

Remote Analgesic Effects Of Conventional Transcutaneous Electrical Nerve Stimulation: A Scientific And Clinical Review With A Focus On Chronic Pain

This article was published in the following Dove Press journal:
Journal of Pain Research

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Background: Transcutaneous electrical nerve stimulation (TENS) is a safe, noninvasive treatment for chronic pain that can be self-administered. Conventional TENS involves stimulation of peripheral sensory nerves at a strong, non-painful level. Following the original gate-control theory of pain, stimulation is typically near the target pain. As another option, remote stimulation may also be effective and offers potential advantages.

Objective: This narrative review examines mechanisms underlying the remote analgesic effects of conventional TENS and appraises the clinical evidence.

Methods: A literature search for English-language articles was performed on PubMed. Keywords included terms related to the location of TENS. Citations from primary references and textbooks were examined for additional articles.

Results: Over 30 studies reported remote analgesic effects of conventional TENS. The evidence included studies using animal models of pain, experimental pain in humans, and clinical studies in subjects with chronic pain. Three types of remote analgesia were identified: at the contralateral homologous site, at sites distant from stimulation but innervated by overlapping spinal segments, and at unrelated extrasegmental sites.

Conclusion: There is scientific and clinical evidence that conventional TENS has remote analgesic effects. This may occur through modulation of pain processing at the level of the dorsal horn, in brainstem centers mediating descending inhibition, and within the pain matrix. A broadening of perspectives on how conventional TENS produces analgesia may encourage researchers, clinicians, and medical-device manufacturers to develop novel ways of using this safe, cost-effective neuromodulation technique for chronic pain.

Keywords: transcutaneous electrical nerve stimulation, TENS, chronic pain, electrode, remote, widespread

Introduction

Transcutaneous electrical nerve stimulation (TENS) is a safe, noninvasive treatment for chronic pain that can be self-administered by patients. It is defined as electrical stimulation of peripheral sensory nerves through electrodes placed on the skin. Conventional TENS uses a stimulation intensity that evokes a strong but non-painful sensation.¹ It is thought to provide pain relief by modulating nociceptive signaling in the central nervous system (CNS).^{2,3} Conventional TENS is a useful component of a chronic pain-treatment plan.^{2,4-9} However, there are questions

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about the effectiveness and optimal applications of TENS.^{10,11} It is likely that TENS efficacy in both clinical trials and real-world use has been adversely impacted by underdosing and poor adherence.^{12–16} There is a need for improved TENS devices and methods.

It is customary to place conventional TENS electrodes near the patient's pain.^{1,17,18} Most TENS devices allow stimulation essentially anywhere on the body through individually wired electrodes. Applying therapy "where it hurts" is readily understood by clinicians and patients. However, it is not always possible to place electrodes near the site of pain, and this is impractical for multisite pain. Moreover, wired electrodes are cumbersome during daily activities and sleep. As another option, remote stimulation may be effective.^{19–21} Use of alternative sites is predicated on the remote analgesic effects of conventional TENS, which are defined as analgesia beyond the site of stimulation.^{22–24}

Remote pain relief is complementary to the traditional use of TENS. In this methodology, stimulation is applied to one or a small number of predetermined locations, rather than specifically within the region of pain.^{23,25} There are several advantages to this approach. First, predefined sites enable a simplified protocol that can be reliably implemented by patients self-administering TENS. Second, such sites as the upper arm²⁴ and lower leg²³ are suitable for wearable TENS devices that may facilitate regular use. These devices can be embedded with sensors which feed algorithms that automatically regulate stimulation and track physiological outcomes.²⁶ Third, there is the potential to treat multisite pain from a single location or small number of sites.^{22,27} A limitation of fixed sites is an inability to optimize stimulation location to each patient's pain distribution.¹⁸

The remote analgesic effects of conventional TENS have been recognized for 40 years;^{19,28–31} however, they have only recently been operationalized. Recent abstracts and published studies have demonstrated innovative uses of conventional TENS applied remotely to pain or to evoke widespread pain relief.^{22–26,32–35} The purpose of this narrative review is to examine mechanisms underlying these remote effects and to appraise the clinical evidence. This is an important topic, because these applications may motivate the development of treatments that increase the utility and adoption of noninvasive neuromodulation for chronic pain.

Methods

The clinical evidence portion of this narrative review was based on a literature search performed on PubMed. The

following keywords were used in various combinations: transcutaneous electrical nerve stimulation, TENS, conventional TENS, AL-TENS, acu-TENS, non-invasive, electrical stimulation, neurostimulation, neuromodulation, electrode placement, fixed site, wearable, remote, widespread, contralateral, segmental, dermatomal, extrasegmental, and acupuncture. Only English-language articles were considered. In most cases, the full text was reviewed. In a small number of instances, only the abstract was available. Citations from primary references and several textbooks^{1,36,37} were examined for additional articles that were not identified in the database search.

Technical Characteristics Of Conventional TENS

Conventional TENS is a noninvasive neuromodulation technique that is defined as high-frequency (>50 Hz) electrical stimulation of sensory nerves at an intensity that evokes a strong sensation that is not painful.¹ In this review, conventional TENS is further characterized by stimulation using discrete monophasic or biphasic pulses to distinguish it from techniques that fall within the broader definition of TENS, but use different stimuli (eg, microcurrent, inferential current therapy).³⁸ Conventional TENS is also intended to encompass electrical stimulation techniques that are functionally equivalent, but use alternative terminology.²⁴ Conventional TENS is distinct from acupuncture-like TENS (AL-TENS), which involves higher intensity and lower frequency (<10 Hz) and is intended to be uncomfortable and provoke phasic muscle contractions.^{39,40} Despite its name, AL-TENS is not specifically applied at acupuncture points. AL-TENS is believed to produce widespread analgesia by activation of opioidergic pathways in the CNS.^{39,40}

Mechanisms Underlying The Remote Analgesic Effects Of Conventional TENS

Peripheral Trigger For Remote Analgesia

All forms of TENS trigger analgesia in the CNS by a strong ascending stimulus carried through peripheral sensory nerves. These nerves are comprised of large-diameter A α and A β (A $\alpha\beta$) fibers that carry nonnociceptive signals and small-diameter nociceptive A δ and C fibers. The analgesic effects of conventional TENS have been attributed to activation of A $\alpha\beta$ fibers and those of AL-TENS with stimulation of A δ fibers.³⁹ In fact, animal and human studies suggest that the threshold for activation of A δ fibers is five to ten times

that of A α fibers. Therefore, it is likely that TENS primarily activates A α fibers up to the patient's maximum tolerable intensity.^{41–45} Noninvasive electrical stimulation of nociceptive fibers is possible, but substantial activation requires high intensity that may be technically challenging and will cause pain.^{35,42,43,46} Interestingly, high-frequency A β -fiber stimulation may be perceived as uncomfortable or painful,⁴³ and robust A β -fiber input may trigger conditioned pain modulation (CPM),⁴⁷ which are both characteristics of AL-TENS. Moreover, electroacupuncture in animal models primarily activates A α nerve fibers.^{48,49} It appears that strong A α -fiber activation is adequate to trigger remote analgesia.

Modulation Of Central Pain Processing

A model for the central regulation of pain was proposed by Melzack and Wall⁵⁰ in 1965. Their theory stipulated that activation of A β sensory afferents closes a “pain gate” in the spinal cord that inhibits the transmission of signals carried by nociceptive afferents (A δ , C fibers) to the brain. This model motivated the development of TENS for pain relief.¹⁷ Fifty years later, the gate-control theory of pain remains a useful concept, although few of the specifics have been confirmed.^{51,52} It is now understood that no specific area of the brain is responsible for pain processing: there is no “pain cortex.” Rather, pain perception is represented across a complex network of neural structures in the brain that are termed the pain matrix.^{53,54} Moreover, these regions are involved with sensory, motor, and cognitive processing, in addition to pain. There are six areas of the brain that appear to be consistently involved in the sensory-discriminative, cognitive, and affective aspects of pain processing. They are the thalamus, the insular cortex, the primary and secondary somatosensory cortices, the anterior cingulate cortex, and the prefrontal cortex.⁵⁴ The pain matrix is not a static structure. It is highly neuroplastic and capable of reorganizing, such as in response to pain and affective stimuli.^{55,56} These changes may be maladaptive, and individuals with chronic pain have been shown to have altered function within the pain matrix.⁵⁷

Pain regulation occurs at multiple levels within the nervous system, including in the periphery, within the spinal cord dorsal horn, in brainstem centers, and in subcortical and cortical structures.⁵¹ Nociceptive circuits in the brain are highly interconnected within the pain matrix, as well as in the brainstem and spinal cord. Specific examples of the latter include midline crossover within the dorsal horn,^{58–60} bilateral projections from neurons in the rostral ventral medulla into the spinal cord dorsal

horn^{61–63} and wide dynamic-range neurons in the spinal cord with whole-body receptive fields.⁶⁴ CPM is a form of central pain regulation that integrates sensory and pain signals from the entire body.^{65–67} This analgesic mechanism decreases nociceptive signal transmission in the spinal cord through supraspinal-mediated descending inhibition. CPM can be triggered by remote noxious^{65,68} and nonnoxious^{24,47,68–70} conditioning stimuli.

The original application of the pain-gate theory to conventional TENS predicted analgesia localized to the area of stimulation.¹⁷ Although pain regulation has subsequently been understood to be more complex, the simple pain-gate formulation continues to influence the clinical application of TENS. Nevertheless, it is now accepted that conventional TENS regulates nociceptive signaling in the spinal cord,^{71–73} brainstem,^{74,75} and subcortical and cortical structures.^{76,77} The remote analgesic effects of conventional TENS are likely derived from its influence on nociceptive signal processing in both spinal and supraspinal neural circuits.^{2,3,24} At the spinal level, activation of peripheral A α fibers will inhibit onward transmission of nociceptive signals that originate in overlapping spinal segments. This mechanism accounts for the traditional local effect of conventional TENS,¹⁷ but also explains remote effects in parts of the body innervated by the same spinal nerves (ie, remote segmental analgesia). Neural connections crossing the spinal cord midline^{58–60} and bilateral descending projections from rostral ventral medulla neurons into the dorsal horn^{61–63,78} may account for contralateral effects of conventional TENS.²⁷ Activation of supraspinal descending pain controls, which have inherently diffuse inhibitory effects, may explain the remote segmental and extrasegmental effects of conventional TENS.^{3,22,24,66,79,80} Finally, activation of brain areas comprising the pain matrix^{76,77} could have profoundly widespread analgesic effects, as well as improve mood, sleep, and other functions.^{25,26,81}

Various neurotransmitters are involved in pain inhibition, including GABA, glycine, noradrenaline, serotonin, and opioids.⁸² The most relevant to remote TENS analgesia are likely to be the opioids.^{3,71,74} Studies by Salar et al⁸³ and Almay et al⁸⁴ in the 1980s demonstrated elevated levels of endogenous opioids in the cerebrospinal fluid (CSF) of healthy subjects and patients with chronic pain in response to high-frequency peripheral nerve stimulation. A statistically significant increase in CSF opioid concentration was measured after 20–45 minutes of stimulation and remained elevated for 60 minutes.⁸³ Despite this early work, the prevailing opinion through the 1990s was that conventional

TENS worked through nonopioid mechanisms, while AL-TENS acted through release of endogenous opioids.^{85,86} However, animal studies by Sluka et al,^{71,74} followed by more recent studies in humans by Leonard et al,^{87,88} demonstrated that conventional TENS also operates through opioidergic pathways, likely involving δ receptors.^{3,89} Increased concentration of endogenous opioids in the CSF may contribute to widespread analgesic effects of conventional TENS.⁸³

Remote Electrode Placement In Clinical Practice

The most common conventional TENS site is around or within the origin of pain. The approach follows a literal interpretation of the pain gate.⁵⁰ Namely, stimulation will result in activation of large-diameter ($A\alpha\beta$) sensory afferents that enter the same spinal segment as nociceptive fibers associated with the pain. Local placement of electrodes might be assumed to have maximal effectiveness, because of direct neural connections between the activated $A\alpha\beta$ afferents and nociceptive relay neurons within the dorsal horn.⁹⁰ However, in practice optimal chronic-pain relief is not necessarily achieved by stimulation at the origin of pain.⁹¹

There are potential issues with traditional TENS-electrode placement. First, electrical stimulation colocalized with pain may not be possible, due to insensate skin, allodynia, wounds, injuries, or amputation in the case of phantom limb pain (PLP).¹ Second, many patients with chronic pain have multisite pain.^{92,93} It is inconvenient, and may be impractical, to treat such conditions with multiple TENS placements. Third, chronic pain is often complicated by maladaptive changes in the CNS, including central sensitization and deficient descending inhibition.⁹⁴ In these patients, peripheral nociceptive signals may have a limited role in maintaining the pain syndrome, and treatment should be directed at modulating central pain processing.^{8,22}

Some of these issues were recognized soon after the development of TENS and alternative electrode configurations proposed. Mannheim published a comprehensive review of TENS-electrode placement in 1978.³⁰ In addition to placement within the painful area, the author described anatomically distant placement within shared dermatomes, contralateral placement, use of acupuncture sites, and placement in extrasegmental locations. In 1996, Walsh published a review of TENS-electrode placement

and outlined similar principles.⁹⁵ Johnson recently had published a textbook on TENS research and clinical practice that describes comparable principles of electrode placement.¹

Evidence For The Remote Analgesic Effects Of Conventional TENS

The evidence in support of remote analgesic effects of conventional TENS includes studies using animal models of pain, experimental pain in humans, and clinical studies in subjects with chronic pain. There are three types of remote analgesia that have been reported in the literature. Contralateral analgesia is defined as analgesia produced by stimulation of the contralateral homologous site. Remote segmental analgesia is defined as analgesia evoked by stimulation within the same spinal segments as the origin of pain. This form of analgesia is consistent with the gate-control theory of pain, whereby the $A\alpha\beta$ -inhibitory signal originates in fibers innervating an area that is anatomically distinct from the pain but segmentally related, ie, in the same dermatome. Extrasegmental analgesia is defined as analgesia generated by stimulation of segments unrelated to the origin of pain. Acupuncture points are often extrasegmental relative to the target pain.⁹⁶

Animal Models Of Pain

Animal models of pain are essential in pain research and development of analgesic therapies.⁹⁷ They have been used to investigate mechanisms of action by which TENS provides pain relief.^{3,46,71,72,74} Table 1 lists studies using animal-pain models that demonstrated remote analgesic effects of conventional TENS. Ainsworth et al

Table 1 Animal Pain-Model Studies Demonstrating Remote Analgesic Effects Of Conventional TENS

Reference	Animal	Pain Model	Remote Analgesic Effects
Ainsworth et al ²⁷	Rat	Muscle inflammation	Contralateral
Somers et al ⁹⁸	Rat	Nerve constriction	Contralateral
Somers et al ⁹⁹	Rat	Nerve constriction	Contralateral
Somers et al ¹⁰⁰	Rat	Nerve constriction	Contralateral
Sabino et al ¹⁰³	Rat	Extremity inflammation	Contralateral
Cho et al ¹⁰⁴	Rat	Nerve ligation	Contralateral
Garrison and Foreman ¹⁰⁵	Cat	None	Contralateral
Neto et al ²¹	Rat	Joint inflammation	Contralateral, segmental

evaluated the analgesic effects of TENS in a rat model of chronic bilateral hyperalgesia induced by unilateral injection of 3% carrageenan into the gastrocnemius muscle.²⁷ Conventional TENS was applied ipsilaterally or contralaterally to the injected muscle. Both TENS applications reduced mechanical hyperalgesia bilaterally. The authors speculated that TENS activates central inhibitory pain pathways or inhibits central facilitatory pain pathways.

In a series of studies, Somers et al evaluated the physiological and analgesic effects of TENS in rats with a chronic nerve-constriction injury, which is a model for neuropathic pain.^{98–100} They showed that daily conventional TENS on the same side as the nerve injury reduced bilateral dorsal horn content of aspartate and glutamate compared to untreated rats.⁹⁸ These excitatory neurotransmitters play a key role in the development and maintenance of neuropathic pain.¹⁰¹ In a later study, these researchers demonstrated that TENS applied contralaterally to the nerve injury reduced the development of allodynia following the nerve-constriction injury.⁹⁹ In a third study, they showed that contralateral TENS elevated the inhibitory neurotransmitter GABA bilaterally in the dorsal horn and also reduced mechanical allodynia on the side of the nerve-constriction injury.¹⁰⁰ GABA plays a key role in mediating antinociception in the spinal cord.¹⁰²

Sabino et al evaluated the effects of conventional TENS applied ipsilaterally and contralaterally to inflammatory pain produced by injection of carrageenan into the rat paw.¹⁰³ Contralateral TENS reversed hyperalgesia in the inflamed paw as effectively as ipsilateral TENS. The authors hypothesized that the contralateral effects were related to the diffuse nature of descending pain inhibition and bilateral projections of sensory afferents in the dorsal horn. Cho et al studied the analgesic effects of conventional TENS in a rat chronic neuropathic pain model created by ligation of the median nerve.¹⁰⁴ Conventional TENS was applied for 20 minutes ipsilaterally or contralaterally to the nerve injury. Ipsilateral TENS application reduced mechanical, cold, and thermal allodynia compared to sham-treated rats. TENS application to the contralateral side reduced mechanical allodynia. The authors hypothesized that conventional TENS works through central mechanisms to reduce pain.

In a study of dorsal horn nociceptive neurons in anesthetized cats by Garrison and Foreman, TENS in both the ipsilateral and contralateral cutaneous receptive fields reduced neuron-firing rates. The ipsilateral effects were quantitatively greater.¹⁰⁵ In a study using a rat joint–

inflammation pain model, Neto et al compared local electrode placement with remote stimulation.²¹ The remote sites included a contralateral homologous location and paraspinal segmental placement. The study found no differences among sites, and the authors concluded that conventional TENS evokes similar levels of antihyperalgesia, regardless of electrode placement. Studies in animal-pain models demonstrate that conventional TENS exhibits remote analgesic effects. The most extensive data are for TENS evoking an analgesic response at the homologous site contralateral to stimulation. There is also evidence that TENS has an analgesic effect on distant sites with common segmental innervation.

Experimental Human Pain

Experimental human-pain models offer an opportunity to study analgesic mechanisms in healthy, pain-free individuals within a laboratory environment.¹⁰⁶ Pain models decrease complexity by controlling key variables, such as pain characteristics. Pain models induce pain in a controlled manner using such stimuli as pressure, heat/cold, ischemia, and electrical stimulation. Table 2 lists studies using experimental pain models that demonstrated remote analgesic effects of conventional TENS.

Table 2 Experimental Human-Pain Studies Demonstrating Remote Analgesic Effects Of Conventional TENS

Reference	Experimental Pain Model	Remote Analgesic Effects
da Silva et al ¹⁰⁸	Mechanical pain	Extrasegmental
Brown et al ²⁰	Ischemic pain	Extrasegmental
Chan and Tsang ¹¹⁰	Nociceptive flexion reflex	Segmental, extrasegmental
Kawamura et al ¹¹³	Thermal pain	Contralateral, segmental
Takiguchi and Shomoto ¹¹⁴	Nociceptive flexion reflex	Contralateral
Peng et al ¹¹⁵	Thermal pain	Contralateral
Zoppi et al ²⁸	Painful electrical stimulation	Contralateral, segmental, extrasegmental
Buonocore et al ¹¹⁷	Thermal pain	Contralateral
Lehmann and Strian ¹¹⁸	Thermal pain	Contralateral
Eriksson et al ¹¹⁹	Thermal pain	Contralateral
Dean et al ¹²⁰	Mechanical pain, thermal pain	Contralateral
Hoshiyama and Kakigi ¹²¹	Painful electrical stimulation	Contralateral

da Silva et al conducted a randomized, double-blinded, sham-controlled trial that evaluated segmental and extrasegmental effects of conventional TENS and two other non-invasive electrical stimulation techniques.^{107,108} The study evaluated 120 healthy subjects randomized into four groups of 30, with each group receiving one intervention (eg, TENS, sham). Stimulation at a strong comfortable level was applied for 30 minutes on the forearm with regular increases in intensity to offset nerve desensitization.¹⁰⁹ Pressure-pain thresholds (PPTs) were measured from the ipsilateral forearm (local) and ipsilateral lower leg (extrasegmental). PPTs were significantly higher during TENS compared to sham at both the segmental and extrasegmental locations. Elevated extrasegmental PPTs persisted for 20 minutes following stimulation. The authors concluded that segmental and extrasegmental hypoalgesic effects may be achieved using TENS.

Brown et al compared TENS administered at the site of experimentally induced ischemic pain on the forearm to TENS administered on the contralateral lower leg, which is an extrasegmental location.²⁰ The study evaluated healthy subjects in a randomized crossover design where each subject was exposed to both local and remote interventions. Outcome measures were VAS scores recorded during TENS administration and short-form McGill Pain Questionnaire scores immediately following intervention. The study found no differences in VAS time-course or McGill questionnaire scores between local and remote TENS. The authors concluded that electrode location did not influence pain-relief outcomes; however, they called for additional research on the topic.

Chan and Tsang used the nociceptive flexion reflex (NFR) to explore the effects of paraspinal conventional TENS at the L4–S1 levels.¹¹⁰ The NFR is a physiological, polysynaptic reflex triggered by a painful stimulus that leads to a withdrawal response recordable by electromyography.¹¹¹ The NFR is usually evoked by painful electrical stimulation at the foot or ankle and measured from lower-extremity muscles. The NFR is an objective assessment of an individual's pain response. In the Chan and Tsang study, the NFR was recorded from the biceps femoris, the tibialis anterior, and the hip flexors. The study demonstrated that paraspinal conventional TENS inhibited the NFR in lower-limb muscles, indicating a widespread segmental influence on pain processing in the lower extremity. In a related study, the authors showed that lower-limb NFRs were inhibited by extrasegmental conventional TENS in the upper extremity.¹¹²

Kawamura et al evaluated the effect of conventional TENS contralaterally and proximally to a painful thermal stimulus applied to the dorsal wrist joint. The contralateral location was at the opposite dorsal wrist joint and the proximal location was at the neck in the same dermatomes as the pain site.¹¹³ The outcome measure was the pain VAS. Both the contralateral and proximal sites produced a statistically significant reduction in pain compared to pretreatment baseline.

Tagiguchi and Shomoto used the NFR to explore contralateral and extrasegmental effects of conventional TENS.¹¹⁴ The NFR was evoked by electrical stimulation of the left sural nerve, and the reflex response was measured by electromyography from the left biceps femoris muscle. Conventional TENS was applied to the right sural nerve (contralateral) and right superficial femoral nerve (extrasegmental). Sham TENS was applied to the right sural nerve. Contralateral TENS significantly reduced NFR after 30 minutes of stimulation compared to both baseline and sham TENS. Extrasegmental and sham TENS did not significantly alter the NFR.

Peng et al used a sham-controlled study of 80 healthy subjects to explore the analgesic and neurobiological effects of conventional TENS.¹¹⁵ The painful stimuli were radiant-heat laser pulses, which selectively stimulate A δ and C cutaneous nociceptors.¹¹⁶ This study was unique in that in addition to assessment of pain and unpleasantness on a numeric rating scale (NRS), laser-evoked potentials (LEPs) were recorded. LEPs quantify the magnitude of the pain signal reaching the somatosensory cortex.¹¹⁶ The authors found statistically significant reductions in pain intensity, pain unpleasantness, and LEPs relative to placebo by both ipsilateral and contralateral conventional TENS. The contralateral effect was qualitatively similar, but quantitatively smaller than the ipsilateral effect.

Zoppi et al examined sensory responses in 59 healthy subjects and 30 subjects with chronic lower-extremity pain who were treated with 24 minutes of conventional TENS applied to the sural nerve.²⁸ Pain was induced by electrical stimulation in the distribution of the sural nerve (“local threshold”) and on the anterior surface of both legs and volar surface of both arms (“general thresholds”). The general thresholds represented contralateral, remote segmental, and extrasegmental sites. Both local and general thresholds were altered by TENS.

Additional studies using experimental human-pain models have shown that TENS applied to one side of the body evokes an analgesic response in the homologous region on

the contralateral side.^{28,113,114,117–122} Buonocore et al showed that TENS applied to the cutaneous distribution of the superficial radial nerve increased the heat-pain threshold in the dorsal hand bilaterally.¹¹⁷ Lehmann and Strian showed that both ipsilateral and contralateral TENS reduced tonic thermal pain relative to placebo.¹¹⁸ Contralateral TENS was about half as effective as ipsilateral TENS. Similar results were found by Eriksson et al, who showed that thermal sensitivity was reduced on both the ipsilateral and contralateral hand in response to TENS applied to the forearm.¹¹⁹ Dean et al evaluated the impact of ipsilateral and contralateral TENS on somatosensory thresholds.¹²⁰ They found that ipsilateral TENS increased mechanical and thermal thresholds, whereas contralateral TENS increased only thermal thresholds. Moreover, ipsilateral effects were greater. Hoshiyama and Kakigi measured pain-related evoked cerebral potentials in response to painful electrical stimulation on the finger.¹²¹ Conventional TENS applied on the ipsilateral and contralateral forearm reduced pain-related evoked cerebral potentials when compared to control.

Not all experimental human-pain studies that evaluated the remote effects of conventional TENS have demonstrated analgesia at a distance from the stimulation site, and some have presented conflicting results.^{123–128} The reasons for this are unclear, but may relate to the particular experimental pain model and to technical factors, such as TENS parameters (eg, stimulation intensity, duration of stimulation). Interestingly, three of the negative studies^{123–125} evaluated mechanical pain thresholds, whereas most of the positive studies examined thermal, ischemic, or electrical pain stimuli. However, studies in subjects with fibromyalgia demonstrated that TENS evoked an increase in mechanical thresholds remotely from the site of stimulation.²² There are profound changes in the CNS that occur in chronic pain that may change the antinociceptive properties of TENS.⁵⁶ Therefore, this limitation of mechanical thresholds may apply only to experimental pain. Danziger et al utilized a lower-extremity NFR to explore local segmental and extrasegmental effects of conventional TENS, high-intensity TENS at a noxious level, and a noxious piezoelectric current.¹²⁶ Conventional TENS had an inhibitory effect on the NFR when placed locally, but not when extrasegmental. High-intensity TENS and the piezoelectric current had effects locally and extrasegmentally. However, stimulation lasted only 2 minutes, which is well below the recommended minimum of 30 minutes¹⁵ and insufficient for endogenous opioid release.⁸³ Jutzeler et al evaluated the local and extrasegmental effects of 10 minutes of

conventional TENS on thermal pain following sensitization by capsaicin in healthy subjects.¹²⁸ Local but not extrasegmental TENS reduced thermal pain ratings. However, the authors also reported that both local and extrasegmental TENS reduced pain related to capsaicin application.

In summary, experimental human-pain studies suggest that conventional TENS has analgesic effects on the contralateral homologous area and distant anatomic sites with shared segmental innervation. There is evidence of extrasegmental analgesia; however, the findings are less consistent. In several studies that compared ipsilateral and contralateral TENS, the former evoked a stronger analgesic response, suggesting the possibility of a gradient whereby efficacy is optimal over the origin of pain. However, it is unclear if such a gradient applies to chronic pain.^{19,79}

Contralateral TENS In Phantom Limb Pain

PLP occurs in more than half of limb amputees¹²⁹ and is considered a form of neuropathic pain.¹³⁰ PLP is a unique clinical model for assessing the remote effects of conventional TENS because of the impossibility of stimulation within the area of pain. Although randomized clinical trials of conventional TENS in PLP have not been conducted,¹³¹ a number of open-label studies and case series have been published that demonstrated reductions in phantom pain in response to contralateral conventional TENS.^{132–136} Theoretical explanations for this analgesic effect include segmental crossover signaling and enhanced descending pain inhibition. In addition, like other forms of chronic pain, PLP is associated with complex CNS changes that may influence the way electrical stimulation modulates pain-regulation circuits.^{130,135}

TENS Over Acupuncture Points

The placement of electrodes over traditional Chinese acupuncture sites was suggested soon after TENS was developed.^{30,31} The motivating principle was the effectiveness of traditional acupuncture in treating pain.¹³⁷ The application of TENS to acupuncture points has relevance to the remote analgesic effects of TENS, as these locations are usually anatomically distant from the origin of pain and often in unrelated segments (ie, extrasegmental). Conventional TENS (or mixed low/high-frequency stimulation) over acupuncture points has been demonstrated to reduce pain.^{138–141} Chao et al showed that mixed-frequency TENS applied to the *hegu* and *sanyinjiao* acupuncture points on the distal extremities decreased labor pain to a greater extent than sham TENS.¹³⁸ Chen et al demonstrated that mixed-frequency TENS applied at the surgical incision site

or to the *zusanli* acupuncture point on the lower leg both reduced postoperative opioid use relative to sham stimulation in patients following abdominal procedures.¹³⁹ Conventional TENS applied over acupuncture points is hypothesized to produce diffuse analgesic effects through activation of descending pain-inhibition systems and by triggering the release of endogenous opioids.⁹⁶

Randomized Controlled Trials

Gibson et al recently described characteristics of studies necessary for inclusion in an evidenced-based Cochrane review of TENS for chronic pain.¹⁴² The key features included randomized controlled trial (RCT), standard TENS method, TENS delivered at a clearly perceptible sensation, and one of the following randomized comparisons: TENS versus sham, TENS versus usual care/no treatment/waiting-list control, and TENS plus active intervention versus active intervention alone/comparisons between different types of TENS/TENS delivered using different stimulation parameters. Table 3 lists RCTs that have evaluated remote applications of conventional TENS and met these criteria.

Jamison et al conducted an RCT of a conventional TENS device placed on the upper calf of either leg in subjects with chronic low-back pain.¹⁴³ A total of 68 subjects were randomized to either daily device use (n=35) or usual care (n=33) and followed for 3 months. Subjects randomized to the device arm self-administered TENS at home, with a recommendation of at least 2 hours per day. Based on actual tracking by the device, average use was 380.6±352.6 hours during the study, which is about 4 hours per day. The primary outcome measure was baseline–follow-up changes in pain intensity and pain interference on

the Brief Pain Inventory (BPI) — short form.¹⁴⁴ Additional outcome measures included the Pain Disability Inventory, the Pain Catastrophizing Scale, and the Hospital Anxiety and Depression Scale. Subjects in the device group had significantly less overall pain, less pain interference with function, and lower pain-catastrophizing scores at follow-up compared to the usual-care group. There were no differences in pain disability or anxiety and depression. The authors concluded that a leg-worn TENS device can have a moderate effect in reducing pain and improving quality of life in primary low-back pain.

Dailey et al conducted a double-blinded, randomized, sham-controlled crossover study to test the effects of a single treatment of TENS applied to the low back or neck in subjects with fibromyalgia.²² A total of 43 subjects were evaluated. Three TENS interventions were assessed in random order: active TENS, sham TENS, and no TENS. The active-TENS intervention was high frequency at a strong non-painful level. Outcome measures included assessment of pain and fatigue at rest and movement based on the VAS, PPTs, 6-minute walk test, range of motion, five-time sit-to-stand test, and single-leg stance. There was a significant decrease in pain and fatigue with movement for active TENS compared to sham and no TENS. Active TENS increased PPTs at the site of stimulation (ie, low back or neck) and remotely in the leg when compared to sham TENS or no TENS. No changes in functional outcomes were found. The authors concluded that TENS improved movement pain and fatigue in subjects with fibromyalgia. Moreover, pain thresholds increased not only at the location of TENS application on the spine but

Table 3 Randomized Controlled Trials Demonstrating Remote Analgesic Effects Of TENS

Reference	Design	Condition	Stimulation Site	Control Group(s)	Remote Analgesic Effects
Jamison et al ¹⁴³ NCT02944513	Parallel (n=68)	Chronic low-back pain	Leg	Usual care	Segmental
Dailey et al ²² NCT00932360	Crossover (n=43)	Fibromyalgia	Back/neck	Sham TENS, no TENS	Segmental, extrasegmental
Crofford et al ³⁴ NCT01888640	Parallel (n=301)	Fibromyalgia	Back/neck	Sham TENS, no TENS	Segmental, extrasegmental
Yarnitsky et al ²⁴ NCT02453399	Crossover (n=71)	Migraine	Arm	Sham TENS	Extrasegmental
Yarnitsky et al ³⁵ NCT03361423	Parallel (n=252)	Migraine	Arm	Sham TENS	Extrasegmental

also remotely on the leg, suggesting widespread effects of TENS.

Crofford et al reported results from an RCT of conventional TENS in subjects with fibromyalgia.^{34,145} A total of 301 subjects with fibromyalgia meeting the American College of Rheumatology 1990 criteria were randomized to active TENS (n=103), sham TENS (n=99), or no TENS (n=99). Active TENS was applied to the cervical and lumbar spine at mixed frequency of 10–100 Hz with strong but tolerable intensity. Subjects were instructed to use their device during activity for at least 2 hours per day for 1 month. Primary outcome measures were pain and fatigue during activity (6-minute walk test) and at rest. Patient-reported outcomes were assessed with the BPI, Multidimensional Assessment of Fatigue, Revised Fibromyalgia Impact Questionnaire, and a global rating of change. At the 1-month follow-up, the active-TENS group exhibited a reduction in activity-induced pain that was significantly greater than sham TENS and no TENS. Similar results were found for activity-induced fatigue. Active TENS also showed significant improvement in the BPI interference domains, Multidimensional Assessment of Fatigue, and Revised Fibromyalgia Impact Questionnaire compared to placebo TENS and no TENS. The global rating of change indicated that 70% of those in the active-TENS group improved compared to 31% in the sham-TENS group, and 9% in the no-TENS group. The authors concluded that active TENS produced significant improvement in pain, fatigue, and disease impact in women with fibromyalgia.

Yarnitsky et al evaluated the ability of high-frequency noninvasive electrical stimulation applied to either upper arm to reduce migraine pain in a double-blinded, randomized, crossover, sham-controlled trial.²⁴ The study evaluated a total of 71 subjects and 299 migraine treatments. The authors described the intensity as well perceived but not painful, which is consistent with conventional TENS as defined in this review. Subjects applied the device to their arm at migraine onset for 20 minutes. The primary outcome measure was reduction in pain measured by NRS from the beginning of each treatment to 2 hours posttreatment. Greater pain reduction was found for active stimulation than sham. The authors concluded that non-painful remote electrical skin stimulation can significantly reduce migraine pain. The authors attributed the mechanism of action to activation of CPM.^{65,146}

The same group that conducted the first remote electrical stimulation study for migraine conducted a larger

follow-on randomized, double-blind, multisite, sham-controlled study of a similar device.³⁵ A total of 252 subjects were randomized to an active or sham device. The stimulator was applied for 30–45 minutes on the upper arm at a perceptible but non-painful intensity within 1 hour of migraine onset. The primary outcome was the proportion of subjects achieving pain relief at 2 hours posttreatment. Active stimulation was more effective than sham stimulation in achieving pain relief (66.7% vs 38.8%). The authors concluded that remote electrical stimulation provides better relief of migraine pain than placebo.

Chronic pain is associated with changes in the CNS, such as central sensitization that decentralizes pain⁹⁴ and may thus enhance spatial responsiveness to focal neurostimulation, such as by TENS.²² A total of five RCTs with over 700 subjects were identified that utilized conventional TENS in remote segmental^{22,34,143} and/or widespread^{22,24,34,35} analgesic configurations. These results build on animal and experimental human-pain data to demonstrate that the remote analgesic effects of conventional TENS translate into chronic pain. Additional controlled studies, including in new indications, such as neuropathic pain,³² should be undertaken.

Observational Studies

RCTs on chronic pain are conducted in structured settings with narrowly selected homogeneous subjects. Although these studies have good internal validity, lack of generalizability may limit their application in practical management of chronic pain.¹⁴⁷ Large-scale observational studies and real-world evidence¹⁴⁸ are also needed to determine the effectiveness of chronic-pain treatments.

Gozani and Kong evaluated 1,676 users of a conventional TENS device located on the lower leg.⁷⁹ The study participants were stratified into two groups: those without foot or leg pain (proximal-pain group, n=296, 17.7%) and those with foot or leg pain (distal-pain group, n=1,380, 82.3%). Participants were followed from baseline (ie, start of TENS use) for 60 days. The primary outcome measure was changes in four BPI domains: pain intensity and pain interference with sleep, activity, and mood. There were no differences in TENS usage between the groups. Mean reductions in pain interference with activity and mood were at the minimum clinically important difference¹⁴⁹ of 1 point for all participants in both groups. Mean reductions in pain intensity and pain interference with sleep were also at the minimum clinically important difference for participants with high utilization (device use >90% of days). Although the proximal-pain

group did not have pain at the site of TENS placement, there were no differences in pain outcomes when compared to the distal-pain group. This result was maintained after adjustment for demographics and pain characteristics by multivariate regression. The authors concluded that leg-worn conventional TENS has analgesic effects beyond the site of stimulation.

Gozani et al evaluated changes in self-reported and objective measures of sleep in 554 participants using conventional TENS located on the lower leg over 10 weeks.²⁶ All participants reported chronic low-back pain with a prior history of back injury. Average TENS use was 40 hours per week. Half the participants reported improvement in pain interference with sleep, measured on an 11-point NRS. These participants exhibited a mean 30-minute increase in total sleep time, which is an objective assessment of sleep measured by actigraphy.¹⁵⁰ Participants that did not report an improvement in pain interference with sleep did not have a change in total sleep time. The authors concluded that regular use of conventional TENS on the lower leg improved self-reported and objective sleep in individuals with chronic low-back pain.

Remote Effects Of Nerve Stimulation In Nonpain Applications

This review focuses on the remote analgesic effects of conventional TENS in patients with chronic pain. Peripheral NS, including conventional TENS, has been shown to produce remote physiological effects in other applications. As an example, symptomatic treatment of pruritus was proposed soon after TENS was developed.¹⁵¹ Although the pathophysiological mechanisms underlying itching are not fully understood, there is substantial overlap between itch and pain signaling.¹⁵² In several studies, conventional TENS reduced the symptoms of generalized (ie, widespread) pruritis.^{153,154}

Percutaneous tibial NS (PTNS) and transcutaneous tibial NS are functionally comparable methods of stimulating the posterior tibial nerve at the ankle.^{155,156} The techniques are similar to conventional TENS in the use of perceptible non-painful stimulation, although the frequency is 20 Hz. The posterior tibial nerve is a mixed nerve originating from segments L4–S3, which overlap with the parasympathetic innervation to the bladder involving segments S2–S4.¹⁵⁷ PTNS and transcutaneous tibial NS have been shown to modulate bladder function, resulting in decreased symptoms of overactive bladder.^{155,158,159} PTNS has also been

demonstrated to decrease chronic pelvic pain.^{160–162} The remote effects of posterior tibial NS are analogous to remote segmental analgesia in chronic pain.

There have been reports of TENS altering sleep patterns in patients with primary CNS disease, potentially through activation of CNS structures that regulate sleep. For example, TENS may partially normalize rest–activity rhythm abnormalities in patients with Alzheimer’s disease.¹⁶³ The study authors hypothesized that TENS activates the hypothalamic suprachiasmatic nuclei, which regulates biological clocks. Interestingly, abnormal rest–activity patterns have also been reported in chronic-pain conditions, including fibromyalgia,¹⁶⁴ painful diabetic neuropathy,¹⁶⁵ and knee osteoarthritis with insomnia.¹⁶⁶ It is possible that some widespread effects of TENS result from modulating physical or emotional functions that are adversely impacted by chronic pain.

Non-Specific Effects

The contribution of a placebo response to the generation of remote analgesic effects by conventional TENS must be considered.^{79,128} Like TENS, the placebo response is partially mediated through descending pain inhibition.^{66,167} However, placebo responses are unlikely to account completely for the remote analgesic effects of conventional TENS. First, the existence of robust animal and human experimental pain data, which are less sensitive to placebo than clinical pain,^{168,169} argues against a primary role for a placebo mechanism. Second, the placebo response is driven by expectation,¹⁷⁰ and it seems unlikely that patients will have a strong expectation of pain relief from a device located at a distance from their pain.⁷⁹ Third, although a TENS placebo that provides robust blinding may not be possible,¹⁴² well-designed sham-controlled studies^{15,171} have been conducted that demonstrated remote analgesic effects of conventional TENS.^{22,24,34,35} Another aspecific effect that may contribute to the remote effects of conventional TENS is distraction. In healthy volunteers, conventional TENS was found to decrease heat-pain perception without a contribution from distraction.¹⁷² Although it is possible that non-painful electrical stimulation from TENS temporarily causes pain distraction, it is unlikely that this effect will be sustained through regular and prolonged TENS use.

Perspectives

Alternative stimulation sites have been noted in descriptions of TENS methodology since soon after its development.^{30,95}

A natural question is why the remote analgesic effects of TENS and conventional TENS in particular have not been utilized more broadly. Perhaps the utilization of remote stimulation sites is less intuitive than placement of electrodes over pain and requires familiarity with the TENS mechanism of action beyond the original pain-gate formulation. Local placement of electrodes may provide better efficacy than distant sites, particularly in the absence of consideration for potential improvements in utilization and adherence using remote analgesia. The strongest analgesic effect may be within the site of pain, because of the potential for nociceptive modulation at peripheral, spinal, and supraspinal levels. As the stimulation site is moved away from the origin of pain, first peripheral and then spinal modulation may be lost, leaving supraspinal regulation. However, the analgesic effects of peripheral, spinal, and supraspinal regulation are not necessarily additive,^{79,80} and thus reduced efficacy with increased spacing between stimulation and pain may not occur.^{19–21,79} It is also likely that a decrease in efficacy due to electrode location can be offset by changes in other treatment variables. For example, as the distance from the pain site increases, stimulation intensity, duration of application, and regularity of use may be increased in a compensatory fashion.^{16,47,173} The importance of maximizing stimulation intensity in conventional TENS, irrespective of the site of stimulation, must be emphasized.^{15,109,174} Stimulation should always be delivered at the highest tolerable intensity.¹⁷⁵

There has been only modest innovation in TENS devices over the past 30 years. Manufacturers have generally focused on differentiated stimulation waveforms of unclear clinical significance.³⁸ This may have contributed to a disconnect between the potential effectiveness of conventional TENS, including remote analgesia, and the current state of the field. However, there has been a resurgence of innovation over the past 5 years that is combining the evolving science of peripheral nerve stimulation with advances in microelectronics and mobile technology to create novel options for the treatment of chronic pain.

Limitations

This review utilized a nonsystematic design, and thus some limitations should be considered. First, although a comprehensive database search was conducted to identify relevant articles, some potential articles may have been missed. This is especially true for non-English-language studies. Second, there was no objective assessment of the

extent or impact of publication bias on the conclusions drawn in this review. Third, negative articles were included when identified; however it is possible that negative results on remote analgesic effects were embedded in studies with other objectives. Fourth, the evidence in support of remote analgesic effects in chronic-pain populations is based on a small number of RCTs and retrospective cohort studies. Additional controlled and observational studies should be performed to further evaluate mechanisms of action and clinical utility in chronic pain.

Conclusion

This narrative review examined the mechanism of action for the remote analgesic effects of conventional TENS and reviewed the clinical evidence. There is an anatomic, molecular, and physiological basis for conventional TENS producing analgesia at sites distant from stimulation. This may occur through modulation of pain processing at the level of the dorsal horn, in brain-stem centers mediating descending inhibition, and within the pain matrix. This scientific foundation is supported by evidence from animal studies, experimental human-pain studies, and clinical studies. Over 30 such studies were identified that reported remote analgesic effects of conventional TENS.

There is a pressing need for effective nonpharmacological treatments for chronic pain, given the economic cost of chronic pain and societal impact of opioid use. TENS has been used to treat chronic pain for 50 years; however, uncertainty remains about its optimal applications. A broadening of perspectives on how conventional TENS produces analgesia and related improvements in functioning may encourage researchers, clinicians, and medical device developers to imagine novel ways of using this inherently safe and cost-effective neuromodulation technique for chronic pain.

Disclosure

The author is an employee and shareholder of NeuroMetrix, which manufactures a device referenced in this review article. In addition, the author has patents 8,948,876, 9,656,070, and 10,112,040 issued to NeuroMetrix. The author reports no other conflicts of interest in this work.

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