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Transcutaneous Electrical Nerve Stimulation in Relieving Neuropathic Pain: Basic Mechanisms and Clinical Applications

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Abstract

Purpose of Review Transcutaneous electrical nerve stimulation (TENS) is widely used as a non-pharmacological approach for pain relief in a variety of clinical conditions. This manuscript aimed to review the basic mechanisms and clinical applications regarding the use of TENS for alleviating the peripheral (PNP) and central neuropathic pain (CNP).

Recent Findings Basic studies on animal models showed that TENS could alleviate pain by modulating neurotransmitters and receptors in the stimulation site and its upper levels, including the spinal cord, brainstem, and brain. Besides, many clinical studies have investigated the efficacy of TENS in patients with CNP (caused by spinal cord injury, stroke, or multiple sclerosis) and PNP (induced by diabetes, cancer, or herpes zoster). Most clinical trials have demonstrated the efficacy of TENS in attenuating neuropathic pain and suggested that appropriate stimulation parameters (e.g., stimulation frequency and intensity) were critical to improving the analgesic effects of TENS. However, there are some conflicting findings related to the efficacy of TENS in relieving neuropathic pain.

Summary With optimized stimulation parameters, TENS would be effective in attenuating neuropathic pain. To obtain sufficient evidence to support the use of TENS in the clinic, researchers recommended performing multicenter clinical trials with optimized TENS protocols for the treatment of various CNP and PNP.

Keywords Transcutaneous electrical nerve stimulation · Peripheral neuropathic pain · Central neuropathic pain · Neural mechanisms · Analgesic effects

Introduction

Although neuropathic pain disorders are known to develop following a disease or lesion of the somatosensory nervous system [1], the underlying pathogeneses and etiologies of these disorders are not completely understood. Wide range patterns of sensory signs and symptoms could be observed in neuropathies of different etiologies and patients with neuropathies of the same etiology [2]. The expression of these sensory signs includes allodynia (excessive pain to a normally non-painful stimulus), hyperalgesia (increased pain to a painful stimulus), and sensory loss [2]. The sensory signs reflect the pathophysiological mechanisms in injured and survived afferent nerve fibers, including ectopic impulse generation, conduction block, and peripheral and central sensitization [3]. Even pathophysiological mechanisms of neuropathic pain cannot be readily examined in patients, the expression of some sensory signs is related to pathogenesis. For example, heat hyperalgesia is mainly related to peripheral sensitization [4, 5], and pinprick hyperalgesia is associated with central sensitization [6, 7]. Thus, the individual somatosensory profile could reveal some clues to the pathophysiological dysfunctions of afferent processing [2, 8].

Neuropathic pain is typically classified into peripheral neuropathic pain (PNP) and central neuropathic pain (CNP) based on the site of the disease or lesion [9]. PNP, resulted from the

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damage or diseases of peripheral nerves, is widely observed in different conditions, such as painful diabetic neuropathy (or diabetic peripheral neuropathic pain [DPNP]), cancer-related neuropathic pain, and postherpetic neuralgia (PHN) [10]. CNP, caused by the damage or diseases affecting different levels of the central nervous system, is popularly reported in various conditions, including stroke, spinal cord injury (SCI), and multiple sclerosis (MS) [11]. Regardless of the site of the disease or lesion, different kinds of neuropathic pain have some common characteristics, such as positive features (e.g., spontaneous pain, hyperalgesia, and allodynia) and negative features (e.g., weakness, sensory loss, and hypoesthesia) [8, 12]. Nevertheless, neuropathic pain is recently suggested to be classified using a different scheme, in which pain is more appropriately differentiated based on the underlying mechanisms [13, 14]. This scheme emphasized the rationale for choosing an optimized treatment strategy based on mechanisms rather than the type of diseases [15–17].

Despite the complexity of pain neurobiology has been well recognized, the pharmacological control of pain-related disorders remains inadequate. Different medications have been introduced to relieve neuropathic pain, whereas almost all have potential side effects [18] and several promising agents have failed in the late phase of the clinical trials [10, 19]. Thus, it is highly important to develop new analgesia strategies that can effectively relieve neuropathic pain with fewer adverse effects. As a noninvasive and non-pharmacological treatment, transcutaneous electrical nerve stimulation (TENS) has been used to treat a variety of neuropathic pains [20••]. The analgesic effects of TENS have been demonstrated to be achieved through different neurobiological mechanisms affecting peripheral and central nervous systems [21]. Specifically, applying electrical pulses to the surface of the skin could activate nerve fibers, and then induce the release of the endogenous opioid, the modification of electrical transmission, and the dilation of blood vessels, ultimately leading to the relief of neuropathic pain [21–23].

Although some clinical studies have demonstrated the efficiency of TENS for alleviating neuropathic pain, there is still much controversy on how to optimize the analgesic effects of TENS. It should be noted that controlled clinical trials investigating the analgesic effects of TENS in PNP and CNP patients are still insufficient. In addition, existing clinical trials investigating the analgesic effects of TENS mainly focused on discussing different TENS parameters rather than the underlying mechanisms, e.g., TENS-induced physiological and histopathological alterations. These situations hindered the popularization of TENS to eliminate neuropathic pain in clinical applications.

In the present investigation, we first describe the characteristics of different types of TENS. After that, we discuss the neurobiological mechanisms of TENS in relieving neuropathic pain. Then, we summarize the efficiency of TENS in treating patients with PNP or CNP caused by different types of diseases or lesions. Finally, we propose the possible directions in future studies for optimizing the TENS-induced analgesic effects in clinical practice.

TENS: Types and Characteristics

As a noninvasive analgesic technique, TENS activates peripheral nerves by delivering electrical pulses to the intact surface of the skin [24], which could modulate the transmission of nerve impulses by inhibiting presynaptic transmission of nociceptive information [25]. In practice, TENS can be implemented using different stimulus parameters in frequency, intensity, and electrode placement [26, 27]. Since TENS with different stimulus parameters could activate different populations of nerve fibers, this technique can be divided into different types, including conventional TENS (low intensity and high frequency), acupuncture-like TENS (high intensity and low frequency), and intense TENS (high intensity and high frequency). The characteristics of these TENS types are detailed below.

Conventional TENS (Low Intensity, High Frequency)

As one of the most commonly used TENS techniques [28], conventional TENS is capable of selectively exciting large diameter, low-threshold non-noxious afferent nerve fibers (Aβ fibers) in pain-related dermatomes [29], which inhibits the activity of the second-order nociceptive transmission neurons. The stimulus parameters of conventional TENS are usually set at a comfortable intensity (below the pain threshold) and a high frequency (> 10 Hz) [30, 31], which can generate a non-painful tingling sensation (strong but comfortable) underneath the TENS electrodes. However, further increased stimulus intensity would undesirably activate small diameter, high-threshold noxious afferent nerves (Aδ fibers) and induce an undesired painful sensation beneath the TENS electrodes [28].

Acupuncture-Like TENS (High Intensity, Low Frequency)

Acupuncture-like TENS can stimulate small diameter, myelinated (Aδ fibers) and unmyelinated (C fibers) afferent nerves, which subsequently activate extrasegmental descending pain inhibitory pathways to produce a spatially diffuse analgesic effect [32, 33]. The stimulus parameters of acupuncture-like TENS are usually set at a high intensity (i.e., reaching pain tolerance threshold) and a low frequency (2–4 Hz) [34], which can produce a painful but tolerable sensation underneath the TENS electrodes. Acupuncture-like TENS can be used in patients who do not respond to

conventional TENS, while it is advised to be applied less frequently than conventional TENS (e.g., 20 min per time and 3 times per day) [28].

Intense TENS (High Intensity, High Frequency)

Similar to acupuncture-like TENS, intense TENS is designed to activate Aδ fibers, which can block the transmission of nociceptive information through extrasegmental analgesic mechanisms [35]. Theoretically, this technique could also produce a spatially diffuse analgesic effect. For the sake of safety, intense TENS is suggested to be applied for a short period (few minutes) on the premise that the stimulus parameters (high intensity, reaching pain tolerance threshold; high frequency, < 200 Hz) are tolerable for the patients.

Placements of TENS Electrodes

The TENS electrodes are normally placed in the proximity of the painful area [36], while the possible influence of electrode placement on TENS-induced analgesic effects is largely ignored previously [37]. In one of our recent studies [38•], we comprehensively investigated the possible interaction between the electrode placement and the type of TENS (i.e., conventional TENS and acupuncture-like TENS). We observed that the analgesic effect of conventional TENS was maximal when the electrodes were placed around the painful area. In contrast, acupuncture-like TENS produced a spatially diffuse analgesic effect, i.e., equally strong analgesic effect regardless of whether the electrodes were placed in the hand ipsilateral or contralateral to the painful area [38•]. Similarly, Cho et al. (2014) evaluated the effectiveness of different electrode placements with conventional TENS (100 Hz, submotor threshold, 20 min) in relieving the chronic neuropathic pain in the upper limb based on the rat model of median nerve injury [39]. When the electrodes were placed at the ipsilateral side of the injured site, the neuropathic pain was greatly alleviated. However, when the electrodes were placed at the contralateral side of the injured site, TENS only decreased the mechanical allodynia in the injured site. These results suggested that the analgesic effect of conventional TENS was maximal when it was delivered on the skin near the painful area. Besides, Sabino et al. (2008) compared the analgesic effect of conventional TENS (130 Hz) and acupuncture-like TENS (10 Hz) in an inflammation model produced by the injection of carrageenan in rat paws [40]. They observed that, while both types of TENS could inhibit the carrageenan-induced hyperalgesia, pretreatment of animals with intraplantar naltrexone reversed the analgesic effect of the acupuncture-like TENS but not that of the conventional TENS. Also, acupuncture-like TENS produced a longer-lasting analgesic effect than conventional TENS, suggesting that the analgesic effect of acupuncture-like TENS is partially due to the release of endogenous opioids. In short, these findings indicated that conventional TENS and acupuncture-like TENS act through different neurobiological mechanisms, which implied that the optimal placement of the TENS electrodes should be determined based on the type of TENS. Specifically, in clinical practice, TENS electrodes are suggested to be placed near the painful area when conventional TENS is adopted, and such requirement is not necessary when acupuncture-like TENS is used (i.e., TENS electrodes could be placed far from the painful area, since its analgesic effect is much less influenced by where TENS electrodes are located).

Peripheral and Central Mechanisms

Different types of TENS have different analgesic mechanisms [41], including peripheral mechanisms, segmental mechanisms, and extrasegmental mechanisms. Conventional TENS is regarded to mainly associate with segmental mechanisms since it can result in a segmental inhibition of the spinal transmission of nociceptive information at the dorsal horn. Acupuncture-like TENS and intense TENS are deemed to largely relate to extrasegmental mechanisms since they can produce analgesia through recruiting descending pain inhibition system. Besides, conventional TENS and intense TENS (both of them are delivered at a high frequency) are demonstrated to relate to peripheral mechanisms since they can generate peripheral blockade of afferent impulses [21, 42].

Peripheral Mechanisms

Both conventional TENS and intense TENS can elicit antidromic activation in peripheral afferent nerves, i.e., the delivery of TENS could elicit nerve impulses traveling away from the central nervous system along the nerve axon [28]. The antidromic activation could result in the peripheral blockade of nociceptive impulses since antidromic nerve impulses would collide with and inhibit afferent impulses arising from the injured tissue [28, 37]. Peripheral blockade induced by conventional TENS is likely to occur in large diameter fibers (e.g., Aβ fibers), which could produce a "busy line effect" and thus generate an analgesic effect for some patients with allodynia. Peripheral blockade of nociceptive impulses is more evident during the intense TENS treatment. The nerve impulses traveling in Aδ fibers induced by intense TENS would collide with nociceptive impulses originated from the injured tissue [35]. Please note that the TENS-induced peripheral blockade is well documented by previous evidence showing that TENS can reduce the conduction velocity and amplitude of action potentials of Aβ and Aδ fibers in isolated nerves [28, 43].

Segmental Mechanisms

Conventional TENS mainly involves in the segmental mechanisms, in which the activation of large-diameter Aβ fibers induced by electrical stimulation could activate the inhibitory interneurons in the dorsal horn of the spinal cord, thus reducing the firing rate of the projection neurons [44]. The segmental mechanisms are in line with the gate control theory of pain proposed by Melzack and Wall [45]. Non-nociceptive inputs close the nerve "gates" to nociceptive inputs, which prevents nociceptive impulses from traveling to the central nervous system. To support the segmental mechanisms, it has been demonstrated that by stimulating large-diameter afferents (i.e., Aβ fibers), conventional TENS suppressed the activation of dorsal horn neurons for up to 2 h after spinal cord transection in cats [46]. In addition, it has been proved that the latency of tail flick responding to heat stimulation enhanced after conventional TENS treatment [47, 48], and this inhibition effect on tail flick was also observed in spinalized animals whose descending pain inhibitory pathways were ruined [48, 49].

Extrasegmental Mechanisms

Acupuncture-like TENS and intense TENS can produce analgesic effects through the recruitment of the descending pain inhibition system [32, 50]. Their analgesic effects are more related to the diffuse noxious inhibitory control (DNIC) phenomenon [51]: a strong noxious input causes the release of endogenous opioids in the periaqueductal gray (PAG) and rostral ventral medulla (RVM), which in turn results in a diffuse descending inhibition of nociception [52, 53]. In addition to the recruitment of the PAG-RVM network, analgesic effects could also be produced through the activation of neurons in the medullary subnucleus reticularis dorsalis which is part of the DNIC system [54, 55]. The analgesic effect of conventional TENS could be partly explained by extrasegmental mechanisms as well [32, 48]. It has been found that conventional TENS could reduce the neuropathic pain in rats with complete spinal transection at the level of the 10th and 11th thoracic vertebrae [48]. Besides, the analgesic effect of conventional TENS would be blocked by naltrindole (a δ-opioid receptor antagonist) microinjected in the spinal cord [56, 57] or RVM [48].

Neurotransmitters and Receptors

Different classes of neurotransmitters (e.g., serotonin, opioid, and norepinephrine) and different types of receptors they bind to (e.g., serotonin receptors, opioid receptors, and adrenergic receptors) in peripheral and central nervous systems have been found to contribute to the analgesic effects of TENS [58]. At the peripheral level, adrenergic receptors play an important role in TENS-induced analgesia. Neither conventional TENS nor acupuncture-like TENS could produce analgesic effects in mutant mice, for which the functional α_{2A}-adrenergic receptors are absent in the periphery [59]. Besides, the analgesic effect induced by acupuncture-like TENS would be reversed when α-adrenergic receptors were blocked by systemic administration of phentolamine [60].

At the central level, TENS-induced analgesia is associated with several classes of neurotransmitters and their receptors. In patients with neurological disorders, conventional TENS and acupuncture-like TENS could respectively increase the concentration of dynorphin and encephalin in lumbar cerebrospinal fluid [61]. In animal studies, the analgesic effects of conventional TENS and acupuncture-like TENS were prevented by the blockade of opioid receptors in the RVM or spinal cord or synaptic transmission in the ventrolateral PAG [48, 57, 62]. Furthermore, the blockade of muscarinic receptors and gamma-aminobutyric acid (GABA) receptors in the spinal cord would prevent the analgesic effects of conventional TENS and acupuncture-like TENS [63, 64]. Besides, acupuncture-like TENS is associated with the increased release of serotonin [65], and its analgesic effect will be inhibited by the blockade of serotonin receptors in the spinal cord [41, 65]. It should be noted that whether the physiological mechanisms of TENS discovered in animal models are the same as those in humans is still on debate.

Clinical Applications: Alleviating Peripheral Neuropathic Pain

Resulted from lesions or diseases of the peripheral nervous system, PNP is normally characterized by spontaneous pain, allodynia, and/or hyperalgesia [66]. There are various etiologies of PNP, including toxin, trauma, metabolic dysfunction, infection/inflammation, tumor invasion/compression, hereditary, etc. [67•]. With the aging of the global population, PNP becomes more common due to the increased incidence of many relevant diseases, e.g., diabetes, cancer, and postherpetic neuralgia [68]. The analgesic effects of TENS on several commonly observed PNP (e.g., DPNP, cancer-related neuropathic pain, and PHN) have been widely investigated, and the relevant findings were summarized in the following sections (Table 1).

Diabetic Peripheral Neuropathic Pain

Diabetes is one of the major causes of peripheral neuropathy. DPNP is defined as a pain directly originated from the abnormalities of the peripheral somatosensory system in people with diabetes [69]. Approximately 10% to 26% of diabetic patients have neuropathic pain [70], which exerts a substantial impact on their quality of life by interfering with sleep and enjoyment of life [71]. The efficiency of TENS in relieving

Table 1 Analgesic effects of TENS on peripheral and central neuropathic pain

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
Kumar et al. (1998) [73]	A single-blind placebo--controlled randomized study	PNP-DPNP	$n = 23$ patients who failed to respond to amitriptyline or who only had partial relief Groups: Sham and amitriptyline ($n = 9$) TENS and amitriptyline ($n = 14$)	–	Four self-adhesive electrodes: 1) 3 in. above the patella and 3 in. medially, over the vastus medialis oblique 2) 3 in. above patella and 3 in. laterally, over the lower portion of vastus lateralis 3) on the neck of fibula 4) on the gastrocnemius muscle about 3 in. below the center of popliteal fossa	4 ms ≤35 mA 25–35 V 2-70 Hz	12 weeks	Symptomatic improvement occurred in 12 (85%) patients Five (36%) of the patients became asymptomatic Effective for patients who failed amitriptyline treatment Pain scores declined from 3.2 ± 0.2 to 1.4 ± 0.4. 66 ± 10% overall reduction in pain
Somers and Somers (1999) [72]	A case report	PNP-DPNP	A 73-year-old woman	HF	1.3 cm (1/2 in) lateral to the left/right posterior superior iliac spine on the back	200–400 ms 44–60 mA 80 Hz	20 min/time occasionally for 1 to 2 h during the day and more often at night 17 days	Following 20 min of TENS on the first day, a 38% reduction in intensity of pain After 17 days, the subject reported no pain following 20 min of TENS and she could sleep through the night
Dubinsky and Miyasaki (2010) [78]	A systematic review	PNP-DPNP	–	LF HF Sham	–	–	–	Modest reduction in pain severity for TENS compared to sham TENS A larger proportion felt benefit with high-frequency external muscle stimulation compared to TENS
Pieber et al. (2010) [77]	A systematic review	PNP-DPNP	–	–	–	–	–	Beneficial effects with prolonged use over an average period of 1.7 years
Jin et al. (2010) [23]	A meta-analysis of RCTs	PNP-DPNP	$n = 78$	LF Sham Other Frequenci-es	–	–	12 weeks	Significant reductions in mean pain score in four to 6 weeks follow-up (16.6%). Improvement in overall neuropathic symptoms in 12 weeks follow-up (70%) No adverse effects
Gossrau et al. (2011) [22]	A single-blind placebo--controlled randomized study	PNP-DPNP	$n = 41$ Groups: TENS ($n = 22$) Placebo ($n = 19$)	LF	Proximal dorsum pedis and the top of the caput fibulae on both legs	30–40 μA 2 Hz	30 min/time 3 times/week 4 weeks	No significant differences in the pain reduction between TENS and sham group No benefit for the patients' general life condition No side effects during and after the therapy
Naderi Nabi et al. (2015) [76]	A single-blind, randomized clinical trial	PNP-DPNP	$n = 60$ Groups: TENS ($n = 30$) PRF ($n = 30$)	HF	Two electrodes: 1) on the upper shin 2) above the ankle	0.2 ms 2 to 3 times sensory threshold 50 Amp 80 Hz	20 min/session 10 sessions every other day	Decreased pain severity (NRS) from 6.10 at baseline to 3.96, 5.23, and 5.90 at the first week, 1 month, and 3 months visits after treatment, respectively Long-term effects remained controversial

Table 1 (continued)

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
Searle et al. (2009) [83]	A case study	PNP-cancer bone pain	A 63-year-old woman	HF	Site of bone pain, over the proximal humerus	200 ms 80 Hz	60 min/time	Reduced overall pain scores both at rest and especially during painful movement The NRS fell from a baseline of 4 at rest and 7 on painful movement to 1 at rest and 2 on painful movement after TENS The short-form McGill pain score fell from a baseline of 8 to a score of 1 after TENS No adverse effects
Hurlow et al. (2012) [82]	A systematic review on RCTs	PNP-cancer-related pain	–	–	–	–	–	Inconclusive results for patients with cancer-relate pain due to a lack of suitable RCTs RCT 1: Cancer bone pain on movement may improve with TENS. On verbal pain relief scores, 12 participants (63.2%) experienced good or very good pain relief with active TENS at one hour, compared with five participants (26.3%) on placebo RCT 2: No significant differences in pain relief scores between TENS or sham transcutaneous spinal electroanalgesia RCT 3: No significant differences between LF-TENS and sham LF-TENS
Loh and Gulati (2015) [84]	A retrospective cohort study	PNP-cancer pain	*n* = 84 patients has a history of chordoma with sacral pain and concurrent knee pain	HF	Dermatomal patterns in the location of pain	180 ms 3 and 3.5 mA ≥80 Hz	30 min–60 min/time 4–6 times/day ≥ 2 months	Benefit in 69.7% of patients over the course of 2 months Decreased VAS scores by 9.8 on a 0 to 100-mm scale in responsive patients Decreased NRS scores by 0.8 on a 1 to 10 scale in responsive patients Improvement of the life quality or pain symptoms in 41% of TENS responsive patients Worsening in the life quality or pain symptoms in 33% of TENS unresponsive patients
Gewandter et al. (2018) [85]	A feasibility study	PNP-Chemot-herapy induced pain	n = 22 n = 22 completed 6 weeks treatment n = 15 completed 6 months treatment	HF	Below the knee	200–400 μs 2 times the sensation threshold 60–100 Hz	6 weeks 1) first 3 weeks: two individual 1-h sessions, once in the morning and once in the evening 2) second 3 weeks: two individual sessions per day or to wear the device between 3 and 12 h per	Improvement in different scales (percent change from baseline): SF-MPQ-2 (52%), EORTC-CIPN20 (13%), and NRS (38%) in the primary follow-up Positive qualitative feedback in most of patients after a 6 months follow-up

Table 1 (continued)

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
							day on the continuous setting that automatically alternates between 1-h treatment and 1-h rest periods (i.e., between 2 and 6 h of stimulation)	
Lee et al. (2019) [111]	A double-blind placebo--controlled randomized pilot study	PNP-cancer pain with radiation	$n = 40$ patients with head and neck cancer with 4 to 6 weeks radiation Groups: Active ($n = 12$) Placebo ($n = 12$) No TENS ($n = 16$)	HF	Four round adhesive electrodes: 1) bilaterally on the TMJ (one third of distance from the ear and nose) 2) bilaterally upper neck area (2 cm from the spine, i.e., cervical 1 and 2)	100 μs 125 Hz	30 min/time once/week over 3 weeks	Active TENS reduced VAS (from 3.2 to 1.9) and MPQ (from 6.8 to 3.7) scores in patients
Kolsek (2012) [90]	A retrospective observational study	PNP-herpes zoster	$n = 102$ patients Groups: TENS ($n = 29$) Antiviral drug ($n = 28$) Antiviral drug with TENS ($n = 24$) No therapy ($n = 21$)	HF	Two patches: 1) paravertebral region 2) the other side along the nerve	1–5 mA 20–40 Hz	30 min/time 5 times/week 2 or 3 weeks	The incidence of PHN was zero in herpes zoster patients treated with TENS
Stepanović et al. (2015) [92]	A multicenter prospective, randomized intervention study	PNP-herpes zoster	$n = 222$ patients with a new onset of HZ Groups: Control ($n = 38$) TENS ($n = 36$) Antiviral agents ($n = 71$) TENS and Antiviral agents ($n = 77$)	HF	Two electrodes: 1) Near the root of affected nerve 2) In the course of that nerve	0.02 ms 3–30 mA 20–40 Hz	30 min/time 10–15 days	The odds for subacute herpetic neuralgia are the lowest in acute herpes zoster patients treated with TENS
Warke et al. (2006) [99]	A randomized, placebo-controlled clinical trial	CNP-MS	$n = 90$ Groups: LF-TENS ($n = 30$) HF-TENS ($n = 30$) Placebo ($n = 30$)	LF HF	Lumbar spine (3 cm distance on either side of the spinous processes)	LF: 200 μs 4 Hz HF: 200 μs 110 Hz	45 min/time 2 times/day 6 weeks	Both methods (LF and HF) reduced pain in 50% of patients Mean weekly VAS score differences were − 16.59 mm for LF-TENS and − 20.60 mm for HF-TENS
Miller et al. (2007) [98]	A single-blind clinical trial	CNP-MS	$n = 32$ Groups: TENS (60 min/day, $n = 16$) TENS (8 h/day, $n = 16$)	HF	Either end of the quadriceps muscle	0.125 ms 100 Hz	60 min/day or 8 h/day daily 2 weeks	TENS does not appear effective in reducing spasticity Significant reduction in muscle spasm (from 4.1 to ~ 2.7) and pain (from 3.9 to ~ 2.2) in 8 h group Longer application (8 h) might be useful in treating MS patients with pain and muscle spasm
Cuypers et al. (2010) [112]	A clinical trial	CNP-MS	$n = 56$ **Groups:** $n = 26$ MS patients ($n = 15$ intervention, $n = 11$ control)	HF	Median nerve region of the dominant hand	250 μs 100 Hz	1 h/day 3 weeks	Long-lasting improvements in tactile sensitivity achieved by repetitive stimulation of sensory afferents in MS patients but not in healthy subjects Increased sensitivity was not only restricted to the median nerve area

Table 1 (continued)

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
			$n = 30$ healthy subjects ($n = 15$ intervention, $n = 15$ control)					but also expanded to the ulnar nerve area
Norrbrink (2009) [101]	A clinical trial	CNP-SCI	$n = 24$ Groups: LF-TENS ($n = 12$) HF-TENS ($n = 12$)	LF HF	Paraspinal site	LF: 180 μs 2 Hz HF: 180 μs 80 Hz	30–40 min/time 3 times/day 2 weeks	Favorable effects for 29% of the patients with HF and 38% of the patients with LF stimulation on a 5-point global pain-relief scale Median values of pain were 4 at baseline and 3.8 after the last HF session Median values of pain were 4 at baseline and 3.9 after the last LF session
Celik et al. (2013) [102]	A prospective, randomized and controlled study	CNP-SCI	$n = 33$ Groups: TENS ($n = 17$) Sham ($n = 16$)	LF	Two channels with four electrodes: 1) 2 electrodes: proximal parts of the region with pain 2) 2 electrodes: distal parts of the region with pain	200 μs 50 mA 4 Hz	30 min/time daily 10 days	Significant reduction of VAS score from 5.79 to 3.88 on the twelfth day in LF-TENS group
Bi et al. (2015) [113]	An RCT	CNP-SCI	$n = 52$ Groups: TENS ($n = 26$) Sham ($n = 26$)	LF	Region with pain	< 200 μs 50 mA 2 Hz	20 min/time 3 times/week 12 weeks	Significant decrease in the pain intensity scores after TENS intervention
Ozkul et al. (2015) [103]	A randomized controlled cross-over trial	CNP-SCI	$n = 24$ Groups: TENS first, then visual illusion ($n = 12$) Visual illusion first, then TENS ($n = 12$)	HF	Both sides of the spinal region	180 μs 0–100 mA 80 Hz	15 min/day 5 days/week 2 weeks	Pain intensity decreased immediately after both applications Significant decrease in most (VAS, from 8.92 to 8.41) and less (VAS, from 2.62 to 2) pain intensity after TENS application for 2 weeks, but not after 2 weeks for visual illusion Significant decrease in negative effect of pain on mood, relationships with others, and sleep after TENS application Both therapies can be used as a supportive or an alternative method separately or together
Price and Pandyan (2001) [108]	A systematic review	CNP-CPSP (shoulder pain)	$n = 170$ ES including TENS, functional ES or other	–	–	–	–	No significant change in pain incidence or change in pain intensity after ES treatment compared with control Significant treatment effect in favor of ES for improvement in pain-free range of passive lateral rotation of humerus ES reduced the severity of glenohumeral subluxation, but no

Table 1 (continued)

Authors (year)	Research type	Type of neuropathic pain	Number of participants	Type of TENS	Electrode placements	Stimulus parameters	Intervention duration	Main results
								significant effect on upper limb motor recovery No negative effects of ES at the shoulder
Vuagnat and Chantraine (2003) [109]	A review	CNP-CPSP (shoulder pain)	–	–	–	–	–	Beneficial effects on pain, subluxation, and mobility

CNP central neuropathic pain, *CPSP* central post-stroke pain, *DPNP* diabetic peripheral neuropathic pain, *EORTC-CIPN20* the European Organization for Research and Treatment of Cancer-CIPN20, *ES* electrical stimulation, *HF* high frequency, *HZ* herpes zoster, *LBP* low back pain, *LF* low frequency, *MPQ* McGill Pain Questionnaire, *MS* multiple sclerosis, *NRS* numerical rating scale, *PHN* postherpetic neuralgia, *PNP* peripheral neuropathic pain, *PRF* pulsed radiofrequency, *PRI-T* pain rating index-total, *RCTs* randomized controlled trials, *SCI* spinal cord injury, *SF-MPQ-2* short-form McGill Pain Questionnaire-2, *TENS* transcutaneous electrical nerve stimulation, *TMJ* temporomandibular joint, *VAS* visual analog scale

DPNP has been proven in many published human studies. In an early case study, conventional TENS (80 Hz) applied to the lumbar skin of a DPNP patient (a 73-year-old woman) reduced pain intensity by 38% after the first 20-min treatment and even eliminated pain after the 17-day treatment (1~2 h during the day and the entire night) [72]. Besides, it has been demonstrated that 12-week TENS (pulse width 4 ms, 25~35 V, ≥ 2 Hz) combined with amitriptyline was effective in reducing neuropathic pain in patients with type 2 diabetes [73], suggesting TENS could augment the analgesic effect of pharmacological agents. Besides, compared with the sham condition, TENS (15~30 Hz) (3 weeks, 3 times per week, 30 min per time) was able to significantly decrease pain intensity and improve physical activity, sense of well-being, and quality of sleep in DPNP patients [74]. Similarly, compared with placebo, 12-week acupuncture-like TENS (4 Hz) treatment could reduce pain and pain-related symptoms in DPNP patients [75]. Another study indicated that conventional TENS (80 Hz; intensity, 2~3 times as much as the sensory threshold, every other day for 20 min) also could reduce pain in both type 1 and type 2 diabetic patients with DPNP [76]. Systematic reviews and meta-analyses concluded that the positive effects of TENS in treating DPNP are consistent and sufficient [23, 77]. In line with the above findings, the American Academy of Neurology regarded TENS as a "probably effective" treatment for reducing DPNP and recommended to apply TENS as a non-pharmacological technique for pain relief in DPNP patients [78].

Cancer-Related Neuropathic Pain

Up to 40% of cancer patients suffer from neuropathic pain that would result in increased analgesic consumption and decreased quality of life [79]. While the majority of neuropathic pain in cancer patients directly resulted from tissue destruction by the tumor, a growing proportion is caused by cancer treatments, such as surgery and/or chemotherapy [80]. Many clinical trials have been performed to investigate the analgesic effects of TENS on cancer-related neuropathic pain [81]. In a systematic review including only randomized controlled trials (RCTs) in adult patients with cancer-related neuropathic pain, the authors concluded that TENS was not more effective than the placebo according to the contradictory results from three RCTs. Notably, the conflicting findings could be caused by the fact that there are no suitable and sufficient RCTs to evaluate the analgesic effects of TENS [82]. In contrast, in a case report, TENS (80 Hz) successfully relieved pain in a 63-year-old woman with cancer bone pain [83]. Moreover, in a research conducted in a major cancer center, researchers found that TENS had positive effects on 69.7% of patients after 2 months follow-up, manifesting as a significant reduction of pain intensity [84]. Researchers also investigated the effects of TENS on relieving the neuropathic pain caused by

chemotherapy. In an open-label feasibility study, a home-based wireless TENS device was used to treat chemotherapy-induced neuropathic pain, and it was proved to significantly reduce self-report pain [85]. In summary, findings about the analgesic effects of TENS on cancer-related neuropathic pain are not conclusive and should be further examined in large multicenter RCTs.

Postherpetic Neuralgia

PHN is a kind of neuropathic pain that occurs due to the damage of peripheral nerves caused by the reactivation of the herpes zoster (HZ) [86]. The lifetime incidence of HZ is about 30%, and about 12.5% of elderly patients (≥ 50 years) with HZ develop PHN [87]. PHN patients are clinically characterized by spontaneous or evoked pain syndromes (e.g., sharp, stabbing, and burning) and by various abnormal sensory symptoms (e.g., hyperalgesia, allodynia, and sensory loss) [8], which profoundly affect patients' quality of life [88]. The analgesic effects of TENS, especially conventional TENS, in relieving PHN and acute pain caused by HZ has been demonstrated in some clinical studies. In an early study, TENS (70 Hz, 10 sessions every day, 20 min per time) was recommended to treat PHN [89]. Also, TENS (20~40 Hz, 5 times/week for 2 or 3 weeks, 30 min per time) was suggested as a safe adjunct or even alternative treatment of acute HZ and could prevent the development of PHN [90]. Combined with pregabalin, conventional TENS (100 Hz) was more effective in reducing PHN in patients (aged 50~80 years) than placebo [91]. Similarly, it has been found that long-term (10~15 days) TENS (20~40 Hz, 3~30 mA, 30 min per time, once per time) could not only serve as an effective treatment strategy for relieving acute pain caused by HZ but could also be capable of reducing the incidence of PHN in patients with HZ [92].

Clinical Applications: Alleviating Central Neuropathic Pain

CNP is induced by lesions or diseases of the spinal cord and/or the brain. In clinic, demyelinating diseases (e.g., MS), injuries (e.g., SCI), and cerebrovascular diseases (e.g., stroke) affecting the central nervous system are the most common CNP-related diseases [11, 93]. It has been widely accepted that TENS can relieve chronic pain in CNP patients as a non-pharmacological therapy [94]. In the following sections, we reviewed the literature investigating the efficiency of TENS in alleviating CNP caused by MS, SCI, and stroke (Table 1).

Multiple Sclerosis

MS is an autoimmune disorder, and there are more than 2.3 million MS patients worldwide [95]. The disease is characterized by inflammation, demyelination, and scar formation, and demyelinating plaques will lead to regional dysfunctions in the brain or spinal cord [96]. Apart from the pain-unrelated dysfunctions (e.g., balance impairment and cognitive impairment), up to 57.5% of MS patients reported pain during the course of their disease [97]. Conventional TENS (100 Hz, delivered for 2 weeks and 8 h per day) significantly reduced muscle spasm and pain in MS patients, while insufficient TENS treatment (2 weeks and 1 h per day) did not produce analgesic effects [98]. In a randomized, placebo-controlled clinical trial, after 6-week (twice a day and 45 min each time) treatment, both acupuncture-like TENS (4 Hz) and conventional TENS (110 Hz) have a positive influence on clinical outcomes (including pain) in MS patients with chronic low back pain [99].

Spinal Cord Injury

About 77.7% of patients with SCI experienced moderate to severe pain [100], and neuropathic pain caused by SCI can be roughly separated into two classes: at-level and below-level neuropathic pain. The below-level neuropathic pain located in dermatomes below the SCI is considered as a CNP, and the at-level neuropathic pain located in dermatomes of SCI is a PNP (nerve injury in the root) and/or CNP (nerve injury in the dorsal horn) [11]. After receiving 2-week treatment (three times per day, 30~40 min per time), conventional TENS (80 Hz) and acupuncture-like TENS (burst of 2 Hz) achieved analgesic effects in 29% and 38% of SCI patients, respectively [101]. The efficiency of acupuncture-like TENS for relieving neuropathic pain in SCI patients was also confirmed using different treatment strategies, e.g., 10 days, 30 min per day [102], and 12 weeks, 3 times per week, 20 min per time [76]. Combination of TENS (80 Hz for 2 weeks, 5 times a week and 30 min a day) and visual illusion (2 weeks) was suggested in clinical practice as an alternative or supportive treatment for pain in SCI patients [103].

Central Post-Stroke Pain (CPSP)

CPSP is one of the most common forms of CNP [104], and the overall incidence of CPSP ranges from 2% to 8%. The risk of CPSP is mostly associated with the location of the stroke, and patients with lateral medullary (Wallenberg syndrome) and thalamic strokes have the highest incidence of CPSP [105, 106]. In an early study, researchers found that conventional TENS and acupuncture-like TENS applied on the contralateral and/or ipsilateral sides of the site of the stroke could relieve pain in a large proportion of patients [107]. However, TENS could also temporarily enhance pain in 1/3 of the patients [107]. In a systematical review, it was found that TENS could increase the painless range of passive humeral lateral rotation and reduce the severity of glenohumeral subluxation, although

it could not relieve the upper limb spasticity and the post-stroke shoulder pain [108]. In a recent review, researchers pointed out that existing evidence to support the effectiveness of TENS for relieving CPSP is still not enough [20••]. On the contrary, some researchers found that TENS had positive effects on reducing pain and increasing mobility in patients with post-stroke shoulder pain [109, 110], thus suggesting to use TENS as a supportive or alternative treatment for CPSP.

Conclusions

The effects of TENS on relieving neuropathic pain have been proved in most studies, thus, it is recommended as a useful non-pharmacological treatment for CNP and PNP in clinical practice. TENS could be delivered using different parameters, which involves different analgesic mechanisms. Even the analgesic effects of TENS have been widely proven in many basic studies, some conflicting results were reported in clinical practice. This inconsistency could be due to unoptimized stimulus parameters, insufficient and inadequate RCTs, and vague treatment selection strategies (e.g., choose treatments based on the type of disease rather than its mechanism). Therefore, future human studies should be performed to optimize the stimulus parameters of TENS for different clinical conditions. Besides, more multicenter clinical trials should be performed to systematically and conclusively evaluate the analgesic effects of TENS in treating different types of neuropathic pain in clinical practice. Furthermore, advanced neuroimaging techniques, such as electroencephalography, magnetoencephalography, and magnetic resonance imaging, should be adopted to investigate the pathological mechanisms of neuropathic pain and the analgesic mechanisms of TENS. These mechanisms would be important for clinicians to determine the optimized TENS strategy.

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Compliance with Ethical Standards

Conflict of Interest Tahmineh Mokhtari, Qiaoyue Ren, Nuo Li, Faguang Wang, Yanzhi Bi, and Li Hu declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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