

For reprint orders, please contact reprints@expert-reviews.com

EXPERT
REVIEWS

Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain

Expert Rev. Neurother. 11(5), 735–753 (2011)

Mark I Johnson^{1,2} and
Jan M Bjordal^{3,4}

¹Faculty of Health and Social Sciences,
Leeds Metropolitan University, Leeds,
LS1 3HE, UK

²Leeds Pallium Research Group,
Leeds, UK

³Department of Physiotherapy, Faculty
of Health and Social Science, Bergen
University College, Bergen, Norway

⁴Section of Physiotherapy Science,
Department of Public Health and
Primary Health Care, Faculty of
Medicine, University of Bergen,
Bergen, Norway

[†]Author for correspondence:

Tel.: +44 113 283 2600

Fax: +44 113 283 3124

m.johnson@leedsmet.ac.uk

The management of neuropathic pain is challenging, with medication being the first-line treatment. Transcutaneous electrical nerve stimulation (TENS) is an inexpensive, noninvasive, self-administered technique that is used as an adjunct to medication. Clinical experience suggests that TENS is beneficial providing it is administered at a sufficiently strong intensity, close to the site of pain. At present, there are too few randomized controlled trials on TENS for neuropathic pain to judge effectiveness. The findings of systematic reviews of TENS for other pain syndromes are inconclusive because trials have a low fidelity associated with inadequate TENS technique and infrequent treatments of insufficient duration. The use of electrode arrays to spatially target stimulation more precisely may improve the efficacy of TENS in the future.

KEYWORDS: chronic pain • electrode array • gate-control theory of pain • neuromodulation • neuropathic pain • randomized controlled clinical trial • systematic review • transcutaneous electric nerve stimulation • TENS

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive self-administered technique that delivers pulsed electrical currents through the intact surface of the skin to activate peripheral nerves (FIGURE 1) [1]. Electrophysiological evidence suggests that TENS-induced afferent activity inhibits onward transmission of nociceptive information in the CNS, and this generates hypoalgesia in healthy humans exposed to non-injurious experimentally-induced pain and pain relief in pain patients [2]. There is widespread use of TENS for acute and chronic pain, yet clinical effectiveness remains in doubt and recommendations for clinical practice appear inconsistent [3]. The UK National Institute for Health and Clinical Excellence (NICE) recommended that TENS should be offered for short-term relief of pain associated with osteoarthritis [4] and rheumatoid arthritis [5], but not for women in established labor [6], or the early management of persistent nonspecific low back pain [7]. By contrast, the North American Spine Society concluded that TENS should be

offered for chronic low back pain because it provided immediate short-term reductions in pain intensity [8].

Recently, attention has been focused on the use of TENS for painful neurological conditions [9–12]. Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system is termed neuropathic pain syndrome [13], and it affects 7–10% of adults in Europe [14]. Management of neuropathic pain is challenging and involves treatment of the underlying disease, and symptom control using systemic medication and regional treatments. First-line treatments for neuropathic pain are tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitor antidepressants, gabapentin and pregabalin. Second-line treatments are strong opioids, including tramadol, although these may be used as first-line treatments for exacerbations of pain [15–17]. Regional treatments are sometimes used on their own or in combination with systemic medication as they are better tolerated than systemic medication. For example, topical

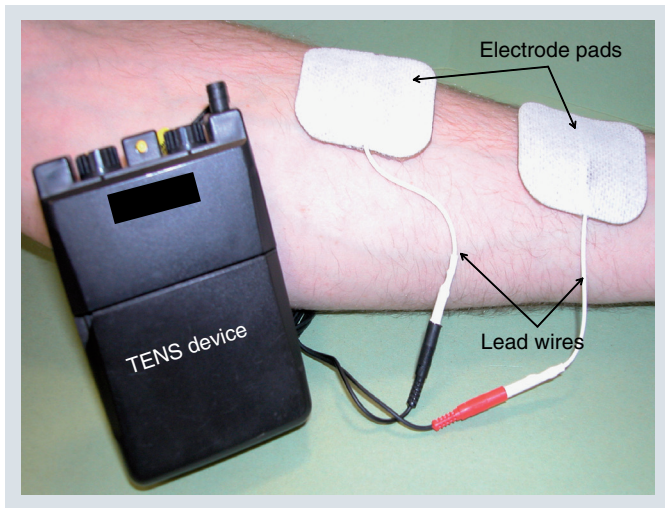


Figure 1. A standard transcutaneous electrical nerve stimulation device.

TENS: Transcutaneous electrical nerve stimulation.

lidocaine is recommended as a first-line treatment for post-herpetic neuralgia (PHN) and where there are concerns about CNS side effects from oral medication (e.g., in the elderly). Regional treatments include regional anaesthetic techniques, such as sympathetic nerve blocks, epidurals and intrathecal pumps; rehabilitation techniques, such as splinting, bracing and exercises; and stimulation-induced analgesia techniques, such as acupuncture, massage, low-level laser therapy, spinal cord stimulation and TENS.

Expert opinion suggests that TENS relieves neuropathic pain when skin sensation is preserved [18–20], although a prospective, randomized, placebo-controlled trial found that individuals with peripheral neuropathic pain (and with osteoarthritis and related disorders of the vertebral column) were less satisfied with TENS than individuals with pain associated with injuries of bone and soft tissue (especially postsurgical pain disorder) [21]. The purpose of this article is to critically review the current uncertainty about the effectiveness of TENS, with particular reference to neuropathic pain.

Principles of TENS

The use of electricity to relieve pain dates back to 2500 BC when the Ancient Egyptians used electric fish to treat various ailments. In 1965, the gate-control theory of pain provided a rational mechanism of action for pain relief by electrically stimulating the skin [22], and clinical observations confirmed that pain relief could be obtained by stimulating the skin, the dorsal columns [23] and structures on the descending pain inhibitory pathways, such as the periaqueductal gray in the

midbrain [24]. TENS was used to predict the success of spinal cord stimulation implants until it was realized that TENS could be used successfully as a treatment in its own right [25].

Nowadays, TENS devices can be purchased without prescription from pharmacy stores or over the internet in many countries and it is prescribed by pain clinicians for symptomatic relief of pain of any origin [26]. TENS can be used as a stand-alone treatment or in combination with pain medication to reduce drug dosage, side effects and costs [27,28]. It has also been used successfully for children as young as 4 years of age [29] and in the management of nonpainful conditions, including alleviating incontinence [30], constipation [31], the progression of dementia [32], postoperative nausea and vomiting [33], and to facilitate wound healing [34], skin-flap survival [35] and bone healing when delivered as micro-ampere currents [36]. The evidence for success in these conditions is inconclusive.

TENS techniques

By strict definition, any technique that delivers electricity across the intact surface of the skin to activate underlying nerves is TENS, although in healthcare the term is used to describe stimulation using a 'standard TENS device' (FIGURE 2). Standard TENS devices are portable battery-powered machines that produce biphasic pulsed electrical currents up to 60 milliamperes (mA) in amplitude, pulse widths (durations) of 50–500 μ s, pulse rates (frequencies) of 1–250 pulses per second (pps) and various pulse patterns (modes), including continuous (normal), burst (intermittent trains of pulses) and modulated amplitude, modulated frequency and modulated pulse duration.

Lead wires take the currents from the TENS device to reusable self-adhering electrode pads made of knitted stainless steel attached to the intact surface of the skin. Commonly, square electrodes 50 \times 50 mm are used, although a variety of other shapes

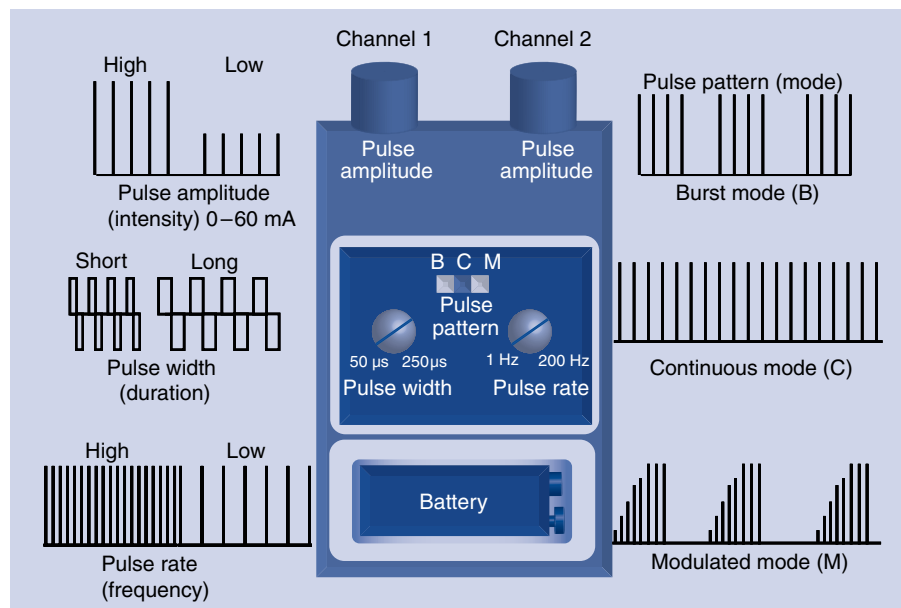


Figure 2. Electrical characteristics of a standard transcutaneous electrical nerve stimulation device.

and sizes of electrodes are readily available. The cathode activates the axonal membrane, so the cathode electrode (normally the black lead) is placed proximal to the anode for monophasic waveforms, although nowadays, most TENS devices use biphasic waveforms with zero net current flow between the electrodes to prevent skin irritation. There is tentative evidence that smaller electrodes (8 × 8 mm) are more comfortable for stimulating superficial nerves lying at depths of 1 mm in the skin and larger electrodes (41 × 41 mm) for stimulating nerves at depths of 11 mm [37]. Glove, sock and belt electrodes are available [38] and electrode arrays have been developed to spatially target stimulation more precisely [39]. The proliferation of TENS-like devices over the last few decades appears to have been driven by developments in technology, rather than proven efficacy or biological rationale (TABLE 1). Evidence suggests that a standard TENS device is most likely to be efficacious in the first instance [40].

The main techniques that are administered using a standard TENS device are conventional TENS (low-intensity, high-frequency) and acupuncture-like TENS (AL-TENS; high-intensity, low-frequency) (TABLE 2). The purpose of conventional TENS is to stimulate low threshold non-noxious afferents (e.g., A-β fibers) without concurrently activating high-threshold noxious afferents (A-δ and C fibers [41]). Activity in A-β afferents reduces transmission of pain-related information in the spinal cord and brainstem (see ‘Mechanism of action’ section). A strong, comfortable, non-painful electrical paresthesia beneath the electrodes or in the painful area is indicative of selective A-β activity and patients titrate current amplitude to achieve this effect. Frequencies of between 10 and 200 pps, with a continuous pulse pattern, are commonly used during conventional TENS, although patients often experiment with stimulator settings to maintain the most comfortable stimulation for that moment in time.

Table 1. Examples of transcutaneous electrical nerve stimulation-like devices.

Device	Characteristics
Action Potential Simulation (APS)	Monophasic square pulse with exponential decay delivered by two electrodes. Pulse amplitude low (<25 mA), duration long (800 μs – 6.6 ms), frequency fixed at 150 pps
Codeatron	Pulsed square wave delivered randomly to one of six electrodes. Pulse amplitude low, duration long (1 ms), frequency low (2 pps)
H-Wave Stimulation	‘Unique’ biphasic wave with exponential decay delivered by two electrodes. Pulse amplitude low (<10 mA), duration long (fixed at 16 ms), frequency low (2–60 pps)
Interferential therapy (Interference currents)	Two out-of-phase currents that interfere with each other to generate an amplitude-modulated wave. Traditionally, delivered by four electrodes; some devices have amplitude-modulated waves that are premodulated within the device (two electrodes). Pulse amplitude low, amplitude-modulated frequency 1–200 Hz (carrier wave frequencies ~2–4 KHz)
Microcurrent, including transcranial stimulation and ‘acupens’	Modified square direct current with monophasic or biphasic pulses changing polarity at regular intervals (0.4 s) delivered by two electrodes. Pulse amplitude low (1–600 μA with no paresthesia), frequency depends on manufacturer (1–5000 pps). Many variants exist (e.g., transcranial stimulation for migraine and insomnia; acupens for pain)
Transcutaneous spinal electroanalgesia (TSE)	Differentiated wave delivered by two electrodes positioned on the spinal cord at T1 and T12 or straddling C3–C5. Pulse amplitude high, yet no paresthetic sensation generated, duration very short (1.5–4 μs), frequency high (600–10,000 pps)
Pain®Gone	Hand-held pen device using piezoelectric elements to deliver a low-ampere, high-voltage, single monophasic spiked pulse (e.g., 6 μA/15000 V) Delivered by giving 30–40 individual shocks at the site of pain or on acupuncture points to generate non-noxious to mild noxious pin-prick sensation – repeated whenever pain returns
InterX®	High-amplitude, short pulse width, dynamic waveform delivered by closely spaced metal electrodes moved across the surface of the skin. Technology claimed to identify changes in tissue properties to identify optimal treatment locations
Limoge current	High-frequency pulses interrupted with repetitive low-frequency cycles delivered by three electrodes (negative electrode between eyebrows and two positive electrodes in retro-mastoid region). Claimed to potentiate the effects of opiates
Salutaris TENS	Dual channel stimulator delivering high- (95 Hz) and low- (4 Hz) frequency pulsed currents delivered by two electrodes using pulse widths of 100 μs or 280 μs and current output up to 70 mA (into a 1-Kohm load). Uniqueness appears to be the use of a rising edge correction circuit, which reduces the ramp time of impulses
MC5-A Calmare (Calmare® Pain Therapy Treatment)	A large trolley-based device that uses surface electrodes to simultaneously treat multiple pain areas using ‘scrambler therapy’. Unable to find details of the output specifications of the device. Technology is claimed to substitute pain information with synthetic nonpain information (Transcutaneous Electrical Modulation Pain Reprocessor)

pps: Pulses per second; TENS: Transcutaneous electrical nerve stimulation.

Table 2. The characteristics of different transcutaneous electrical nerve stimulation techniques.

Characteristic	Conventional TENS	AL-TENS
Goal of peripheral nerve stimulation	Activate cutaneous non-noxious afferents (A- β)	Activate small-diameter cutaneous (A- δ) and muscle (A- δ ; Group III) afferents
TENS sensation	Strong nonpainful TENS paresthesia (minimal muscle activity)	Strong pulsating TENS sensation with simultaneous muscle twitching, at or just below pain threshold
Electrode positions	Straddle site of pain (dermatomal). In presence of hyper- or hypo-sensitive skin, use main nerve bundle or contralateral positions	Over muscle belly or motor nerves (myotomal) at site of pain. In presence of hyper- or hypo-sensitive skin, use main nerve bundle or contralateral positions Trigger points or acupuncture points sometimes used
Pulse amplitude (intensity)	Sufficient to achieve nonpainful TENS sensation – usually no more than 60 mA (low intensity)	Sufficient to achieve nonpainful pulsating TENS sensation or nonpainful muscle twitching – usually no more than 70 mA (high intensity)
Pulse frequency (rate)	High (10–200 pulses per second) determined by patient preference	Low (<5 pulses per second or <5 bursts [trains] per second of high-frequency pulses)
Pulse width (duration)	Between 50–200 μ s determined by patient preference	Between 100–200 μ s. Lower pulse width will generate a weaker TENS sensation yet still create muscle twitching
Pulse pattern (mode)	Continuous in first instance but determined by patient preference	Burst or amplitude modulated in first instance. If delivering low-frequency single-pulsed currents then use continuous
Dose	Use whenever pain relief is required. Can be used throughout the day although have a break every hour or so	Use for no more than 30 min at a time a few times each day as muscle fatigue may develop resulting in delayed-onset muscle soreness the following day
Time course of pain relief	Rapid onset and offset of effects. Pain relief tends to be via segmental mechanisms (i.e., spinal gating)	Rapid onset, delayed offset of effects. Pain relief tends to be a combination of segmental (i.e., spinal gating) and extrasegmental mechanisms (i.e., descending pain inhibitory pathways)

AL-TENS: Acupuncture-like transcutaneous electrical nerve stimulation; TENS: Transcutaneous electrical nerve stimulation.

The purpose of AL-TENS is to activate A- δ afferents from deeper (muscular) structures in order to release opioid peptides in the CNS [42,43]. AL-TENS is a form of ‘hyperstimulation’ and is delivered using high-intensity currents (maximum tolerable sensation) at a low frequency (either single pulses <5 pps or <5 Hz bursts of high-frequency pulses [\sim 100 pps] [41]). AL-TENS is delivered at painful sites, on acupuncture points, and over muscles, motor points and trigger points. There has been debate about whether muscle twitching is a prerequisite for AL-TENS [43]. Clinical practice is variable and the presence or otherwise of muscle twitching will depend on whether electrodes are positioned over muscles or motor nerves.

It is claimed that AL-TENS is useful for patients resistant to conventional TENS and for patients with radiating neurogenic pain, pain associated with altered skin sensitivity and pain arising from deep structures [44].

Other types of TENS include ‘Acu-TENS’ to describe TENS on acupuncture points using a wide variety of parameters [45] and ‘intense TENS’ to describe high-frequency painful TENS given for short durations for wound-dressing changes, suture removal and venepuncture.

Adequate TENS technique

The critical factors in TENS outcome are electrode position and pulse amplitude (intensity), with evidence suggesting that an adequate TENS technique is achieved when a strong nonpainful TENS sensation is produced within the site of pain [27,46].

Optimal electrode placement

In clinical practice, TENS electrodes are usually positioned over the site of pain so that the TENS sensation covers the pain (FIGURE 3). However, this may not be appropriate for neuropathic pain as TENS may aggravate tactile allodynia and dysesthesias. Paradoxically, this is not always the case. In addition, it may be difficult to achieve TENS paresthesia when there is diminished skin sensitivity from nerve damage (e.g., numbness following peripheral neuropathy). In these circumstances, electrodes are positioned over nerves that are proximal to the site of pain. Sometimes it is possible to project TENS sensations into distal body parts, for example, into phantom limbs to relieve phantom limb pain.

There have been relatively few studies that have systematically compared different electrode sites on outcome. Cheing and Chan found that TENS over acupuncture points or over peripheral nerves was superior to placebo (no current) TENS at elevating mechanical pain thresholds in healthy humans, although there were no differences in the magnitude of response between the two active TENS interventions [47]. Brown *et al.* found no differences in the relief of ischemic pain in the arm in healthy humans during the submaximal effort tourniquet technique when TENS was administered at the site of pain, compared with a location not related to pain (contralateral lower leg) [48]. A series of studies by Chesterton and colleagues using pressure algometry in healthy humans [49–51] suggest that TENS outcome is due to

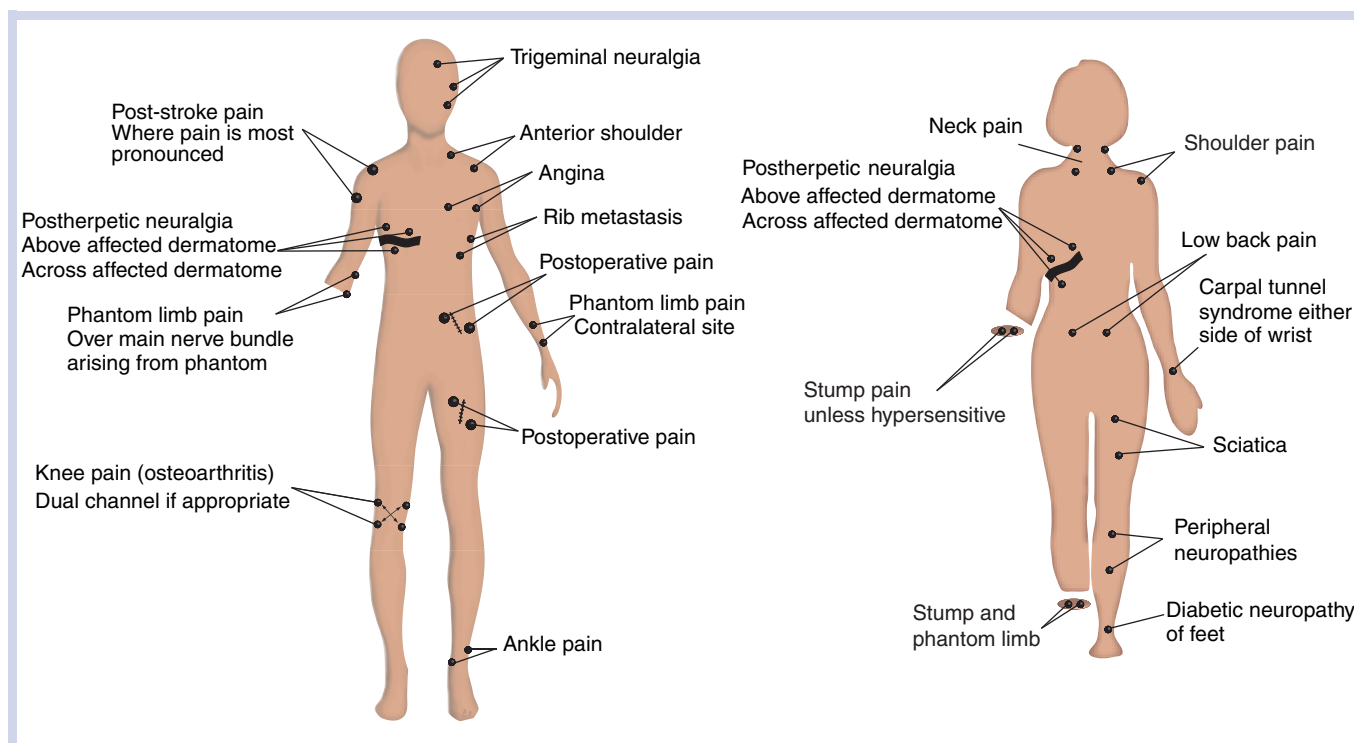


Figure 3. Common electrode-placement sites during conventional transcutaneous electrical nerve stimulation.

a combination of site, intensity and frequency, and that TENS at segmental and extrasegmental sites can generate hypoalgesia, providing that sufficiently high-intensity stimulation is used, regardless of frequency.

Optimal TENS amplitude (TENS intensity)

Studies using healthy pain-free human volunteers exposed to non-injurious experimental pain have found that strong nonpainful TENS is superior to barely perceptible TENS [52–54], implying that patients need to learn to titrate current to achieve a strong nonpainful sensation. The intensity of interferential current therapy, which delivers sinusoidal currents across the intact surface of the skin in a similar manner to TENS, has been demonstrated to fade during treatment [55]. Thus, TENS users should increase amplitude to maintain a strong nonpainful TENS.

Optimal TENS frequency & pulse width

Electrophysiological research suggests that different TENS frequencies activate different neurophysiological mechanisms [56], although a systematic review of human studies concluded that hypoalgesia during strong nonpainful TENS was not influenced by pulse frequency [57]. Most of the human studies were underpowered, and recent appropriately powered studies have found that strong nonpainful TENS at 80 pps was superior to 3 pps stimulation at reducing experimental mechanical pain and ischemic pain in healthy participants [58,59], yet 3 pps was superior to 80 pps for cold-pressor pain [60]. Long-term TENS users demonstrate preferences for TENS frequencies based on the comfort of TENS sensation, with evidence of a relationship between

frequency and the magnitude of analgesia and/or medical diagnosis being limited [21,61]. Reducing pulse width (duration) can aid the passage of currents through the skin, leading to stimulation of deeper nerves, which can be useful when attempting to stimulate muscles without generating a strong TENS sensation in the skin.

Optimal dosage

Evidence suggests that pain relief is rapid in onset and offset, and that maximal benefit occurs during stimulation, with successful long-term TENS users administering TENS for many hours each day [61]. Over 50% of chronic pain patients who try TENS gain short-term benefit from TENS, but this declines in the long-term because effects wear off over time and/or the effort to use TENS regularly is disproportionate to the amount of pain relief obtained [62–64]. Animal studies suggest that repeated use of TENS leads to opioid tolerance [65], with cholecystokinin [66] and NMDA receptors [67] involved, and that this may lead to a reduction in hypoalgesia in humans [68]. The use of modulated patterns of TENS may reduce habituation and tolerance [69–71]. It has been suggested that delivering strong nonpainful TENS punctuated with intense TENS may be useful for background pain with incidents of breakthrough pain [72].

Contraindications & precautions for TENS

Active implants such as pacemakers and ventricular assist devices (artificial hearts) are absolute contraindications for TENS [73]. TENS also produces inadvertent shocks with internal cardiac defibrillators [74] and generates artefacts on fetal monitoring equipment [75]. In exceptional circumstances, TENS has been used in

these situations, using electrode positions that are distant from the chest following approval from the medical specialist [76]. TENS should not be administered on the neck or head in individuals with epilepsy, or close to bleeding tissue, malignancy (except in palliative care), active epiphysis or on the abdomen during pregnancy [201]. Care should be taken when TENS is administered for patients with metal implants, stents, percutaneous central catheters or drainage systems, and close to transdermal drug delivery systems. Adverse events from TENS appear to be rare and are due to inappropriate technique [77–80]. TENS worsens pain in some individuals, may produce mild erythema and produce a vasovagal response, leading to nausea, dizziness and even syncope.

Mechanism of action

In recent years, much attention has been paid to quantitative sensory testing to characterize the spectrum of sensory abnormalities in neuropathic pain patients, with a view to developing a mechanism-based classification system [81,82]. Nerve injury causes sustained amplification of normal sensory input via peripheral and central sensitization, ectopic impulse generation due to expression of ion channels (Na^+), neurotransmitters and receptors, and re-organization of neural connections [83]. TENS may interact with many of these physiological processes underlying neuropathic pain because it has effects on peripheral, spinal and supraspinal structures (FIGURE 4).

Electrophysiological studies provide strong evidence that TENS inhibits nociceptive transmission cells (i.e., nociceptive-specific and wide dynamic range neurons) that are spontaneously active or responding to evoked noxious stimuli [84–87]. High-frequency TENS applied close to an inflamed area at an intensity just below motor threshold reduced central sensitization in rats [88], although to date there has been little research on the effects of TENS on central sensitization induced by nerve injury. Inhibition disappears within 1 h of TENS being switched off, although when TENS recruits higher threshold peripheral A- δ fibers, central nociceptive cell inhibition persists and lasts up to 2 h poststimulation [72,89]. Large-diameter primary afferent fibers from deep tissue appear to produce stronger antihyperalgesia during TENS than cutaneous fibers [90]. TENS effects are mediated, in part, via supraspinal structures, such as the ventrolateral periaqueductal gray, which sends projections to the rostroventromedial medulla and to the spinal cord [91]. Brain imaging studies have found that TENS modulates excitability in pain-related cortical areas, including the primary and secondary somatosensory regions, primary motor cortex, supplementary motor cortex and the parahippocampal gyrus [92,93].

Behavioral studies using models of joint inflammation in rats have demonstrated that TENS at motor threshold reduced flexion reflexes and increased tail flick latencies to noxious heat and mechanical stimuli, suggesting that TENS reduces primary and secondary hyperalgesia [90,94–96]. Interestingly, TENS did not reduce edema in this inflammatory model [97] and the antihyperalgesic effects of low-frequency TENS appear to persist longer than high-frequency TENS [98]. Serotonin, noradrenaline and μ -opioid receptors appear to be involved in the antihyperalgesic

effects of low-frequency TENS and GABA, noradrenaline and δ -opioid receptors in the antihyperalgesia mediated by high-frequency TENS [94,99,100]. TENS has also been demonstrated to reduce hyperalgesia in an inflamed limb when applied to the contralateral uninjured limb [98,101], and when given repeatedly in arthritic rats, opioid tolerance has been demonstrated [65], with cholecystokinin receptors involved [66].

Studies on TENS actions using models of neuropathic pain are less common. Leem *et al.* found that low-frequency, high-intensity TENS (2 Hz, 4–5 mA) applied to somatic receptive fields reduced the responses of sensitized wide dynamic range neurons to brush and pinch stimuli in a rat model of peripheral neuropathy induced by a tight ligation of L5–6 spinal nerves [87]. These effects persisted for 30–45 min for brush stimuli and 60–90 min for pinch after TENS had been switched off. Hanai found that TENS of the posterior tibial nerve and sciatic nerve inhibited responses of wide dynamic range neurons in the lumbosacral dorsal horn to C-fiber input in anesthetized cats [102]. Nam *et al.* found that low-frequency, high-intensity TENS reduced injury-induced mechanical allodynia but not cold hyperalgesia in rats with nerve injury [103]. TENS appeared to operate via an endogenous opioid system that was dependent on whether or not the pain was mediated by sympathetic activity.

A series of studies by Somers and Clemente using rats with chronic constriction injuries to the sciatic nerve found that daily high-frequency TENS prevented thermal, but not mechanical, allodynia [104], although follow-up studies found that high-frequency TENS reduced mechanical allodynia when TENS was delivered on the side contralateral to the injury [105]. This suggested that early intervention with TENS contralateral to a nerve injury with a combination of high- and low-frequency TENS may reduce allodynia in humans with neuropathic pain. They also found that high-frequency TENS elevated the synaptosomal content of GABA bilaterally in the dorsal horn and a combination of high- and low-frequency TENS elevated the axon terminal content of aspartate, glutamate and glycine [106,107]. Thus, different TENS parameters affect the CNS neuropharmacology and the responsiveness of TENS to allodynia in different ways.

Transcutaneous electrical nerve stimulation also reduces nociceptive input to the CNS via a 'busy-line' effect in peripheral nerves [108,109]. This is achieved by antidromic impulses, traveling toward the periphery, which have been generated by TENS, colliding and extinguishing orthodromic impulses arising from nociceptors, mechanoreceptors and thermoreceptors in response to injury. Antidromic activity in smaller diameter afferents caused by high-intensity TENS will generate axon reflexes and the release of substance P and calcitonin gene-related peptide (CGRP) at the distal ends of sensory receptors. Changes in activity in blood vessels, sweat glands and mast cells resulting from axon reflexes have been suggested as a putative mechanism for the tissue-healing effects of TENS [110,111]. TENS also affects autonomic efferent activity, which may lead to increased blood flow and sweat responses in the peripheral tissues [112]. Studies on the effects of TENS on the sympathetic division of the autonomic nervous system are therefore conflicting [113,114].

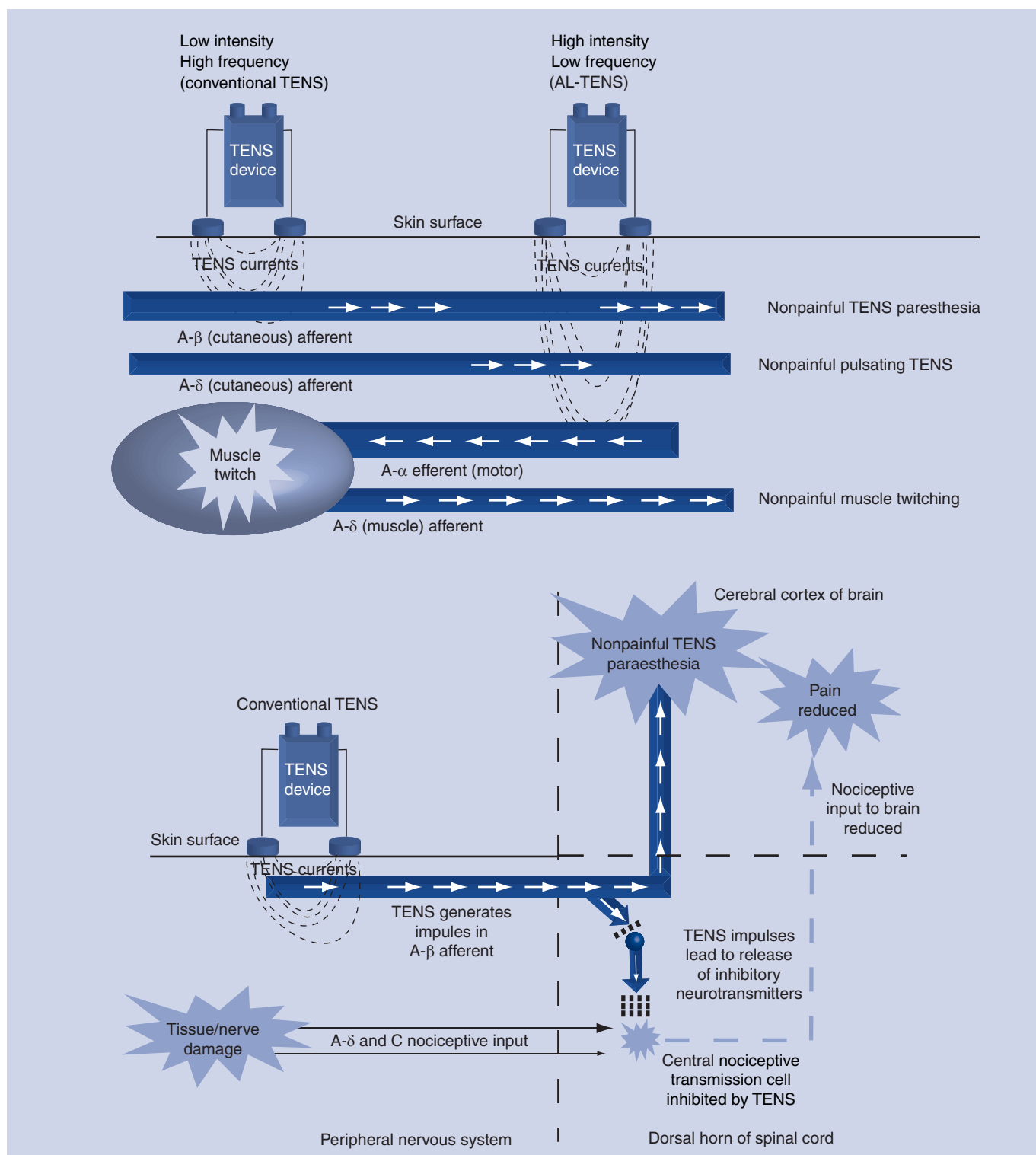


Figure 4. Mechanism of action of transcutaneous electrical nerve stimulation. The white arrows indicate nerve impulses. AL-TENS: Acupuncture-like transcutaneous electrical nerve stimulation; TENS: Transcutaneous electrical nerve stimulation.

Electrical stimulation techniques have been demonstrated to regenerate soft tissue [115], skin [34] and bone [116,117]. This seems to be dependent on various factors, including characteristics of currents, site of stimulation, type of electrodes and the timing

of stimulation. Evidence suggests that TENS delivered above 10 mA may hinder tissue regeneration by reducing ATP concentrations [118]. Baptista *et al.* investigated the effect of high- and low-frequency TENS delivered at or just below motor threshold,

delivered for 30 min a day, 5 days a week, for 5 weeks, on nerve regeneration following crush lesions in mice [119]. When compared with a no stimulation control TENS was found to impair nerve regeneration, producing more axons with dark axoplasm, signs of edema, less organized cytoarchitecture, fewer and thinner myelinated fibers and an increase in the number of Schwann cell nuclei. However, Static Sciatic Index values did not differ between the groups. Gigo-Benato *et al.* generated sciatic nerve crush injuries in rats and delivered six sessions of TENS every other day from 3 days postinjury to day 14, using a variety of electrical characteristics on the tibialis anterior muscle [120]. TENS delivered at amplitudes to induce a visible contraction increased muscle fiber atrophy and decreased muscle excitability and functional recovery at day 14 postinjury compared with no stimulation.

Transcutaneous electrical nerve stimulation delivered at micro-ampere amplitudes using microcurrent therapy devices (e.g., 1–1000 μ A) appears to facilitate tissue healing [121]. For example, Alrashdan *et al.* reported that 30 min of microcurrent (20-Hz pulse rate, 2- μ A amplitude) applied directly over a crushing injury to the sciatic nerves of rats could improve nerve regeneration when compared with a no stimulation control [122]. Microcurrent improved functional and sensory recovery 3 weeks after injury, with higher values for sciatic functional index, mean conduction velocity, the number of retrogradely labeled sensory neurons, axon counts and myelin thickness. Microcurrents delivered using invasive techniques have produced similar findings. Mendonca *et al.* found delayed axonal degeneration, accelerated nerve sprouting, myelin sheath regeneration and an increased number and diameter of vasa nervorum, following direct currents at 1 μ A delivered by an anode fixed to muscles proximally and a cathode fixed below the nerve, distally to the lesion site [123]. Lu *et al.* found that low-frequency (2 Hz) percutaneous electrical stimulation augmented regeneration between proximal and distal nerve stumps when administered at 1 and 2 mA, yet 4 mA hindered regeneration of the nerves [124]. Thus, there appears to be a therapeutic window for current intensity for regeneration of nerve fibers.

Studies using rat models of sciatic nerve injury have demonstrated that low-frequency alternating-current electrical stimulation (2 or 20 Hz), via implanted or percutaneous electrodes, accelerates axon outgrowth from proximal nerve stumps to distal nerve stumps to accelerate the time for muscle reinnervation and reduce facilitation of spinal motor response [125,126]. Tyrosine kinase B receptors and their ligands, BDNF and NT4/5 seem to have a role in response [127–140]. Low-frequency stimulation of proximal nerves has been demonstrated to regenerate median nerves following carpal tunnel release surgery so that they reinnervate thenar muscles within 6–8 months, compared with failure of reinnervation in nontreated individuals [131].

Clinical effectiveness

Neuropathic pain

There is a vast research literature on TENS, with over 1000 hits for clinical trials, over 700 hits for randomized controlled clinical trials (RCTs) and over 30 hits for meta-analyses identified during an unfiltered search on the PubMed database using the

medical subject heading (MeSH) term ‘transcutaneous electric nerve stimulation’ (1 December 2010). Expert opinion suggests that neuropathic pain responds well to TENS, with peripheral neuropathic pain responding better than central neuropathic pain [18]. Benefit has been reported for PHN, trigeminal neuralgia, phantom limb and stump pain, radiculopathies (cervical, thoracic and lumbar), diabetes, HIV-associated neuropathy, complex regional pain syndromes, entrapment neuropathies, such as carpal tunnel syndrome, cancer pain and its treatment, including pain from nerve compression by a neoplasm and infiltration by a tumor and postsurgical pain, central post-stroke pain, spinal cord injury pain, spinal surgery and multiple sclerosis. There is a case report of long-term remission of neuropathic pain following TENS [132]. Many of these clinical reports lack control groups, and although they can be a rich source of documented clinical experience about the usefulness of TENS, they cannot prove that beneficial effects were due to electrical currents *per se*.

Placebo-controlled RCTs using sham TENS devices with no current output are used to isolate the effects of electrical currents on pain. To date, there have been no systematic reviews of RCTs evaluating the effectiveness of TENS for neuropathic pain, although a Cochrane protocol for a review has been published [133]. A review of studies by the European Federation of Neurological Societies (EFNS) Task Force for neurostimulation therapy for neuropathic pain found that TENS was superior to placebo, based on nine controlled trials with data extracted for 200 patients with neuropathic pain (TABLE 3) [9]. The methodological quality of the RCTs was low and there were no class I RCTs (i.e., adequately powered prospective RCT with masked outcome assessment in a representative population). Trial reports suggested beneficial effects of TENS compared with placebo TENS for painful diabetic neuropathy [134–136], peripheral mononeuropathies of traumatic origin [137,138], painful cervical radiculopathy [139] and chronic pains, including neuropathic elements [140]. One small RCT found no benefit for PHN [141] and one study found reductions in painful diabetic neuropathy, although this was using percutaneous electric nerve stimulation rather than TENS [142]. EFNS recommended that TENS may be useful as a preliminary or add-on therapy as it was noninvasive, safe and could be self-administered, based on level C evidence (i.e., possibly effective based on at least two convincing class III nonrandomized controlled trials).

Peripheral neuropathic pain conditions

Painful diabetic peripheral neuropathy

It is estimated that between 26 and 47% of patients with diabetes present with neuropathy, and that 26.8% of participants with diabetes present with neuropathic pain [143]. Studies using models of diabetes in rats suggest that electrical stimulation can normalize nerve conduction velocities and improve endoneurial blood flow [144]. A meta-analysis of three RCTs (78 patients) claimed that TENS was superior at reducing mean pain scores compared with placebo (no current) TENS at 4- and 6-week follow-up and improved overall neuropathic symptoms measured at 12-week follow-up. The reviewers concluded that TENS was safe and effective

Table 3. Systematic reviews of transcutaneous electrical nerve stimulation for pain relief.

Study (year)	Condition	Data set and analysis	Reviewers' conclusion	Comment	Ref.
<i>Acute pain</i>					
Walsh <i>et al.</i> (2009) Cochrane review	Acute pain	12 RCTs (919 patients) Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes	[162]
Carroll <i>et al.</i> (1996)	Postoperative pain	17 RCTs (786 patients) Descriptive analysis	Evidence of no effect	Comparison groups consisted of active and inactive interventions. Patients allowed free access to analgesic medication in some RCTs	[165]
Bjordal <i>et al.</i> (2003)	Postoperative analgesic consumption	21 RCTs (964 patients) Meta-analysis	Evidence of effect	Demonstrated that adequate TENS technique was critical for effect	[27]
Freyne <i>et al.</i> (2010)	Post-thorocotomy pain	Nine RCTs (645 patients) Descriptive analysis	Evidence of no effect as stand-alone treatment Evidence of effect as adjuvant	Most studies low-quality with small sample sizes	[166]
Carroll <i>et al.</i> (1997)	Labor pain	Ten RCTs (877 patients) Descriptive analysis	Evidence of no effect	Comparison groups consisted of active and inactive interventions. Patients allowed free access to analgesic medication in some RCTs	[187]
Dowswell <i>et al.</i> (2009) Cochrane review	Labor pain	19 RCTs (1671 patients) Descriptive analysis	Evidence inconclusive	Low-quality studies	[164]
Proctor <i>et al.</i> (2003) Cochrane review	Primary dysmenorrhea	Seven RCTs, (213 patients) Descriptive analysis	Evidence of effect – pain relief for high-frequency TENS only	Low-quality studies with small sample sizes	[188]
<i>Chronic pain</i>					
Nnoaham and Kumbang (2008) Cochrane review	Chronic pain	25 RCTs (1281) Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes and possibility of underdosing TENS	[168]
Johnson and Martinson (2007)	Musculoskeletal pain	32 RCTs on TENS, six RCTs on PENS (1227 patients) Meta-analysis	Evidence of effect	Criticized for using multiple diseases creating heterogeneity	[171]
Khadiilkar <i>et al.</i> (2008) Cochrane review	Low back pain	Three RCTs (197 patients) Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes and possibility of underdosing TENS	[189]
Poitras <i>et al.</i> (2008)	Low back pain	Six RCTs (375 patients) Descriptive analysis	Evidence of effect	Low-quality studies with small sample sizes	[8]
Dubinsky and Miyasaki (2010) Expert panel report	Painful neurological conditions Low back pain	Two RCTs (201 patients) Descriptive analysis	Evidence of no effect	Small sample sizes and possibility of underdosing TENS	[11]
Rutjes <i>et al.</i> (2009) Cochrane review	Knee osteoarthritis	18 RCTs (275 patients) Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes with some RCTs not using standard TENS device	[173]
Bjordal <i>et al.</i> (2007)	Knee osteoarthritis	Seven RCTs (414 patients) Meta analysis	TENS effective in short term	Accounted for adequate TENS technique in analysis	[174]
CT: Controlled trial; ES: Electrical stimulation; PENS: Percutaneous electrical nerve stimulation; RCT: Randomized controlled trial; TENS: Transcutaneous electrical nerve stimulation.					

Table 3. Systematic reviews of transcutaneous electrical nerve stimulation for pain relief.

Study (year)	Condition	Data set and analysis	Reviewers' conclusion	Comment	Ref.
<i>Chronic pain</i>					
Brosseau <i>et al.</i> (2003) Cochrane review	Rheumatoid arthritis	Three RCTs (78 patients) Meta-analysis	Evidence of effect	Low-quality studies with small sample sizes	[175]
Robb <i>et al.</i> (2008) Cochrane review	Cancer pain	Two RCTs (64 participants) Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes and possibility of underdosing TENS	[190]
Kroeling <i>et al.</i> (2009) Cochrane review	Neck disorders (whiplash-associated disorders and mechanical neck disorders)	Seven RCTs on TENS (88 patients) Descriptive analysis	Evidence of effect but low-quality studies	Low-quality studies with small sample sizes and possibility of underdosing TENS. Included any surface ES including microcurrent devices	[191]
Bronfort <i>et al.</i> (2004) Cochrane review	Chronic headache	Three RCTs Descriptive analysis	Evidence inconclusive	Low-quality studies with small sample sizes and possibility of underdosing TENS	[192]
<i>Neuropathic pain</i>					
Price and Pandyan (2000) Cochrane review	Post-stroke shoulder pain	Four RCTs (170 patients) of any surface ES	Evidence inconclusive	Low-quality studies with small sample sizes and possibility of underdosing TENS. Two RCTs used TENS to produce muscle contractions	[193]
Cruccu <i>et al.</i> (2007) Task force report	Various neuropathies	Nine CTs (200 patients) Descriptive analysis	Evidence of effect	Low-quality studies with small sample sizes	[9]
Mulvey <i>et al.</i> (2010) Cochrane review	Postamputation pain	Zero RCTs	No evidence available		[147]
Jin <i>et al.</i> (2010)	Painful diabetic neuropathy	Three RCTs (78 patients) Meta-analysis	Evidence of effect	Low-quality studies with small sample sizes. Used nonstandard TENS devices	[10]
Dubinsky and Miyasaki (2010) Expert panel report	Painful neurological conditions Painful diabetic neuropathy	Three RCTs (two RCTs used in evaluation 55 patients) Descriptive analysis	Evidence of effect	Low-quality studies with small sample sizes	[11]

CT: Controlled trial; ES: Electrical stimulation; PENS: Percutaneous electrical nerve stimulation; RCT: Randomized controlled trial; TENS: Transcutaneous electrical nerve stimulation.

for symptomatic diabetic peripheral neuropathy [10]. However, the included studies did not use standard TENS devices. Kumar *et al.* used a H-wave therapy device that delivers currents across the intact surface of the skin using waveforms that differ from a standard TENS device [136]. They found that H-wave therapy (n = 18) administered to lower extremities for 30 min per day for 4 weeks was superior to placebo (no current) H-wave therapy (n = 13) for reducing pain and symptoms of diabetic peripheral neuropathy. In a follow-up study, Kumar *et al.* assessed the efficacy of a 12-week course of H-wave therapy combined with amitriptyline for diabetic peripheral neuropathy and found significant reductions in pain scores during H-wave therapy (n = 14) compared with placebo H-wave therapy (n = 9) [145]. Forst *et al.* assessed a 12-week course of low-frequency TENS using a Salutaris® TENS

device on 19 patients with symptomatic diabetic neuropathy [135]. They applied electrodes over the common peroneal nerve using a stimulation rate of 4 Hz and pulse width of 280 µs, with intensities to produce a strong nonpainful sensation. They found improvements in pain, Neuropathy Total Symptom Score-6 (NTSS-6) scores of numbness, lancinating pain and allodynia compared with placebo (no current). The manufacturers market Salutaris stimulation specifically for the treatment of peripheral diabetic neuropathy, although the electrical output characteristics of the device are similar to those found in a standard TENS device.

An assessment of the use of TENS for painful diabetic neuropathy by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) concluded that TENS was “probably effective” (level B evidence

– i.e., at least one RCT) [11]. This was based on RCTs by Kumar *et al.* [136], Forst *et al.* [135] and Reichstein *et al.* [134], although the assessment has been criticized as only 31 participants in total received TENS and 24 received placebo TENS [3,146].

Other peripheral neuropathic pain conditions

Evidence for the effectiveness of TENS in other peripheral neuropathic pain conditions is limited. A Cochrane review by Mulvey *et al.* found no RCTs on which to judge the effectiveness of TENS for the management of phantom pain and stump pain [147]. Recently, two case studies found improvements in phantom limb pain and sensations following TENS delivered to the contralateral limb that was maintained for at least 1 year [148]. A placebo-controlled RCT on 30 patients with PHN found that a 4-week treatment with TENS reduced pain intensity and sleep interference when combined with pregabalin [149]. A cross-over study on 24 patients with neuropathic pain associated with spinal cord injury failed to detect any difference in ratings of pain intensity, mood, coping or sleep quality between high- (80 Hz) and low-frequency (2-Hz bursts) TENS that was self-administered three times each day for 2 weeks [150]. A placebo-controlled trial on 19 patients with allodynia of the hand found that 2-week treatment with daily high-frequency TENS reduced pain and increased rankings of dowel textures on the Downey Hand Centre Hand Sensitivity Test [137]. There were no significant intergroup differences in grip strength. Interestingly, improvements in tactile sensitivity of the fingers resulting from long-term TENS treatment applied over the median nerve for 1 h per day for 3 weeks has been reported in patients with multiple sclerosis [151].

Two RCTs suggest that TENS may be useful at reducing radicular pain. A single-blinded, randomized, placebo-controlled cross-over trial found that 30 min of low-frequency (4 Hz) TENS or percutaneous electrical nerve stimulation (PENS) given three times per week for 3 weeks decreased pain and daily oral analgesic requirements for radicular pain in 64 patients with sciatica due to lumbar disc herniation [152]. PENS was more effective than TENS in improving physical activity, quality of sleep and Short Form (SF)-36 score, with 73% of patients opting for PENS as the most desirable modality. A prospective, randomized, double-blinded, placebo-controlled study found that a TENS-like device that delivered random electrical pulses or stochastic-frequency pulses was superior than conventional TENS for chronic radicular pain, although only 13 patients took part in the study [139].

Recently, attention has turned to the use of TENS to manage cancer pain, which often presents with neuropathic symptoms. A case series of 16 patients found that 1-h daily interventions of electrical stimulation delivered over 10 working days using a novel TENS-like device (MC5-A Calmare[®]) reduced pain associated with refractory chemotherapy-induced peripheral neuropathy [153]. A feasibility study provided preliminary evidence that TENS may be of benefit for cancer-induced bone pain [154]. However, a Cochrane review failed to find sufficient RCTs to judge the effectiveness of TENS in cancer-related pain [155].

Central neuropathic pain conditions

There are very few clinical trials on the use of TENS for central neuropathic pain and most are nonrandomized or lacking control groups. A Cochrane review on electrical stimulation for post-stroke shoulder pain [156] included four trials that delivered TENS (170 patients), although three of these trials delivered TENS as functional electrical stimulation, with a view of improving motor function to generate muscle contractions [157–159]. One trial found that high-intensity TENS (at 100 Hz) delivered at three-times the sensory threshold was superior, compared with TENS at sensory threshold and placebo (no current) TENS, at relieving hemiplegic shoulder pain and improving passive range of motion for flexion [160]. The Cochrane reviewers concluded that there was insufficient evidence to judge effectiveness of TENS for post-stroke shoulder pain, although there was evidence that TENS may improve passive humeral lateral rotation. Recently, a meta-analysis of eight studies found that functional electrical stimulation and TENS was effective at improving gait speed in post-stroke patients, although it was noted that the type of stimulation device, location of electrodes and dose varied between the studies [161].

TENS & acute pain

Despite the vast research literature on TENS, there is a continuing debate about its effectiveness for acute and chronic pain. A Cochrane review concluded that evidence was inconclusive for acute pain [162], yet supported effectiveness for dysmenorrhea [163]. Evidence was inconclusive for established labor pain [164], with NICE recommending that TENS should not be offered to women in established labor, although it may be beneficial in the early stages of labor [6].

Systematic reviews on TENS for postoperative pain concluded that TENS was not effective [165], although a meta-analysis of 21 RCTs (1350 patients) with a subgroup analysis of 11 trials (964 patients) [27] found larger reductions in analgesic consumption in RCTs using adequate TENS technique (i.e., a strong stimulation at the site of pain). Recently, a systematic review of TENS for relieving acute post-thoracotomy pain, which often includes neuropathic pain elements, found that TENS was superior to placebo TENS as an adjuvant to analgesics for pain relief in seven of the nine included RCTs [166]. The reviewers concluded that TENS was ineffective as a stand-alone therapy for posterolateral thoracotomy incision (severe post-thoracotomy pain), but useful as an adjunct to analgesics for muscle sparing thoracotomy incision (moderate post-thoracotomy pain) and very effective as the sole pain-control treatment in video-assisted thoracoscopy incision (mild post-thoracotomy pain). Evidence also suggested that TENS reduced the duration of the recovery room stay and increasing tolerance to coughing and pulmonary ventilatory function. RCTs suggest that TENS may be beneficial for a wide range of acute pain conditions, including orofacial pain, painful dental procedures, fractured ribs and acute lower back pain, and angina pectoris (for a review, see [167]).

TENS & chronic pain

A similar picture of conflicting evidence emerges for chronic pain. A Cochrane review of 25 RCTs with a total of 1281 participants found that TENS was superior to an inactive TENS control in 13

out of 22 studies [168]. Only one RCT was specifically for neuropathic pain (diabetic neuropathy) [136] and three others included mixed populations of patients [140,169,170]. Reviewers did not perform meta-analysis due to large variations in TENS technique and methodological quality. To date, the largest meta-analysis of TENS was performed from trials on patients with chronic musculoskeletal pain and included 32 RCTs on TENS, six studies on PENS and a total of 1227 patients. Reviewers concluded that TENS and PENS were superior to the placebo control [171]. The review was criticized for combining multiple diseases at the expense of homogeneity, although this approach did increase the statistical power of the analysis [172].

A Cochrane review on osteoarthritic knee pain included 18 RCTs (813 patients), of which 11 RCTs used a standard TENS device, with 275 participants receiving TENS and 190 receiving either placebo or no intervention. Evidence was inconclusive, although the meta-analysis found a large standard-mean difference of -0.85 (-1.36, -0.34) equating to approximately 20 mm on a 100-mm Visual Analogue Scale (VAS) [173]. The magnitude of this effect was consistent with an earlier meta-analysis of seven RCTs delivering TENS at optimal doses that found that TENS reduced pain by 22.2 mm (95% CI: 18.1–26.3) on a 100-mm VAS in the short-term [174]. A Cochrane review of TENS for rheumatoid arthritis of the hand included three RCTs (78 patients), and only two of these compared TENS (27 patients) against a placebo (27 patients) [175]. The evidence was inconclusive. NICE recommended that TENS should be used as an adjunct to core treatment for short-term relief of osteoarthritic knee pain [4] and for rheumatoid arthritis of the hand [5,176].

However, NICE recommended that TENS should not be offered for early management of persistent nonspecific low back pain based on three RCTs conducted by two investigating teams, with 331 participants receiving TENS and 168 receiving placebo TENS [7]. **By contrast, the North American Spine Society recommended that TENS has immediate short-term effects to reduce pain intensity but not in the long-term, which was based on six RCTs with 375 participants receiving TENS and 192 receiving placebo TENS [8].** A Cochrane review of three RCTs with 110 patients receiving TENS and 87 receiving placebo TENS found inconclusive evidence for an effect on pain intensity, although TENS did not improve back-specific functional status, based on two RCTs with 271 participants receiving TENS and 95 receiving placebo. A meta-analysis of several therapies for nonspecific chronic low back pain concluded that the effect size for pain relief for TENS was small, but of a similar magnitude to analgesic medication, including NSAIDs and muscle relaxants [177].

The Therapeutics and Technology Assessment Subcommittee of the AAN concluded that there was level A evidence (i.e., good-quality RCTs) that TENS should not be recommended for the relief of chronic low back pain [11]. The assessment included “clinical trials ... for well-defined painful neurologic disorders...”, although it is debatable whether low back pain is a well-defined painful neurological disorder and it is usually considered as a mixed pain pattern even when radiculopathy is present. There was no mention of neuropathic pain in the analysis. The conclusion was based

on two RCTs, with 114 patients receiving TENS and 87 receiving placebo. One of the RCTs included etiologies not commonly associated with neurological pathology [178], for example, arthritis (30%), and the RCT was criticized at the time of publication for clinical heterogeneity, use of a suboptimal TENS technique and the concurrent use of hot packs, which could have masked the effects of TENS. Interestingly, placebo TENS on its own was associated with considerable improvements in pain up to 2 months postintervention. The other RCT used participants with multiple sclerosis and the original trial authors argued for the presence of clinically important effects from TENS, despite a lack of statistical difference between active and placebo groups, as some participants in the placebo TENS group were taking additional analgesics [179].

Expert commentary

Transcutaneous electrical nerve stimulation is inexpensive, readily accessible, safe and can be self-administered by the patient, and is useful as an adjunct to analgesic medication providing it is administered at a sufficiently strong intensity, close to the site of pain. At present, it seems sensible to try TENS as part of the pain management package for patients with neuropathic pain until sufficient gold standard clinical research says otherwise.

The current focus of research on the translation of pathophysiological mechanisms into sensory signs of neuropathic pain is likely to lead to a more effective and specific mechanism-based treatment approach in the future. TENS is advantageous over systemic interventions because it is better tolerated and can target the neuropathic pain with more precision. Many clinicians consider TENS to be less effective than systemic medication, although there is insufficient good quality evidence to make an informed judgement.

The uncertainty over the effectiveness of TENS for acute and chronic pain has continued for over four decades, despite a continuous flow of new RCTs. Randomized controlled trials on TENS continue to use too few participants, resulting in a failure to provide robust answers (i.e., underpowering the study). A review of 38 RCTs from Cochrane systematic reviews on TENS for acute, chronic and cancer pain quantified significant sources of implementation fidelity, including suboptimal dosing of TENS and inappropriate outcome assessment [180]. Frequently, TENS trials use inadequate TENS technique (i.e., intensity too weak or electrodes placed at inappropriate sites) and infrequent treatments of insufficient duration leading to underdosing. Not measuring TENS effects during stimulation (i.e., using a pre-post assessment) and not monitoring concurrent medication during the trial are also problematic issues. These shortcomings are likely to lead to low fidelity (i.e., bias toward an underestimation of treatment effects) and may account for inconclusive findings.

Blinding of TENS interventions has been a recurrent challenge as it is not possible to truly blind TENS because a prerequisite of adequate TENS technique is the presence of a strong nonpainful TENS sensation. Hence, participants are likely to guess that TENS with no sensation is the placebo intervention. Attempts to reduce this bias include informing participants that some TENS devices generate ‘tingling sensations’, whereas others, such as

microcurrent, do not [60], and the use of transient sham TENS devices that deliver currents to produce a TENS sensation for a short period of time before fading away to zero current output [181]. Nonblinded trials tend to introduce positive bias toward the active intervention, yet paradoxically, systematic review evidence for TENS is inconclusive for most conditions.

There is a need for universally accepted practice guidelines for TENS to reduce variability in clinical trial delivery and *ad hoc* clinical practice leading to a negative impact on patient care.

Five year view

The financial cost of repeating the errors of previous RCTs should be challenged, therefore, there needs to be careful consideration regarding the design of future TENS trials. In future, there needs to be pragmatic trials on TENS that follow similar principles to recent RCTs on acupuncture analgesia, which include thousands of participants [182,183], clear guidelines on adequate dosage [184] and reporting the intervention [185], and authentic placebo controls [186]. Criteria for judging directions of bias in future studies of TENS have been proposed for allocation, application and assessment of TENS interventions in future RCTs [180].

In addition, there is a need for studies assessing patients' experiences of using TENS. This would help to inform practices to calibrate new TENS users about realistic expectations from TENS treatment and ways to help them sustain motivation to continue to

use TENS in the long term. There is tentative evidence that a barrier to effective use is the disproportionate amount of effort needed to regularly apply TENS for the amount of pain relief achieved [63,65], yet there has been limited research on the relationship between patient expectations of TENS with clinical outcome.

Attempts to resolve the perceived awkwardness of applying TENS, such as removing electrode lead wires by clipping the TENS directly onto a single electrode, have met with only partial success. Developments in electronic technology have led to a variety of TENS-like devices on the market, some of which are specifically designed for neuropathic pain. However, the scientific principles on which these devices are designed are tenuous. The development of electrode arrays to spatially target stimulation more precisely may improve the efficacy and efficiency of locating appropriate electrode location [39]. The use of smart electrodes that communicate with the TENS device (current generator) without the need for electrode lead wires are likely to improve adherence and long-term use.

Financial & competing interests disclosure

Mark Johnson has taken part in TENS symposia that have been sponsored by TENS and pharmaceutical companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

Key issues

- Neuropathic pain syndrome affects 7–10% of adults in Europe and management is challenging with first-line treatments being systemic medication and second-line treatments consisting of regional treatments including stimulation-produced analgesic techniques such as transcutaneous electrical nerve stimulation (TENS).
- TENS is a noninvasive self-administered technique that delivers pulsed electrical currents through the intact surface of the skin to activate peripheral nerves.
- There is strong neurophysiological evidence that TENS inhibits transmission of nociceptive information in the CNS with much detail about the neurochemicals involved.
- Clinical experience suggests that TENS is useful as an adjunct to analgesic medication for any type of pain providing it is administered at a sufficiently strong intensity close to the site of pain.
- The findings of systematic reviews are inconclusive or conflicting, leading to uncertainty about the effectiveness of TENS.
- Most trials have low fidelity (i.e., bias toward an underestimation of treatment effects) due to inadequate TENS technique (i.e., intensity too weak or electrodes placed at inappropriate sites), infrequent treatments of insufficient duration, and not measuring TENS effects during stimulation.
- There are few randomized controlled trials on TENS for neuropathic pain, with insufficient evidence to judge effectiveness.
- In the future, the use of smart electrodes using electrode arrays to spatially target stimulation more precisely may improve the efficacy and efficiency of locating appropriate electrode location, without the need for electrode lead wires.
- As TENS is inexpensive, readily accessible, safe and can be self-administered by the patient themselves, it seems sensible for patients to try TENS as part of the pain management package for patients with neuropathic pain until sufficient gold standard clinical research says otherwise.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- 1 Jones I, Johnson MI. Transcutaneous Electrical Nerve Stimulation (TENS). *Cont. Educ. Anaesth. Crit. Care Pain* 9(4), 130–135 (2009).
- 2 DeSantana JM, Walsh DM, Vance C, Rakel BA, Sluka KA. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Curr. Rheumatol. Rep.* 10(6), 492–499 (2008).
- 3 Johnson MI, Walsh DM. Pain: continued uncertainty of TENS' effectiveness for pain relief. *Nat. Rev. Rheumatol.* 6(6), 314–316 (2010).
- 4 National Institute for Health and Clinical Excellence. NICE clinical guideline 59. *Osteoarthritis: the Care and Management*
- Critique of the American Academy of Neurology's assessment of the efficacy of transcutaneous electrical nerve stimulation (TENS) in neurologic disorders (low back pain and diabetic neuropathy), also see [11].

- of Osteoarthritis in Adults. NICE, London, UK, 1–22 (2008).
- 5 National Institute for Health and Clinical Excellence. NICE clinical guideline 79. *Rheumatoid Arthritis: the Management of Rheumatoid Arthritis in Adults*. NICE, London, UK, 1–35 (2009).
 - 6 National Institute for Health and Clinical Excellence. NICE clinical guideline 55. *Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth*. NICE, London, UK, 1–65 (2007).
 - 7 National Institute for Health and Clinical Excellence. NICE clinical guideline 88. *Early Management of Persistent Non-Specific Low Back Pain*. NICE, London, UK, 1–25 (2009).
 - 8 Poitras S, Brosseau L. Evidence-informed management of chronic low back pain with transcutaneous electrical nerve stimulation, interferential current, electrical muscle stimulation, ultrasound, and thermotherapy. *Spine J.* 8(1), 226–233 (2008).
 - 9 Cruccu G, Aziz TZ, Garcia-Larrea L *et al.* EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur. J. Neurol.* 14(9), 952–970 (2007).
 - **Current clinical guidelines from the European Federation of Neurological Societies on the use of TENS for neuropathic pain.**
 - 10 Jin DM, Xu Y, Geng DF, Yan TB. Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: a meta-analysis of randomized controlled trials. *Diabetes Res. Clin. Pract.* 89(1), 10–15 (2010).
 - **Most recent meta-analysis of TENS for diabetic peripheral neuropathy.**
 - 11 Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 74(2), 173–176 (2010).
 - **Most recent evidence-based review of TENS for neurologic disorders (including low back pain) by the American Academy of Neurology, see critique in [3].**
 - 12 Pieber K, Herceg M, Paternostro-Sluga T. Electrotherapy for the treatment of painful diabetic peripheral neuropathy: a review. *J. Rehabil. Med.* 42(4), 289–295 (2010).
 - 13 Treede RD, Jensen TS, Campbell JN *et al.* Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 70(18), 1630–1635 (2008).
 - 14 Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 136(3), 380–387 (2008).
 - 15 Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 150(3), 573–581 (2010).
 - 16 Dworkin RH, O'Connor AB, Audette J *et al.* Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin. Proc.* 85(3 Suppl.), S3–S14 (2010).
 - 17 Attal N, Cruccu G, Baron R *et al.* EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur. J. Neurol.* 17(9), e1113–e1188 (2010).
 - 18 Barlas P, Lundeberg T. Transcutaneous electrical nerve stimulation and acupuncture. In: *Textbook of Pain*. McMahon S, Koltzenburg M (Eds). Elsevier Churchill Livingstone, PA, USA, 583–590 (2006).
 - 19 Somers DL, Somers MF. Treatment of neuropathic pain in a patient with diabetic neuropathy using transcutaneous electrical nerve stimulation applied to the skin of the lumbar region. *Phys. Ther.* 79, 767–775 (1999).
 - 20 Carrol EN, Badura AS. Focal intense brief transcutaneous electric nerve stimulation for treatment of radicular and postthoracotomy pain. *Arch. Phys. Med. Rehabil.* 82(2), 262–264 (2001).
 - 21 Oosterhof J, Samwel HJ, de Boo TM, Wilder-Smith OH, Oostendorp RA, Crul BJ. Predicting outcome of TENS in chronic pain: a prospective, randomized, placebo controlled trial. *Pain* 136(1–2), 11–20 (2008).
 - 22 Melzack R, Wall P. Pain mechanisms: a new theory. *Science* 150, 971–979 (1965).
 - 23 Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth. Analg.* 46(4), 489–491 (1967).
 - 24 Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 164(878), 444–445 (1969).
 - 25 Shealy CN, Maurer D. Transcutaneous nerve stimulation for control of pain. A preliminary technical note. *Surg. Neurol.* 2(1), 45–47 (1974).
 - 26 Chipchase LS, Williams MT, Robertson VJ. A national study of the availability and use of electrophysical agents by Australian physiotherapists. *Physiother. Theory Pract.* 25(4), 279–296 (2009).
 - 27 Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur. J. Pain* 7(2), 181–188 (2003).
 - 28 Chabal C, Fishbain DA, Weaver M, Heine LW. Long-term transcutaneous electrical nerve stimulation (TENS) use: impact on medication utilization and physical therapy costs. *Clin. J. Pain* 14, 66–73 (1998).
 - 29 Merkel SI, Gutstein HB, Malviya S. Use of transcutaneous electrical nerve stimulation in a young child with pain from open perineal lesions. *J. Pain Symptom Manage.* 18, 376–381 (1999).
 - 30 Hagstroem S, Mahler B, Madsen B, Djurhuus JC, Rittig S. Transcutaneous electrical nerve stimulation for refractory daytime urinary urge incontinence. *J. Urol.* 182(4 Suppl.), 2072–2078 (2009).
 - 31 Clarke MC, Chase JW, Gibb S, Hutson JM, Southwell BR. Improvement of quality of life in children with slow transit constipation after treatment with transcutaneous electrical stimulation. *J. Pediatr. Surg.* 44(6), 1268–1272; discussion 1272 (2009).
 - 32 Cameron M, Lonergan E, Lee H. Transcutaneous electrical nerve stimulation (TENS) for dementia. *Cochrane Database Syst. Rev.* (3), CD004032 (2003).
 - 33 Ezzo JM, Richardson MA, Vickers A *et al.* Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst. Rev.* (2), CD002285 (2006).
 - 34 Gardner SE, Frantz RA, Schmidt FL. Effect of electrical stimulation on chronic wound healing: a meta-analysis. *Wound Repair Regen.* 7(6), 495–503 (1999).
 - 35 Atalay C, Yilmaz KB. The effect of transcutaneous electrical nerve stimulation on postmastectomy skin flap necrosis. *Breast Cancer Res Treat.* 117(3), 611–614 (2009).
 - 36 Goldstein C, Sprague S, Petrisor BA. Electrical stimulation for fracture healing: current evidence. *J. Orthop. Trauma* 24(Suppl. 1), S62–S65 (2010).

- 37 Kuhn A, Keller T, Lawrence M, Morari M. The influence of electrode size on selectivity and comfort in transcutaneous electrical stimulation of the forearm. *IEEE Trans. Neural. Syst. Rehabil. Eng.* 18(3), 255–262 (2010).
- 38 Cowan S, McKenna J, McCrum-Gardner E, Johnson MI, Sluka KA, Walsh DM. An investigation of the hypoalgesic effects of TENS delivered by a glove electrode. *J. Pain*, 10(7), 694–701 (2009).
- 39 Kuhn A, Keller T, Micera S, Morari M. Array electrode design for transcutaneous electrical stimulation: a simulation study. *Med. Eng. Phys.* 31(8), 945–951 (2009).
- 40 Johnson MI. Transcutaneous electrical nerve stimulation (TENS) and TENS-like devices. Do they provide pain relief? *Pain Rev.* 8, 121–128 (2001).
- 41 Charlton J. Task force on professional education. In: *Stimulation-Produced Analgesia*. Charlton J (Ed.). IASP Press, WA, USA, 93–96 (2005).
- 42 Eriksson M, Sjölund B. Acupuncture-like electroanalgesia in TNS resistant chronic pain. In: *Sensory Functions of the Skin*. Zotterman Y (Ed.). Pergamon Press, NY, USA, 575–581 (1976).
- 43 Johnson MI. Acupuncture-like transcutaneous electrical nerve stimulation (AL-TENS) in the management of pain. *Phys. Ther. Rev.* 3, 73–93 (1998).
- 44 Sjölund B, Eriksson M, Loeser J. Transcutaneous and implanted electric stimulation of peripheral nerves. In: *The Management of Pain*. Bonica J (Ed.). Lea & Febiger, PA, USA, 1852–1861 (1990).
- 45 Brown L, Holmes M, Jones A. The application of transcutaneous electrical nerve stimulation to acupuncture points (Acu-TENS) for pain relief: a discussion of efficacy and potential mechanisms. *Phys. Ther. Rev.* 14(2), 93–103 (2009).
- 46 Claydon L, Chesterton L. Does transcutaneous electrical nerve stimulation (TENS) produce ‘dose-responses’? A review of systematic reviews on chronic pain. *Phys. Ther. Rev.* 13(6), 450–463 (2008).
- 47 Cheing GL, Chan WW. Influence of choice of electrical stimulation site on peripheral neurophysiological and hypoalgesic effects. *J. Rehabil. Med.* 41(6), 412–417 (2009).
- 48 Brown L, Tabasam G, Bjordal JM, Johnson MI. An investigation into the effect of electrode placement of transcutaneous electrical nerve stimulation (TENS) on experimentally induced ischemic pain in healthy human participants. *Clin. J. Pain* 23(9), 735–743 (2007).
- 49 Chesterton LS, Barlas P, Foster NE, Lundeberg T, Wright CC, Baxter GD. Sensory stimulation (TENS): effects of parameter manipulation on mechanical pain thresholds in healthy human subjects. *Pain* 99(1–2), 253–262 (2002).
- 50 Chesterton LS, Foster NE, Wright CC, Baxter GD, Barlas P. Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects. *Pain* 106(1–2), 73–80 (2003).
- 51 Claydon LS, Chesterton LS, Barlas P, Sim J. Effects of simultaneous dual-site TENS stimulation on experimental pain. *Eur. J. Pain* 12(6), 696–704 (2008).
- 52 Lazarou L, Kitsios A, Lazarou I, Sikaras E, Trampas A. Effects of Intensity of Transcutaneous Electrical Nerve Stimulation (TENS) on Pressure Pain Threshold and Blood Pressure in Healthy Humans: a randomized, double-blind, placebo-controlled trial. *Clin. J. Pain* 25(9), 773–780 (2009).
- 53 Aarskog R, Johnson MI, Demmink JH *et al.* Is mechanical pain threshold after transcutaneous electrical nerve stimulation (TENS) increased locally and unilaterally? A randomized placebo-controlled trial in healthy subjects. *Physiother. Res. Int.* 12(4), 251–263 (2007).
- 54 Moran F, Leonard T, Hawthorne S *et al.* Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity *J. Pain* (2011) (In press).
- 55 Defrin R, Ariel E, Peretz C. Segmental noxious versus innocuous electrical stimulation for chronic pain relief and the effect of fading sensation during treatment. *Pain* 115(1–2), 152–160 (2005).
- 56 DeSantana JM, Santana-Filho VJ, Guerra DR, Sluka KA, Gurgel RQ, da Silva WM Jr. Hypoalgesic effect of the transcutaneous electrical nerve stimulation following inguinal herniorrhaphy: a randomized, controlled trial. *J. Pain* 9(7), 623–629 (2008).
- 57 Chen CC, Tabasam G, Johnson MI. Does the pulse frequency of transcutaneous electrical nerve stimulation (TENS) influence hypoalgesia? A systematic review of studies using experimental pain and healthy human participants. *Physiotherapy* 94(1), 11–20 (2008).
- 58 Chen CC, Johnson MI. An investigation into the hypoalgesic effects of high- and low-frequency transcutaneous electrical nerve stimulation (TENS) on experimentally-induced blunt pressure pain in healthy human participants. *J. Pain* 11(1), 53–61 (2010).
- 59 Chen CC, Johnson MI. Differential frequency effects of strong non-painful transcutaneous electrical nerve stimulation (TENS) on experimentally-induced ischaemic pain in healthy human participants. *Clin. J. Pain* DOI: 10.1097/AJP.0b013e318208c926 (2011) (Epub ahead of print).
- 60 Chen CC, Johnson MI. A comparison of transcutaneous electrical nerve stimulation (TENS) at 3 and 80 pulses per second on cold-pressor pain in healthy human participants. *Clin. Physiol. Funct. Imaging* 30(4), 260–268 (2010).
- 61 Johnson MI, Ashton CH, Thompson JW. An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for clinical use of TENS. *Pain* 44(3), 221–229 (1991).
- 62 Johnson MI, Ashton CH, Thompson JW. Long term use of transcutaneous electrical nerve stimulation at Newcastle Pain Relief Clinic. *J. R. Soc. Med.* 85(5), 267–268 (1992).
- 63 Davies HT, Crombie IK, Brown JH, Martin C. Diminishing returns or appropriate treatment strategy? – An analysis of short-term outcomes after pain clinic treatment. *Pain* 70, 203–208 (1997).
- 64 Koke AJ, Schouten JS, Lamerichs-Geelen MJ *et al.* Pain reducing effect of three types of transcutaneous electrical nerve stimulation in patients with chronic pain: a randomized crossover trial. *Pain* 108(1–2), 36–42 (2004).
- 65 Chandran P, Sluka KA. Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration. *Pain* 102(1–2), 195–201 (2003).
- 66 DeSantana JM, da Silva LF, Sluka KA. Cholecystokinin receptors mediate tolerance to the analgesic effect of TENS in arthritic rats. *Pain* 148(1), 84–93 (2010).
- 67 Hingne PM, Sluka KA. Blockade of NMDA receptors prevents analgesic tolerance to repeated transcutaneous electrical nerve stimulation (TENS) in rats. *J. Pain* 9(3), 217–225 (2008).
- 68 Liebano RE, Rakel B, Vance CG, Walsh DM, Sluka KA. An investigation of the development of analgesic tolerance to TENS in humans. *Pain* 152(2), 335–342 (2011).

- 69 Desantana JM, Santana-Filho VJ, Sluka KA. Modulation between high- and low-frequency transcutaneous electric nerve stimulation delays the development of analgesic tolerance in arthritic rats. *Arch. Phys. Med. Rehabil.* 89(4), 754–760 (2008).
- 70 Chen CC, Johnson MI. An investigation into the effects of frequency-modulated transcutaneous electrical nerve stimulation (TENS) on experimentally-induced pressure pain in healthy human participants. *J. Pain* 10(10), 1029–1037 (2009).
- 71 Pomeranz B, Niznick G. Codetron, a new electrotherapy device overcomes the habituation problems of conventional TENS devices. *Am. J. Electromed.* First quarter, 22–26 (1987).
- 72 Sandkuhler J. Long-lasting analgesia following TENS and acupuncture: Spinal mechanisms beyond gate control. In: *9th World Congress on Pain: Progress in Pain Research and Management*. Devor M, Rowbotham MC, Wiesenfeld-Hallin Z (Eds). IASP Press, Austria, 359–369 (2000).
- 73 Chartered Society of Physiotherapy C. *Guidance for the Clinical Use of Electrophysical Agents*. Chartered Society of Physiotherapy, London, UK (2006).
- 74 Holmgren C, Carlsson T, Mannheimer C, Edvardsson N. Risk of interference from transcutaneous electrical nerve stimulation on the sensing function of implantable defibrillators. *Pacing Clin. Electrophysiol.* 31(2), 151–158 (2008).
- 75 Bundsen P, Ericson K. Pain relief in labor by transcutaneous electrical nerve stimulation. Safety aspects. *Acta Obstet. Gynecol. Scand.* 61(1), 1–5 (1982).
- 76 Eriksson M, Schuller H, Sjolund B. Hazard from transcutaneous nerve stimulation in patients with pacemakers. *Lancet* 1(8077), 1319 (1978).
- 77 Scherder E, Van Someren E, Swaab D. Epilepsy: a possible contraindication for transcutaneous electrical nerve stimulation. *J. Pain Symptom Manage.* 17, 152–153 (1999).
- 78 Mann C. Respiratory compromise: a rare complication of transcutaneous electrical nerve stimulation for angina pectoris. *J. Accid. Emerg. Med.* 13(1), 68 (1996).
- 79 Llamas M, Santiago D, Navarro R, Sanchez-Perez J, Garcia-Diez A. Unusual allergic contact dermatitis produced by a transcutaneous electrical nerve stimulator. *Contact Dermatitis* 62(3), 189–190 (2010).
- 80 Ford KS, Shrader MW, Smith J, McLean TJ, Dahm DL. Full-thickness burn formation after the use of electrical stimulation for rehabilitation of unicompartmental knee arthroplasty. *J. Arthroplasty* 20(7), 950–953 (2005).
- 81 Maier C, Baron R, Tolle TR *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 150(3), 439–450 (2010).
- 82 Haanpaa M, Attal N, Backonja M *et al.* NeuPSIG guidelines on neuropathic pain assessment. *Pain* 152(1), 14–27 (2010).
- 83 Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* 9(8), 807–819 (2010).
- 84 Garrison DW, Foreman RD. Effects of prolonged transcutaneous electrical nerve stimulation (TENS) and variation of stimulation variables on dorsal horn cell activity in cats. *Eur. J. Phys. Med. Rehabil.* 7, 87–94 (1997).
- 85 Garrison DW, Foreman RD. Decreased activity of spontaneous and noxiously evoked dorsal horn cells during transcutaneous electrical nerve stimulation (TENS). *Pain* 58(3), 309–315 (1994).
- 86 Garrison DW, Foreman RD. Effects of transcutaneous electrical nerve stimulation (TENS) on spontaneous and noxiously evoked dorsal horn cell activity in cats with transected spinal cords. *Neurosci. Lett.* 216, 125–128 (1996).
- 87 Leem J, Park E, Paik K. Electrophysiological evidence for the antinociceptive effect of transcutaneous electrical stimulation on mechanically evoked responsiveness of dorsal horn neurons in neuropathic rats. *Neurosci. Lett.* 192(3), 197–200 (1995).
- 88 Ma YT, Sluka KA. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Exp. Brain Res.* 137, 94–102 (2001).
- 89 Sandkuhler J, Chen JG, Cheng G, Randic M. Low-frequency stimulation of afferent A δ -fibers induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat. *J. Neurosci* 17, 6483–6491 (1997).
- 90 Radhakrishnan R, Sluka KA. Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve stimulation-induced antihyperalgesia. *J. Pain* 6(10), 673–680 (2005).
- 91 Desantana JM, da Silva LF, de Resende MA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience* 163(4), 1233–1241 (2009).
- 92 Murakami T, Takino R, Ozaki I, Kimura T, Iguchi Y, Hashimoto I. High-frequency transcutaneous electrical nerve stimulation (TENS) differentially modulates sensorimotor cortices: an MEG study. *Clin. Neurophysiol.* 121(6), 939–944 (2010).
- 93 Kara M, Ozcakar L, Gokcay D *et al.* Quantification of the effects of transcutaneous electrical nerve stimulation with functional magnetic resonance imaging: a double-blind randomized placebo-controlled study. *Arch. Phys. Med. Rehabil.* 91(8), 1160–1165 (2010).
- 94 Sluka KA, Lisi TL, Westlund KN. Increased release of serotonin in the spinal cord during low, but not high, frequency transcutaneous electric nerve stimulation in rats with joint inflammation. *Arch. Phys. Med. Rehabil.* 87(8), 1137–1140 (2006).
- 95 King EW, Audette K, Athman GA, Nguyen HO, Sluka KA, Fairbanks CA. Transcutaneous electrical nerve stimulation activates peripherally located α -2A adrenergic receptors. *Pain* 115(3), 364–373 (2005).
- 96 Vance CG, Radhakrishnan R, Skyba DA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies reduces primary hyperalgesia in rats with joint inflammation in a time-dependent manner. *Phys. Ther.* 87(1), 44–51 (2007).
- 97 Resende MA, Sabino GG, Candido CR, Pereira LS, Francischi JN. Local transcutaneous electrical stimulation (TENS) effects in experimental inflammatory edema and pain. *Eur. J. Pharmacol.* 504(3), 217–222 (2004).
- 98 Sabino GS, Santos CM, Francischi JN, de Resende MA. Release of endogenous opioids following transcutaneous electric nerve stimulation in an experimental model of acute inflammatory pain. *J. Pain* 9(2), 157–163 (2008).
- 99 Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *J. Pharmacol. Exp. Ther.* 298(1), 257–263 (2001).

- 100 Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J. Pharmacol. Exp. Ther.* 289, 840–846 (1999).
- 101 Ainsworth L, Budelier K, Clinesmith M *et al.* Transcutaneous electrical nerve stimulation (TENS) reduces chronic hyperalgesia induced by muscle inflammation. *Pain* 120(1–2), 182–187 (2006).
- 102 Hanai F. Effect of electrical stimulation of peripheral nerves on neuropathic pain. *Spine (Phila Pa 1976)*, 25(15), 1886–1892 (2000).
- 103 Nam TS, Choi Y, Yeon DS, Leem JW, Paik KS. Differential antinociceptive effect of transcutaneous electrical stimulation on pain behavior sensitive or insensitive to phentolamine in neuropathic rats. *Neurosci. Lett.* 301, 17–20 (2001).
- 104 Somers DL, Clemente FR. High-frequency transcutaneous electrical nerve stimulation alters thermal but not mechanical allodynia following chronic constriction injury of the rat sciatic nerve. *Arch. Phys. Med. Rehabil.* 79, 1370–1376 (1998).
- 105 Somers DL, Clemente FR. Transcutaneous electrical nerve stimulation for the management of neuropathic pain: the effects of frequency and electrode position on prevention of allodynia in a rat model of complex regional pain syndrome type II. *Phys. Ther.* 86(5), 698–709 (2006).
- 106 Somers DL, Clemente FR. The relationship between dorsal horn neurotransmitter content and allodynia in neuropathic rats treated with high-frequency transcutaneous electric nerve stimulation. *Arch. Phys. Med. Rehabil.* 84(11), 1575–1583 (2003).
- 107 Somers DL, Clemente FR. Contralateral high or a combination of high- and low-frequency transcutaneous electrical nerve stimulation reduces mechanical allodynia and alters dorsal horn neurotransmitter content in neuropathic rats. *J. Pain* 10(2), 221–229 (2009).
- **Evidence for the mechanism by which TENS reduces allodynia.**
- 108 Nardone A, Schieppati M. Influences of transcutaneous electrical stimulation of cutaneous and mixed nerves on subcortical and cortical somatosensory evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* 74(1), 24–35 (1989).
- 109 Walsh DM, Lowe AS, McCormack K, Willer JC, Baxter GD, Allen JM. Transcutaneous electrical nerve stimulation: effect on peripheral nerve conduction, mechanical pain threshold, and tactile threshold in humans. *Arch. Phys. Med. Rehabil.* 79(9), 1051–1058 (1998).
- 110 Burssens P, Forsyth R, Steyaert A, Van Ovost E, Praet M, Verdonk R. Influence of burst TENS stimulation on collagen formation after Achilles tendon suture in man. A histological evaluation with Movat's pentachrome stain. *Acta Orthop. Belg.* 71(3), 342–346 (2005).
- 111 Burssens P, Forsyth R, Steyaert A, Van Ovost E, Praet M, Verdonk R. Influence of burst TENS stimulation on the healing of Achilles tendon suture in man. *Acta Orthop. Belg.* 69(6), 528–532 (2003).
- 112 Sommer P, Kluschina O, Schley M, Namer B, Schmelz M, Rukwied R. Electrically induced quantitative sudomotor axon reflex test in human volunteers. *Auton. Neurosci.* 159(1–2), 111–116 (2011).
- 113 Reeves JL 2nd, Graff-Radford SB, Shipman D. The effects of transcutaneous electrical nerve stimulation on experimental pain and sympathetic nervous system response. *Pain Med.* 5(2), 150–161 (2004).
- 114 Olyaei GR, Talebian S, Hadian MR, Bagheri H, Momadjed F. The effect of transcutaneous electrical nerve stimulation on sympathetic skin response. *Electromyogr. Clin. Neurophysiol.* 44(1), 23–28 (2004).
- 115 Akai M, Hayashi K. Effect of electrical stimulation on musculoskeletal systems; a meta-analysis of controlled clinical trials. *Bioelectromagnetics* 23(2), 132–143 (2002).
- 116 Goldstein C, Sprague S, Petrisor BA. Electrical stimulation for fracture healing: current evidence. *J. Orthop. Trauma* 24(Suppl. 1), S62–S65 (2010).
- 117 Mollon B, da Silva V, Busse JW, Einhorn TA, Bhandari M. Electrical stimulation for long-bone fracture-healing: a meta-analysis of randomized controlled trials. *J. Bone Joint Surg. Am.* 90(11), 2322–2330 (2008).
- 118 Cheng N, Hoof HV, Bockx E. The effects of electric current on ATP generation, protein synthesis, and membrane transport in rat skin. *Clin. Orthop.* 171, 264–272 (1982).
- 119 Baptista AF, Gomes JR, Oliveira JT, Santos SM, Vannier-Santos MA, Martinez AM. High- and low-frequency transcutaneous electrical nerve stimulation delay sciatic nerve regeneration after crush lesion in the mouse. *J. Peripher. Nerv. Syst.* 13(1), 71–80 (2008).
- 120 Gigo-Benato D, Russo TL, Geuna S, Domingues NR, Salvini TF, Parizotto NA. Electrical stimulation impairs early functional recovery and accentuates skeletal muscle atrophy after sciatic nerve crush injury in rats. *Muscle Nerve* 41(5), 685–693 (2010).
- 121 Poltawski L, Watson T. Bioelectricity and microcurrent therapy for tissue healing – a narrative review *Physical Ther. Rev.* 14(2), 104–114 (2009).
- 122 Alrashdan MS, Park JC, Sung MA *et al.* Thirty minutes of low intensity electrical stimulation promotes nerve regeneration after sciatic nerve crush injury in a rat model. *Acta Neurol. Belg.* 110(2), 168–179 (2010).
- 123 Mendonca AC, Barbieri CH, Mazzer N. Directly applied low intensity direct electric current enhances peripheral nerve regeneration in rats. *J. Neurosci. Methods* 129(2), 183–190 (2003).
- 124 Lu MC, Tsai CC, Chen SC, Tsai FJ, Yao CH, Chen YS. Use of electrical stimulation at different current levels to promote recovery after peripheral nerve injury in rats. *J. Trauma* 67(5), 1066–1072 (2009).
- 125 Gordon T, Sulaiman OA, Ladak A. Chapter 24: electrical stimulation for improving nerve regeneration: where do we stand? *Int. Rev. Neurobiol.* 87, 433–444 (2009).
- 126 Vivo M, Puigdemasa A, Casals L, Asensio E, Udina E, Navarro X. Immediate electrical stimulation enhances regeneration and reinnervation and modulates spinal plastic changes after sciatic nerve injury and repair. *Exp. Neurol.* 211(1), 180–193 (2008).
- 127 Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. *J. Neurosci.* 20(7), 2602–2608 (2000).
- 128 English AW, Schwartz G, Meador W, Sabatier MJ, Mulligan A. Electrical stimulation promotes peripheral axon regeneration by enhanced neuronal neurotrophin signaling. *Dev. Neurobiol.* 67(2), 158–172 (2007).
- 129 Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VM. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. *Exp. Neurol.* 205(2), 347–359 (2007).
- 130 Brushart TM, Hoffman PN, Royall RM, Murinson BB, Witzel C, Gordon T. Electrical stimulation promotes motoneuron regeneration without increasing its speed or conditioning the neuron. *J. Neurosci.* 22(15), 6631–6638 (2002).

- 131 Gordon T, Udina E, Verge VM, de Chaves EI. Brief electrical stimulation accelerates axon regeneration in the peripheral nervous system and promotes sensory axon regeneration in the central nervous system. *Motor Control* 13(4), 412–441 (2009).
- 132 Thorsen SW, Lumsden SG. Trigeminal neuralgia: sudden and long-term remission with transcutaneous electrical nerve stimulation. *J. Manipulative Physiol. Ther.* 20, 415–419 (1997).
- 133 Claydon L, Chesterton L, Johnson MI, Herbison G, Bennett M. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst. Rev.* (10), CD008756 (2010).
- 134 Reichstein L, Labrenz S, Ziegler D, Martin S. Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation. *Diabetologia* 48(5), 824–828 (2005).
- 135 Forst T, Nguyen M, Forst S, Disselhoff B, Pohlmann T, Pfutzner A. Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device. *Diabetes Nutr. Metab.* 17(3), 163–168 (2004).
- 136 Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care* 20, 1702–1705 (1997).
- 137 Cheing GL, Luk ML. Transcutaneous electrical nerve stimulation for neuropathic pain. *J. Hand Surg. Br.* 30(1), 50–55 (2005).
- 138 Thorsteinsson G, Stonnington HH, Stillwell GK, Elveback LR. Transcutaneous electrical stimulation: a double-blind trial of its efficacy for pain. *Arch. Phys. Med. Rehabil.* 58(1), 8–13 (1977).
- 139 Bloodworth DM, Nguyen BN, Garver W *et al.* Comparison of stochastic vs. conventional transcutaneous electrical stimulation for pain modulation in patients with electromyographically documented radiculopathy. *Am. J. Phys. Med. Rehabil.* 83(8), 584–591 (2004).
- 140 Tulgar M, McGlone F, Bowsher D, Miles JB. Comparative effectiveness of different stimulation modes in relieving pain. Part II. A double-blind controlled long-term clinical trial. *Pain* 47(2), 157–162 (1991).
- 141 Rutgers M, Van-Romunde L, Osman P. A small randomised comparative trial of acupuncture versus transcutaneous electrical neurostimulation in postherpetic neuralgia. *Pain Clinic* 2, 87–89 (1988).
- 142 Hamza MA, White PF, Craig WF *et al.* Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. *Diabetes Care* 23, 365–370 (2000).
- 143 Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS. Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: a review. *Pain Med.* 8(Suppl. 2), S50–S62 (2007).
- 144 Cameron NE, Cotter MA, Robertson S, Maxfield EK. Nerve function in experimental diabetes in rats: effects of electrical stimulation. *Am. J. Physiol.* 264(2 Pt 1), E161–E166 (1993).
- 145 Kumar D, Alvaro MS, Julka IS, Marshall HJ. Diabetic peripheral neuropathy. Effectiveness of electrotherapy and amitriptyline for symptomatic relief. *Diabetes Care* 21(8), 1322–1325 (1998).
- 146 Riker DK. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review); utility of transcutaneous electrical nerve stimulation in neurologic pain disorders. *Neurology* 74(21), 1748–1749; author reply 1749 (2010).
- 147 Mulvey MR, Bagnall AM, Johnson MI, Marchant PR. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. *Cochrane Database Syst. Rev.* (5), CD007264 (2010).
- 148 Giuffrida O, Simpson L, Halligan PW. Contralateral stimulation, using TENS, of phantom limb pain: two confirmatory cases. *Pain Med.* 11(1), 133–141 (2010).
- 149 Barbarisi M, Pace MC, Passavanti MB *et al.* Pregabalin and transcutaneous electrical nerve stimulation for postherpetic neuralgia treatment. *Clin. J. Pain* 26(7), 567–572 (2010).
- 150 Norrbrink C. Transcutaneous electrical nerve stimulation for treatment of spinal cord injury neuropathic pain. *J. Rehabil. Res. Dev.* 46(1), 85–93 (2009).
- 151 Cuyppers K, Levin O, Thijs H, Swinnen SP, Meesen RL. Long-term TENS treatment improves tactile sensitivity in MS patients. *Neurorehabil. Neural. Repair* 24(5), 420–427 (2010).
- 152 Ghoname EA, White PF, Ahmed HE, Hamza MA, Craig WF, Noe CE. Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica. *Pain* 83(2), 193–199 (1999).
- 153 Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare®) for chemotherapy-induced peripheral neuropathy. *J. Pain Symptom Manage.* 40(6), 883–891 (2010).
- 154 Bennett MI, Johnson MI, Brown SR, Radford H, Brown JM, Searle RD. Feasibility study of transcutaneous electrical nerve stimulation (TENS) for cancer bone pain. *J. Pain* 11(4), 351–359 (2010).
- 155 Robb K, Oxberry SG, Bennett MI, Johnson MI, Simpson KH, Searle RD. A Cochrane systematic review of transcutaneous electrical nerve stimulation for cancer pain. *J. Pain Symptom Manage.* 37(4), 746–753 (2008).
- 156 Price CI, Pandyan AD. Electrical stimulation for preventing and treating post-stroke shoulder pain: a systematic Cochrane review. *Clin. Rehabil.* 15(1), 5–19 (2001).
- 157 Sonde L, Gip C, Fernaeus SE, Nilsson CG, Viitanen M. Stimulation with low frequency (1.7 Hz) transcutaneous electric nerve stimulation (low-TENS) increases motor function of the post-stroke paretic arm. *Scand. J. Rehabil. Med.* 30, 95–99 (1998).
- 158 Linn SL, Granat MH, Lees KR. Prevention of shoulder subluxation after stroke with electrical stimulation. *Stroke* 30(5), 963–968 (1999).
- 159 Faghri PD, Rodgers MM, Glaser RM, Bors JG, Ho C, Akuthota P. The effects of functional electrical stimulation on shoulder subluxation, arm function recovery, and shoulder pain in hemiplegic stroke patients. *Arch. Phys. Med. Rehabil.* 75(1), 73–79 (1994).
- 160 Leandri M, Parodi CI, Corrieri N, Rigardo S. Comparison of TENS treatments in hemiplegic shoulder pain. *Scand. J. Rehabil. Med.* 22(2), 69–71 (1990).
- 161 Robbins SM, Houghton PE, Woodbury MG, Brown JL. The therapeutic effect of functional and transcutaneous electric stimulation on improving gait speed in stroke patients: a meta-analysis. *Arch. Phys. Med. Rehabil.* 87(6), 853–859 (2006).
- 162 Walsh D, Howe T, Johnson M, Sluka KA. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst. Rev.* 15(2), CD006142 (2009).
- 163 Proctor ML, Smith CA, Farquhar CM, Stones RW. Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. *Cochrane Database Syst. Rev.* (1), CD002123 (2002).

- 164 Dowswell T, Bedwell C, Lavender T, Neilson JP. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database Syst. Rev.* (2), CD007214 (2009).
- 165 Carroll D, Tramer M, McQuay H, Nye B, Moore A. Randomization is important in studies with pain outcomes: systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain. *Br. J. Anaesth.* 77(6), 798–803 (1996).
- 166 Freynet A, Falcoz PE. Is transcutaneous electrical nerve stimulation effective in relieving postoperative pain after thoracotomy? *Interact. Cardiovasc. Thorac. Surg.* 10(2), 283–288 (2010).
- 167 Johnson MI, Oxberry S, Simpson K. Transcutaneous Electrical Nerve Stimulation (TENS) and acupuncture for acute pain. In: *Acute Pain. Clinical Pain Management, Second Edition*. Macintyre P, Walker S, Rowbotham D (Eds). Hodder Arnold, London, UK, 271–290 (2008).
- 168 Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst. Rev.* (3), CD003222 (2008).
- **Most comprehensive systematic review of TENS for chronic pain.**
- 169 Tulgar M, McGlone F, Bowsher D, Miles JB. Comparative effectiveness of different stimulation modes in relieving pain. Part I. A pilot study. *Pain* 47(2), 151–155 (1991).
- 170 Nash T, Williams J, Machin D. TENS: does the type of stimulus really matter? *The Pain Clinic* 3, 161–168 (1990).
- 171 Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain* 130(1–2), 157–165 (2007).
- **Largest meta-analysis of randomized controlled trials on TENS to date.**
- 172 Novak S, Nemeth WC. How clinically relevant is a meta-analysis of electrical nerve stimulation when based on heterogeneous disease states? *Pain* 131(1–2), 228–229; author reply 229–230 (2007).
- 173 Rutjes AW, Nuesch E, Sterchi R *et al.* Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database Syst. Rev.* (4), CD002823 (2009).
- 174 Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskelet. Disord.* 8, 51 (2007).
- 175 Brosseau L, Judd MG, Marchand S *et al.* Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. *Cochrane Database Syst. Rev.* (3), CD004377 (2003).
- 176 Ottawa Panel. Ottawa Panel Evidence-Based Clinical Practice Guidelines for Electrotherapy and Thermotherapy Interventions in the Management of Rheumatoid Arthritis in Adults. *Phys. Ther.* 84(11), 1016–1043 (2004).
- 177 Machado LA, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. *Rheumatology (Oxford)* 48(5), 520–527 (2009).
- 178 Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N. Engl. J. Med.* 322(23), 1627–1634 (1990).
- 179 Warke K, Al-Smadi J, Baxter D, Walsh DM, Lowe-Strong AS. Efficacy of transcutaneous electrical nerve stimulation (TENS) for chronic low-back pain in a multiple sclerosis population: a randomized, placebo-controlled clinical trial. *Clin. J. Pain* 22(9), 812–819 (2006).
- 180 Bennett M, Hughes N, Johnson MI. Methodological quality in randomised controlled trials of TENS for pain: low fidelity may explain negative findings. *Pain* DOI: 10.1016/j.pain.2010.12.009 (2011) (Epub ahead of print).
- **Systematic review of research methodologies used in randomized controlled trials on TENS.**
- 181 Rakel B, Cooper N, Adams HJ *et al.* A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *J. Pain* 11(3), 230–238 (2010).
- 182 Witt CM, Jena S, Selim D *et al.* Pragmatic randomized trial evaluating the clinical and economic effectiveness of acupuncture for chronic low back pain. *Am. J. Epidemiol.* 164(5), 487–496 (2006).
- 183 Jena S, Witt CM, Brinkhaus B, Wegscheider K, Willich SN. Acupuncture in patients with headache. *Cephalalgia* 28(9), 969–979 (2008).
- 184 White A, Cummings M, Barlas P *et al.* Defining an adequate dose of acupuncture using a neurophysiological approach – a narrative review of the literature. *Acupunct. Med.* 26(2), 111–120 (2008).
- 185 MacPherson H, Altman DG, Hammerschlag R *et al.* Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med.* 7(6), e1000261 (2010).
- 186 Enblom A, Hammar M, Steineck G, Borjeson S. Can individuals identify if needling was performed with an acupuncture needle or a non-penetrating sham needle? *Complement. Ther. Med.* 16(5), 288–294 (2008).
- 187 Carroll D, Moore A, Tramer M, McQuay H. Transcutaneous electrical nerve stimulation does not relieve in labour pain: updated systematic review. *Contemp. Rev. Obstetrics Gynecol.* 195–205 (1997).
- 188 Proctor ML, Smith CA, Farquhar CM, Stones RW. Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrhoea. *Cochrane Database Syst. Rev.* (1), CD002123 (2003).
- 189 Khadilkar A, Odebiyi DO, Brosseau L, Wells GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst. Rev.* (4), CD003008 (2008).
- 190 Robb KA, Bennett MI, Johnson MI, Simpson KJ, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database Syst. Rev.* (3), CD006276 (2008).
- 191 Kroeling P, Gross A, Goldsmith CH *et al.* Electrotherapy for neck pain. *Cochrane Database Syst. Rev.* (4), CD004251 (2009).
- 192 Bronfort G, Nilsson N, Haas M *et al.* Non-invasive physical treatments for chronic/recurrent headache. *Cochrane Database Syst. Rev.* (3), CD001878 (2004).
- 193 Price CI, Pandyan AD. Electrical stimulation for preventing and treating post-stroke shoulder pain. *Cochrane Database Syst. Rev.* (4), CD001698 (2000).
- Website**
- 201 Coldron Y, Crothers E, Haslam J *et al.* ACPWH guidance on the safe use of Transcutaneous Electrical Nerve Stimulation (TENS) for musculoskeletal pain during pregnancy (2007) www.electrotherapy.org/downloads/Modalities/TENS%20in%20pregnancy%20guidelines.pdf