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REVIEW

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Transcutaneous electrical nerve stimulation for pelvic pain: A scoping review of treatment protocols, practical indications, and caveats

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Abstract

Background: Neuromodulation (NM) is a family of therapies based on electrical stimulation to target specific nerves that control LUTS (Lower Urinary Tract Symptoms) and pain. The aim is to modulate what is happening within the nervous system to achieve therapeutic effects. A particular type of neuromodulation, called TENS (Transcutaneous Electrical Nerve Stimulation), has proven effective for treating pelvic pain. The available evidence provides indications regarding the many aspects of TENS that influence therapeutic effects, but a comprehensive review has yet to be conducted.

Methods: Scoping review on Pubmed, CINAHL, Embase, Scopus, and Web of Science, including clinical trials, reviews, case studies or series, and other descriptive studies, according to the Joanna Briggs and PRISMA methodology.

Results: The 31 papers retrieved allowed the formulation of precise indications about the DOs and DON'Ts of electrode placement, waveform, pulse duration, pulse frequency, amplitude, session duration, and frequency of sessions. This paper also discusses the biochemical and neuro urological mechanisms of TENS.

Conclusion: TENS effectiveness is influenced by many factors, some self-evident, others subtle, which this paper elucidates. Pelvic pain requires a multimodal approach, of which TENS is just a part. TENS should therefore be viewed as one of the components of the rehabilitation program in the frame of thorough and continuous patient assessment.

KEYWORDS

neuromodulation, pelvic pain, rehabilitation, TENS

1 | INTRODUCTION

Neuromodulation (NM) is a family of therapies based on electrical stimulation to target specific nerves that control LUTS (Lower Urinary Tract Symptoms) and pain. The aim is to modulate what is happening within the nervous system to achieve therapeutic effects (e.g., reduction of pain or LUTS). NM includes electrical stimulation of the pelvic floor (ES) with vaginal, anal and surface electrodes, interference therapy (IF), magnetic stimulation (MS), percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS).

When used to control pain, NM is based on the gate control theory, first described in 1965 by Melzack and Wall. The gate control mechanism is an anatomical mechanism located in the Substantia Gelatinosa ("gelatinous substance," also known as Rolando's substance), contained in the dorsal horn of the spinal cord. This substance contains interneurons that synapse with primary afferent neurons; the substantia gelatinosa then modulates sensory information from these neurons.[1] Consequently, painful stimuli can reach the brain or be attenuated at the level of the spinal cord in a mechanism similar to a gate that can be opened or closed.[2] In the former case, pain signals pass through the gate and reach the brain; in the latter, stimulus conduction is interrupted in the spinal cord and does not reach the brain. Based on these considerations, it is possible to reduce pain by applying a non-noxious stimulus, such as NM, to activate the gate mechanism and reduce pain intensity.[3]

A particular type of neuromodulation, called TENS (Transcutaneous Electrical Nerve Stimulation), has proven effective for treating pelvic pain. This treatment's effectiveness is based on gate control and another mechanism called "extra-segmental TENS." The latter consists of releasing endogenous opioids through stimulating small motor and afferent fibers. This extra-segmental analgesic effect is linked to the activation of structures that constitute the descending pathways of pain inhibition, including the periaqueductal gray substance, the raphe magnus nucleus, and the gigantocellular raphe nucleus.[4] The periaqueductal substance in the midbrain (originating directly from the neural tube) is the primary center of descending pain modulation. At the same time, the raphe magnus is the point of origin of a descending pathway that produces noradrenaline and serotonin. The latter inhibits the interneurons in the gelatinous substance and stimulates the encephalinergic interneurons in the spinal cord. As the name suggests, these interneurons react to enkephalins as neurotransmitters, a family of molecules involved in pain perception.[5] Finally, TENS activates peripheral and central opioid receptors, including those located in the spinal cord, nucleus raphe magnus and periaqueductal gray matter.[6]

In the many papers on TENS published to date, including systematic reviews, several different treatment protocols have been proposed, as highlighted by a recent meta-analysis whose authors also pointed out the poor quality of most of the papers retrieved.[7] The electrical parameters chosen by the authors of the studies show considerable variability. Although the results of most articles report a certain clinical benefit with TENS despite these differences, the size of the effect of this benefit varies considerably. Other articles have discussed practical indications, such as the criteria for electrode placement and for deciding the amplitude of the current, sometimes presenting partial results. Very few articles discussed tolerance to TENS. Finally, no author has critically summarized all these aspects by adding specific considerations on pelvic pain. Therefore, it is useful to conduct a scoping review to provide scientific criteria for applying TENS to pelvic pain and to favor patients with optimal pain relief.

2 | METHODS

2.1 | Study design

We conducted a scoping review, which allows a systematic literature search, although it does not require grading or methodological appraisal.[8] This work was conducted under the indications of the Joanna Briggs Institute[9] and the Preferred Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).[10]

2.2 | Searches and information sources

2.2.1 | Systematic database search

The research questions were:

- Based on the neurophysiology of pain, what is the rationale behind TENS for pelvic pain?
- Based on the mechanisms of action of TENS, which electrical parameters can be recommended to treat pelvic pain?
- Which caveats should be considered during clinical practice with TENS for pelvic pain?

We performed a preliminary search on Pubmed only to inform the development of the final search strategy with relevant keywords (Table 1). We then searched Pubmed again, CINAHL, Scopus, Embase, and Web of Science for studies published in the last 10 years in English, French, Spanish and Italian (the four languages known by the authors).

TABLE 1 Preliminary search in PubMed.

1	"Chronic Pain"[Mesh] OR "Pelvic Pain"[Mesh] OR "chronic pain" OR "Pelvic Pain" OR "Chronic Pelvic Pain"
2	"TENS"[Mesh] OR "Electrical Nerve Stimulation"[Mesh]
4	#1 AND #2
5	Limits: English, Italian, French and Spanish language, from 10 years ago.

TABLE 2 Neuromodulators and neuropeptides.[15,16]

Name	Action	Mechanism
Glutamate	Excitatory neurotransmitter	Activates NMDA[a] receptors increasing receptive field size, decreasing activation threshold, and extending depolarization, thus activating the dorsal horn neurons
Glycine	Inhibitory neurotransmitter	Activates NMDA receptors
Gamma-amino-butyric-acid (GABA)	Inhibitory neurotransmitter	Activates GABA[b] receptors in supraspinal sites that coordinate the perception and response to painful stimuli. GABA regulates the control of sensory information processing in the spinal cord
Substance P	Excitatory neuropeptide	Found in C fibers, it responds to tissue damage by causing vasodilation, inflammation, and pain.
Endorphins, serotonin	Inhibitory neurotransmitters	Released in the descending pathway of the spinal cord, they help with pain modulation (and therefore gate control)

[a]NMDA, N-metil-d-aspartate.

[b]GABA, Gamma-amino-butirric acid.

2.2.2 | Eligibility criteria

We included primary studies (both descriptive and interventional), reviews, and guidelines regarding the mechanisms of action and the electrical parameters of TENS for treating pelvic pain.

2.2.3 | Exclusion criteria

We excluded grey literature, but we used such sources to check for additional references, as done by other authors[11] and suggested by the Jonna Briggs method.[9]

2.2.4 | Study selection

Zotero software was used to eliminate duplicates and manage citations of retrieved articles. Two independent researchers (both with PhDs in nursing) performed the literature search from October 21 2022, to December 5, 2022; two research team members screened the papers using the Rayyan platform for systematic reviews. Disagreements were resolved through discussion after the full-text analysis. To report the results, we used the PRISMA-SR criteria for systematic reviews.[10]

3 | RESULTS

Figure 1 reports the study selection process. Of note, since many papers on neuroanatomy and biochemistry of nociception were published in the early 2000s, recent reviews and reference textbooks often referred to such articles. We, therefore, chose to include them in this revision after checking for the existence of more recent papers providing additional insights or up-to-date recommendations of clinical relevance.

3.1 | Synthesized findings

The results of the included studies are summarized in the following paragraphs, based on the research questions.

3.2 | Research question #1: Based on the neurophysiology of pain, what is the rationale behind TENS for pelvic pain?

On its journey to the brain, the pain signal initially reaches first-order afferent neurons (also called primary neurons), whose endings form receptors. Next, these neurons synapse with second-order neurons in the spinal cord. Finally, at the level of the thalamus, third-order

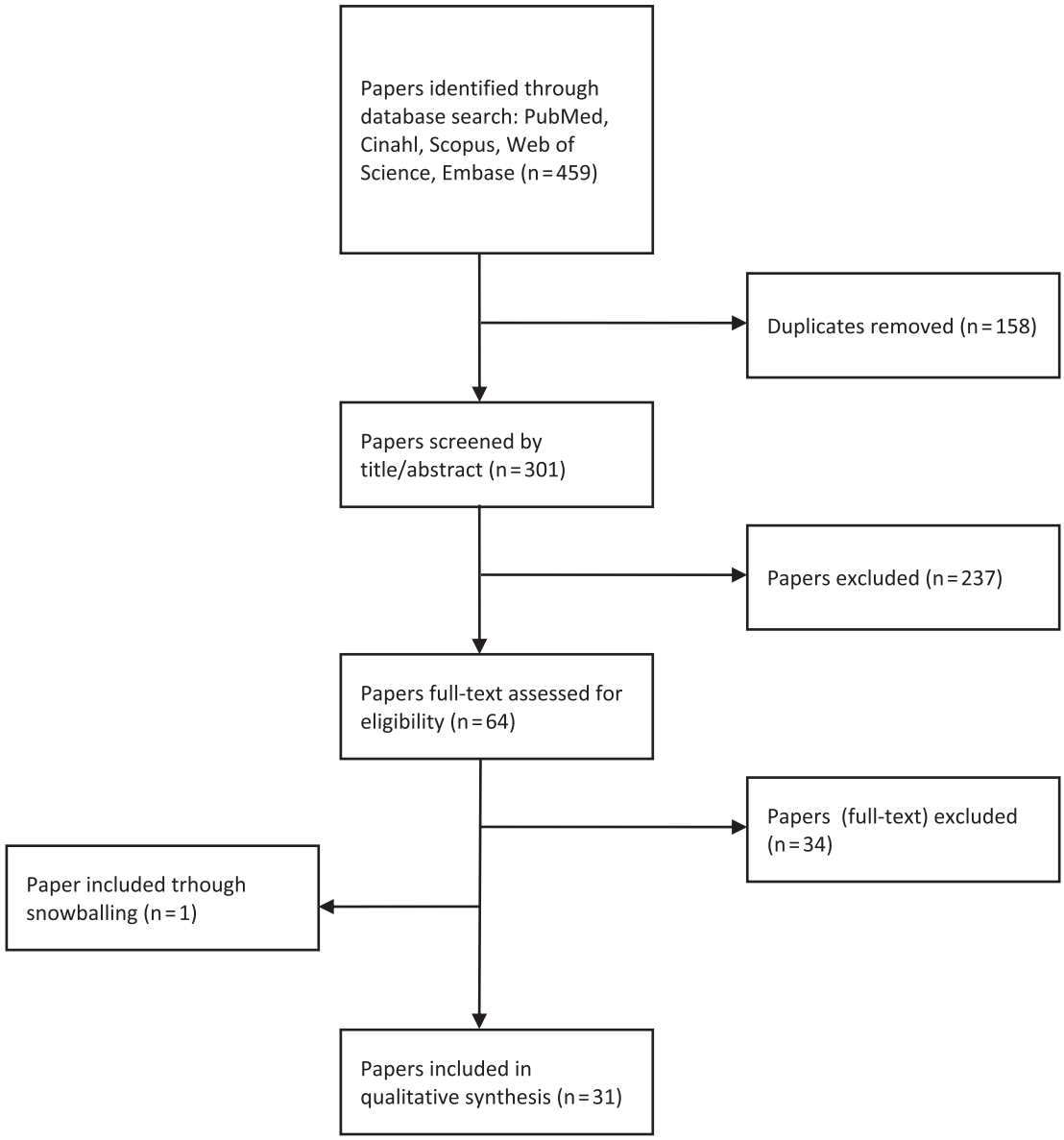

FIGURE 1 PRISMA flowchart.

neurons pick up the signal and carry it to the cortex.[12] In humans, there are three different types of fibers produced by primary neurons: A-beta fibers are large and myelinated and are activated by non-noxious stimuli such as light touch. A-delta fibers are small, poorly myelinated, and conduct noxious stimuli related to acute sensations. Finally, C-fibers are unmyelinated (and therefore slow) and, like A-delta fibers, conduct painful stimuli but are mainly involved in prolonged sensations (e.g., burning). A-delta and C-fibers terminate in the skin, muscles, joints, and visceral organs, with their cell bodies located in the dorsal root ganglia and trigeminal ganglia.[13] Second-order neurons can be nociceptive-specific (NS) or wide dynamic spectrum (WDR) neurons. The latter synapse with all the fibers mentioned above (A-beta, A-delta, and C), whereas nociceptive-specific neurons only synapse with A-delta and C-fibers. This means that WDR neurons are activated by all noxious and non-noxious, whereas noxious stimuli only activate NS neurons.[14]

Suppose the interneurons of the substantia gelatinosa are stimulated by non-noxious stimuli through the A-beta fibers. In that case, an inhibitory response is produced, and the pain door closes, thus preventing pain from reaching the brain.[2] In contrast, when stimulation passes through the A-delta or C-fibers, the result is an excitatory response that opens the door to pain. Once the signals reach the brain, they are sent back down through a descending modulation and perceived as painful sensations of varying intensity. Pain transmission

through the A-delta and C-fibers can, however, be inhibited by activation of the A-beta fiber [2] (Figure 2).

From a biochemical point of view, primary afferent neurons from the periphery synchronize with second-order neurons in the dorsal horn of the spinal cord. During the synapse, neurotransmitters or neuropeptides are released, of which the most important for understanding pain control are shown in Table 2.

Among the neurotransmitters shown in Table 1, glutamate is particularly important for chronic pain. It is involved in central sensitization (CS), which is associated with chronic pain. From a physiological point of view, CS is a sign of plasticity of somatosensory nerve pathways in case of inflammation or injury; it results from increased membrane excitability, increased synaptic efficiency, and reduced inhibition. Chronic pain is linked to hyperexcitability of the glutamatergic system, which leads to the development of the main sensory symptoms.[17] The action of glutamate is mediated by ionotropic (iGluRs) and metabotropic (mGluRs) receptors. The former are ligand-gated ion channels involved in the fast synaptic response to glutamate. The mGluRs are protein-coupled receptors responsible for the slow neuromodulatory response to glutamate. Both iGluRs and several mGluRs are involved in the onset and maintenance of CS, as they are expressed throughout the pain neuraxis and modulate the transmission of pain information.[18] Glial cells in the spinal cord, such as microglia and astrocytes, also contribute to CS, while cortical and subcortical structures modulate pain.[19] In neuropathic pain, the loss of function of inhibitory neurons in the spinal cord contributes to increased arousal. In chronic inflammatory pain, GABAergic inhibition is reduced in the spinal cord.[20]

Concerning other substances involved in pain perception, preclinical studies have shown that TENS inhibits the upregulation of substance P,[21] N-methyl-D-aspartate receptor 1 (NMDA-1) and cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-alpha).[22] In addition, it suppresses the expression of the p-extracellular signal-regulated kinase (both -1 and -2) and cyclooxygenase-2 in the dorsal horn and reduces serum levels of the pro-inflammatory cytokine interleukin-6.[23,24]

3.3 | Research question #2: What is the rationale behind the electrical parameters of TENS?

Regardless of the type of pain (acute or chronic), the logic of TENS remains the same, that is, to close the pain door by providing a non-noxious stimulus through the A-beta fibers; this is achieved by eliciting physiological NM. The electrical parameters used to stimulate the nerves are dictated by the effects of the electrical currents on the target fibers. As a general concept, the parameters to be considered during treatment are the electric current waveform, pulse amplitude (expressed in milliAmps, mA), pulse frequency, and duration. The literature offers insights into each of these concepts.

3.3.1 | Waveform

The pulse waveform can be monophasic or biphasic; in the latter case, unlike the monophasic waveform, there is an exchange of electrode polarity, that is, the alternation

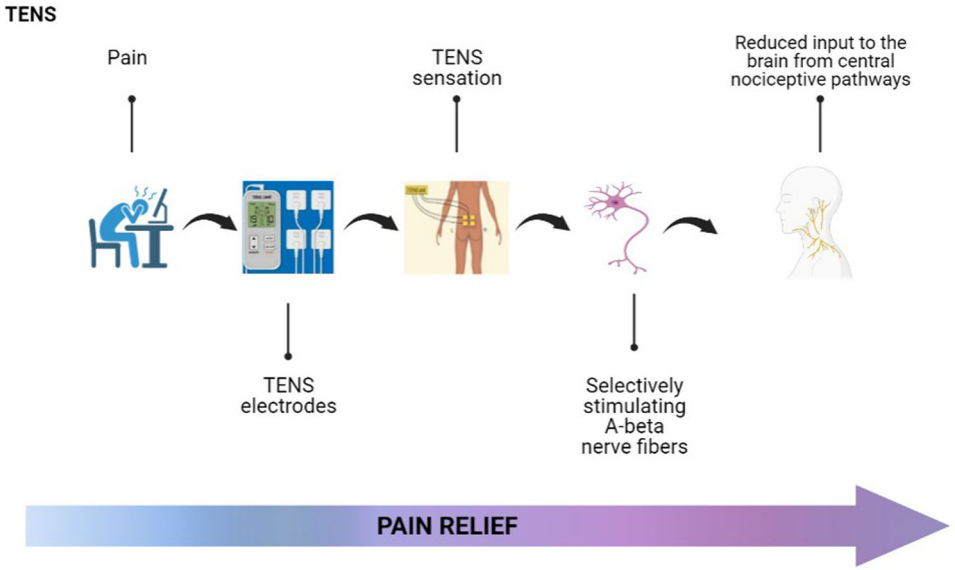

FIGURE 2 Basic mechanisms of TENS (authors' original artwork).

of cathode and anode between the two electrodes. Biphasic waveforms can be further divided into symmetrical and asymmetrical. In the first case, the first phase of the wave has a mirror image with opposite polarity to the second phase of the wave. This leads to the same amount of electrons between the electrical flow under the cathodic and anodic electrodes, with a net current flow of zero, which means no concentration of ions under the electrodes, unlike the monophasic and asymmetric biphasic waveforms. For this reason, TENS is usually delivered through symmetric biphasic waveforms, which have been shown to reduce the incidence of skin reactions because they prevent the accumulation of ions under the surface electrodes.[25] The literature, however, reports conflicting evidence on this concept, as some authors report discomfort related to the asymmetrical waveform.[26] In contrast, others report no differences between the different waveforms in pain thresholds.[27]

3.3.2 | Pulse amplitude (intensity)

TENS induces the blocking of afferent input from peripheral neurons. The TENS-generated impulses are conducted in both directions along the axon; the antidromic impulses (those conducted towards the periphery) counteract the orthodromic signals (those from the sensory receptor cells, which travel towards the central nervous system). The nociceptive input conducted in the higher threshold afferents of the A-delta and C-fibers is effectively blocked by high-amplitude TENS currents, but this often produces an uncomfortable sensation that patients have difficulty tolerating.[25] Therefore, the amplitude of the currents (measured in mA, milliAmps) is titrated to activate low-threshold nerve fibers (A-beta) selectively. This produces excitatory impulses that reach the inhibitory interneurons of the central nervous system, reducing the excitability of central nociceptive cells and, thus, a decrease in pain sensation. The amplitude directly influences the effectiveness of TENS; the literature points out that higher pulse amplitudes activate deeper tissue afferents, allowing for greater analgesia. For this reason, some authors suggest a "strong, non-painful intensity", that is, patients must perceive the electrical stimulus in the treatment area without experiencing pain due to excessive current amplitude, as lower intensities are ineffective.[28]

3.3.3 | Pulse and session duration

Pulse duration is usually classified into major and minor (<200 μs). The evidence is conflicting, with some authors stating that longer duration evokes more intense sensations of pain relief, related to greater inhibition of neuronal activity in the dorsal horn, and others reporting no effect on anti-hyperalgesic effects.[27] Pulse duration currents of 30–100 μs activate large-diameter fibers without activating smaller nociceptive fibers. Pulse durations around 100 μs stimulate both types of fibers, providing analgesia derived from the activation of the descending pain inhibitory pathways instead of gate control. As a general recommendation, a pulse duration of 50–100 μs can activate A-beta fibers and obtain antalgic effects. As regards the total session duration, the length suggested by the literature is 20–30 min.[29]

3.3.4 | Pulse frequency

The frequency of the electric current pulses is classified as high frequency (50–100 Hz), low frequency (5–10 Hz), and burst (bursts of high-frequency current applied at a much lower frequency). Over the years, several studies have distinguished between the effects of high-frequency and low-frequency TENS, with the former activating delta opioid receptors (thus reducing the release of glutamate and aspartate in the spinal cord receptors) and the latter acting on mu receptors.[30] Another study on healthy volunteers concluded that the frequency of the TENS pulses does not influence the analgesic effect, provided that the intensity, waveform, and duration of the electrical impulse are constant.[31] It should be noted that frequency modulation (offered by some commercially available electrical stimulators) does not affect the hypoalgesia induced by TENS.[31] However, some authors report that it overcomes the accommodation of nerve fibers, thus providing higher comfort to the patient.[32]

According to other authors, HF and LF TENS have effects at the site of stimulation: HF TENS reduces substance P, which increases dorsal root ganglion neurons in animals after tissue injury. In contrast, blood flow increases with LF TENS at intensities above 25% of the motor threshold.[28] This last finding is important because one of the factors maintaining chronic pelvic pain and chronic pelvic pain syndromes is hypoxia[14] (also often related to pathological breathing patterns[11]), which can be alleviated by increased blood flow. In most studies, the frequency varies from 1 to 100 Hz, depending on the levels of the painful response.[29] A study on chronic pelvic pain syndrome and chronic prostatitis suggested frequencies with optimal values around 50 Hz.[33] However, as a general consideration, it should be noted that the amplitude of current, and not frequency, is the fundamental parameter in TENS applications.[34] In women with vulvodynia, some authors

suggest the efficacy of biphasic currents between 2 and 100 Hz and 50–100 μs in relieving pain.[35]

3.4 | Research question #3: Which caveats should be considered during clinical practice with TENS for pelvic pain?

3.4.1 | Position of the electrodes

The electric current consists of a flow of electrons; the cathodic electrode of TENS (commonly marked with a black wire) attracts these particles toward the outside of the nerve membrane, thus causing depolarization on the axonal membrane and the consequent onset of the action potential. Conversely, the anodic electrode (red wire) causes hyperpolarisation resulting in blockage of nerve transmission. For this reason, the cathode is the active electrode in TENS. For these reasons, the literature recommends placing the electrodes in line along a peripheral nerve.[27] The application of TENS on acupoints reduces pain. It may be more effective than non-acupuncture sites when measuring pain and pain threshold to heat and pressure in normal subjects.[28]

When this is impossible due to the absence of healthy skin tissue or abnormal hypersensitivity, electrodes can be applied in the correct vertebral area on the corresponding spinal nerve.[27] For example, some authors reported the successful use of "box" stimulation in a patient with painful perineal lesions; with this set-up, they achieved 'crossed' stimulation and reached the pudendal and genitofemoral nerves.[36] This stimulation requires two channels, with the respective electrodes positioned as shown in Figure 3, and is consistent with the suggestions made by other authors on quadripolar stimulation.[27]

As a general consideration, close positioning of the electrodes may result in the electric field being limited to superficial tissues, as the penetration depth of the force lines increases in parallel with the distance between the electrodes.[37] This distance must be determined based on the anatomical margins of the region to be treated. In addition, the size of the electrodes must be considered for the possible effect on the electric field strength. When using electrodes of different sizes, electrons usually accumulate under the smaller one; this increases the current density (i.e., the amount of current per unit area of conduction), causing heat due to the Joule effect and feelings of discomfort.[37] The shape of the electrodes (square or circular) does not make a difference in the distribution of electrons, although this result comes from only one study conducted in vitro.[38]

3.4.2 | Tolerance to repeated TENS

Attention should be paid to the frequency of the sessions: the literature[39] reports the development of analgesic tolerance by the fourth and fifth day of treatment in healthy volunteers undergoing high-frequency and low-frequency TENS, respectively. Analgesic tolerance with TENS LF results in cross-tolerance to mu-opioid receptors in the spinal cord. In contrast, analgesic tolerance with TENS HF results in cross-tolerance to delta-opioid receptors in the spinal cord.[28] The same authors suggest that the prevention of analgesic tolerance occurs by

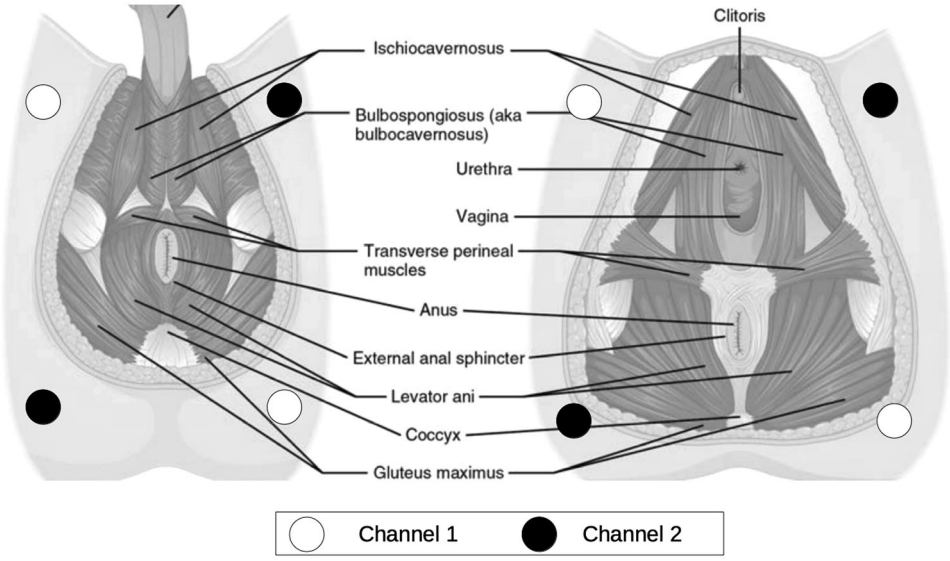

FIGURE 3 Crisscross stimulation (adapted from a public domain image, reproduced with permission from www.openstax.org).

TABLE 3 DOs and DON'Ts to consider during clinical practice with TENS.

Aspect of TENS	DOs and DON'Ts
Position of electrodes	• DO Place the electrodes on acupoints, in line, along a nerve • DO apply the electrodes in the vertebral area on the corresponding spinal nerve in case of hypersensitivity or damaged skin • DO apply quadripolar (boxed) stimulation with two channels in case of perineal tissue lesion to stimulate the pudendal and genitourinary nerves • DO use square or round electrodes indifferently, as electrode shape does not influence the distribution of electrons • DO NOT place the electrodes too close, as this will reduce the depth of penetration of the electric field • DO NOT use electrodes of different sizes, as the current density will be greater under the smaller one, and the patient will perceive heat and discomfort
Waveform	• DO prefer biphasic current waveform, as patients often perceive less discomfort than monophasic waveforms • DO prefer symmetrical waveform, as it reduces patient discomfort compared to asymmetrical current[a]
Pulse amplitude	• DO use the strongest current amplitude that the patient can stand without pain, as lower intensities are ineffective • DO remember that amplitude is the most important parameter of TENS to obtain therapeutic efficacy
Pulse duration	• DO use a pulse duration between 50 and 100 microseconds, which activates A-beta fibers and produces an antalgic effect by gate control. In comparison, a duration of about 100 microseconds also activates smaller nociceptive fibers, activating descending pain inhibitory pathways. • DO NOT use pulse duration currents shorter than 30 μs, as this is the threshold to activate large-diameter fibers
Pulse frequency	• DO use frequencies between 1 and 100 Hz as a general principle, with 50 Hz as an optimal value for chronic pelvic pain syndrome and chronic prostatitis • DO use frequencies between 2 and Hz for treating vulvodynia • DO remember that frequency is not important as current amplitude • DO NOT use frequency modulation to increase the antalgic effect of TENS, as there is no relationship between modulation and pain reduction
Session duration	• DO apply TENS for 20–30 min per session
Frequency of sessions	• DO increase current amplitude by 10% (as long as the patient experiences no pain) to prevent analgesic tolerance[b] • DO use frequency modulation to prevent analgesic tolerance • DO perform biweekly stimulations as a maximum frequency of sessions • DO NOT perform daily sessions, as this is likely to induce analgesic tolerance in 4–5 days

[a]Conflicting evidence in literature.

[b]Preclinical study.

pharmacological modulation of the pathways involved in opioid tolerance. In particular, blocking NMDA-glutamate receptors or CCK (cholecystokinin) receptors in the spinal cord prevents analgesic tolerance to both LF and HF TENS. Interestingly, while frequency modulation does not affect antalgic outcomes of TENS,[31] others suggest that it helps prevent the onset of tolerance.[40] However, their evidence comes from a preclinical study on pain unrelated to the pelvic floor. Finally, another animal study suggests increasing the intensity of TENS by 10% per session to prevent tolerance.[41]

Some authors[29] suggest that, for vulvodynia, a twice-weekly or an alternate-day regimen should be preferred to the commonly reported daily regimen concerning the site of application of the TENS electrode, based on the delicate tissues of the vagina. They also reported, as anecdotal evidence based on their clinical experience, that the nociceptive system is best suited to the new situation through a gradual increase of day numbers between TENS sessions. Based on this anatomical consideration and the findings on analgesic tolerance expressed in the previous paragraphs, we agree with the recommendation of biweekly stimulations.

3.4.3 | Summary of evidence-based recommendations

Based on the literature findings reported in the previous paragraphs, we can formulate a summary of recommendations for clinical practice, which we report in Table 3.

4 | DISCUSSION

The literature retrieved covers all three research questions of this review. Some of the findings came from preclinical studies conducted in vitro or on animals, and caution should be used when applying such results to clinical practice. Nonetheless, the available studies allowed the identification of relevant aspects that no existing review had summarized in a single paper. Some conflicts remain, as in the case of symmetrical and asymmetrical currents; however, from a practical point of view, these discrepancies can be easily solved by choosing the parameters of TENS that most studies indicated are most comfortable for patients.

5 | LIMITATIONS

The main limitation of this review is the nature of some of the studies, as only a few high-quality papers exist, as pointed out by other authors in a recent systematic review.[7]

6 | CONCLUSION AND PERSPECTIVES

As the European Guidelines[42] pointed out, pelvic pain requires a multimodal approach, of which TENS is just a part. TENS should therefore be viewed as one of the components of the rehabilitation program in the frame of thorough and continuous patient assessment.[11]

AUTHOR CONTRIBUTIONS

Stefano Terzoni performed the literature search and drafted the manuscript; Cristina Mora prepared the tables and revised the parts regarding the electrical parameters of TENS; Constantina Cloconi authored Figure 2 and reviewed the manuscript draft; Giorgia Gaia, Maria Chiara Sighinolfi, Serena Maruccia, Bernardo Rocco and Barbara Pinna retrieved additional literature; Paolo Ferrara and Mauro Parozzi performed the literature search and selected the papers according to the PRISMA methodology; Anne Destrebecq wrote the methods sections.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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