REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cutaneous Electroanalgesia for Relief of Chronic and Neuropathic Pain

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Chronic pain, defined as pain that persists for more than 3 months, is a major global health problem and affects as many as 100 million adults in the United States alone. Besides the suffering, chronic pain costs the nation up to $894 billion each year in medical treatment and lost productivity.[1] Many common pharmacologic pain treatments do not always manage chronic pain effectively (especially neuropathic pain, which is caused by a lesion or disease of the somatosensory nervous system),[2] and their use may increase the risk of drug-related adverse outcomes such as addiction (e.g., opioid addiction) and polypharmacy.

Contemporary clinical guidelines recommend nonpharmacologic therapies.[3] One such approach is electroanalgesia, which has been used since Greco-Roman times, when Pliny, Aristotle, and Plutarch recommended that patients with chronic pain stand in a pool of water containing electric rays in order to receive analgesia from electrical currents.[4] Today, common forms of cutaneous electroanalgesia include transcutaneous electrical nerve stimulation (TENS) and scrambler therapy. This focused review provides an overview of the physiological effects of each approach; details the technology and safety of these two forms of cutaneous electroanalgesia; reviews clinical results of randomized trials evaluating electroanalgesia for pain related to cancer, pain due to other diseases, and neuropathic pain; and discusses limitations of the data.

TENS Therapy

Physiology of Electroanalgesia with TENS

TENS devices administer low-intensity electrical signals through conductive gel pads placed over the skin at the sites of pain. Most TENS devices can be adjusted by the patient to vary the intensity and frequency of stimulation and the width of the electrical pulse.[5] The mechanism of action of TENS devices was initially based on the premise of the gate-control theory, first proposed in 1965.[6] In this theoretical framework, stimulation of Aβ fibers activates inhibitory dorsal-horn interneurons that "close the gate" on the transmission of afferent nociceptive signals from Aδ and C fibers, leading to decreased pain perception. It has since been recognized that TENS induces numerous proanalgesic effects, such as blockade of glutamate and aspartate in the spinal cord, reduction of dorsal-horn neuron sensitization, facilitation of endogenous opioid release, and activation of peripheral α_{1A}-adrenergic receptors.[7,8] Although the electrophysiological properties have not been fully worked out at this time, differences in waveform intensity are likely to influence whether central or peripheral nervous system effects of stimulation predominate, and variations in waveform shape and frequency may confer differential effects. For example, high-frequency, low-intensity stimulation preferentially re-

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cruits Aβ fibers, whereas low-frequency, high-intensity stimulation preferentially recruits Aδ and C fibers.

TENS DEVICES

Each TENS unit consists of a pair of electrodes and a central unit that transmits waveforms with various settings that can be adjusted by the patient. The most common waveforms are shown in Figure 1. The operator, usually the patient, can vary the width of the electrical pulse and the magnitude of stimulation, which usually ranges from 3 to 80 mA. The pair of electrodes is placed on the skin across the area of pain, as shown in Figure 2A. The operator increases the current or tries different patterns of waveforms until the pain is relieved. The instructions for most TENS devices suggest using the device for an hour. With a TENS device, the analgesic effects dissipate within minutes to hours after discontinuation of the stimulation.

TENS devices are contraindicated in patients with cardiac pacemakers or epilepsy and in areas of the skin above vascular, neurologic, or dermatologic injury.[8] Minor skin irritation or erythema and tenderness at the site of electrode application appear to be the most common adverse effects, and no serious adverse events have been reported.[7]

USE IN PATIENTS WITH CHRONIC, REFRACTORY PAIN

Since their introduction to the market in 1974, TENS devices have been used for a broad range of refractory, chronic pain conditions. The evidence of their effectiveness is largely based on open-label trials or case series, with the largest randomized trial comprising three groups of women with fibromyalgia: 103 receiving TENS, 99 receiving placebo TENS, and 99 receiving neither TENS nor placebo TENS.[9] Movement-evoked pain intensity (the primary outcome) was rated on a scale from 0 (no pain) to 10 (worst pain possible) after measurement of the distance a person could walk in 6 minutes and the sit-to-stand test, which measures how long it takes a person to move from sitting to standing five times. Baseline scores for pain with movement in the three groups ranged from 6.2 to 6.5 after the 6-minute walk test and from 5.5 to 5.8 after the sit-to-stand test. After 4 weeks, the decrease in pain after the 6-minute walk test was −1.8 points (95% confidence interval [CI], −2.3 to −1.2), a 27% decrease, in the TENS group, as compared with −0.8 points (95% CI, −1.4 to −0.2) in the placebo TENS group (P=0.008) and −0.006 points (95% CI, −0.5 to 0.6) in the no-treatment group (P<0.001). The results were similar with the change from baseline in the sit-to-stand test. The 1.8-point difference between active TENS and placebo TENS meets the minimum clinically important difference in the pain-rating scale of 1 point on a scale of 0 to 10.[10]

In a large two-group trial, Buchmuller et al. randomly assigned 236 patients with chronic low back pain to TENS plus analgesic medications (117 patients) or to placebo TENS plus analgesic medications (119 patients).[11] The primary outcome — function — did not differ significantly between the two groups at 3 months. Adverse events were reported in 10.4% and 10.6% of the patients in the TENS and placebo TENS groups, respectively.

The results of Cochrane systematic reviews of TENS trials for chronic pain that have been completed since 2000 are reported in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The largest disease-specific effect size seen was in patients with neuropathic pain, with a change from baseline of −1.58 points on an 11-point visual-analogue scale[11]; on these scales, a 1-point change is considered to be clinically significant.[10] Despite the magnitude of the change, the authors were unable to conclude that TENS was effective because of the low quality of the evidence (e.g., small samples and heterogeneous study populations and outcome measures), as designated on the basis of the Cochrane reviewers' grading system.

Johnson et al. performed a meta-analysis of 381 randomized, controlled trials.[12] They noted that with both acute and chronic pain, patient-reported pain intensity was lower during TENS than during placebo TENS (the same lead placement but without electrical current). The meta-analysis showed that the standardized mean difference (SMD, the mean difference divided by the standard deviation in each trial and averaged) in pain intensity was −0.96 (with the minus sign denoting pain reduction). The authors predefined an SMD value of at least 0.4 to less than 0.7 in magnitude as a moderate effect and a value of 0.7 or higher in magnitude as a large effect. Although the precise correlative relation-

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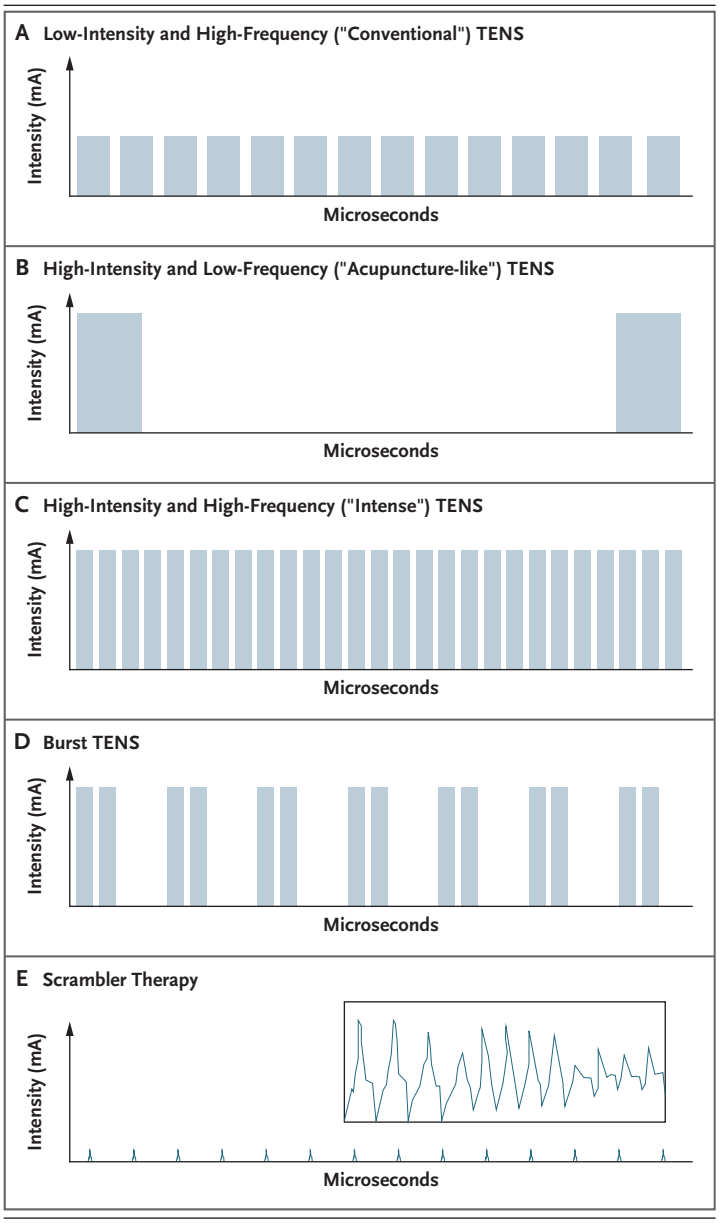


Figure 1. Waveform Patterns, Intensity, and Frequency in Transcutaneous Electrical Nerve Stimulation (TENS) and Scrambler Therapy.

Shown are the differences between TENS and scrambler therapy with regard to waveform shape and pattern, stimulation magnitude (amplitude), pulse width, and frequency. Panels A, B, C, and D show various types of TENS waveforms. The amplitude can range from 5 to 80 mA in current, but 20 to 50 mA is most common, with applied voltages of 3 to 9 V. Pulse widths (in microseconds) vary among devices, as shown in the first four panels. Panel E shows the scrambler therapy signal. It is grouped into packets of four similar but distinct waveforms, which are constantly varied by a proprietary algorithm. At the maximum magnitude of stimulation from scrambler therapy, the peak current achieved is 3.5 to 5.5 mA, with a voltage of 6.5 to 12.5 V. Each stimulation wave in Panel A (conventional TENS) represents a pulse width of 100 μsec and a stimulation magnitude of 25 mA. The waveforms in all five panels are shown in proportion and to scale. In scrambler therapy, the maximum pulse width (7 to 11 μsec) and amperage (3.5 to 5.5 mA) are significantly lower than those in TENS; the inset in Panel E shows the morphologic features of a few representative waveforms in greater detail (with frequency not to scale).

ship between SMDs and scores on visual-analogue scales has not been established, an SMD approaching 1.0 would be considered a large effect. When TENS was compared not with placebo but with pharmacologic treatments or other nonpharmacologic treatments, the SMD in pain intensity was −0.72, a value considered to represent a moderate effect. In the 20 studies specifically assessing chronic pain, the SMD was −0.66, a moderate effect. The authors concluded that there was evidence of moderate certainty that pain intensity decreases during or immediately after TENS, without serious side effects.

Of the 17 Cochrane reviews listed in Table S1, 5 clearly showed no effect of TENS on pain relief, 1 review showed a benefit in patients with rheumatoid arthritis of the hand, and 11 reviews of trials in various therapeutic settings showed evidence that was equivocal with respect to a benefit. In the single review of TENS for phantom limb pain, there were no randomized, controlled trials for inclusion in the review. Dose-limiting toxic effects were not a concern in any of the reviews.

HETEROGENEOUS RESULTS WITH TENS

Given the wide variety of TENS devices available, most of the systematic reviews or meta-analyses comprise studies with a high degree of heterogeneity in applied waveforms (e.g., intensity, frequency, or proprietary patterns). TENS might be conceptualized as a treatment category with specific options that can be tailored to patient-specific factors, much like a pharmacologic class, rather than as a homogeneous group consisting of nearly identical and interchangeable options. Despite the absence of high-quality evidence of the analgesic benefit of TENS devices for chronic or neuropathic pain, they nonetheless have value by virtue of their accessibility and safety. A key point is that

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the pain relief disappears as soon as the TENS unit is turned off.

COST AND AVAILABILITY

TENS devices are available over the counter and can be used without medical supervision. The cost of one device generally ranges from $20 to more than $300.

SCRAMBLER THERAPY

Scrambler therapy was invented by Giuseppe Marineo at the University of Rome Tor Vergata during the early 1990s.[13] It was approved by the Food and Drug Administration (FDA) in 2009 for professionally supervised treatment sessions in patients with chronic or neuropathic pain.

PHYSIOLOGY AND MECHANISMS OF ELECTROANALGESIA

Although both scrambler therapy and TENS devices administer electrical stimulation through cutaneous adhesive electrodes, scrambler therapy is a distinct type of treatment, not a variation or subcategory of TENS. Table 1 summarizes the main differences between the two approaches.

Scrambler therapy is based on the theory that an electrical stimulus on the skin can activate particular sodium–calcium channels to produce action potentials and sensations perceived as non-noxious and innocuous instead of painful.[13] The scrambler therapy signal output comprises 16 waveforms that vary slightly (Fig. 1), combined into 256 distinct sequences that are continuously changed by a proprietary software algorithm. By "scrambling" noxious stimuli into nonpainful sensations, scrambler therapy is theorized to mitigate continuous pain input and reduce central sensitization (increased responsiveness of the central nervous system to afferent input).

Recent data have shown that the optimal waveform for stimulating A fibers is rectangular, whereas for C fibers, it is sinusoidal, half-sinusoidal, or "shark fin"–like in appearance, such as the waveforms produced by scrambler therapy.[14] C-fiber stimulation, in turn, is associated with changes in cerebral blood flow associated with the inhibition of nociception and possibly central sensitization, as seen on magnetic resonance imaging in patients with burn injuries who have received scrambler therapy.[15] In one randomized trial, pain hypersensitivity was lower after scrambler therapy than with a sham approach, and scrambler therapy dramatically reduced serum messenger RNA levels of peptides associated with

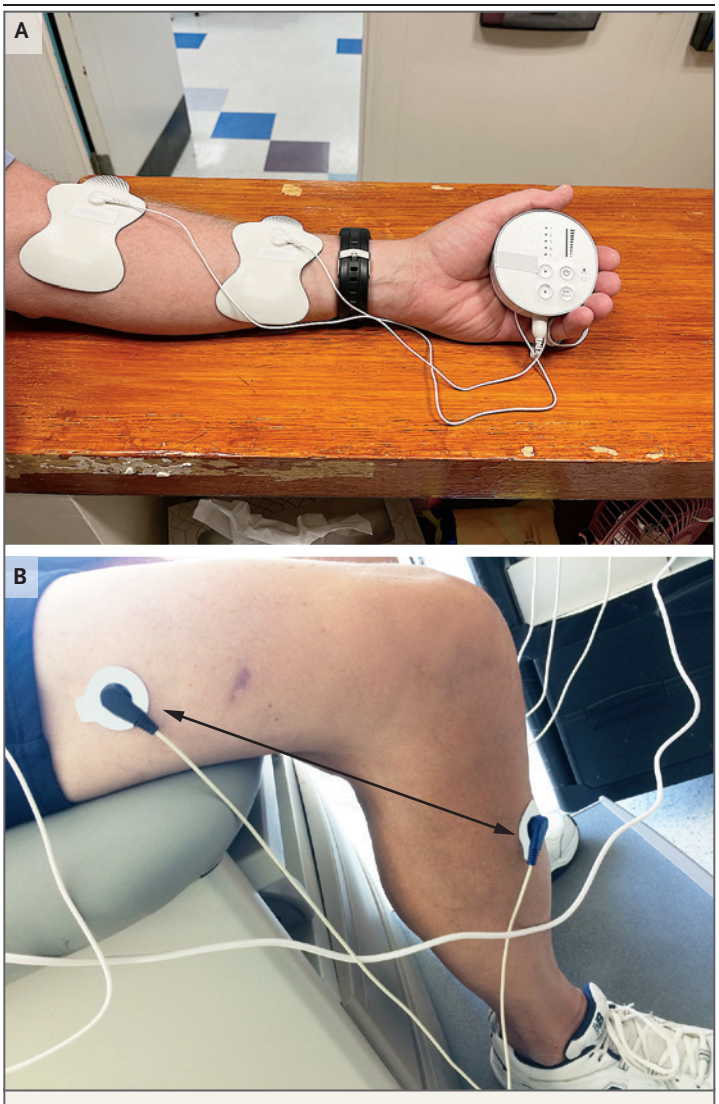


Figure 2. Application of TENS Electrodes and Use of Scrambler Therapy in a Patient with Chemotherapy-Induced Neuropathy.

Panel A shows TENS electrodes applied on either side of the area of pain. Most TENS devices allow the patient to choose among various settings for the magnitude or pattern of stimulation. Panel B shows the use of scrambler therapy in treating oxaliplatin-induced pain, numbness, and tingling on the soles of the feet. The electrodes are placed on the L5 dermatome (which innervates most of the sole), always above the area of diminished sensation, to ensure that there are enough healthy nerves to carry the scrambler therapy signal to the central nervous system. If sufficient relief is not obtained, the operator can add similar sets of electrodes on the L4 and S1 dermatomes. One session relieved this patient's symptoms for 6 weeks, and remission of pain occurred again with additional treatments.

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Table 1. Differences between Transcutaneous Electrical Nerve Stimulation (TENS) and Scrambler Therapy.

Feature	TENS	Scrambler Therapy
Theoretical model	Gate-control theory	Artificial neurons replace the chronic pain signal with nonpain waveforms, potentially resetting central sensitization and reducing peripheral inflammation
Target	Aβ fibers in peripheral nerves of affected dermatomes	Surface receptors of C fibers in affected dermatomes
Signal	Linear pulse, typically a rectangular wave, 30–150 mA, 80 Hz	Constantly varying signals that resemble action potentials; maximum, 5.5 mA, 43–52 Hz; charge per phase is 38.8 microcoulombs (μC), like the charge in TENS
Main indications	Acute musculoskeletal pain, physiotherapy	Designed specifically for chronic neuropathic and cancer pain, especially opioid-resistant pain
Duration of action	Beneficial effects generally stop when stimulation stops but may persist for several hours	Beneficial effects have been reported to persist for weeks, months, or years after sessions
Restrictions on use	No restrictions; available over the counter	Use restricted to physicians or to other qualified health care professionals under the direct supervision of a physician
Technology	Settings such as magnitude and frequency of stimulation can be modified by the patient; devices vary with respect to the number of settings and the extent to which they can be adjusted	Scrambler machine that administers electrical stimulation through cutaneous adhesive electrodes, stimulating artificial neurons (output not modifiable by the operator)

inflammation, such as nerve growth factor.[16] The latter finding may account for the potentially prolonged analgesic effects of scrambler therapy. Additional preclinical studies are needed to clarify the mechanisms of action and to correlate physiological changes (e.g., in cytokine levels) or anatomical changes (e.g., dorsal-horn alterations) with analgesia.

APPLICATION

Up to five pairs of electrodes are placed proximally and distally to the site (or sites) of pain, along the affected dermatome (or dermatomes), or only proximally to the pain along the same dermatome. Unlike TENS, scrambler therapy is delivered in scheduled sessions at a health care facility where the treatment is available. In a session, electrodes are placed on skin without known pathological changes (e.g., small-fiber nerve damage from chemotherapy) or symptoms of neuropathy (e.g., hyperesthesia or allodynia). The scrambler machine is then connected and activated, at which point patients perceive a nonpainful sensation between the electrodes. This sensation is commonly described as being bitten by electrical ants. In this regard, scrambler therapy is similar to TENS. The operator gradually increases the magnitude of the electrical stimulation in intervals of 5 to 10 minutes until the pain is relieved or the patient reaches a maximal threshold, below any perception of pain. As the current is increased, the operator says at each interval, "Tell me when you feel something," to confirm that any changes in stimulation magnitude are being perceived, and then says, "Tell me when enough is enough — the stimulus should be tingling and tolerable," to prevent excessive stimulation. Treatment is continued for 30 to 40 minutes total per day. Given the resistance of skin changes from day to day, the process is repeated anew at each treatment session to find the optimal lead placement and stimulation settings. Figure 2B shows the use of scrambler therapy in a patient with chemotherapy-induced neuropathy.

Clinically, a treatment session is judged to be successful if neuropathic pain, tingling, or numbness is relieved. If there is no relief, a different pattern of electrode placement or signal intensity is attempted. The therapeutic goal is to replace nociceptive signals in the affected field with the scrambler therapy signal, such that the patient's usual pain is reduced as much as possible during the treatment session. The duration of relief usually increases with each day of treatment, and in contrast to TENS, analgesic effects have been reported to last for weeks,[16] months,[17,18] or even years[19] after a treatment course. If identical pain symptoms recur, retreatment is likely to induce remission, according to case reports showing successful repeat treatments, but data on actual percentages are lacking.

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Scrambler therapy is contraindicated in patients with an implanted pacemaker, defibrillator, or spinal cord or peripheral-nerve stimulator and should not be used in a patient with uncontrolled epilepsy. In a recent systematic review specifically assessing the safety of scrambler therapy in a total of 1152 patients, 3 patients had complications (0.26%): contact dermatitis in 2 patients and minor ecchymosis in 1 patient. There were no serious adverse events.[20]

COST AND AVAILABILITY

The FDA restricts the sale and use of the scrambler therapy device to physicians or to health care personnel operating under the supervision of a physician. The current cost of a scrambler therapy device is $65,000, and practitioners are required to complete several days of training in its use, though there is no official certification process. Patients must travel to a health care facility that offers scrambler therapy. Unlike TENS, scrambler therapy is administered through one specific device that is licensed and distributed by a single manufacturer.

USE IN PATIENTS WITH CHRONIC, REFRACTORY PAIN

Data from several randomized clinical trials suggest an analgesic benefit with the use of scrambler therapy in patients who have chronic pain (Table S2). One of the difficulties in conducting randomized, placebo-controlled clinical trials of scrambler therapy is that the operator must use patient feedback to guide adjustments in lead placement and the magnitude of stimulation. This makes masking of active scrambler therapy difficult and is likely to result in a bias in favor of scrambler therapy.

Marineo et al. randomly assigned 52 patients with conditions involving refractory neuropathic pain (e.g., post-herpetic neuralgia, postsurgical pain, and spinal stenosis) to the best medical management provided by physicians with experience in pain management or to scrambler therapy plus the continuation of current medications.[18] The group receiving scrambler therapy had a 91% reduction in pain (as measured on a scale from 0 [no pain] to 10 [the most severe pain]), from 8.0 to 0.7, a 7.3-point difference, which persisted for at least 3 months. This result met the criterion of a 1-point reduction for a minimum clinically important difference.[10] Allodynia decreased, and the doses of opioids and other analgesic drugs were reduced by 75%. The control group had a 28% reduction in pain but no decrease in the use of drugs for pain. Because the treatment groups were not blinded, reporting biases against medical management alone could not be ruled out.

Scrambler therapy has been shown to provide a greater benefit than a sham mechanical device in patients with neuromyelitis optica spectrum disorder, which often causes neuropathic pain that is difficult to control pharmacologically.[21] With the use of an 11-point rating scale (0 to 10), pain scores for the 11 patients receiving scrambler therapy were reduced by 70%, from 5.0 (range, 4 to 8) to 1.5 (range, 0 to 3), a reduction of 3.5 points ($P<0.01$), and for 4 of the 11 patients, the pain score was reduced to 0. The 3.5-point reduction met the minimum clinically important difference of 1 point on the 11-point scale.[10] Analgesic effects were still significant 30 days after treatment but not at 60 days ($P=0.05$). Although the operator was aware of the treatment assignments, the actual device was kept behind a curtain so that the patients did not know which intervention they were receiving. Masking of the intervention was adequate, since the patients in the scrambler therapy group were not more likely than those in the control group to have accurately guessed which intervention they were receiving.

A recent meta-analysis of seven randomized trials involving 287 patients showed that scrambler therapy decreased pain scores, with an SMD of −0.85, a large effect, between the active-treatment group and the control group.[22] Use of analgesic medications was also decreased, with an SMD of −0.54, a moderate effect. The authors concluded that scrambler therapy appeared to be effective in patients with chronic pain, but larger randomized trials are needed. Several systematic reviews of scrambler therapy have shown evidence of a benefit in patients with chronic pain, neuropathic pain, or pain from cancer or other disorders.[23-26]

Some of the largest reviews and reports[17,27] indicate that 10 to 20% of patients have no analgesic response to scrambler therapy, whereas approximately 80 to 90% have a favorable response. Data from these reviews and reports on the responses and duration of the therapeutic effect are provided in Table S3.

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LIMITATIONS OF KNOWLEDGE AND FUTURE DIRECTIONS

The major limitation with respect to our understanding of electroanalgesia is the small number of well-designed, large, randomized, sham-controlled clinical trials of TENS and scrambler therapy. A general limitation in the neuromodulation literature is the lack of definitive knowledge regarding both mechanisms and pain conditions or patient-specific factors that might predict the success of electroanalgesia. Additional preclinical trials are needed to further our understanding of the relationship between cutaneous electroanalgesic stimulation and established markers of neuroinflammation (e.g., changes in dorsal-horn activation). Moreover, to minimize the potential effects of placebo on patient-reported pain outcomes that are common in the pain literature, future research should prioritize larger sham-controlled trials or, when these are operationally unfeasible, trials evaluating the comparative effectiveness of various electroanalgesic devices.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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