urticaria [235] and cervical myofascial pain syndrome [40]. Comorbidity has been shown also for back pain and temporomandibular disorders [248], migraine and temporomandibular disorders [91], irritable bowel syndrome and functional dyspepsia, fibromyalgia and chronic pelvic pain [185], and finally between migraine and irritable bowel syndrome, chronic fatigue and fibromyalgia [232]. There is also an overlap between urological disorders like chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis and vulvodynia with fibromyalgia, chronic fatigue, temporomandibular disorders and irritable bowel syndrome [187], and more specifically between vulvodynia, fibromyalgia and irritable bowel syndrome [10].

The overwhelming conclusion from these diverse epidemiological studies is that chronic pain hypersensitivity in the absence of inflammation or nerve damage results in apparently phenotypically different syndromes depending on the tissue/organs affected. However, the overall similarity of the sensitivity changes may reflect a common contribution of central sensitization, and this may account for the unexpectedly high comorbid rate of the apparently different different syndromes. To test if there are indeed **central sensitization syndromes,** we will need a clear set of diagnostic criteria and biomarkers for the phenomenon. If this hypothesis is correct, the implications may be that treatment strategies targeted at normalizing hyperexcitability in the CNS may have a shared efficacy for the different manifestations of the central sensitization syndrome.

Conclusions

Clinical pain is not simply the consequence of a “switching on” of the “pain system” in the periphery by a particular pathology, but instead reflects to a substantial extent, the state of excitability of central nociceptive circuits. The induction of activity-dependent increases in synaptic function in these circuits, triggered and maintained by dynamic nociceptor inputs, shifts the sensitivity of the pain system such that normally innocuous inputs can activate it and the perceptual responses to noxious inputs are exaggerated, prolonged and spread widely. These sensory changes represent the manifestation of central sensitization, and extensive experimental medicine and clinical investigations over the past twenty years, have revealed it to be an important component of the pain hypersensitivity present many patients. While considerable progress has been made in teasing out the cellular and molecular mechanism responsible [148], much remains still to be learned, particularly which genetic and environmental contributors increase the risk of developing central sensitization in particular systems, exactly what triggers and sustains the phenomenon, and what is responsible in some individuals for its persistence. Nevertheless, the identification of the contribution of central sensitization to many “unexplained” clinical pain conditions has both provided a mechanistic explanation, and offered a therapeutic target.

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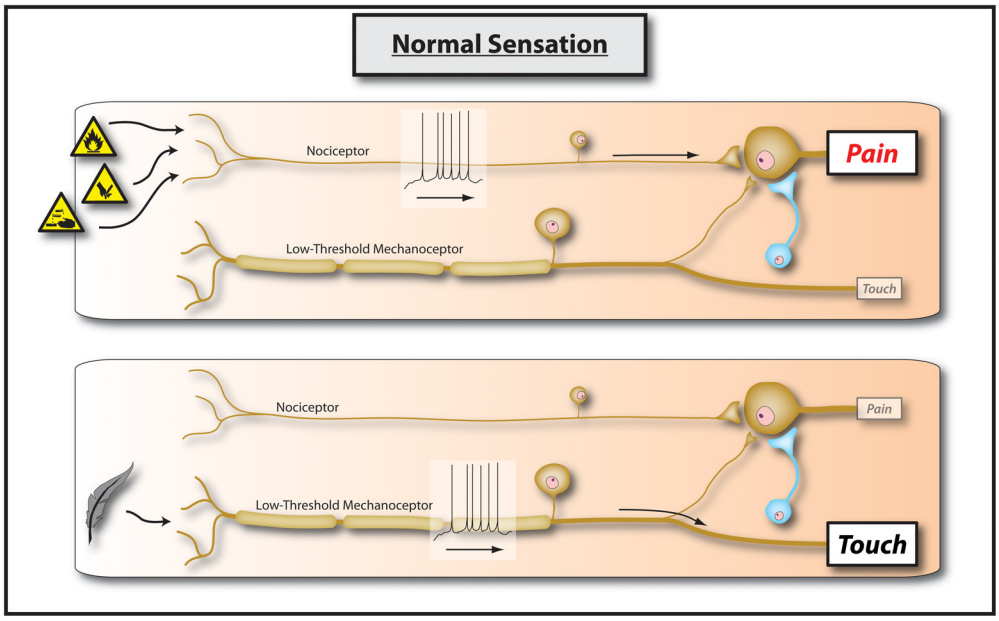

Figure 1.
Normal sensation. The somatosensory system is organized such that the highly specialized primary sensory neurons that encode low intensity stimuli only activate those central pathways that lead to innocuous sensations, while high intensity stimuli that activate nociceptors only activate the central pathways that lead to pain and the two parallel pathways do not functionally intersect. This is mediated by the strong synaptic inputs between the particular sensory inputs and pathways and inhibitory neurons that focus activity to these dedicated circuits.

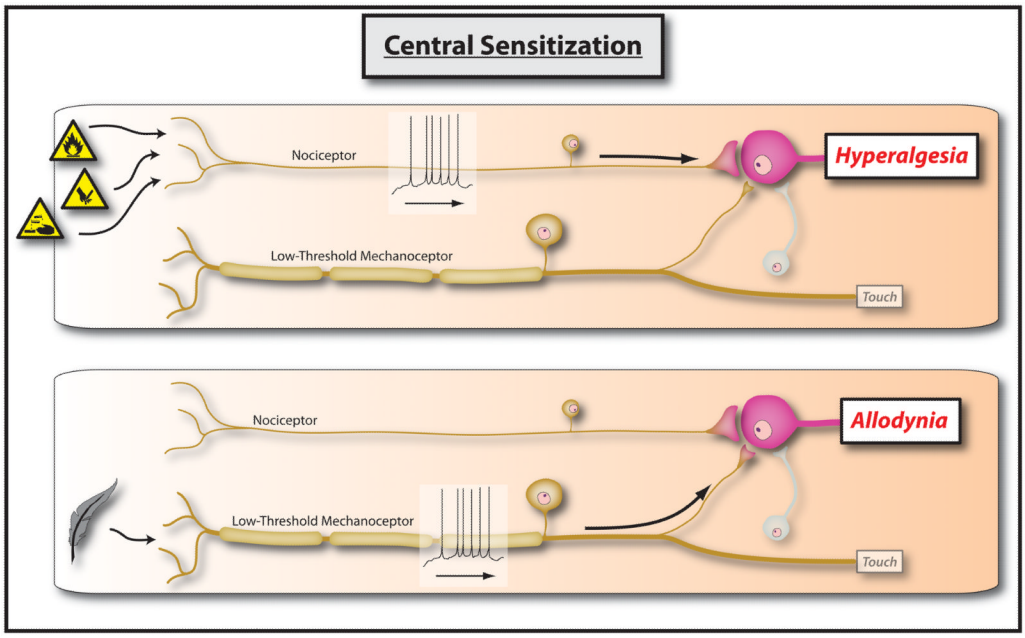

Figure 2.
Central sensitization. With the induction of central sensitization in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge.

Clinical Evidence

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Original article

Pulsed electromagnetic fields in knee osteoarthritis: a double blind, placebo-controlled, randomized clinical trial

Gian Luca Bagnato[1], Giovanni Miceli[1], Natale Marino[1], Davide Sciortino[1] and Gian Filippo Bagnato[1]

Abstract

Objectives. This trial aimed to test the effectiveness of a wearable pulsed electromagnetic fields (PEMF) device in the management of pain in knee OA patients.

Methods. In this randomized [with equal randomization (1:1)], double-blind, placebo-controlled clinical trial, patients with radiographic evidence of knee OA and persistent pain higher than 40 mm on the visual analog scale (VAS) were recruited. The trial consisted of 12 h daily treatment for 1 month in 60 knee OA patients. The primary outcome measure was the reduction in pain intensity, assessed through VAS and WOMAC scores. Secondary outcomes included quality of life assessment through the 36-item Medical Outcomes Study Short-Form version 2 (SF-36 v2), pressure pain threshold (PPT) and changes in intake of NSAIDs/analgesics.

Results. Sixty-six patients were included, and 60 completed the study. After 1 month, PEMF induced a significant reduction in VAS pain and WOMAC scores compared with placebo. Additionally, pain tolerance, as expressed by PPT changes, and physical health improved in PEMF-treated patients. A mean treatment effect of −0.73 (95% CI − 1.24 to − 0.19) was seen in VAS score, while the effect size was −0.34 (95% CI − 0.85 to 0.17) for WOMAC score. Twenty-six per cent of patients in the PEMF group stopped NSAID/analgesic therapy. No adverse events were detected.

Conclusion. These results suggest that PEMF therapy is effective for pain management in knee OA patients and also affects pain threshold and physical functioning. Future larger studies, including head-to-head studies comparing PEMF therapy with standard pharmacological approaches in OA, are warranted.

Trial registration: ClinicalTrials.gov, http://www.clinicaltrials.gov, NCT01877278

Key words: OA, pain, pain threshold, knee, clinical trial.

CLINICAL SCIENCE

Rheumatology key messages

- Pulsed electromagnetic fields therapy is safe and effective in improving knee osteoarthritis symptoms.
- Pain threshold increases after pulsed electromagnetic field therapy in knee osteoarthritis patients compared with placebo.

Introduction

OA affects a large proportion of the population, especially the elderly, leading to pain and disability [1]. Knee OA is the most common form of joint disease [2] and the major cause of pain and physical disability among middle-aged and elderly people [3]. To relieve pain, many patients, in order to avoid the side effects of long-term use of conventional therapies, are turning towards non-pharmacological

[1]Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Messina, Italy

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Correspondence to: Gian Luca Bagnato, Division of Internal Medicine, University of Messina, Via Consolare Valeria n°1, 98100 Messina, Italy.
E-mail: gbagnato@unime.it

therapies [4]. Several non-pharmacological interventions for OA are in different stages of development, investigation and application. Conservative and effective approaches for relieving pain are needed for knee OA patients and, among these, pulsed electromagnetic fields (PEMF) are emerging with promising results. *In vitro* studies have demonstrated that PEMF therapy is effective in reducing chondrocyte apoptosis and MMP-13 expression of knee cartilage in ovariectomized rats [5] and in favourably affecting cartilage homeostasis [6].

Nonetheless, data from human studies are contradictory [7–9], suggesting that further studies using different types of electromagnetic devices, treatment protocols and patient populations are warranted to confirm the efficacy of PEMF therapy in OA. A recent review, comprising 482 patients in the treatment group and 448 patients in the placebo group, highlighted that in trials employing high-quality methodology PEMF therapy was effective in reducing pain and improving function [10]. When the efficacy of PEMF was evaluated for function, a significant improvement was observed 8 weeks after initiation of treatment, and no significant association was found between the use of PEMF and the occurrence of adverse events.

The aim of the present study, therefore, was to evaluate the efficacy for reduction of pain intensity, measured by visual analog scale (VAS) and WOMAC, in patients affected by knee OA treated for 1 month with a wearable device using PEMF. The secondary aim was to evaluate the pain threshold, measured by an algometre, the improvements in quality of life and the changes in intake of NSAIDs/analgesics.

Methods

Patients

This randomized, with equal randomization (1:1), double-blind, placebo-controlled clinical trial, parallel group study, was approved by the ethics committee of the Faculty of Medicine at the University of Messina. The trial was performed in compliance with the Declaration of Helsinki and ICH-GCP. All patients provided their written informed consent. This trial was registered on clinicalTrials.gov (NCT01877278).

Eligibility criteria were: a diagnosis of primary OA of the knee according to the ACR criteria, including radiological evidence of OA [11]; age >40 years; symptomatic disease for at least 6 months prior to enrolment; persistent pain despite receiving the maximal tolerated doses of conventional medical therapy, including acetaminophen and/or an NSAID, with persistent pain defined as a minimal mean score of 40 mm on the VAS for global pain (0–100 mm range for each); daily pain during the month prior to study enrolment; ability to attend follow-up appointments; and no change in pain medication during the last month. Patients affected by secondary causes of OA, DIP joint OA, local or systemic infection, secondary FM, diabetes mellitus, systemic arthritis, coagulopathy, patients on anticoagulant therapy and patients who had received previous intra-articular steroid injection or with avascular necrosis of bone were excluded. The study took place at the rheumatology outpatient clinic of AOU G. Martino Policlinico Universitario of the University of Messina from June 2013 to December 2014.

Randomization and blinding

Both the placebo and the PEMF devices were provided by Bioelectronics Corporation. Before the randomization and blinding procedures, every device was tested through an electromagnetic field detector in order to allocate each device to the proper group.

Randomization and blinding of treatment was conducted by the research coordinator, which ensured similarity between preparations. Devices were consecutively numbered for each patient according to the randomization schedule. For allocation of the participants, a computer-generated list of random numbers was used.

An outcome assessor maintained the randomization codes in sealed envelopes, while another assessor, blinded to the randomization codes, dispensed the devices. Each patient was assigned an order number and received the device in the corresponding pre-packed envelope. Patients continued to remain blinded to the original treatment allocation. Outcome assessors and data analysts were kept blinded to group allocation of patients.

Treatment groups

Patients were randomly allocated to one of two treatment groups, either placebo or PEMF wearable device. Patients in the treatment group were given a PEMF wearable device (PEMF group). Patients in the placebo group were given a device with no electromagnetic properties (placebo group).

The device is manufactured by Bioelectronics Corporation, MD, USA (www.bielcorp.com), and is commercially available. The device used in the present study is a pulsed radiofrequency energy device (ActiPatch) that emits a safe form of non-ionizing electromagnetic radiation. The carrier frequency is 27.12 MHz, the assigned Federal Communications Commission medical frequency, and it has a pulse rate of 1000 Hz and a 100 μs burst width. The peak burst output power of the 12 cm antenna is ~0.0098 W and covers a surface area of ~103 cm^2. The circuitry consists of low-voltage (3 V) digital/analog electronics that control all timing functions to produce the therapeutic radiofrequency field, with the antenna field placed directly above the therapeutic site. This closed-loop system of the antenna, low-energy signal generator circuit and battery power supply transfers the radiofrequency energy to the tissue. The placebo devices do not emit a radiofrequency electromagnetic field but are identical to the active devices, including a light-emitting diode light showing operation. The energy from the active device is not felt by the user, and the active device cannot be distinguished in any way from the placebo device.

Study procedures and assessments

Patients were trained in the use of the PEMF device, which was worn consecutively for a minimum of 12 h,

mainly at night, with the antenna placed over the knee. The device was kept in place with a wrap and switched off when not in use. Patients were asked, during the enrolment phase, to record wear/hours per day and to report, at the end of the study, the hours per day of device use.

Study end points and outcome measures

Each patient was re-evaluated at 4 weeks, to assess the safety and efficacy of treatment, by an assessor who was blinded to the treatment. The primary end point for assessment of efficacy was set at 1 month. The primary outcome measure was the pain score improvement response to treatment from baseline to 1 month in the VAS and in WOMAC. In addition, in order to complete the core set of three primary efficacy variables, recommended by the Outcome Measures in Rheumatology Clinical Trials group [12], quality-of-life assessment [36-item Medical Outcomes Study Short-Form 36 version 2 (SF-36 v2)] was performed.

The secondary end point was to evaluate pain threshold measured by a pressure algometre applied on the anterior aspect of the thigh and at the DIP joint. The algometre consists of a mechanical digital pressure component carrying a sharp section, which could evoke a major painful stimulus. The device, powered by electricity, has a pressure-sensitive terminal connected to an electronic converter that records on a display in real time the amount of pressure in Bar as units of measurement (Wagner FPX 25 Algometer; Wagner Instruments; http://wagnerforce.com/). One rheumatologist, trained in quantitative sensory testing, performed all testing.

The pain threshold test was performed twice on the same day, with 2–5 min separating tests. The first test was designated as a trial run, to accustom participants to the testing procedures. The second test was designated as the test run, from which all data were obtained. The tests were performed on the same day to minimize heterogeneity caused by daily changes in environment, disease activity and mental status. Previous studies have indicated that pressure pain thresholds (PPTs) are highly reproducible when testing is done on the same day [13]. The pain threshold is defined as the pressure at which the participant first feels pain. The pain threshold was measured in two distinct anatomical areas, namely the DIP joint of the second finger and the anterior portion of the quadriceps muscle.

Another secondary outcome measure was to analyse the change in daily intake of NSAIDs per week at baseline and after 4 weeks of treatment. Patients reported analgesic and anti-inflammatory medications taken in the last week prior to each assessment.

Statistical analysis

Statistical analyses were performed using SPSS version 21. We used analysis of covariance on the post-intervention values to assess the group differences with P-values, mean difference and 95% CI. Baseline values were included as covariates. A value of $P < 0.05$ was considered to be statistically significant. It was calculated that a sample size of 66 (33 in each group, allowing for 10% withdrawals) was sufficient, with a power of 80% using a two-tailed test with α level of 0.05, to detect a 10-point difference in VAS, WOMAC total score and SF-36, set as primary outcomes of the study. Calculations were based on standard deviations data from Nelson *et al*. [14] (Pain VAS), Pipitone and Scott [15] (WOMAC total score) and Iannitti *et al.* [16] (SF-36).

Results

A total of 72 patients affected by knee OA were assessed for eligibility. Two patients with concomitant diabetes mellitus, one patient with concomitant DIP joint OA, two patients with persistent pain lower than 40 mm on the VAS and one patient with symptomatic disease for <6 months were not enrolled. Sixty-six patients were recruited into this study. Participants attended clinic visits at the time of randomization (baseline) and at 1 month for a total period of 1 month. Three patients from the PEMF group and three patients from the placebo group were lost to follow-up. Thus, each group comprised 30 (in the PEFM group) and 30 (in the placebo group) completers (see Fig. 1 for flow chart of participants). Baseline characteristics, such as, sex, age, BMI, duration of disease and outcome parameters are reported in Table 1. During the study, the rates of compliance with the different devices were similar. Patients from PEMF group reported an average use of 11.3 ± 0.8 h/day, whereas patients treated with the placebo device reported 11 ± 0.7 h/day. No statistically significant difference was observed in daily use of the devices between the two groups. No adverse events were detected during the study.

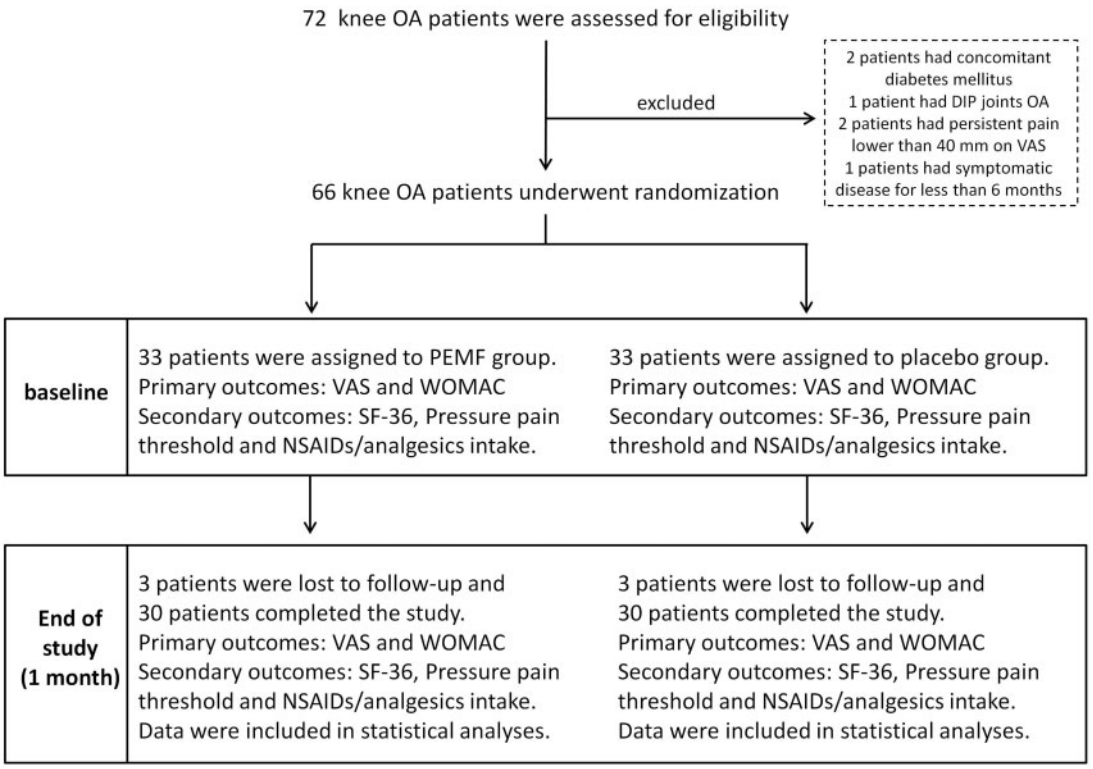
PEMF treatment reduced pain intensity and improved physical functioning

In the initial analysis, we sought to compare the primary outcome in the PEMF and placebo groups. In patients treated with the PEMF device, we found that VAS pain and WOMAC pain scores decreased significantly after 1 month of treatment compared with placebo. Consistently, WOMAC stiffness and function scores improved after PEMF treatment (Table 2).

After 1 month of treatment, there was a 25.5% reduction in VAS pain scores for subjects treated with the PEMF device and a 3.6% reduction in those who received placebo, with a standardized effect size of −0.73 (95% CI −1.24 to −0.19) in VAS score.

There was a 23.4% reduction in WOMAC pain subscale and 18.4% reduction in WOMAC total score compared with 2.3% reduction for both WOMAC pain and total in the placebo group. The standardized effect size was −0.61 (95% CI −1.12 to −0.09) for WOMAC pain and −0.34 (95% CI −0.85 to 0.17) for WOMAC total score (Fig. 2).

Fig. 1 Flow chart of knee OA patients recruited in the trial



Among 72 eligible patients, 6 were excluded (diabetes mellitus, OA of DIP joints, pain duration <6 months, persistent pain lower than 40 on VAS). A total of 66 patients underwent randomization and 6 patients (3 for each group) were lost to follow-up. A total of 60 subjects, 30 for each group, completed the study. The primary outcomes, VAS and WOMAC, and the secondary outcomes, quality of life measured through the 36-item Medical Outcomes Study Short-Form version 2 (SF-36), pain pressure threshold, measured through a pressure algometer and intake of NSAIDs/analgesics, were assessed at baseline and after 1 month for statistical analysis.

Table 1 Baseline demographic and clinical characteristics of patients affected by knee OA treated with pulsed electromagnetic fields or placebo device

Characteristic	All patients (n = 60)	PEMF (n = 30)	Placebo (n = 30)
Age, mean (S.D.), years	67.7 (10.9)	68.6 (11.9)	66.9 (10)
Gender (female/male)	43/17	21/9	22/8
BMI, mean (S.D.), kg/m^2	27.4 (4.3)	27.7 (4.6)	27.1 (4.1)
Disease duration, mean (S.D.), years	12.1 (8.2)	12.4 (9.1)	11.9 (7.4)
Pain score (100 mm VAS), mean (S.D.), MM	65.3 (15.8)	67 (16.6)	63.6 (15.1)
WOMAC total score, mean (S.D.)	132.9 (45.2)	136.6 (49.6)	129.2 (40.8)
SF-36 v2 physical health, mean (S.D.)	52.1 (6.8)	52 (7.4)	52.2 (6.2)
SF-36 v2 mental health, mean (S.D.)	41.1 (5.9)	40.4 (5.8)	41.8 (5.6)
DIP PPT, mean (S.D.)	3.3 (1.3)	3.4 (1.4)	3.3 (1.2)
QDR PPT, mean (S.D.)	12.3 (5.8)	12.4 (6)	12.4 (5.8)
NSAIDs, n (%)	21 (35)	10 (33)	11 (36)
Analgesics, n (%)	26 (43)	12 (40)	14 (46)

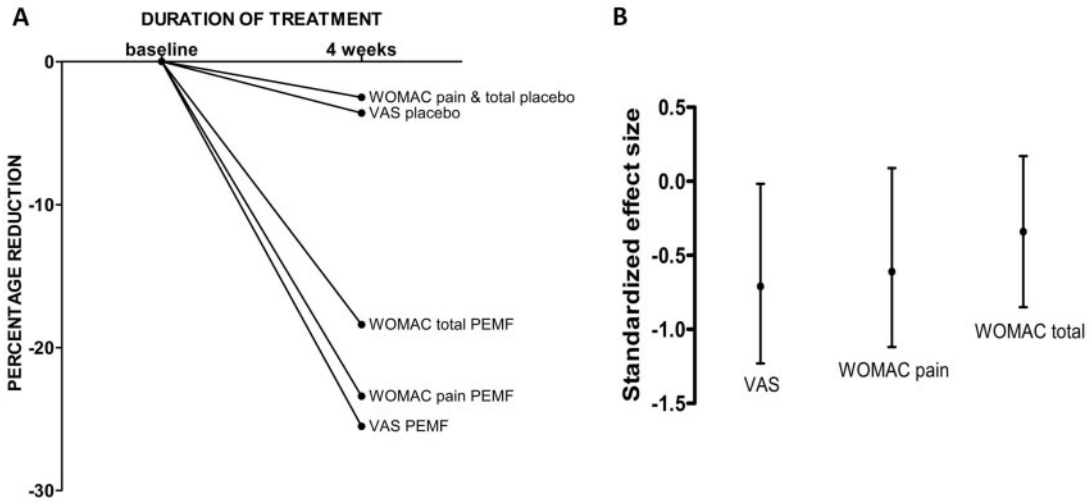
PEMF: pulsed electromagnetic fields; PPT: pressure pain threshold; QDR: quadriceps femoris; SF-36 v2: 36-item Medical Outcomes Study Short-Form version 2; VAS: visual analog scale.

Table 2 Effect of electromagnetic field device therapy on pain and clinical status

Outcomes	PEMF (n = 30)		Placebo (n = 30)		Estimated mean group difference (95% CI)	P-values
	Baseline	1 month	Baseline	1 month		
VAS, mean (S.D.)	67 (16.6)	50 (16.1)	63.6 (15.1)	61.3 (15)	−13.6 (−19.3 to − 7.9)	0.0005
WOMAC pain, mean (S.D.)	28.2 (9.9)	21.6 (9.6)	27.6 (7.4)	26.8 (8.2)	−5.6 (−8.4 to − 2.9)	0.0005
WOMAC function, mean (S.D.)	97.6 (39.9)	81.7 (37.9)	91.2 (36.7)	89.7 (34.4)	−13 (−23.3 to − 2.8)	0.013
WOMAC stiffness, mean (S.D.)	10.8 (4.2)	8.1 (3.8)	10.4 (2.9)	9.6 (3.1)	−1.7 (−2.9 to − 0.6)	0.004
WOMAC total, mean (S.D.)	136.6 (49)	111.5 (48)	129.2 (40)	126.2 (39)	−20.8 (−32.6 to − 8.9)	0.001
SF-36 v2, physical health, mean (S.D.)	52 (7.4)	55.8 (6.1)	52.2 (6.2)	53.1 (6.2)	2.7 (0.3 to 5.2)	0.024
SF-36 v2, mental health, mean (S.D.)	40.4 (5.8)	43.8 (3.6)	41.8 (6.0)	43.6 (4.7)	0.5 (−1.5 to 2.6)	0.6
DIP PPT, mean (S.D.)	3.4 (1.4)	4 (1.6)	3.3 (1.2)	3.4 (1.2)	0.6 (0.1 to 1)	0.015
QDR PPT, mean (S.D.)	12.4 (6)	13.5 (6.2)	12.3 (5.8)	12 (5.3)	1.4 (0.7 to 2.1)	0.0005

Differences between the groups in post-intervention (1 month) values were evaluated with analysis of covariance, with baseline values as covariates. PEMF: pulsed electromagnetic fields; PPT: pressure pain threshold; QDR: quadriceps femoris; SF-36 v2: 36-item Medical Outcomes Study Short-Form version 2; VAS: visual analog scale.

Fig. 2 Changes over time and standardized effect size of VAS pain, WOMAC pain and WOMAC total score



(**A**) The percentage reduction in VAS pain, WOMAC pain and WOMAC total in knee OA participants according to the group of treatment. (**B**) The standardized size effect induced by PEMF treatment is higher for the parameters evaluating pain (VAS score: −0.73 (95% CI −1.24 to −0.19); WOMAC pain: 0.61, 95% CI − 1.12 to − 0.09), while the effect size associated with an improvement in WOMAC, considering all the subscales, is −0.34 (95% CI − 0.85 to −0.17). PEMF: pulsed electromagnetic fields; VAS: visual analog scale.

Pain threshold and physical health improved during electromagnetic treatment

Our results showed that both measurements of PPT improved in OA patients after 1 month of treatment with the PEMF device compared with placebo. Next, we assessed whether quality of life, measured through the SF-36 questionnaire, was modified by the treatment. Only physical health scores improved in the PEMF group (Table 2).

PEMF treatment reduced intake of NSAIDs/analgesics

Given that recruited patients continued to take prescribed analgesic therapy as needed, we analysed the changes in intake of NSAIDs/analgesics. Among the patients from the PEMF group, eight patients (26%) stopped previously prescribed medications, whereas in the placebo group one patient (3%) stopped and 3 (10%) started a new therapy for chronic pain (Table 3).

Discussion

In this randomized clinical trial, PEMF therapy improved pain and dysfunction in knee OA patients. Although previous studies have reported contradictory results on the efficacy of this non-pharmacological approach, our results support previous high-quality randomized clinical trials. In our study, the electromagnetic therapy was applied

Table 3 Changes in intake of NSAIDs/analgesics

NSAID/analgesic intake	PEMF (n = 30)	Placebo (n = 30)
Subject's daily drug intake at 1 months		
NSAIDs, n (%)	6 (20)	12 (40)
Analgesics, n (%)	8 (26)	15 (50)
Changes in drug intake at 1 month follow-up		
Started NSAIDs/ analgesics, n (%)	- (0)	3 (10)
Stopped NSAIDs/ analgesics, n (%)	8 (26)	1 (3)

At the end of the trial, 46% subjects from the PEMF group and 90% patients from the placebo group were under treatment with NSAIDs/analgesics. In the PEMF group, 26% (n = 8) stopped the pharmacological therapy compared with baseline, whereas in the placebo group 10% (n = 3) started a new therapy with NSAIDs/analgesics and 3% (n = 1) stopped previous treatment. PEMF: pulsed electromagnetic fields.

for 12 h each day for a treatment duration of 4 weeks, whereas previous studies ranged from 20 min in nine sessions for 3 weeks [17] to 2 h a day in 30 sessions for 6 weeks [18]. Thus, the absence of a standardized treatment protocol limits the comparison with previous studies.

Additionally, the pulse frequency and duration were different among the randomized clinical trials available, further limiting the possibility of comparing efficacy and safety. Significant pain reduction has been observed in trials using both low pulse frequency and duration (3–7.8 Hz and 10 μs) [15] and relatively high pulse frequency and duration (145 Hz and 400 μs) [19].

In order to explore pain perception, in addition to the self-reported pain scores, such as the VAS and WOMAC scores, we measured pain threshold using pressure algometry, which is the most commonly used quantitative and objective sensory testing method used in rheumatic diseases [20]. It has been clearly shown that patients with rheumatic disease, including OA, have decreased pain thresholds [21–26]. We compared quantitative sensory testing scores, performed on an osseous anatomical surface, the DIP joint, and a muscular anatomical site, the quadriceps muscle, between baseline and 4 weeks of treatment, and we found that pain threshold increased in the PEMF group compared with placebo. The induction of changes in the neuronal sensory mechanism underlying pain perception and threshold remains debated and complex. Exposure to PEMF can increase pain thresholds toward an analgesic response, without affecting thermal sensory threshold, in healthy subjects [27, 28]. Recently, it has been demonstrated that exposure to PEMF can reduce the pain threshold in lateral epicondylitis [29] and also in refractory carpal tunnel syndrome [30]. Neuromodulation could be related to nociceptive C and large A-fibre activity, probably through ion–ligand binding modifications or through changes in the excitability of cell membranes [31]. Another interesting aspect of the interaction between electromagnetic fields and pain is related to opioid function; it has been demonstrated in mice that the induction of analgesia by electromagnetic exposure was equivalent to a moderate dose of morphine [32].

Patients with knee OA have significantly poorer quality of life compared with healthy controls, and this is related to functional disability and chronic pain [33]. We assessed quality of life using the SF-36 v2 questionnaire, as a sensitive health status measure for clinical evaluation, and we found that physical health improved after the exposure to PEMF.

OA is the most prevalent form of joint disease, and the incidence is rising because of the ageing population [1]. Although NSAIDs remain the gold standard for the treatment of pain in OA, there is an increasing need to find conservative and alternative approaches, in order to avoid the toxicity associated with the chronic use of the analgesics, mostly in the elderly population [34]. In our study, OA patients treated with the PEMF device significantly reduced their intake of NSAIDs compared with the placebo group. Given that the factors influencing pain perception in each individual patient remain complex, an attempt to define the mechanisms of pain modulation of this form of therapy in relationship to previously described biological effects remains speculative. Our data on the evidence for the regulation of pain threshold at two different anatomical sites indicates the need for specific studies designed to explore neuronal adaptation in a pulsed electromagnetic environment.

Given that our data are limited to a low number of participants, and the long-term efficacy of the wearable device is unknown, the generalizability of the results needs to be confirmed in a larger clinical trial with a longer duration of treatment. However, the use of a wearable PEMF therapy in knee OA can be considered as an alternative safe and effective therapy in knee OA, providing the possibility for home-based management of pain compared with previous studies.

Taken together, these results suggest that PEMF therapy is a plausible option for the treatment of chronic pain in knee OA. The possibility that some of the effects of this therapeutic approach might be derived from neuromodulation of the pain mechanism needs to be explored further in order to identify the interactions between cartilage function, pain perception and electromagnetic fields.

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Original Research

Pulsed Radiofrequency Electromagnetic Field Therapy: A Potential Novel Treatment of Plantar Fasciitis

Joel Brook, DPM, FACFAS [1], Damien M. Dauphinee, DPM, FACFAS [2], Jaryl Korpinen, DPM, FACFAS [3], Ian M. Rawe, PhD [4]

[1] *Dallas Podiatry Works, Dallas, TX; and Education Director, Podiatric Surgery Residency Program, Hunts Regional Medical Center, Greenville, TX*
[2] *Complete Foot and Ankle Care of North Texas, PA, Denton, TX*
[3] *Premier Foot and Ankle, Plano, TX*
[4] *Director, Clinical Research, BioElectronics Corp, Frederick, MD*

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ABSTRACT

Plantar fasciitis is a common cause of heel pain, and although treatments are usually conservative, they can take up to 2 years to achieve resolution. A double-blind, multicenter, randomized, placebo-controlled study was used to evaluate a small, wearable, extended-use pulsed radiofrequency electromagnetic field (PRFE) device as a treatment of plantar fasciitis. A total of 70 subjects diagnosed with plantar fasciitis were enrolled in the present study. The subjects were randomly assigned a placebo or active PRFE device. The subjects were instructed to wear the PRFE device overnight, record their morning and evening pain using a 0- to 10-point visual analog scale (VAS), and log any medication use. The primary outcome measure for the present study was morning pain, a hallmark of plantar fasciitis. The study group using the active PRFE device showed progressive decline in morning pain. The day 7 AM-VAS score was 40% lower than the day 1 AM-VAS score. The control group, in comparison, showed a 7% decline. A significantly different decline was demonstrated between the 2 groups ($p = .03$). The PM-VAS scores declined by 30% in the study group and 19% in the control group, although the difference was not significant. Medication use in the study group also showed a trend downward, but the use in the control group remained consistent with the day 1 levels. PRFE therapy worn on a nightly basis appears to offer a simple, drug-free, noninvasive therapy to reduce the pain associated with plantar fasciitis.

The plantar fascia is a thick fibrous band of connective tissue originating on the bottom surface of the calcaneus (heel bone) and extending along the sole of the foot toward the 5 toes. It acts to support the arch of the foot and aids in resupination of the foot during propulsion (1). The condition "plantar fasciitis" is the most common cause of heel pain, and estimates indicate that 1 million physician visits annually involve the diagnosis and treatment of plantar fasciitis (2). In addition, it is a common complaint in athletes, resulting in approximately 8% of all running-related injuries (3,4).

The pain from plantar fasciitis is usually felt in the heel of the foot and is usually most acute during the first steps in the morning because the fascia tightens up during the night during sleep. As the tissue warms, the pain subsides but can return with activity and long periods of standing. The underlying condition is a degenerative condition, caused by microscopic tears in the collagen of the fascia. The condition has a detrimental effect on the quality of life, and although conservative treatments are often effective, the period to resolution can be up to 2 years. However, most patients experience improvement by 9 months (5). Conservative therapies include rest, nonsteroidal anti-inflammatory medication, night splints, foot orthotics (6), and stretching protocols (7) of the plantar fascia and gastrocnemius/soleus muscle (8). For persistent plantar heel pain, extracorporeal shock wave therapy has been used but with mixed success. Surgery is sometimes used as a last resort but complications can arise, and it is not always successful (9).

Pulsed radiofrequency electromagnetic field (PRFE) therapy or pulsed electromagnetic field therapy has a long history in treating medical conditions. In 1947, the Federal Communications Commission assigned 3 frequencies at the short end of the radiofrequency band for medical use (40.68 MHz, 13.56 MHz, and 27.12 MHz) (10). The frequency of 27.12 MHz is the most widely used in clinical practice. The first PRFE device, the Diapluse (Daipulse, Great Neck, NY) was commercially available in the 1950s and was followed by other commercially available machines. PRFE is a noninvasive therapy that

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Address correspondence to: Ian M. Rawe, PhD, Director, Clinical Research, BioElectronics Corp, 4539 Metropolitan Court, Frederick, MD 21704.
E-mail address: irawe@bielcorp.com (I.M. Rawe).

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delivers electromagnetic energy into soft tissue, generating an electric field that is thought to mediate the therapeutic effects (11). Many studies have shown the clinical efficacy and safety of PRFE therapy recently reviewed by Guo et al (12). For soft tissue injury, these include ankle inversion treatment, in which studies showed a reduction in pain and swelling (13,14). PRFE therapy has shown to be beneficial in the treatment of neck pain (10,15). The treatment of osteoarthritis with PRFE has been reported to improve joint mobility and decrease pain and stiffness (16–18). Recently, there has been a focus on PRFE therapy and its application in controlling postoperative pain and in promoting the healing of chronic wounds. Significant decreases in postoperative pain have been reported after breast augmentation (19,20) and breast reduction surgery (21), with a corresponding decreased need for narcotic pain medication during recovery. Healing of chronic wounds has also been reported in a number of case reports (22–26), and a retrospective study of a wound registry showed that PRFE holds promise to effectively promote the healing of chronic wounds (27). Significantly, studies on animal models of Achilles tendon repair showed increased tensile strength and collagen alignment (28,29) after PRFE treatment. At 3 weeks after transection of the rat Achilles tendon, the tensile strength had increased by 69% compared with the nontreated control rats (29). Also, in a model of Achilles tendonitis, increased collagen alignment, decreased inflammation, and better tissue normality was seen (28). In vitro cuts in primary human tenocyte cultures from supraspinatus and quadriceps tendons exposed to electromagnetic field stimulation showed significantly accelerated cut closure 12 and 24 hours after the injury (30).

Classically, most studies of PRFE have used large, fixed main-powered devices, in which therapy is delivered in the clinic. In the present exploratory study for the treatment of plantar fasciitis, we used an innovative, small, wearable PRFE device (ActiPatch, BioElectronics, Frederick, MD) that can be used for extended periods. In the present study, it was used as a home-based therapy delivered nightly during sleep.

Patients and Methods

The study was a multicenter, prospective, randomized, double-blind, and placebo- and positive-controlled trial to determine the effects of nightly use of a wearable PRFE device (ActiPatch, Bioelectronics). The North Texas institutional review board at Medical City Dallas approved the study, the study participants provided signed consent forms, and all rights of the enrolled subjects in the present study were protected. The primary outcome measure for the study was morning pain, selected because morning pain is the hallmark of plantar fasciitis. Subjects who had been diagnosed with plantar fasciitis were recruited from the clinical practices of the podiatrist authors. The primary diagnostic criteria was defined as the presence of tenderness at the insertion of the plantar fascia into the heel bone, either plantar medially or plantarly. Radiography was used in all cases to rule out osseous causes of heel pain, including stress fracture or bone tumor. Although patients with fat pad atrophy were not excluded, those with pain directly under the osseous prominence of the calcaneal tuber rather than at the insertion of the plantar fascia, were excluded. Patients in whom neuritis was found to be the primary cause of heel pain as determined by palpation or percussion of the branches of the medial and lateral calcaneal nerves were excluded. Each subject recruited into the study randomly selected a coded PRFE device. The device used in the present study was a pulsed radiofrequency energy device (ActiPatch) that emits a safe form of nonionizing electromagnetic radiation. The carrier frequency is 27.12 MHz, the assigned Federal Communications Commission medical frequency, and it has a pulse rate of 1000 pulses/s and a 100-μs burst width. The peak burst output power of the 12-cm antenna is approximately 0.0098 W and covers a surface area of approximate 103 cm^2. The circuitry consists of low voltage (3 V) digital/analog electronics that control all timing functions to produce the therapeutic radiofrequency field, with the antenna field placed directly above the therapeutic site. This closed loop system of the antenna, low-energy signal generator circuit, and battery power supply transfers the radiofrequency energy to the tissue. The placebo devices did not emit a radiofrequency electromagnetic field but were identical to the active devices, including a light-emitting diode (LED) light showing operation. The energy from the active device is not felt by the user, and the active device cannot be distinguished in any way from the placebo device. Subjects were trained in the use of the PRFE device, which was worn nightly for 7 days with the antenna placed over the heel, the site of pain. The device was kept in place with a wrap and switched off when not in use. No other new treatments were started during the study period.

The subjects were asked to record their pain levels using a 0 to 10 visual analog scale (VAS). The VAS scores were recorded in the morning (AM), assessed on the first steps after awakening, and at night (PM), before bed, for the 7 days of the study. Medication use was also recorded, and medication use was left to the discretion of the patients during the study period.

Statistical Analysis

After completion of the study period and the collection of all available data, the data were analyzed using Excel 2007 (Yuma, AZ) with QI macros (KnowWare International, Denver, CO). Analysis of variance was performed using a generalized linear model, a flexible generalization of ordinary linear regression using SAS software (SAS Institute, Cary, NC). The generalized linear model generalizes linear regression by allowing the linear model to be related to the response variable by way of a link function and by allowing the magnitude of the variance of each measurement to be a function of its predicted value. The slope or rate of decline was compared using repeated measure analysis, which allows for the comparison of the mean variables with time. This analysis allows for a statistical comparison between the rate of decline in the control and study groups. The slope is considered significantly different at the 95% confidence level. Trends in VAS scores were analyzed using the Friedman test for nonparametric repeated measures. The base rates for each group were done relative to the first VAS score taken in the morning of day 1.

Although not typically used, to show the group trends in medication use during the 7-day study period, the following method was used. Medications were converted to 1 pill doses using a base dose for each medication used by the study participants. One pill was recoded as 200 mg ibuprofen, 250 mg acetaminophen, 250 mg naproxen, or 100 mg celecoxib. The use of a diclofenac topical patch was recorded as 1 dose.

Results

The planned enrollment for the study was 140 patients, and 70 active- and 70 placebo-coded devices were mixed in boxes. The patients randomly chose a device, and the device code was recorded. The planned enrollment was not met owing to time constraints, and only 70 patients were enrolled in the study (42 active and 28 placebo). Given the shortness of the study period and the simplicity of the treatment, no patients were lost to follow-up and no data were missing. Although this was a multicenter study, an intersite analysis was not performed because subject site recruitment data were not recorded by the study coordinator.

The demographic data indicated the randomization was successful (Table 1). No significant difference was found in age, height, weight, or plantar fasciitis duration between the 2 groups. The percentage of females in the 2 groups was 75% in the control group and 73.8% in the study group.

The PRFE therapy devices were well tolerated by all the patients, and no adverse effects were noted. Data were obtained from all 70 enrolled patients and were available for statistical analysis. The mean AM-VAS scores and the standard deviation for the 7 days of the study are presented in Table 2.

The day 1 VAS scores were not significantly different between the study and control groups. The VAS pain scores for the 7 days of the study showed a consistency in the control group with a day 1 to day 7 difference of 0.26 VAS points. In contrast, the AM-VAS score in the study group showed a steady decline. The day 1 to day 7 VAS score difference was 1.74 VAS points, for a 7.5-fold greater reduction in pain than in the control group (Fig. 1). Regression analysis of the

Table 1
Demographic data (N = 70 patients)

Variable	Control Group (n = 28 patients)	Study Group (n = 42 patients)	*p* Value
Age (y)	49.7 ± 15.2	53.2 ± 14.7	.35
Height (in.)	64.3 ± 2.9	65.5 ± 3.0	.09
Weight (lb)	196.4 ± 58.6	176.0 ± 28.8	.14
Plantar fasciitis duration (mo)	13.1 ± 8.7	11.9 ± 8.1	.60

Data presented as mean ± standard deviation, with no significant difference ($p \leq .05$) detected between the 2 groups.

Table 2
Mean morning visual analog scale scores (N = 70 patients)

Day	AM-VAS Score	
	Control Group (n = 28 patients)	Study Group (n = 42 patients)
1	3.67 ± 2.01	4.38 ± 2.39
2	3.75 ± 2.30	3.64 ± 2.15
3	3.28 ± 2.40	3.45 ± 2.11
4	3.13 ± 2.37	3.26 ± 1.91
5	3.54 ± 2.86	2.87 ± 2.16
6	3.30 ± 2.59	3.01 ± 2.13
7	3.41 ± 2.80	2.64 ± 1.88

Abbreviation: AM-VAS, morning visual analog scale.
Data presented as mean ± standard deviations.
Friedman test for nonparametric repeated measures showed significant difference ($p = .036$) between mean values for control and study groups.

study group showed an R^2 of 0.887 ($p = .002$, slope = −0.252; i.e., y = 4.33 − 0.252 × day). For the control group, the R^2 was 0.239 ($p = .265$, slope = −0.051; i.e., y = 3.643 − 0.051 × day). The regression analysis showed a significant downward slope of 0.25 VAS points/day in the study group. A standard repeated measure analysis using the SAS generalized linear model routine showed significantly different rates of improvement in morning pain between the 2 groups ($p = .03$). An F test was also performed using Excel 2007 QI macros and showed the group means to be significantly different ($p = .036$).

The AM-VAS scores from day 2 through day 7 were compared with the day 1 AM-VAS scores using the Student's *t* test (Table 3). The AM-VAS scores from day 2 to day 7 in the control group show no significant differences compared with the day 1 scores. In contrast, the steady decline in pain scores in the study group had become significantly different at day 4 ($p = .021$) compared with the day 1 score. The decline in pain continued to be significant through day 7.

The mean PM-VAS score with standard deviation is listed in Table 4. The control and study groups showed declines compared with the day 1 VAS scores.

The decline in the control group was 1.05 VAS points or 19%, and the decline in the study group was 1.49 VAS points or 30%. The SAS analysis of variance and F test showed no significant difference between the 2 groups. However, the decline in the control group from day 1 to day 2 was 0.64 VAS point and an additional 0.36 VAS point from day 2 to day 3. From day 3 to day 7, no additional decline occurred in the mean VAS score (4.46 and 4.41 points, respectively). In contrast, the VAS score decline was more evenly spread in the study group, with a day 1 to day 2 decline of 0.33 VAS point and a day 2 to day 3 decline of 0.39 point. The VAS point decline from day 3 to day 7 was 0.77 VAS point in the study group. Fig. 2*A* shows the mean decline in the PM-VAS score for both groups during the 7-day study period, and Fig. 2*B* shows the day 3 to 7 mean decline.

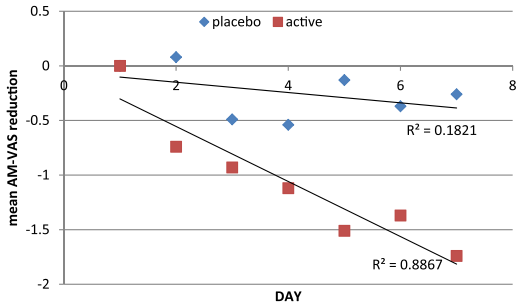

Fig. 1. Effect of overnight use of ActiPatch device on morning pain. Data presented as mean reduction in morning visual analog scale (AM-VAS) score for pain from day 1 to day 7. As can be clearly seen, the level of pain decrease in the treated group was greater than that of the control group by a factor of 7.5.

Table 3
AM-VAS scores on day 2 through day 7 compared with day 1 score using Student's *t* test (N = 70 patients)

Day	*p* Value	
	Control Group (n = 28 patients)	Study Group (n = 42 patients)
2	.90	.15
3	.52	.06
4	.36	.021*
5	.83	.0035*
6	.61	.0076*
7	.69	.00045*

Abbreviation: AM-VAS, morning visual analog scale.
* Statistically significant difference.

The results of the PM-VAS analysis were similar to those of AM-VAS analysis, when comparing the scores of day 2 through day 7 with the day 1 scores using the Student's *t* test. Significance was shown for days 4 through 7 in the study group, with no significant decrease seen in the control group (Table 5).

Medication

The medication used by each group is shown in Table 6. Although the randomization of the study was successful as shown by the demographic data (Table 1), a greater percentage of patients were taking medication in the control group (9/28, 32.1%) compared with the study group (10/42, 23.8%) on day 1. However, of those patients in the 2 study groups taking medication, the average pill use on day 1 was very similar (control group, 2.55; study group, 2.44 pills per subject; Table 7). This was also shown by the total pill use, which was similar at day 1 (study group, 22; control group, 23). The daily total pill use and average patient pill use in the control group showed day to day variability but showed no decline overall. In contrast, in the study group, the total pill and patient average use showed a downward trend (Table 7 and Fig. 3). By day 7, the pill use in the control group was 28 and in the study group was 11, and the average pill use was 2.8 pills per patient in the control group and 1.57 pills per patient in the study group. The number of patients taking pills in the control group was 10 (35.7%) of 28 and in the study group was 7 (16.6%) of 42 at day 7. However, no significant difference was found between the 2 groups.

Discussion

In the present study, we have presented the results from a prospective study using a small, lightweight wearable PRFE device as a treatment for plantar fasciitis. The subjects were instructed to wear the device overnight and the pain experienced in the morning and evening was recorded for 7 days. The results showed that overnight wear of the PRFE device was effective at significantly reducing morning pain, a hallmark of plantar fasciitis. The significant decline in

Table 4
Mean daily PM-VAS scores

Day	Control Group		Study Group	
	Mean Score	Day to Day Decline	Mean Score	Day to Day Decline
1	5.46 ± 2.7	—	4.97 ± 2.5	—
2	4.82 ± 2.9	−0.64	4.64 ± 2.5	−0.33
3	4.46 ± 2.9	−0.36	4.25 ± 2.7	−0.39
4	4.59 ± 3.1	+0.13	3.74 ± 2.2	−0.51
5	4.45 ± 3.0	−0.14	3.81 ± 2.4	+0.06
6	4.14 ± 2.8	−0.31	3.79 ± 2.5	−0.02
7	4.41 ± 2.9	+0.33	3.48 ± 2.4	−0.31
Total	—	−1.05	—	−1.49

Abbreviation: PM-VAS, evening visual analog scale.
Data presented as mean ± standard deviation.

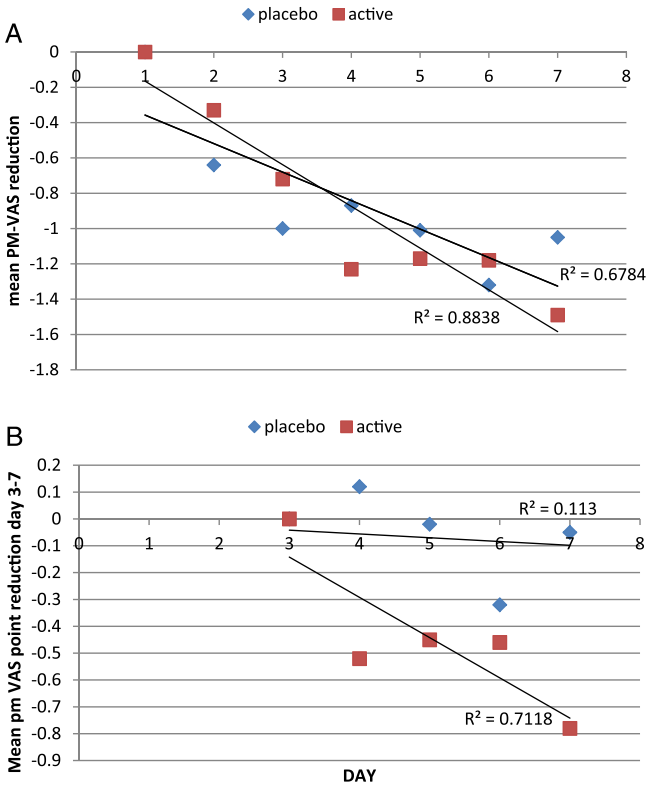

Fig. 2. (*A*) Mean evening visual analog scale (PM-VAS) point reduction after overnight use of Actipatch device. Data are presented as mean reduction in evening visual analog scale pain from day 1 to day 7, with no significant difference between the 2 groups. The study group decreased 1.49 visual analog scale points compared with 1.05 visual analog scale points in the control group. (*B*) Mean evening visual analog scale score reduction from days 3 to 7. Data show that the control group mean evening visual analog scale score remained essentially unchanged from day 3 through day 7 but study group mean evening visual analog scale score showed a continued decline.

morning pain in the study group wearing the active PRFE device was 40% compared with the 7.9% in the control group during the 7-day study period. The analysis of the nighttime pain showed no significant difference between the 2 groups. The pain declined 30% in the study group and 19% in the control group. The control group had a day 1 to day 3 decline of 1.00 VAS point in the evening, although very little decline (0.05 VAS points) was seen for the following 3 to 7 days. This suggests that there was a strong initial placebo effect for the first few days of the study. The decline in the study group was more consistent, indicating a longer study period would have resulted in a significance difference between the 2 groups. Medication use in the study group showed a downward trend during the 7-day study but remained more consistent in the control group, although the results were not significantly different. The consistent decreases in morning pain seen in the study group would be expected to lead to decreased medication use, which occurred.

Table 5
PM-VAS scores on day 2 through day 7 compared with day 1 score using Student's *t* test (n = 70 patients)

Day	*p* Value	
	Control Group (n = 28 patients)	Study Group (n = 42 patients)
2	.41	.55
3	.20	.21
4	.28	.02*
5	.20	.03*
6	.08	.03*
7	.17	.007*

Abbreviation: PM-VAS, evening visual analog scale.
* Statistically significant.

Table 6
Group medication use (N = 70 patients)

Medication	Control Group (n)	Study Group (n)
Acetaminophen 250 mg	3	24
Ibuprofen 200 mg	85	46
Naproxen 250 mg	38	22
Celebrex	28	0
Flector patch (diclofenac)	0	7
Loratab	0	2
Total	154	101

Control group used 154 pain medication pills compared with 101 pain medication pills in the study group. (1 pill counted as 200 mg ibuprofen, 250 mg acetaminophen, 250 mg naproxen, 100 mg celebrex, or 1 Flector patch).

The PRFE device used in the present study is based on work pioneered by Bentall (31) in the 1980s who first showed that reducing the power and size but extending the use time produced equivalent results to larger, more powerful devices. A study by Nicolle and Bentall (32) on surgical recovery showed that extended-use PRFE devices were able to control edema after blephoraplasty. There has been a new focus on small, extended-use PRFE devices, and a number of studies on post-operative recovery and wound healing have been published (19–21,26).

The current treatment for most plantar fasciitis cases results in positive resolution with conservative modalities (6,33–36). Conservative forms of treatment, including nonsteroidal anti-inflammatory drugs, heel pads or orthotics, physical therapy, stretching of the gastrocnemius-soleus, and corticosteroid injections, provide substantial relief for about 80% of patients. However, along with the long interval to resolution, these treatments have additional drawbacks. Injection of corticosteroids for the treatment of plantar fasciitis is almost always painful and can cause both local and systemic side effects (37). Long-term use of nonsteroidal anti-inflammatory drugs can have significant side effects such as gastrointestinal complications and an increased risk of serious cardiovascular events (38). Although custom orthotics are often prescribed, they may only show a short-term benefit in reducing the pain associated with plantar fasciitis (39).

After failure of conservative therapy, treatments such as extracorporeal shock wave therapy and surgery, are used. Extracorporeal shock wave therapy has been reported to be effective in some studies after conservative treatment has failed. Metzner et al (40) reported good results with extracorporeal shockwave therapy. In their study, success was defined as a 30% VAS reduction, which was seen in 81% of patients at 6-week follow-up. However, other studies have reported conflicting results, with the treatment seeming no better than sham therapy (41–43). Although surgery to treat plantar fasciitis is used as a last resort, it has had a variable (70–90%) success rate, and recovery from surgery can vary from several weeks to a few months. Potential complications include transient swelling of the heel, heel hypoesthesia, rupture of plantar fascia, flattening of the longitudinal arch, and calcaneal fracture (9).

Table 7
Medication use (N = 70 patients)

Variable	Day						
	1	2	3	4	5	6	7
Control group (n = 28 patients)							
Subjects using medication	9	8	10	8	9	8	10
Total medication use	23	21	24	19	20	19	28
Average pill use	2.55	2.65	2.4	2.37	2.22	2.37	2.80
Study group (n = 42 patients)							
Subjects using medication	9	7	7	5	7	8	7
Total medication use	22	16	12	7	17	16	11
Average pill use	2.44	2.28	1.71	1.4	2.42	2.0	1.57

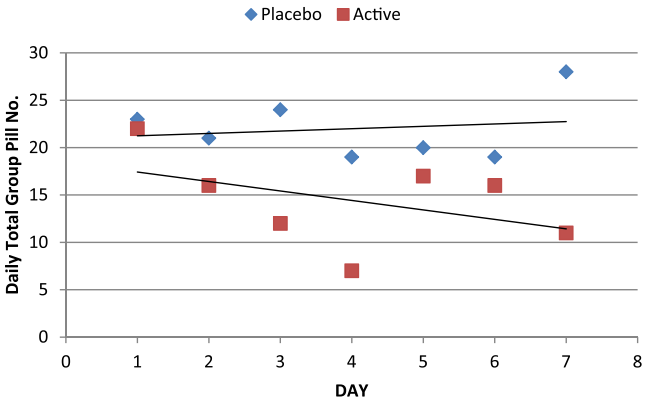

Fig. 3. Mean daily pill use for study and control groups showing decline in pill use in the study group from 22 pills on day 1 to 11 pills on day 7. In contrast, no decline in pill use was seen in the control group (23 pills on day 1 and 28 pills on day 7).

This is the first study to show that PRFE therapy used in this format can potentially treat plantar fasciitis. PRFE therapy for plantar fasciitis appears to offer a therapy that is easy to use, noninvasive, and drug free, with no reported side effects. The results from the present initial study indicate that PRFE therapy results in a relatively rapid decline of pain, given the usually protracted nature of the condition. However, the present study had a number of limitations, including the length of time that data was collected (7 days), the lack of long-term follow-up, and the lack of intercenter analysis. Also, no power analysis was performed to calculate the study size, owing to the lack of data on the effects of this form of therapy on plantar fasciitis heel pain. The sample size was determined by the amount of time the podiatric authors could allot to do the study, which resulted in lower than anticipated recruitment goals. However, the study results suggest that PRFE therapy in this form holds promise as a new treatment of plantar fasciitis.

This is the first study using this form of therapy for plantar fasciitis heel pain. The results from our study indicate that additional studies are warranted to confirm these initial findings.

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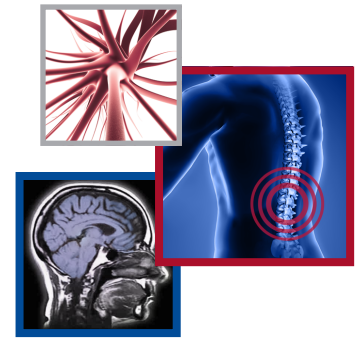
CLINICAL TRIAL EVALUATION

Pain Management

A UK registry study of the effectiveness of a new over-the-counter chronic pain therapy



Ian M Rawe*,[1] & Deepak C Kotak**,[1]

Practice points

- Musculoskeletal pain is widespread in the community.
- Wearable pulsed shortwave therapy is a new over-the-counter pain therapy in the UK and has not been shown to have any significant side effects, even in the elderly or subjects with diabetes.
- This registry study included 44,000 subjects who tried the device, with 5000 submitting an assessment.
- Subjects reported on average severe baseline pain which was present despite using on average two pain modalities including analgesics, heat wraps, transcutaneous electrical nerve stimulation and other pain therapies.
- Current pain modalities appear to be inadequate and ineffective for many individuals.
- In the study over 65% reported a clinically meaningful reduction in pain from a wide variety of etiologies and locations of pain.
- The average pain reduction reported in these individuals was 57%.
- The 3-month follow-up showed sustained pain relief, decreased oral analgesic medication use and quality of life improvement.
- Pulsed shortwave therapy offers a new alternative safe chronic pain therapy.

Background: The ActiPatch® (BioElectronics Corporation, MD, USA) pulsed shortwave therapy device has been shown to be clinically effective in three double-blind randomized controlled pain studies. However, the effectiveness of this device in a broader population of chronic musculoskeletal pain sufferers, affected by a variety of etiologies in different regions of the body, has not been studied. **Aim:** The objective of this registry study was to assess the effectiveness and satisfaction of the ActiPatch device in the general population of chronic pain sufferers. **Methods:** A total of 44,000 subjects completed the trial, with 5000 assessments of the device collected. **Conclusion:** The ActiPatch device appears to provide a clinically meaningful reduction of chronic musculoskeletal pain affecting different locations of the body caused by a variety of etiologies.

Chronic pain is a major burden for individuals and poses a significant public health challenge [1]. Its incidence and prevalence are increasing with an aging population and the rise in obesity. Prevalence of chronic pain is estimated to be 37% in the USA, with an estimated annual cost of US$635 billion [2]. Similar estimates have been put forward for the EU, with an annual cost calculated to be

KEYWORDS
• chronic pain • noninvasive • over-the-counter • pulsed shortwave therapy • therapy

[1]BioElectronics Corporation, 4539 Metropolitan Ct, Frederick, Maryland, MD 21704, USA
*Author for correspondence: Tel.: +1 781 325 2439; Fax: +1 301 874 6935; ian.rawe@gmail.com
**Author for correspondence: Tel.: +1 781 325 2439; Fax: +1 301 874 6935; deekotak@bielcorp.com

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around €300 billion [3]. In a large European pain survey, Breviek *et al.* [4] reported that nearly one-fifth (19%) of adults across Europe suffer from moderate to severe chronic pain. When considering the location of the pain and its etiology, back pain was the most common location with arthritis/osteoarthritis being the most common cause [4]. Chronic back pain has a high economic outlay due to the direct costs of treatment, lost productivity, employment and disability compensation and negative impacts on quality of life [5,6].

Options for treating pain appear to be diminishing with a recent report highlighting the lack of efficacy of paracetamol for spinal pain and osteoarthritis, as well as the lack of improved function and durability of response to opioids [7,8]. Guidelines for NSAID use recommend use for the shortest duration and lowest effective dose due to risk of adverse effects [9]. These adverse effects include gastrointestinal tract injury [10,11], kidney injury, worsening of heart failure and hypertension, increased risk of stroke, heart attack [12] and deep vein thrombosis, as well as death [10,13]. The use of poorly tolerated and ineffective medications is a major driver in direct healthcare costs [14]. Therefore, identification of new safe pain therapies that are efficacious and cost effective are urgently needed.

Nonpharmacological therapies for chronic pain including therapies such as transcutaneous electrical nerve stimulation [15], heat wraps, physical therapy, acupuncture, nutrition, biofeedback and cognitive behavioral therapy have been used for chronic pain with varying degrees of efficacy [16,17].

ActiPatch® (BioElectronics Corporation, MD, USA) has been recently introduced into the UK as an over-the-counter (OTC) 'topical' analgesic for localized musculoskeletal pain. Before this introduction, there was almost no awareness of this medical technology and device. ActiPatch is a noninvasive, low power, easy to use, pulsed shortwave therapy device for localized musculoskeletal pain. The device does not produce heat or any sensation. There are two basic requirements to use the device, switching it on via an on/off switch, and affixing the device over the target area of the body. The area of treatment is confined to the area within the 11.5-cm diameter loop antenna covering an area of 100 cm^2, the antennae is circular, soft and flexible and can be shaped to fit the area/location being treated as required.

As an acute muscle pain treatment, the ActiPatch device significantly reduced postoperative pain in submuscular breast augmentation patients, and significantly reduced the requirement for narcotic pain medications [18]. In two chronic musculoskeletal pain conditions, plantar fasciitis [19] and osteoarthritis of the knee [20], the device was found to significantly reduce pain and medication use [19,20]. However, the effectiveness of ActiPatch has not been studied in a large cohort of musculoskeletal pain subjects with pain in different locations due to a variety of etiologies. To achieve this goal we conducted a registry study of subjects who signed up to receive a trial device. The trial device, once activated has a 7-day power supply and is recommended to be used continuously for the 7 days. The study was designed to evaluate effectiveness (where a treatment is defined to be effective if the user reports a significant reduction in pain when used in real life and in nonideal circumstances) of the device in the common areas of the body affected by different causes of musculoskeletal pain as well as acceptance of subsequent use of the device by the subjects.

Methods

• Subjects

A registry of 44,000 subjects who submitted a request via the ActiPatch website to try a trial device was established between July 2014 and April 2015. Most of these consumers first heard of this medical device via a company sponsored message found on Facebook or a direct response TV testimonial message, although some first heard of the trial offer from a friend or family or a few magazine advertisements. All subjects were from the UK and Ireland, ActiPatch is classified as a class IIa over the counter medical device in the EU but is not available in the USA over the counter. Subjects paid GB£2.95 to obtain the device that was shipped to their home.

• ActiPatch

ActiPatch is a low power pulsed shortwave therapy device operating at 27.12 MHz, emitting pulses at a rate of 1000 pulses per second, each sustained for a 100 µs. The peak power is 73 µWatts/cm^2 with an electromagnetic flux density of 30 µT. The mechanism of action is beginning to be elucidated. Unpublished data suggest a noninvasive neuromodulation effect, with the ability to stimulate afferent nerves through inductive coupling and stochastic resonance. The device

can be used up to 24 h per day and is placed over the area of localized pain either using medical tape or a specifically designed wrap.

• Data collection & processing

The survey objectives were to assess self-reported effects of ActiPatch on chronic pain from an array of etiologies. Three to four weeks after receiving a trial device, subjects were emailed a web-based assessment form using Constant Contact email software. An initial email was followed by a second reminder email 6 days later.

A total of 44,000 subjects registered, and received a trial device and the email assessment form generated 5002 responses, a response rate of approximately 11%. Raw data were outputted and analyzed with Excel 2013 (Microsoft Corp. WA, USA). The trial device was considered effective or of benefit when there was a reported 2 or greater visual analogue scale (VAS) point reduction (0–10 scale). The defined minimal VAS pain reduction for a treatment to be deemed clinically significant has been reported to be between 9 and 14 mm (0–100 mm scale) or 0.9–1.4 on the 0–10 scale [21] and so the 2-point VAS cut off level for determining the effectiveness is conservative. Tests for non-response bias were conducted by using the well validated approach of comparing first wave and second wave responses [22]. Validation was also done by grouping data by month to show the consistency of the data, and conducting a second assessment, after a minimum of 3 months, to determine durability of pain management, impact on quality of life and pain medication use. This assessment was sent to those reporting an intention to purchase the commercial device.

According to European regulations on non-interventional studies with medical devices (CE directive 93/42 and ISO 13485), this survey did not require ethics committee approval.

Results

A total of 5002 responses were acquired between June 2014 and April 2015. All responses were included in the data with the exception of responses that included comments that stated that the trial ActiPatch had not been received or used. There was a total of 250 exceptions with the majority reporting that they had not received the trial device and these were not included in the total of responses. There was a preponderance of females (74%), compared with males in the respondent population (26%), with the majority of subjects over the age of 35 years **(Box 1)**.

Box 1. Demographics of the trial device subjects.

- Gender:
  - Male: 26%
  - Female: 74%
- Age:
  - 18–24 years: 0.9%
  - 25–34 years: 2.9%
  - 35–44 years: 15%
  - 45–54 years: 25.4%
  - 55–64 years: 29.5%
  - 65 years or over: 26.3%

• Cause of pain

In a number a cases multiple causes of pain were reported with an overall average of 1.1 per subject **(Box 2)**. The most frequently reported etiologies were osteoarthritis (31%), rheumatoid arthritis 15% and fibromyalgia (15%).

• Location of pain

Multiple concurrent locations of pain were reported with an average of 1.7 per subject **(Table 1)**. Back pain was reported by 58% of respondents and sample use of the device for back pain was 44%; the knee and shoulder were the next most frequent areas of use at 21 and 15%, respectively. If it is assumed the sample user applied the device on the area that was causing the most pain, conditional that they reported that that location was causing some pain. The 'other' group mainly consisted of elbow, wrist, ankle, foot and legs for locations of use.

• Baseline pain

Baseline VAS score pain for all the responses was an average of 8.02, indicating the majority of

Box 2. Causes of chronic pain.

Percentage reporting

- Osteoarthritis: 31%
- Rheumatoid arthritis: 15%
- Fibromyalgia: 15%
- Sports injury: 8%
- Postsurgery pain: 6%
- Tendonitis: 3%
- Neuropathy: 5%
- Other: 29%

Table 1. Location of pain and location of sample use.

Location	Location of pain (%)	Location of sample use (%)
Back	58	44
Knee	34	21
Neck	17	5
Shoulder	26	14
Hip	20	7
Other	14	8

subjects were experiencing severe pain. Baseline pain was present despite the use of on average of 1.97 pain modalities being used per subject. These were 84% analgesic tablets, 20% transcutaneous electrical nerve stimulation, 27% heat wrap, 32% topicals, 19% physical therapy and 10% other. Paracetamol and NSAIDs were the most frequently used medications at 43 and 48%, respectively (Box 3). For subjects who took pain medications, an average of 1.9 different pain medications were used.

• Pain data

The assessment of pain duration shows that chronic pain is a long standing issue for many individuals (Figure 1). Baseline pain increased with the duration of pain, with subjects reporting pain for more than 20 years recording the highest baseline pain at 8.48 (Figure 1) and less than 6 months the lowest baseline pain 7.63. There is a clear trend of increasing baseline pain with the duration of pain.

Assessment of the trial device

• Pain duration

Using the 2 VAS reduction criteria for benefit, the percentage reporting benefit from the trial device was 65% with an average pain reduction of 57% (Table 2). The percentage reporting benefit was consistent through the range of pain duration groups. However, there was a steady decrease in percentage effectiveness with duration of pain. With pain present for 20 years plus, these subjects reported an average 50% decrease in pain, compared with a 60% average reduction in pain for those with pain present for less than 2 years. Baseline pain shown in Table 2 is the baseline pain of those reporting benefit and is, therefore, slightly different than the baseline pain shown in Figure 1.

Box 3. Analgesic medications being used.

Analgesic: percentage using

- Paracetamol (acetaminophen): 43%
- NSAIDs: 48%
- COX-2 inhibitors: 2%
- Weak opioids: 23%
- Strong opioids: 21%
- Other: 22%

• Gender

Gender comparisons show that females have higher baseline pain (8.11) compared with males 7.79 (Table 3). The percentage reporting that the trial device was beneficial was higher in females at 67%, whereas with males it was 59%. However, there was no difference in the effectiveness between the genders for those reporting benefit, with females posting only a slightly higher VAS reduction (Table 3).

• Pain response by location

The following results represent data from the >6 month or chronic pain group only, a total of 4308 responses were subgrouped by location of sample use (Table 4). The percentage that reported benefit of the trial device and the level of pain reduction was consist in the major areas of the body varying from 61 to 70% effectiveness with a 4.37–4.81 VAS decrease or a 53–60% reduction in the reported pain level. The 'other' locations of use, consisted of use of the trial devices in areas of the body such as ankle, foot, elbow, wrist and hand and had the lowest effectiveness rate – 51% but highest percentage pain reduction at 60% (4.93 VAS points).

• Pain response by cause of pain

Average baseline pain was reported to be in the 8 VAS range for all causes of pain except sports injury (Table 5). The percentage reporting benefit was highest in rheumatoid arthritis and tendonitis at 71% and lowest in neuropathic pain at 59%. Effectiveness was fairly consistent with all causes of pain showing a greater than 50% pain reduction. To confirm the pain reductions were significant, a T-test was performed on the data, all locations of use and causes of pain reported in Tables 4 & 5 were statistically significant $p < 0.001$.

• VAS score distribution

The distribution of VAS scores for the 5002 respondents at baseline are predominantly in the 6–10 VAS point range totaling 4689 in this range, indicating that the registry was composed of mostly people in moderate to severe pain. However, after trial device use, repørted VAS

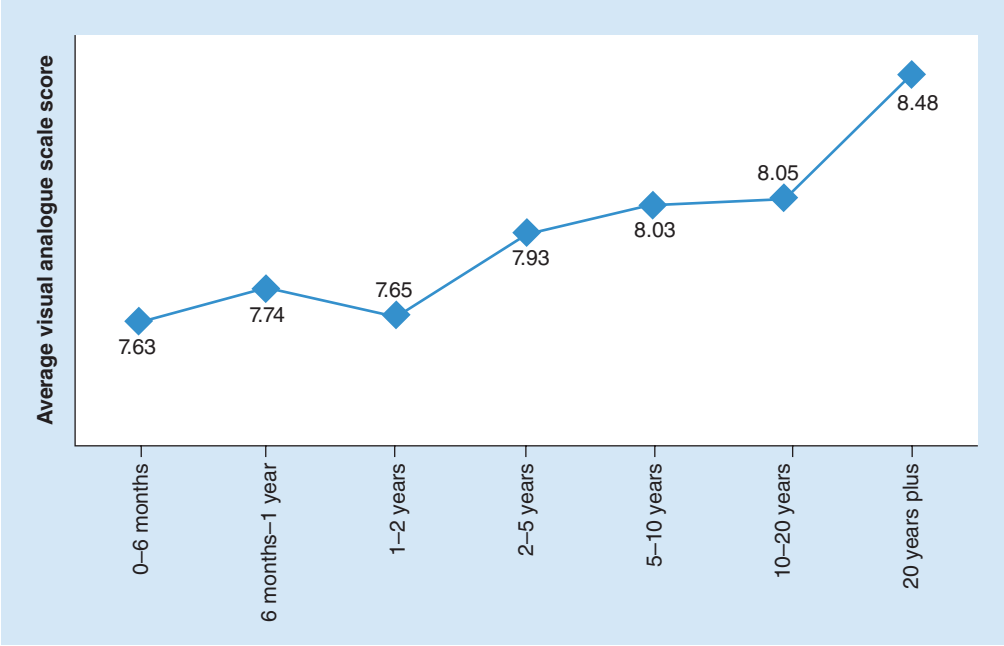

Figure 1. Baseline pain in relation to duration. Baseline pain showed a trend of increasing with the duration of pain.

scores have shifted and are fairly evenly distributed from 0 to 10, with 2879 in the 0–5 range and 2123 in the 6–10 range (Figure 2).

• Days to pain relief

The time in days needed for pain relief over the 7-day trial varied with the most reporting pain reductions by day 1 (31%) and day 2 (31%) followed by day 3 (19%). Therefore the majority, 81% required 3 days to experience pain relief (Figure 3). The data were from subjects that reported pain relief of two or more VAS points.

• Validation of the data

Baseline pain, the percentage reporting benefit and effectiveness of pain reduction with the responses are grouped by month (Table 6). These data show very strong consistency when compared across different assessment time periods. The percentage reporting benefit varied between 61 and 70% and percentage of pain reduction 53–59%.

• Non-response bias testing

Non-response bias testing was used to help validate the data [22]. This consisted of comparing the responses from the first email containing the survey – the first wave, to responses from a second reminder email 1 week later – the second wave (Table 7). The non-response testing shows only very small differences in first wave and second wave responses.

Table 2. Effectiveness and percentage benefiting from the trial device by duration of pain.

Pain duration	Percentage	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
0–6 months	13	65	7.83 ± 1.56	2.94 ± 1.83	4.89	62
6 months to 1 year	11	62	7.92 ± 1.47	3.14 ± 1.91	4.78	60
1–2 years	14	61	7.81 ± 1.49	3.15 ± 1.75	4.66	60
2–5 years	20	69	8.10 ± 1.49	3.29 ± 1.82	4.81	59
5–10 years	21	67	8.16 ± 1.38	3.41 ± 1.90	4.75	58
10–20 years	12	66	8.02 ± 1.59	3.51 ± 1.86	4.51	56
20 years plus	9	70	8.51 ± 1.59	4.14 ± 2.13	4.29	50
All	100	65	8.17 ± 1.50	3.49 ± 1.98	4.68	57

VAS: Visual analogue scale.

Table 3. Effectiveness by gender.

Gender	Response number	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
Female	3641	67	8.24 ± 1.45	3.51 ± 2.00	4.73	57
Male	1337	59	7.95 ± 1.62	3.37 ± 1.92	4.58	58

VAS: Visual analogue scale.

• Consumer acceptance

Of the responses 49% indicated that they would purchase, 22% indicated that they might purchase and 29% indicated that they did not plan to purchase the retail ActiPatch device. This response was highly correlated with the percentage improvement reported. Thus, those who reported substantial improvement in pain level also indicated a higher likelihood of purchasing the retail device. Similar patterns were found when asked if they would recommend to a friend or family member, 52% very likely recommend, 19% somewhat likely, 11% somewhat unlikely and 17% very unlikely to recommend the device.

• Three month follow-up survey data

A second follow-up assessment was sent to the 71% who reported an intention to purchase/maybe purchase the retail ActiPatch device. The assessments were sent after a minimum 3-month interval. The data from these surveys indicated a high purchase rate of 80% of the retail device. (Approximately half of 20% indicated that the reason for not purchasing was financial limitations, the retail cost is GB£19.99 equating to 66p a day) Long-term pain control was reported with 93% experiencing sustained benefit. Asked again for baseline pain, this was on average 8.34, very close to the baseline pain in the 7-day survey of 8.21 and was not significantly different ($p = 0.24$). Directly comparing the two baseline scores from the subjects 83% were either 0 or 1 point difference, with an average variation of 0.84 VAS points for all the subjects offering a strong validation to the VAS scoring used in this study. Pain levels at the 3-month time point with ActiPatch use were on average 3.99 or 51% lower than the reported baseline. Quality of life improvement was also reported with 84% reporting a moderate to a great improvement in quality of life. Along with this pain control, systemic medication use was reduced on average by 50%. These data are currently from 658 responses and data collection is ongoing.

• Attachment issues

The sample was sent with adhesive medical strips for attachment. This attachment method is adequate for most individuals, but a number of individuals, estimated at 3–6% commented on the difficulty of use.

• Safety

No major adverse events were reported. Minor issues centered on attachment of the device and a reaction to the adhesive medical tape and occurred in 0.4% of the responses. This issue can be mitigated by attachment of the device to clothing instead of directly to skin. The commercial device is supplied with wraps for back or knee to help with attachment issues.

Discussion

This registry survey provides data on a large cohort of over 5002 predominantly severe pain sufferers regarding the new OTC pain therapy device in terms of its effectiveness in the general musculoskeletal pain population. Therefore, the

Table 4. Pain reduction and effectiveness in relation to location of use for those reporting chronic pain (>6 months).

Location	Response number	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
Back	2080	65	8.17 ± 1.51	3.61 ± 2.03	4.56	56
Knee	946	69	8.22 ± 1.52	3.41 ± 1.89	4.81	59
Neck	211	61	7.97 ± 1.46	3.71 ± 1.89	4.26	53
Shoulder	603	68	8.11 ± 1.41	3.48 ± 1.94	4.63	57
Hip	339	70	8.25 ± 1.44	3.48 ± 2.00	4.77	58
Other	351	54	8.24 ± 1.47	3.31 ± 2.10	4.93	60

VAS: Visual analogue scale.

Table 5. Effectiveness and pain reduction by cause of chronic pain for those reporting chronic pain (>6 months).

Etiology	Response number	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
Rheumatoid arthritis	688	71	8.54 ± 1.41	3.62 ± 2.06	4.92	58
Osteoarthritis	1519	66	8.32 ± 1.38	3.63 ± 2.03	4.67	56
Fibromyalgia	787	68	8.57 ± 1.33	4.16 ± 2.09	4.41	51
Sports injury	370	69	7.68 ± 1.62	3.23 ± 1.81	4.45	58
Postsurgery pain	270	65	8.26 ± 1.62	3.72 ± 2.08	4.54	55
Tendonitis	128	67	8.38 ± 1.50	3.84 ± 1.85	4.54	54
Neuropathic	241	59	8.39 ± 1.36	3.82 ± 2.21	4.57	54
Other	1414	63	8.00 ± 1.57	3.36 ± 1.92	4.64	58

VAS: Visual analogue scale.

study population was defined by having musculoskeletal pain and not by a specific medical diagnosis as to the cause of pain. Demographics of the cohort favored females by 74% to 26% male and these percentages differ substantially from the reported epidemiology of chronic pain [4] (56% female/44% male) though chronic pain syndromes generally have a higher prevalence in women [1,4,23]. However, they were in line with the population segment targeted by the company with its messages concerning the opportunity to obtain the trial medical device. Specifically, the messages were targeted at women over 35 years of age who indicated on Facebook that they had some interest in pain or causes of pain, for example they were likely to discuss issues associated with arthritis. The locations of use of the trial device are similar to those reported in general surveys of chronic pain [4], with back pain being the most prominent issue reported by the subjects and the highest area of use of the trial device. The frequencies of the causes of pain reported in the registry also reflect a strong similarity to the general population of chronic pain sufferers surveyed in prior studies. However, some targeted marketing, for example, for fibromyalgia may have increased the percentage reporting this etiology as the cause of their pain.

The data presented here show a very high baseline pain scores among the respondents, with the majority – 89% reporting severe pain and the average pain score falling in the severe end of pain

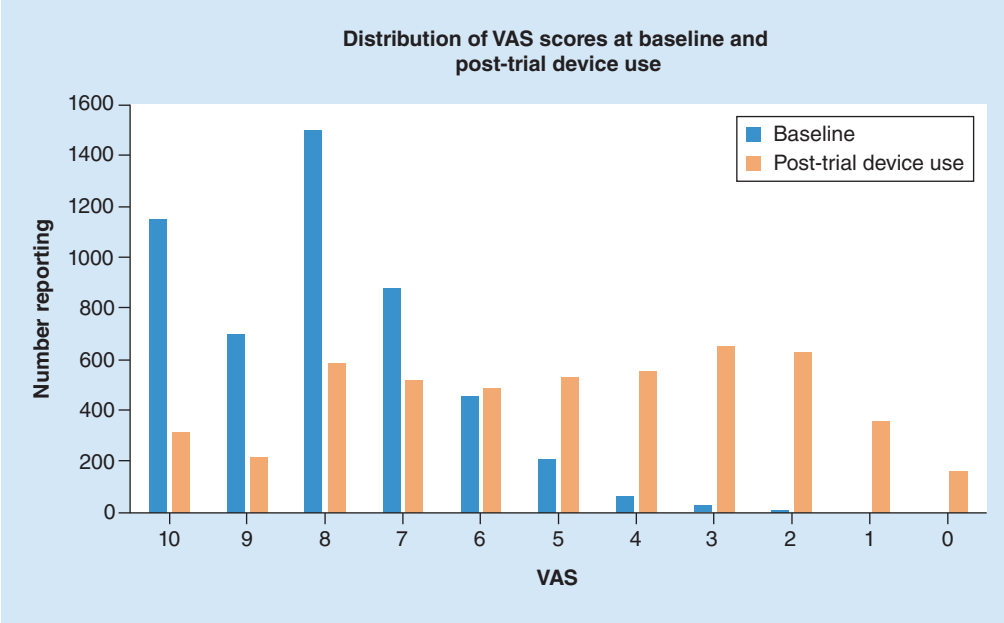

Figure 2. Distribution of visual analogue scale scores at baseline and after trial device use for all the subjects.
VAS: Visual analogue scale.

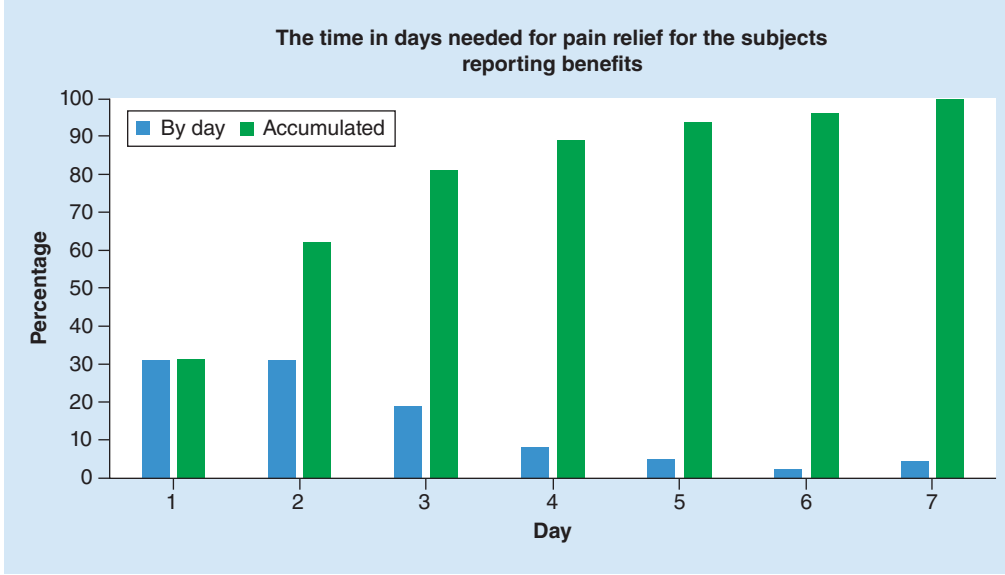

Figure 3. The days needed to experience pain relief shown as the percentage reporting pain relief by day, and accumulated percentage.

scale (8.02). This high baseline pain is present despite the use, on average, of two concurrent pain therapy modalities. This clearly demonstrates that pain treatment is often ineffective and inadequate in many individuals. Underscoring this point is the fact that 84% reported taking pain medications, and these subjects used on average 1.9 types of medication per individual clearly demonstrating that many patients respond poorly to a pharmacological approach for chronic pain [7,14]. Given this severe chronic pain segment of the general population has not found any solution to reducing this pain to an acceptable level, it is clear that there is a need for new innovative pain therapies that are effective, safe and economically acceptable. While reported baseline pain levels may seem to be high, baseline pain levels were duplicated in the 3-month follow-up assessment, suggesting the VAS scoring is reflected of the pain being experienced. These data indicate that ActiPatch is an effective pain modality; for those reporting benefit (2 or > VAS reduction) for all the responses was 65%, with an average pain reduction of 4.68 VAS points or 57%. The percentage reporting benefit from those reporting chronic pain, pain >6 months, was 65% with a 57% pain reduction demonstrating equal effectiveness for chronic pain. This is true regardless of the length of time pain was present, with only a slight decrease in effectiveness with the increased time of the chronic pain. The percentage reporting benefit was also consistent across all major areas of the body varying between 61 and 70%, except the option 'other' which included elbow, wrist, hand, fingers, legs, ankle and feet, where the benefit was reported by 54% (though the extent of effectiveness was higher at 60% or 4.93 VAS point pain decrease). This may be due to the difficulty of attachment of the device to these areas of the body and only those experiencing rapid pain relief persisted with the use of the sample device.

The percentage reporting that the device was beneficial showed consistency with different causes of pain, rheumatoid arthritis showed the highest rate of benefit at 71%, whereas neuropathy was the lowest reported at 55%. Effectiveness of the trial device was shown, with average VAS point decreases ranging from 4.41 to 4.92, with rheumatoid arthritis at 4.92 the largest VAS point decrease. Effectiveness of the ActiPatch sample was matched by subject interest in purchasing the full retail device, with 71% reporting a 'yes' or maybe purchase and consumer likelihood of recommending the device to family and friends.

The VAS scale has been used widely in clinical and research settings where a quick index of pain intensity is required and to which a numerical rating can be assigned. VAS scoring has been shown to have reliability and validity [24]. It is accepted by the authors that it is a unidimensional pain rating scale that does not fully capture the complexity of the pain. Note, however, that the follow-up study also assessed the quality of life and the use of medication which are other indicators of the person's pain level [25].

Table 6. Response data grouped by month.

Month and year	Response number	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
June–August 2014	444	70	8.47 ± 1.44	3.72 ± 2.16	4.75	56
September 2014	231	67	8.35 ± 1.40	3.95 ± 2.05	4.4	53
October 2014	611	62	8.22 ± 1.50	3.47 ± 2.02	4.75	58
November 2014	344	61	8.11 ± 1.39	3.36 ± 1.86	4.75	59
December 2014	452	68	8.10 ± 1.48	3.32 ± 1.91	4.78	59
January 2015	800	63	8.16 ± 1.55	3.51 ± 2.04	4.65	57
February 2015	441	69	8.11 ± 1.56	3.34 ± 2.00	4.77	59
March 2015	1216	63	8.08 ± 1.53	3.41 ± 1.93	4.62	58
April 2015	460	68	7.98 ± 1.48	3.39 ± 1.83	4.59	58
Other	5002	65	8.17 ± 1.50	3.49 ± 1.98	4.68	57

VAS: Visual analogue scale.

While this study is not a randomized controlled trial, and lacks in this regard, there are strengths to this study. This is a large-scale report of a new OTC pain device being used in the community. The registry data come from 58 separate assessments that generate remarkably consistent results when grouped on a month by month basis. Baseline pain scores vary by only a few tenths between each of the sets of data collected, as does the extent of reported benefit in terms of both the level of and average pain reduction, and the effectiveness of the device. The data were also non-response bias tested. Non-response bias testing was conducted by examining trends in data over successive waves of data collection, and is a validated approach for determining non-response bias from just the obtained data [22]. Non-response bias testing did not reveal bias in the data as first wave and second wave baseline and device use VAS scores were very closely matched, as well as having the same level of effectiveness in percentage pain reduction. In fact, we noted that the second wave there was slight improvement in the percentage that reported benefit. Thus, the data suggest that the first wave contains a slightly higher level of people reporting no change in their pain levels. This may reflect that they were disappointed or frustrated that another pain therapy had failed for them and thus were quick to respond.

• Study limitations

This study involved participants who self-selected into the sample and thus may not represent a random sample of all chronic pain sufferers. In this way it is similar to many clinical trials where the patient volunteers to participate. In addition, our results are based only on users who responded to our survey. Although non-response bias testing did not reveal evidence of responder bias, it is still possible that bias could have been present.

Due to the open nature of the study, it could be argued that the reported benefit is due to a strong placebo effect. However, there is no evidence for placebo analgesia except for early time points in chronic pain [26]. Also the 3-month follow-up survey on subjects who reported effectiveness with the trial device indicated a substantial relationship between reported pain relief and actual consumer behavior. This was shown by subjects acquiring the commercial device as well as continued benefit over the longer period, with 93% who purchased the commercial device reporting continued benefit. Moreover, pain control was consistent with an average 51% reduction in pain. Pain control was matched by improvements in quality of life and reductions of systemic medication use. These data indicate that the benefit experienced with the trial device was not due to a placebo effect. Furthermore, three published

Table 7. Non-response bias testing.

Response number	Benefit (%)	Baseline VAS	Trial device VAS	VAS difference	Pain reduction (%)
Total 1231 responses (both waves)	63	8.05 ± 1.49	3.34 ± 2.78	4.71	59
First wave 829 responses	62	8.12 ± 1.49	3.36 ± 2.77	4.76	59
Second wave 319 responses	66	7.92 ± 1.56	3.25 ± 2.95	4.67	59

VAS: Visual analogue scale.

randomized controlled trials using placebo controls indicate that the placebo effect is minimal with this medical device. In plantar fasciitis the placebo effect was reported to be 7% in the control group [19], compared with a 40% pain reduction in the study group. In a knee osteoarthritis study placebo effect was reported to be small compared with the reduction in the study group [20]. Therefore, it would appear unlikely that a placebo effect had a major role in the reported effectiveness of the ActiPatch device though it can not be entirely ruled out as a contributing factor. What is clear overall, is that by using the device, subjects reported that they were in less pain and that they went on to purchase the commercially available device to continue to obtain the therapeutic benefit of pain reduction and as a result reported improvements in their quality of life.

The mechanism of action of ActiPatch is thought to be through a mechanism of noninvasive neuromodulation via stimulation of afferent nerves [McLeod KJ, Unpublished Data]. Though ActiPatch is a very low power device, the pulsed signal is adapted to influence afferent nerve firing through inductive coupling and stochastic resonance. Stochastic resonance is a process where the background noise amplifies the signal, in this case the inherent noise of the body amplifying the signal from the ActiPatch. The time response to pain relief reported supports the mechanism of neuromodulation as the potential mechanism of action. The time for pain relief was spread out over the 7-day trial period though the majority (81%) experienced pain relief by 3 days of use of the trial device.

Conclusion & future perspective

This registry study of 5002 individuals, of which 4301 reported chronic pain, demonstrated that 65% experienced a 2 or greater VAS point reduction, a clinically meaningful reduction in chronic musculoskeletal pain. Along with an excellent risk/benefit ratio profile of ActiPatch, the data supports its use in the community as an OTC product.

The completion of further randomized controlled studies of this device in chronic musculoskeletal pain are needed, as well as presenting a clear mechanism of action, which is believed to be noninvasive neuromodulation. This will help gain acceptance of the technology by patients and in the medical community. Further research and refinement of the technology may well enhance its clinical effect and offer a safe alternative chronic musculoskeletal pain therapy for many individuals in the years ahead.

Financial & competing interests disclosure

IM Rawe and DC Kotak are paid employees of BioElectronics Corporation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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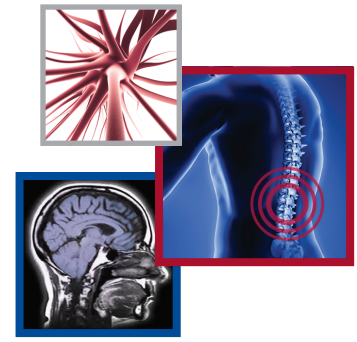
SHORT COMMUNICATION

Pain Management



An over-the-counter central sensitization therapy: a chronic back pain registry study of pain relief, medication use and their adverse effects

Richard Staelin[1], Sree N Koneru[2,3] & Ian M Rawe*[,2]

Practice points

- Subjects in this study had chronic back pain (CBP), with a mean pain duration averaging 6.1 years.
- Pain etiologies demonstrated a heterogeneous subject population of CBP sufferers.
- About 96% of the subjects were using analgesics medications averaging 2.5 per subject, with 71% using prescription analgesics.
- The majority of individuals using analgesic medications for CBP report less than adequate pain relief.
- Adverse effects from pain medications are common (66%) for CBP sufferers.
- CBP sufferers, who report chronic pain for longer than 2 years, also detail using approximately 25% more prescription analgesics than those who have experienced the pain for less than 2 years.
- The number of adverse effects is directly proportional to the number of prescription analgesics being used.
- The increase in the number of adverse side effects negatively impacts quality of life.
- The majority of CBP users, upon using the ActiPatch®, reported a clinically significant reduction in pain within 7 days.
- Nearly 50% of the study subjects were able to eliminate or decrease analgesic medications after 7 days of use of the medical device.
- The ActiPatch was effective in reducing CBP for the majority of subjects as well as reducing their analgesic use.

Aim: Back pain, the most prevalent musculoskeletal chronic pain condition, is usually treated with analgesic medications of questionable efficacy and frequent occurrence of adverse side effects. **Objective:** The objective was to determine the effectiveness of the ActiPatch medical devices in reducing chronic back pain, document medication related adverse side effects and establish their impact on quality of life. **Methods:** Upon completing a 7-day trial, subjects were contacted via email with an assessment form using the Constant Contact email program. A total of 1394 responses were collected from subjects who used the device for back pain. **Conclusion:** Medication adverse effects are common and impact quality of life in the lay population. ActiPatch is an effective intervention for the majority of subjects for treating chronic back pain, although this requires further investigation in randomized clinical trials.

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[1]Fuqua School of Business, Duke University, Durham, NC, USA
[2]BioElectronics Corporation, Frederick, MD, USA
[3]Clinical Science & Engineering Research Laboratory, Binghamton University, Binghamton, NY, USA
*Author for correspondence: Tel.: +1 781 325 2439; Fax: +1 301 874 6935; ian.rawe@gmail.com

Future Medicine part of fsg

KEYWORDS
• adverse side effects • analgesics • chronic back pain • medication reduction • pain relief • pulsed shortwave therapy (PSWT)

Chronic pain, defined as pain which has persisted for greater than 3 months, is a widespread and complex condition [1]. Over 40% of all chronic musculoskeletal pain conditions are associated with chronic back pain (CBP) [2,3] and CBP has been documented to present a significant financial and emotional burden both to the individual and society [2,4–6]. Treatments that are ineffective and poorly tolerated can drive up direct healthcare costs [7]. Although delivering effective therapy for CBP is challenging, the most successful approach is to utilize a multimodal treatment program that necessitates management by a multidisciplinary team of healthcare specialists [8–10].

Currently, most chronic pain sufferers rely heavily on both over-the-counter (OTC) and prescription analgesic medications to treat their pain. The OTC analgesics include acetaminophen (paracetamol) [11] and NSAIDs [12], while prescription drugs include tricyclic antidepressants [13], serotonin and norepinephrine re-uptake inhibitors [14], corticosteroids [15], anticonvulsant [16,17] as well as opiate pain relievers [18]. A major drawback of analgesics, especially of prescription origin, is the significant number of adverse effects that often negatively impact the quality of life (QoL) [19–21]. A US Pain Foundation study showed that 45% of users of OTC drugs do not fully realize the implications of the prescription drugs they are taking and 65% do not consider the possible interactions of other OTC medications they are taking [22]. Moreover, analgesic medications are often ineffective for many individuals [23]. A recent survey by Arthritis UK [24] indicates that only 46% of respondents were satisfied with their pain management, with up to 80% reporting that their mobility was still affected and 64% reporting difficulties in sleeping from a lack of pain relief. Although these facts are well known, the full extent of the adverse effects resulting from the use of multiple analgesics and their impact on QoL in the lay population has not been well documented. This is a central objective of this study.

Safer, more effective alternatives for CBP are now emerging. One such alternative is the ActiPatch, which is a commercially available medical device in the UK, Canada and parts of Europe that uses pulsed shortwave therapy (PSWT) [25] to provide relief from chronic pain [26,27]. Randomized, double-blind, placebo-controlled studies that utilized the ActiPatch indicate clinically significant decreases in pain, along with a decrease in the use of medication [26–28]. For example, in a 4-week study investigating osteoarthritis of the knee [26], 26% of subjects in the ActiPatch treatment group stopped the use of prescribed analgesics, mainly NSAIDs, while 0% added a new therapy for pain management. In comparison, only 3% of the subjects in the control group reported eliminating analgesics, while 33% initiated a new therapy for pain management.

In a previously published, 5000 cohort registry study [29] that investigated general chronic pain, subjects reported high levels of baseline pain (8.03 visual analog scale [VAS] pain score) despite the wide, and often multiple use of analgesic medications in addition to other modalities such as transcutaneous electrical nerve stimulation (TENS) and heat wraps. After using a special trial device that lasts for 7 days, 65% of chronic pain subjects reported effective pain relief, defined as a decrease of ≥2 points on the VAS pain scale over this 7-day period. Of those reporting effectiveness, baseline pain was reduced from 8.17 ± 1.50 to 3.49 ± 1.98, or a 57% pain decrease.

The current study investigates the effectiveness of this 7-day trial ActiPatch device for CBP by assessing a new cohort of subjects. In addition, the study collects data on a wider analgesic profile, a rating of how effective these medications are, the fraction of users who report adverse effects, the details of these adverse effects and how likely it was for the CBP sufferer to reduce medication use after using the medical device for 7 days. In all, 1394 subjects were part of this study.

Methods

• Subjects

A registry of 31,125 subjects was established between January and May 2016 who tested a 7-day trial device, ActiPatch® (BioElectronics Corporation, MD, USA) for musculoskeletal pain after responding to formal company messaging or recommendation from family or friends. There were no formal inclusion/exclusion criteria, except for the contraindications of the medical device (women, who are pregnant, and children) and pain duration greater than 6 months. All the subjects in this study were from the UK and Ireland where the device is classified as class IIa and sold OTC as a pain therapy. The subjects paid a fee for the device which was shipped to their home. Email addresses were collected in the ordering process. A trial completion date was estimated based on the sample

order data, following which an assessment was emailed to the subjects using Constant Contact (Constant Contact, MA, USA) email marketing software (see **Supplementary Materials** for assessment details). A second reminder email was sent 4 days after the first email. Subjects' response to the email survey was completely voluntary, and no other method was used to collect the data. The assessment was designed to collect data on age, gender, pain level, duration of pain, location and cause of pain, as well as analgesic profile, adverse effects* reported, the effect of adverse events on QoL on a 0–10 scale (0 being no effect and 10 being the worst effect) and any change in medication after using the medical device.

*A list of adverse effects was provided in the assessment form, where respondents could select one or more applicable adverse effects. This list was created after observing responses from the first 400 subject assessments in this study, where subjects were allowed to comment on the adverse side effects they were experiencing.

• ActiPatch

ActiPatch is a low power PSWT device that is classified as an OTC, class II(a) medical device in the EU. The device operates at a carrier frequency of 27.12 MHz and pulses 1000-times per second, each sustained for a duration of 100 µs. There are two versions of the device. The 7-day trial device has no on/off switch and the battery life is approximately 168 h or 7 days (cost £5). This trial device comes with medical adhesives that allow the user to attach the device to the skin (or a thin piece of clothing) and is to be applied over the area of pain. The OTC retail device last for 720 h and has on/off capability, and is supplied with a choice of a back wrap medical adhesive tape **(Supplementary Figure 1)**. The retail device sells for £23. The wraps have a pocket designed for the device and straps with Velcro fastening to secure the device in place.

• Data handling

Data from the responses were exported as a comma-delimited (CSV) file, and analyzed using Microsoft Excel (Microsoft Corporation, WA, USA) and an Excel add-on (Regressit). Cross tabs and multivariate regression analysis were used to explore the relationship between a number of characteristics of the subjects and adverse side effects, a person's QoL and medication use and change in medication use.

Results

• Demographics

Of the 31,125 users who were contacted, over a 5-month period (from January to May 2016), approximately 40% opened the email and 32% of these people agreed to 'consider being part of the registry' by clicking onto the link to the assessment. Of those who consented, 88% completed the assessment resulting in a total response of 3735 individuals and an overall response rate of 12%. Of this group, 1394 subjects indicated that they used the device for CBP. The gender, age and duration of pain distributions are given in **Tables 1 & 2**. In general, the sample was predominately a woman, over 35 years of age and experiencing long-standing pain of 2 or more years with a median of 6.1 years.

Etiologies reported by the study subjects **(Table 3)** demonstrate that the population was heterogeneous and, on average, subjects reported pain caused by 1.57 etiologies, and some of these are therefore not related to CBP.

• Analgesics

The most commonly used analgesics were NSAIDs (46%) and paracetamol (52%), followed by weak opioids (typically tramadol) at 30% and amitriptyline at 29%. In addition, many CBP sufferers indicated that they were using other treatment modalities such as TENS, heat wraps and physical therapy **(Table 4)**. On average, each subject using medications in the study used 2.5 analgesics, including topical analgesics (NSAIDs or opiate). Only 3.7% reported not using analgesics.

Subjects were asked to rate the pain relief they experienced from pain medications **(Figure 1)**. Only 7.5% reported good pain relief, while 31.8% reported adequate pain relief, leaving 60.4% who reported less than adequate pain relief or no real pain relief. The mean number

Table 1. Gender distribution.

Gender	n = 1394 (%)
Male	25
Female	75
Age (years)	
18–24	1.4
25–34	3.4
35–44	14.9
45–54	29.4
55–64	27.6
65 or more	22.4

Table 2. Duration of pain.

Pain duration	n = 1394 (%)
6 months to 1 year	7.6
1–2 years	21.9
2–5 years	24
5–10 years	21.2
10–20 years	18.4
20 years +	16

of analgesics used for those reporting good pain relief was 2.34 (1.52 prescription, 0.82 OTC), 2.48 (1.46 prescription, 1.02 OTC) for adequate pain relief, 2.6 (1.52 prescription, 1.08 OTC) for less than adequate pain relief and 2.42 (1.82 prescription, 0.6 OTC) for no real pain relief.

• Pain data

The mean baseline pain reported by the CBP subjects before using the medical device was 8.04 ± 1.46 (Figure 2 & Table 4). The pain score, post-trial was 4.83 ± 2.66, or a 39.9% decrease ($p < 0.001$). The percent of subjects that reported effectiveness, defined as a minimum of 40% pain decrease, was 52% (Table 5). These positive responders reported a mean pain decrease of 5.40 VAS points, or 66% reduction in pain. Conversely, 26% reported no improvement in pain levels, while 1.5% reported an increase in pain.

Table 3. The reported etiologies show a heterogeneous pain population.

Etiology	%
Not sure what causes my pain	11.5
Accident	7.0
Ankylosing spondylitis	4.2
Cervical issues	2.3
Complex regional pain syndrome	1.1
Disc issues	18.0
Fibromyalgia	11.8
Frozen shoulder	0.9
Ligament damage	1.4
Multiple sclerosis	0.6
Neuropathy	2.4
Osteoarthritis	13.7
Osteoporosis	2.5
Rheumatoid arthritis	6.1
Sciatica	11.8
Sports injury	1.3
Surgery	3.0
Tendinitis	0.9
Tennis elbow	1.1
Trapped nerve	4.4
Other	5.9

• Continuation of therapy

Intent to continue the use of the device by subjects was determined, this ranged from 'definitely' to 'definitely not' (Table 6). Intent was closely associated with the degree of VAS reduction with those reporting the greatest VAS reduction indicating a 'definite' intent, whereas those reporting no pain relief indicated 'definitely not' intent to continue the therapy.

• Changes in analgesic medication use

Data were also collected on any changes in analgesic medication use over the 7-day period (Figure 3). The available responses and percent response were increased medication use (0.6%), added a new therapy (0.3%), decreased medication use (36%), eliminated medications (14%) and made no change (49%).

• Analgesic adverse effects – QoL

The impact of analgesic adverse effects on QoL of subjects was assessed on a 0–10 scale (0 being no effect and 10 being the worst effect). A total of 996 or 71.4% of the 1394 CBP subjects were asked about possible adverse effects associated with their medication use. Of these individuals, 66.1% (658) reported adverse effects. In total, there were 3010 adverse effects reported by this group, with the most frequent being constipation (332), followed by dry mouth (279), drowsiness (273), sleep problems (237) and weight gain (191) (see Figure 4). The mean number of adverse effects was 4.6 ± 3.3 per person, for those 658 subjects reporting adverse effects. When asked how adverse effects negatively impacted the QoL on a 0–10 scale, the mean reported was 5.7 ± 2.8.

• Analgesics use – relation to pain duration

The percent of people reporting adverse effects, the number of adverse effects and the impact of these medications on the QoL are segmented by the duration of pain in Table 7. These results indicate that there are significant correlations between duration of pain, the use of analgesics and the number of reported adverse side effects. This is driven in part by the use of prescription analgesics which is seen to increase from approximately 1.1 per individual in the two groups with the shortest pain duration (0–6 months and 6 months to 2 years) to a mean of 1.45 per individual at the 2–5-year pain duration, before peaking for the 5–10

year group at a mean of 1.74 per individual. The percent of subjects experiencing adverse effects is less than 50% when the pain duration is 2 years or less, but it increases to 68.3% with a pain duration of 2–5 years and continues to increase with pain duration, even though prescription use decreases for the longer levels of pain duration. This indicates that pain duration could influence the number of adverse effects in individuals above and beyond to any use of prescription drugs. Finally, we see a comparable increase in the negative impact of pain on the QoL, increasing by almost 50% from the shortest pain duration to the longest pain duration (Table 7).

• Analgesics use & QoL – relation to age

Analgesic use, adverse effects and their impact on QoL are categorized by age of the subjects (Table 8). It is interesting to note that younger age groups report using higher rates of medications and consequently experience a higher number of mean adverse effects as well as greater impact on QoL. The 25–34-year age group has the highest analgesic use and experienced the highest number of adverse effects per individual. A reduction in both these factors is seen with increasing age. Thus, the oldest age group, 65 years plus, has the lowest medication use and consequently the lowest mean adverse effects and lowest impact on QoL. There was no significant statistical relationship between age and duration of pain, in other words, older subjects are not more likely to have a longer duration of pain. Thus, these two variables should be thought of as being independent.

Table 4. Medication use of the subjects in the study.

Analgesic	%
Paracetamol (acetaminophen)	52
NSAIDs	46
Weak opioids (codeine, tramadol)	30
Strong opioids	13
Cox-2 inhibitors	1
Pregabalin (e.g., Lyrica)	13
Amitriptyline	29
Topical opioid (e.g., morphine)	10
Topical NSAIDs (e.g., Voltarol)	17
Gabapentin	16
Duloxetine (e.g., Cymbalta)	1
Steroids (e.g., prednisone)	2
Epidural	2
Other	7
No analgesics	3.7
Other modalities	
TENS	24
Heat wraps	30
Physical therapy	20

TENS: Transcutaneous electrical nerve stimulation.

Regression analysis

• Side effects & therapy

The relationship between the number of reported side effects and the quantities of the different types of therapy being used was explored. These were the number of different OTC medications, the number of different prescription drugs and the number of different other treatments (e.g., TENS and heat wraps) where larger

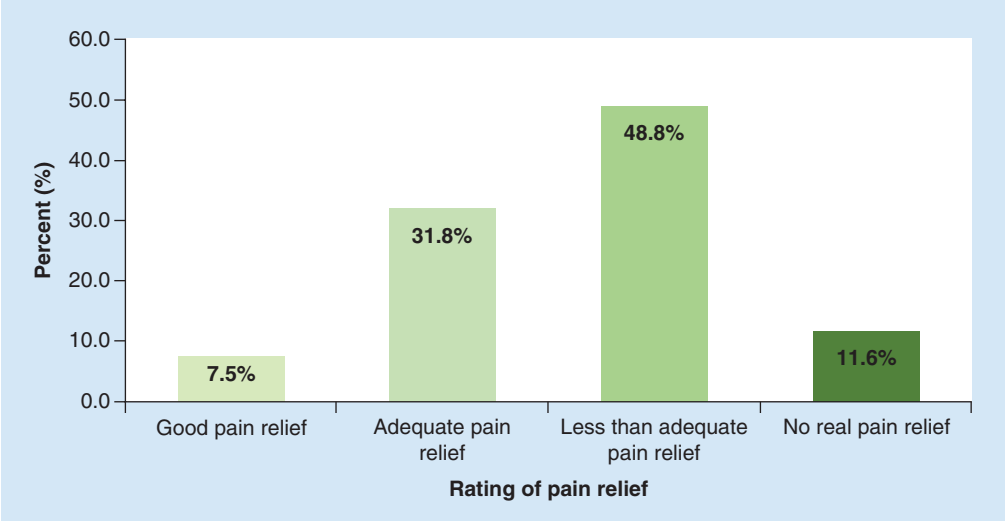

Figure 1. Ratings of pain relief by subjects indicate that only 7.5% get good pain relief, with 60.4% experiencing less than adequate pain relief.

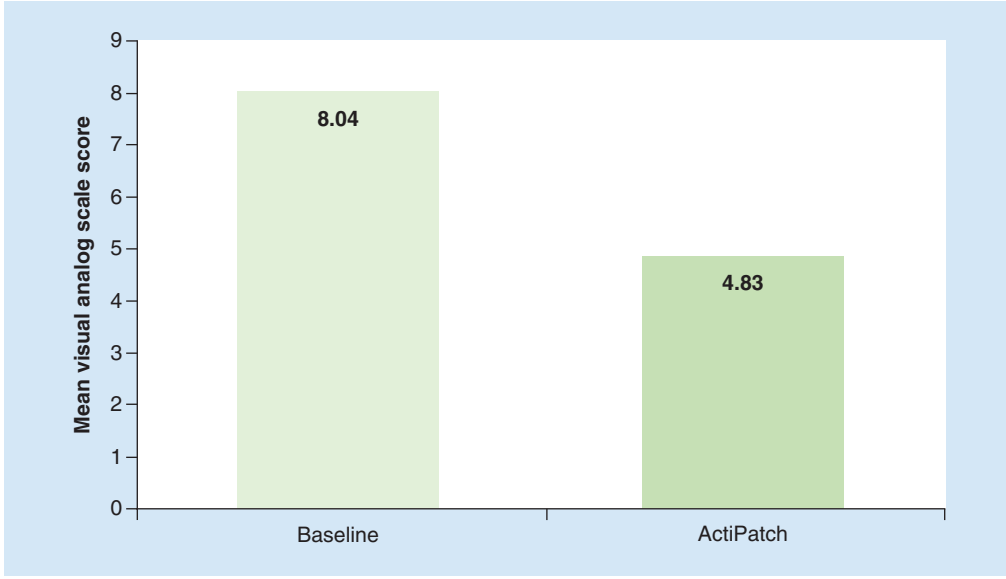

Figure 2. Visual analog scale scores at baseline and after device use shows a mean pain reduction of 39.9% across all the chronic back pain subjects in the study.

numbers for each therapy indicate that the subject was using more types of the particular therapy. A number of control variables were included, these being age, gender, duration of the pain and baseline pain. All the variables in this multivariate regression were significant ($p < 0.02$) except age and gender. However, the most significant variable as measured by the standardized coefficients was the number of prescription drugs taken ($p < 0.0001$). The estimated coefficients for the regression analysis were that a reduction of one prescription drug would result in an estimated reduction of 1.45 side effects per subject. In contrast, the reduction of one OTC medication would only result in a reduction of 0.35 side effects per individual, indicating that the prescription drug effect is four-times greater than OTC medication.

• Side effects & QoL impact

The next regression has QoL as the dependent variable where higher numbers indicate a greater negative impact on the person's QoL. A number of control variables were included, these being age, gender, duration of pain, reduction in the use of medications after using the medical device and the reported reduction in pain as measured by the difference between before and after pain levels. The number of side effects was found to have a strong, negative impact on a subject's QoL ($p < 0.0005$). The only other variable significant at $p < 0.05$ was the reported decreases in medication use. Subjects who reported a greater medication reduction were less likely to report a negative effect on the QoL. Decreases in the person's level of pain were not significant after controlling for the number of side effects reported and the reduction of medication.

• Reduction in pain & medications taken

The data show that using the medical device for 7 days is associated with subjects reducing their pain levels and also reducing medication use **(Figures 2 & 3)**. This relationship was quantified through regression analysis, where the

Table 5. The percent of individuals who reported a 40% or greater visual analog scale scores reduction was 726/1394 or 52%.

Pain measure	All n = 1394	Effective ≥40% pain reduction n = 726 (52%)
Baseline VAS	8.04 ± 1.46	8.16 ± 1.41
Post-trial VAS	4.83 ± 2.68	2.76 ± 1.40
VAS difference	3.21	5.40
Percent reduction (%)	39.9	66.2
p-value	p < 0.001	p < 0.001

These individuals had a mean pain reduction of 66%.
VAS: Visual analog scale.

Table 6. The intent to continue therapy.

Intent	Percent	Baseline VAS	Trial VAS	VAS difference
Definitely	40.6	8.34 ± 1.40	3.09 ± 1.93	5.25
Probably	13.4	7.92 ± 1.39	4.02 ± 1.96	3.90
Possibly	14.8	7.80 ± 1.58	5.25 ± 2.16	2.55
Probably not	16.3	7.67 ± 1.38	6.70 ± 1.99	0.97
Definitely not	14.9	8.00 ± 1.49	7.87 ± 1.75	0.13

VAS: Visual analog scale.

dependent variable is medication reduction. This variable is coded -1 if the persons indicated that they increased the use of medications and/or added other treatment therapies over the 7-day trial period, 0 if they indicated no changes, +1 for decreased use and +2 if they eliminated medication use. Therefore, higher numbers indicate increased reduction in medication. The independent variables in this analysis were reduction in pain, age, gender, duration, baseline pain and the number of treatments used in the three different therapy classes, in other words, OTC analgesics, prescription analgesics and other treatments. The largest impact, as measured by the standardized coefficients, was reported reduction in pain ($p < 0.0005$). This estimated effect was three-times as great as initial baseline pain (which was negative, i.e., higher baseline pain subjects were less likely to reduce their medication all else equal), four-times as great as the negative effect of the number of prescription drugs initially taken (both significant at the 0.0005 level) and seven-times greater than the number of other treatments initially used ($p < 0.01$). This latter effect was positive, in other words, those subjects using other pain therapies were more likely to reduce medication, with other factors unchanged. No other variables were significant at $p < 0.05$.

• Device adverse effects

No significant adverse events were reported. Adverse advents were increased pain in 1.5% of individuals and adverse reaction to the medical adhesive tape which was reported in less than 1% of individuals.

Discussion

Given the limitation of the study design, strong conclusions cannot be drawn as to the efficacy of the device used in this registry study. The limitations of the study are discussed further

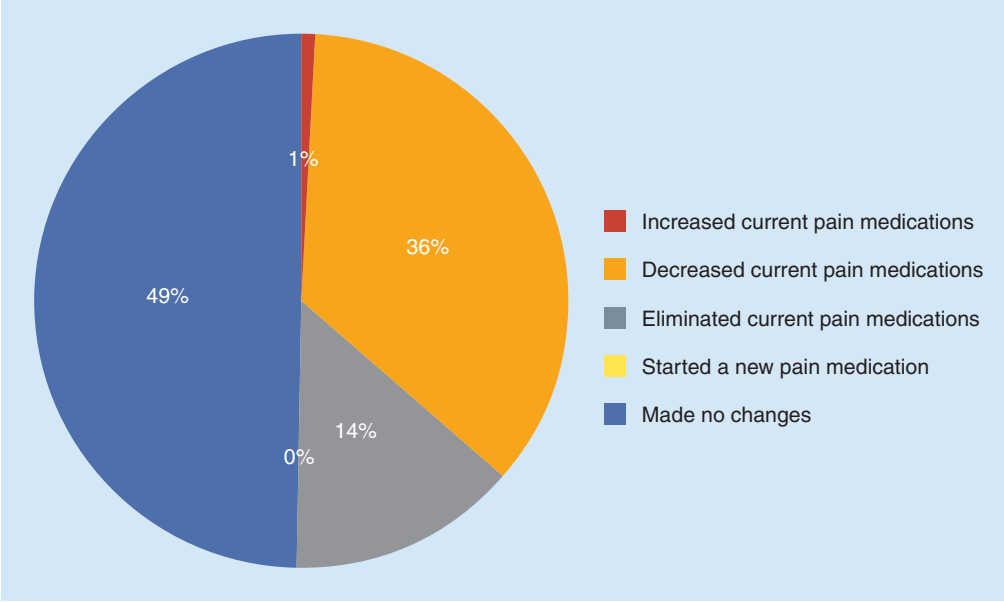

Figure 3. The percent of subjects who made changes in medication use during the 7-day trial: no change (49%), increased (0.6%), decreased (36%), eliminated (14%) and started a new medication (0.3%).

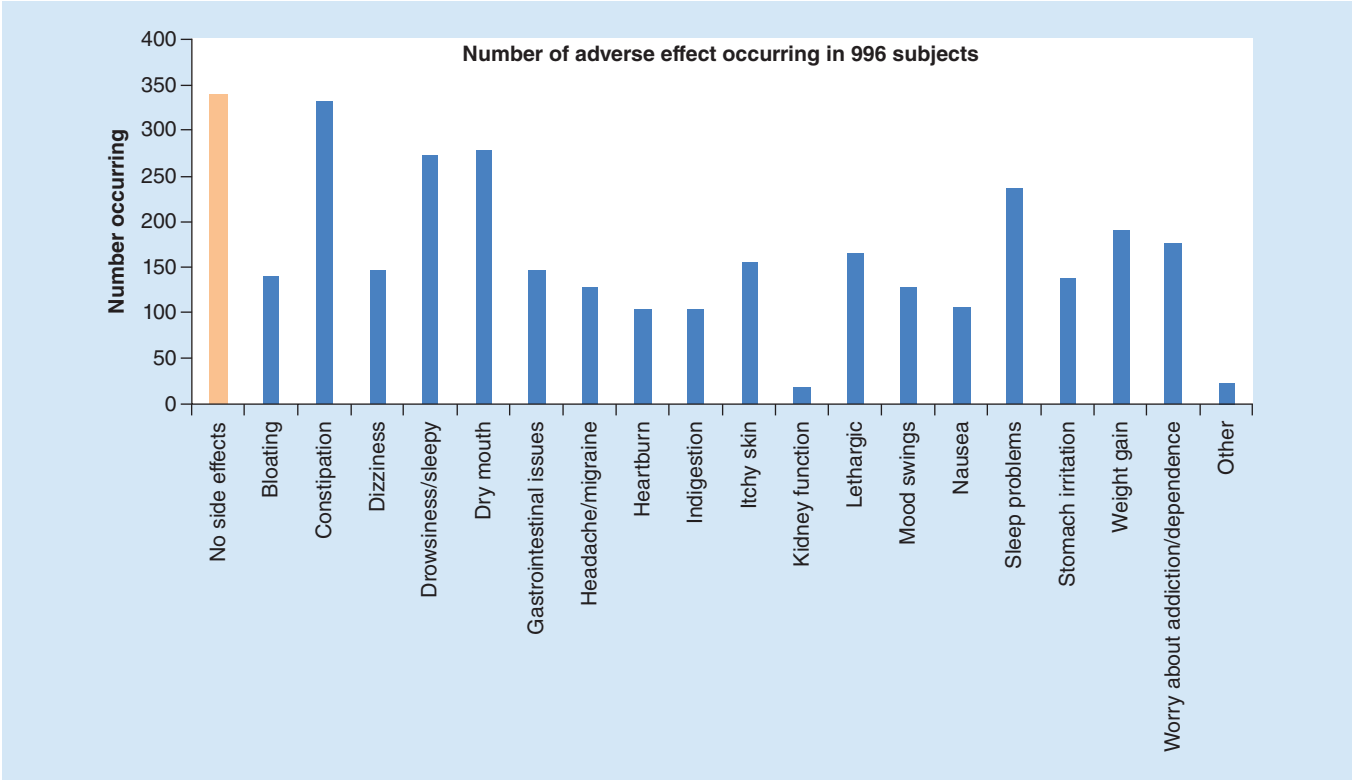

Figure 4. Types of adverse effects and the number who reported these effects for the 66% (n = 658) who reported having side effects. The mean number of adverse effects was 4.6 per subject.

below. However, this CBP registry study documents a number of important findings including the level of unresolved chronic pain in many individuals, significant adverse side effects from analgesic medications that impact patients' QoL and the potential of this new OTC pain therapy to help manage CBP.

The results presented here are consistent with, and others which compliment, the results of a prior published 5000 cohort registry study of chronic pain sufferers who used the same device [29]. However, the results from that study were not limited to back pain, nor did that study document detailed information on medication use, medication side effects or the negative impact of these medications on a person's QoL. The results are very similar across the two studies in terms of initial pain levels and pain reduction. In the prior study, the baseline mean VAS pain score was 8.02 and the average pain reduction was 37.9% [29]. In comparison, the current study found that the baseline mean VAS pain score was 8.04 ± 1.46 which decreased to 4.83 ± 2.68, or a 39.9% decrease, after using the trial device for 7 days. In addition, these reductions are consistent with two randomized

Table 7. Pain duration, analgesic use, percent subjects reporting adverse effects, mean adverse effects and their impact on patients' quality of life.

Pain duration	Mean number of meds used	Mean number of prescription meds	Percent of subjects with adverse effects	Mean number of adverse effects (per subject)	Impact on QoL
6 months to 1 year	2.29	1.19	48.2	4.3	4.2
1–2 years	2.23	1.07	50	3.9	5.5
2–5 years	2.48	1.45	68.3	4.1	5.6
5–10 years	2.72	1.74	70.0	5.3	5.9
10–20 years	2.63	1.64	76	4.8	5.8
20 years +	2.61	1.56	72	4.9	6.1

QoL: Quality of life.

Table 8. Subject age group, analgesic use, percent of subjects reporting adverse effects, mean adverse effects and their impact on patients' quality of life.

Age (years)	Mean number of meds used	Mean number of prescription meds	Percent of subjects with adverse effects	Mean number of adverse effects (per subject)	Impact on QoL
25–34	3.25	2.03	72.7	7.0	6.2
35–44	2.92	1.84	76.7	5.3	6.1
45–55	2.62	1.58	69.6	4.9	5.8
56–64	2.51	1.39	66.2	4.5	5.9
65 +	2.08	1.18	55.6	3.2	5.0

QoL: Quality of life.

controlled trials (RCTs) that investigated the efficacy of the ActiPatch medical device in reducing chronic pain. In one such study that investigated the analgesic effect of the medical device for plantar fasciitis pain [27], the reported mean VAS score reduction was 40%, while in the second study that investigated the analgesic effect in osteoarthritis of the knee [26], the reported mean VAS score reduction was 25%.

In this study, the device was considered effective if the VAS pain score was reduced by at least 40%. This 40% figure was chosen to account for a lack of a placebo control and reflects the fact that the two RCTs using this device reported placebo effects of 7 and 3%, respectively [26,27]. Although the understanding of placebo has changed substantially and is now seen as being related to patient's perception of treatment, ways are being investigated to incorporate the placebo effect into medical treatment [30]. At this 40% effectiveness threshold, 52% of subjects reported effective pain relief and averaged a 66% reduction in their mean VAS scores. In the prior registry study of all chronic pain sufferers, a 2-point reduction on the mean VAS pain score was set as the threshold for effective pain relief. In that case, 65% met this 2-point or greater reduction threshold and reported a 57% mean VAS reduction. Using this 2-point reduction for the current study, we find that 66% of the CBP subjects meet these criteria and average a 58% reduction in pain.

The high level of baseline pain in both registry studies, coupled with the high use of multiple therapies, indicates that many chronic pain sufferers have not been able to find adequate treatment from other available therapies. In addition, their willingness to purchase the trial unit indicates that they were still actively seeking solutions to find pain relief. This need for an adequate solution is also compatible with the finding that the majority of subjects (60%) do not receive adequate pain relief from commonly used analgesics. This latter finding is similar to what was reported by the Arthritis UK/Daily Telegraph survey [24], which indicated that 54% of chronic pain sufferers were not satisfied with the current pain treatment they were receiving from their GP or healthcare professional. Despite the fact that subjects in this study were using a wide range of analgesics from OTC to prescription drugs, averaging 2.5 analgesics per subject (including topical analgesics), they were unable to reduce their pain to acceptable levels. In addition, many subjects reported using nonanalgesic pain therapies such as TENS, heat wraps and physical therapy.

It is common knowledge that relying heavily on analgesic medications for pain control can result in adverse effects. This study indicates that 66% of the subjects experience adverse effects from their medications, averaging 4.6 ± 3.3 per individual. Not surprisingly, there were correlations between the numbers of analgesics (both prescription and OTC) being used and the number of adverse effects being observed.

These findings are relevant, since they document the magnitude and implications of the adverse effects experienced by individuals using multiple analgesic medications in an attempt to control their chronic pain, outside of a controlled healthcare setting.

Also investigated was how these adverse effects impacted a subject's QoL on a 0–10 scale. The regression results demonstrate that increases in adverse effects also tend to increase the negative impact on a person's QoL, even after controlling for the baseline measure of pain. Importantly, we found that the ActiPatch medical device was able to significantly reduce the pain level for the majority of subjects. We also find a strong relationship between this reduction in pain and the reduction or elimination of analgesic medication after the 7-day trial. Importantly, we find that less

than 1% report increasing medication use or trying some new therapy while using the ActiPatch, thus indicating little or no adverse side effects of the treatment. This behavioral change in medication use gives credence to reported reductions in pain levels while the regression analyses make clear that this reduction in medication is also associated with an improvement in the subject's QoL by reducing adverse side effects.

• Mechanism of action – negating central sensitization

The biophysical and clinical community has been plagued for decades with a lack of a clear mechanism explaining how low power, PSWT can result in biological effects. With empirical evidence highlighting the therapeutic potential of the ActiPatch for chronic pain, there is a need to better understand how PSWT can provide analgesia. Recently, PSWT has been shown to regulate activity of peripheral afferents in the body through stochastic (random; stochastic neuromodulation is a process where subthreshold levels of input combine with resting 'afferent noise' to nondeterministically activate nerves), subsensory, neuromodulation [McLeod KJ, Koneru SN, Unpublished Data], which indicates that the ActiPatch's analgesic effects occur through neuromodulation.

The CNS continuously receives large amounts of information from the periphery of the body and internal organs, including noxious, mechanical, chemical and motor/sensory stimuli. The background level of this activity is referred to as 'afferent noise' [31]. In order to appropriately process critical afferent inputs, the CNS must constantly adapt to the background levels of these inputs. In this way, differences from the background are easily detected and sent to the brain for processing. Habituation is the process by which sensation thresholds are raised, while the process of sensitization results in a lowering of sensation thresholds. Habituation and sensitization are normal physiologic processes that allow our nervous system to operate optimally. In the case of 'central sensitization,' the normal habituation/sensitization process has been disrupted such that even normal 'afferent noise' can be sensed as being painful. As such, when long-standing acute pain hypersensitizes the CNS, it results in increased pain facilitation pathways and decreased inhibition pathways [32–35]. This results in pain that does not reduce over time (chronic) and therefore the sufferer is left in a persistent, sensitized state of pain. Central sensitization is now well established as an integral factor in many chronic pain states, including the commonly occurring knee and back pain [32,34,35]. Since peripheral information plays a crucial role in central sensitization, the key to reversing central sensitization, and moving the system out of the pain state, also lies in providing new peripheral information [33].

The challenge in re-establishing normal background pain threshold levels is that the most common means for stimulating musculoskeletal sensation is through movement or touch (e.g., manual therapy or exercise) [36]. But initiating an exercise regime is painful, and therefore it is a barrier to successful therapeutic activity [33], and this is compounded by the effect of chronic pain on the subjects' motivation [37]. There is some evidence that TENS can help reduce pain and hyperalgesia, while restoring healthy levels of central inhibition in patients with another clinical syndrome of central sensitization, fibromyalgia [38]. In other studies, TENS has been consistently shown to decrease central excitability and increase central inhibition [39–41], which are key to mitigating central sensitization. Complications such as discomfort from the tingling sensation, skin irritation from electrode gel and potential skin damage from electrical heating make prolonged TENS use inconvenient for long-term use. However, since sensory information constitutes only a fraction of all the 'afferent noise' that reaches the spinal cord [33], sensation-free neuromodulation has the potential to be used continuously for mitigating central sensitization. Given the sensation-free and contactless nature of the ActiPatch, it can be used to regulate peripheral afferent activity such that the CNS 'sees' an increase in nonsensory 'afferent noise' and, over time, raises the pain tolerance thresholds through the habituation process.

The prior and current registry studies [29] documented that pain relief associated with using the medical device often occurred over the course of days, with the majority of subjects reporting that it took up to 3 days to experience pain relief. These results indicate that the mechanism of action is unlikely a masking phenomenon. It has previously been proposed that chronic pain resulting from osteoarthritis of the knee may involve central sensitization [42–44]. In the knee osteoarthritis pain study [26] discussed earlier, when subjects were tested for pain pressure thresholds

post-trial, the treatment group demonstrated a significantly higher pain tolerance than the placebo group, both locally and peripherally, indicating a decreased sensitivity to pain. This indicates that the repetitive input nature of the ActiPatch is indicative of a mechanism supporting reversal of central sensitization. Importantly, this could mean that ActiPatch therapy is not simply masking the underlying pain, as pain medications do, but is in fact, over time, treating the pain. However, this interesting possibility needs to be explored further in prospective clinical studies investigating long-term relief from chronic pain.

• Study limitations

The registry-style, self-reported method of data collection differs from methods used in randomized, blinded clinical studies. The strength of these data is that it is real world data that reflect a heterogeneous population of CBP sufferers who have turned to a new OTC therapy to combat long-standing CBP. However, we acknowledge that the study has many limitations which add caution to the findings presented in this study. As such, this study does not allow for causal statements since there is neither a positive or placebo-controlled group, nor it is possible to control and/or rule out other unobserved causal factors. However, the substantial decreases in pain seen in the study are unlikely to be entirely the result of the placebo effect for three reasons: the reduction in pain scores seen here are consistent with the results of prior responses acquired over a period of 2 years; published RCT studies that utilized the same device report that the associated placebo effect is relatively small (<10%); and a longer term, registry study of 254 positive responders (i.e., those who indicated substantial 7-day relief) assessed over a 6-month period demonstrates the durability of the analgesic effect in a vast majority of the subjects (>90%) as well as >90% reporting improvements in QoL and continued decreased reliance on analgesic medications [45].

Another possible limitation of the study is the self-reported nature of the information collected since there is no way to check for consistency by accessing actual medical records. However, a statistically significant correlation is seen between the reported pain reduction and many behavioral variables that can be theoretically linked. For instance, those reporting higher decreases in pain were also more likely to reduce analgesic medication use, while those reporting more analgesic use were also more likely to report more adverse effects and a greater negative impact on QoL. Moreover, the core data collected by subjects over 2 years are consistent; for example, the baseline pain range on monthly averaged data over a 2-year period had been 7.91–8.29 VAS.

Conclusion & future perspective

This registry study of 1394 CBP subjects indicates that 66% of subjects experience adverse effects from pain medications use, and these effects had a significant negative impact on their QoL. Furthermore, the perceived benefit of their analgesic therapy was found to be inadequate for the majority of individuals. After using the ActiPatch medical device for 7 days, 52% of these CBP subjects achieved a large and clinically significant pain reduction (40% or more), with an average reduction of 66%. Additionally, 49% of the CBP sufferers were able to reduce or eliminate their dependence on analgesic medications, which is consistent with the number who reported significant pain reduction. These results are encouraging, and need investigation in further RCTs, but imply that this new therapy can complement multimodal therapies for chronic pain patients, and in some cases, reduce the use of analgesic medications and in the process improve QoL of those suffering from CBP.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pmt-2016-0046

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