# Medical Policy

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| **Subject:** | Electrical Stimulation as a Treatment for Pain and Other Conditions: Surface and Percutaneous Devices | | |
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## Description/Scope

This document addresses certain types of electrical stimulation devices. These include auricular electrostimulation, external lower extremity nerve stimulation devices, H-Wave stimulation, interferential stimulation therapy, microcurrent electrical nerve stimulation, pulsed electrical stimulation, percutaneous neuromodulation therapy, supraorbital transcutaneous neurostimulation, sympathetic therapies, cranial electrical stimulation and remote electrical neuromodulation. The devices differ in various ways including the type and intensity of electrical impulse and technique for delivering electrical stimulation.

**Note:** For further information on similar technologies, please see the following related documents:

- CG-DME-03 Neuromuscular Stimulation in the Treatment of Muscle Atrophy
- CG-DME-04 Electrical Nerve Stimulation, Transcutaneous, Percutaneous
- DME.00022 Functional Electrical Stimulation (FES); Threshold Electrical Stimulation (TES)
- SURG.00158 Implantable Peripheral Nerve Stimulation Devices as a Treatment for Pain

**Note:** For additional information concerning acupuncture services, please see the following document:

- CG-ANC-03 Acupuncture

## Position Statement

**Investigational and Not Medically Necessary:**

**Note**: For examples of devices, see Types of Devices Used for Treatment in the Background/Overview section.

Electrical stimulation using the following techniques is considered **investigational and not medically necessary** for all indications:

A. Auricular electrostimulation
B. Cranial electrical stimulation (CES)
C. Electrical stimulation wound treatment device
D. Electromagnetic wound treatment device
E. External lower extremity nerve stimulation devices
F. H-Wave electrical stimulation devices
G. Interferential therapy (IF)
H. Microcurrent electrical nerve stimulation (MENS) devices
I. Non-implantable percutaneous neuromodulation therapy
J. Percutaneous electrical nerve field stimulation (PENFS)

K. Pulsed electrical stimulation
L. Pulsed electromagnetic field stimulation (PEMF)
M. Remote electrical neuromodulation (REN)
N. Supraorbital transcutaneous neurostimulation
O. Sympathetic Therapy
P. Transcutaneous electrical modulation pain reprocessing

## Rationale

*Auricular Electrostimulation Devices*

Auricular electrostimulation, also referred to as auricular electroacupuncture, is a type of ambulatory electrical stimulation of acupuncture points intended to provide continuous or intermittent stimulation over a period of several days. It is primarily proposed for the treatment of pain. A number of randomized controlled trials (RCTs) evaluating auricular electrostimulation for pain treatment have been published, and RCTs have been summarized in several systematic reviews. Most recently, Zhao and colleagues (2015) published a systematic review and meta-analysis of RCTs investigating the efficacy and safety of auricular therapy for chronic pain. In meta-analyses of RCTs comparing auricular therapy to sham treatment (4 trials) and comparing auricular therapy to interventions other than sham (7 trials), statistically significant greater benefits were found for auricular therapy. However, the effect was primarily in trials with short-term follow-up (less than 1 month). In a meta-analysis of RCTs with follow-up longer than 3 months (3 trials), there was not a significant difference in effect size between auricular therapy and control interventions.

Previously, Yeh and colleagues (2014) conducted a systematic review and meta-analysis of RCTs published in English or Chinese that compared auricular therapy (including auricular electroacupuncture) to a control intervention and used a validated pain assessment tool. A total of 22 RCTs were included; findings of 13 of these (10 in English and 3 in Chinese) were included in the meta-analysis. The pooled analysis found a statistically significantly greater reduction in pain after auricular therapy versus control (SMD [standard mean difference], -1.59, 95% confidence interval [CI], -2.36 to 0.82). There was heterogeneity among trials and most had short-term follow-up (that is, assessed immediate relief or relief after 24 or 48 hours).

RCTs comparing the P-Stim® device (Octus Spine Laguna Hills, CA) to other therapies have had limitations including a small number of participants (Holzer, 2011; Sator-Katzenschlager, 2004), a high participant withdrawal rate, outcome measures reporting limited clinical improvement in pain intensity during the treatment period (Bernateck, 2008), and no significant difference between the active treatment and sham treatment groups (Holzer, 2011; Michalek-Sauberer, 2007).

In summary, the available evidence in the peer-reviewed medical literature is insufficient to evaluate the treatment effect of auricular electrostimulation on improving health outcomes, including the treatment of acute and chronic pain and other conditions. To date, no evidence-based clinical practice guidelines recommend the use of auricular electrostimulation devices for any indication. Additional randomized studies with larger number of subjects measuring long-term outcomes are needed to evaluate the efficacy of this treatment approach.

*Cranial Electrical Stimulation (CES) Devices*

Several systematic reviews of the literature on CES devices, using low-level electrical stimulation, have been published. A 2014 Cochrane review by Kavirajan and colleagues focused on CES for treatment of depression. No studies met the review's eligibility criteria which were RCTs comparing CES to sham CES in the acute treatment of depression in adults aged 18 to 75 years. The authors concluded that there is insufficient evidence supporting CES for treating depression.

In 2018, Shekelle and colleagues published a systematic review of RCTs on the benefits and harms of CES for treatment of pain, depression, anxiety, and insomnia. To be eligible for inclusion in the review, studies needed to evaluate adults in the outpatient setting, compare CES to a sham control or an alternative intervention, and report outcome measures using standardized instruments. A total of 26 studies (28 articles) met the eligibility criteria. These included 14 studies evaluating CES for painful conditions, 3 on depression, 5 on depression and anxiety, 2 on insomnia, 1 on anxiety and 1 on anxiety and insomnia. Trial results were not considered to be suitable for pooling in meta-analyses. Studies on each of the indications were found to have methodological limitations. For example, most trials were small with fewer than 30 participants. The quality of evidence was judged to be insufficient for all conditions except one, anxiety and depression, for which the quality of evidence was judged to be low. Four of the 5 trials on anxiety and depression were published in the 1970s and used devices that are no longer available. The fifth trial (Barclay, 2014) enrolled 115 individuals with anxiety disorder, 23 of whom had co-morbid depression. The study used an Alpha-Stim device and compared active to sham treatment. Compared with sham CES, the active CES group had statistically significantly lower scores on the Hamilton Rating Scale for Anxiety (HAM-A) and the Hamilton Depression Scale (HAM-D) from baseline to the study endpoint at 5 weeks, p=0.001. A limitation of the study was a relatively short follow-up.

A 2021 systematic review by Price and colleagues evaluated the literature on AlphaStim CES for treatment of depression. The authors identified 5 RCTs and 17 non-randomized controlled trials. All of the RCTs were published prior to 2015, with the exception of one more recent and as yet unpublished study. A pooled analysis of data from the RCTs found a standard mean difference in means of -0.695 (95% CI, -0.959 to 00.430), a statistically lower result for the CES group. A pooled analysis of 16 non-randomized studies found a standard difference in means of -0.43 (SE [standard error], 0.03), significantly lower for the CES group. Studies used a variety of outcome measures and length of follow-up was not reported.

An RCT comparing the AlphaStim device to a sham device in individuals with major depression was published by Morriss and colleagues in 2023. Eligibility included age 16 or older, moderate to severe depressive symptoms defined as a score of 10-19 on the Patient Health Questionnaire (PHQ-9) and a diagnosis of current primary major depression. The authors randomized 236 individuals to active treatment or sham control (n=118 in each group). Participants were advised to use the device for 60 minutes a day for 8 weeks. The primary study outcome was change on the GRID Hamilton Depression Rating Scale (GRID-HDRS-17) from baseline to 16 weeks. The authors stated that a difference of 3 points between groups is accepted internationally as the minimally clinically important difference for depression. Analysis was intention to treat (ITT), including all randomized individuals. In the ITT analysis, mean change in the GRID-HDRS-17 at 16 weeks was -5.9 (95% CI, -7.1 to -4.8) in the Alpha-Stim group

and -6.5 (95% CI, -7.7 to -5.4) in the placebo group. The difference between group was not statistically significant (mean change difference, 0.6 (95% CI, -1.0 to 2.2, p=0.46). The between-group difference was also not statistically significant in a per protocol analysis.

Several RCTs have evaluated transcranial direct current stimulation (tDCS), a type of CES with a higher level of electrical stimulation, above 1 milliamp (mA). Ko and colleagues (2022) studied the MINDD Stim device for enhancing cognition in individuals who had strokes. The study included 30 adults at least 6 months following a stroke who had cognitive dysfunction, defined as scoring less than 26 on the Korean version of the Montreal Cognitive Assessment (K-MoCA) tool. Individuals were randomized to 20 sessions home-based active or sham stimulation. Individuals were instructed to conduct five 30-minute sessions per week of 2 mA for 4 weeks. A total of 26 individuals completed study and were evaluated at the 4- and 8-week follow-up sessions. The primary outcome, increase in the K-MoCA score, did not differ significantly between groups (p=0.264). Moreover, there were not statistically significant between-group differences in secondary outcomes including the Korean version of the Dementia Rating Scale-2 (K-DRS-2), the Stroop Word Test and the Korean-Boston Naming Test.

Leffa and colleagues (2022) used a home-based tDCS device developed at a hospital in Brazil (and not commercially available in the United States) and evaluated its impact on inattention in adults with attention deficit/hyperactivity disorder (ADHD). They randomized 64 individuals (32 per group) to 4 weeks of daily 30-minute sessions with an active or sham tDCS device. Eligibility criteria included age 18 to 60 years old, meeting DSM-5 criteria for ADHD, combined or inattentive subtypes, and having moderate or severe symptoms, defined as an inattention score of at least 21 on the clinician-administered version of the adult ADHD self-report scale (CASRS). Individuals with a diagnosis of depression, anxiety, bipolar disorder, schizophrenia or other psychiatric disorders or autism spectrum disorders were excluded. Individuals received instruction on use of the device prior to initiating use and received text messages to remind them to conduct their sessions. At the 4-week follow-up, the prespecified primary outcome, symptoms of inattention as evaluated with CASRS, was 18.88 (SD, 5.79) in the tDCS group and 23.63 (SD, 3,97) in the sham group. There was a statistically significant treatment by time interaction for the CASRS score, p<0.001, indicating a greater decrease in the active versus sham group over the 3 assessment periods (baseline, 4 weeks, and 8 weeks). It is not clear whether the difference between groups in change in inattention symptoms was clinically significant and there was no follow-up beyond the end of the treatment period at 8 weeks. There were no statistically significant differences between groups in any of the secondary outcomes, including symptoms of hyperactivity-impulsivity, depression, or anxiety.

A pilot study evaluating the feasibility and safety of high-definition cathodal transcranial direct current stimulation (HD C-tDCS) for treatment of acute ischemic stroke was published by Bahr-Hosseini and colleagues in 2023. The study randomized 10 individuals who were within 24 hours of acute ischemic stroke onset to one of two doses of HD C-tDCS or a sham intervention. The doses were 1 milliamp (mA) for 20 minutes or 2 mA for 20 minutes. The primary outcome was tolerability, which was assessed with two measures, the rate of individuals completing the study intervention period and a tolerability technician questionnaire. All individuals completed the intervention and thus the first tolerability endpoint was met. For the second endpoint, no skin discoloration or rash was noted after stimulation. One individual reported mild skin burning, which resolved quickly. One symptomatic intracranial hemorrhage occurred in an individual assigned to the active treatment group; this individual was determined as not

having met study eligibility criteria and was thus at higher risk. The authors recommend larger trials of HD C-tDCS.

The American Psychiatric Society guideline on treatment of major depressive disorder (2010) did not address CES.

*Electrical and Electromagnetic Wound Treatment Devices*

Electrostimulation refers to the application of electrical current through electrodes placed directly on the skin near the wound. Electrical stimulation for wound treatment can involve low-intensity direct current, high-voltage pulsed current and alternating current devices. Electromagnetic therapy is a related but distinct form of treatment that involves the application of electromagnetic fields, rather than direct electrical current.

Published literature on electrical and electromagnetic wound treatment has been addressed in systematic reviews. Two Cochrane reviews have been published evaluating RCTs. One of these, published by Arora and colleagues in 2020, addressed electrical stimulation and the other, by Aziz and colleagues (2015) addressed electromagnetic stimulation.

The Arora et al Cochrane review (2020) identified 20 RCTs comparing electrical stimulation plus standard care to standard care only or standard care plus sham electrical stimulation for treatment of pressure ulcers. The review had 4 primary efficacy outcomes. For the outcome, proportion of pressure ulcers healed, a meta-analysis of 13 studies found that electrical stimulation increased the proportion of ulcers healed versus the control intervention (RR, 1.99, 95% CI, 1.39 to 2.85). The authors stated that they downgraded the evidence to moderate certainty due to serious risk of bias in the studies. For the outcomes, time to complete healing and a composite measure of ulcer severity, there were no significant differences between the treatment and control groups in pooled analyses. For the fourth primary outcome, ulcer surface area, the authors did not pool study findings due to heterogeneity among studies. The authors concluded:

> Electrical stimulation (ES) probably increases the proportion of pressure ulcers healed, but its effect on time to complete healing is uncertain, and the certainty of evidence for all outcomes is moderate, low or very low. The evidence to date is insufficient to support the widespread use of ES for pressure ulcers other than for research purposes.

The Aziz (2015) Cochrane review identified two RCTs comparing electromagnetic stimulation to standard care or sham stimulation for treating pressure ulcers. The authors considered both trials to have unclear risk of bias. The authors did not pool study findings. They stated that neither of the studies found a statistically significant difference in complete healing between treatment and control groups.

No systematic reviews or RCTs more recent than the Aziz study were identified evaluating electromagnetic stimulation for treatment of wounds.

*External Lower Extremity Nerve Stimulation Devices*

The tonic motor activation (TOMAC) system is a type of external lower extremity nerve stimulation device for restless leg syndrome (RLS). It is comprised of bilateral external therapy units worn on the legs over the peroneal nerve at the head of the fibula bone, with electrical stimulation provided through the therapy units to stimulate the peroneal nerve fibers and increase tibialis anterior muscle tone.

Following a proof-of-concept study with an earlier version of the device (Buchfuhrer, 2021), a multicenter double-blind sham controlled RCT evaluating TOMAC, known as the RESTFUL study, was conducted (Bogan, 2023). The RCT included individuals aged 22-79 with medication-refractory moderate-to-severe RLS. Medication-refractory was defined as having failed at least one medication prescribed for RLS due to adverse effects or insufficient response at maximum approved or tolerated dose. An International RLS Study Group Rating Scale (IRLS) total score > 15 was required for participation. Eligibility criteria also included having symptoms at least 2 nights per week, with symptoms most significant 2 hours before bedtime, at bedtime or after bedtime. Key exclusion criteria included being on unstable doses of RLS medications, sleep medications or antidepressants, having sleep disorders other than RLS and severe peripheral neuropathy in the lower legs.

A total of 133 individuals were randomized to receive TOMAC (n=68) or an identically appearing sham device (n=65). Participants were trained in use of the device and instructed to self-administer a 30-minute session when they experienced RLS symptoms, with a maximum of 4 sessions per day. The device automatically recorded usage data. The randomized comparison lasted for 4 weeks; at which time the primary endpoint was assessed. The primary efficacy endpoint was response rate according to the clinician-rated 7-point Clinical Global Impressions-Improvement (CGI-I) scale; response was defined as a rating of "much improved" or "very much improved" (score of 1 or 2). Secondary endpoints were self-reported by participants and included the Patient Global Impressions-Improvement (PGI-I) scale, Medical Outcomes Sleep (MOS) Study Problem Indices and symptom severity according to the IRLS score. After 4 weeks, the sham-group received active treatment and there was a 4-week open-label follow-up period for all participants.

In the ITT analysis of the primary efficacy endpoint at 4 weeks, 29 of 68 (45%) individuals in the TOMAC group and 10 of 65 (16%) individuals in the sham control group were considered responders per the CGI-I; the difference between groups was statistically significant (p=0.00011). Secondary endpoint analyses also favored the TOMAC group. The PCI-I responder rate was 33 of 68 (51%) individuals in the TOMAC group and 12 of 65 (19%) in the sham group, p<0.001. At the end of the additional 4 weeks of open-label follow-up, there were no differences in outcomes in the group originally assigned to TOMAC versus sham treatment. There was a high degree of TOMAC utilization. In the first 4 weeks, participants assigned to TOMAC used the device on all days they reported RLS symptoms (71% of total days). Utilization in the sham group was not reported. A limitation of this study was that there was only 4 weeks of a randomized blinded comparison of the intervention versus a sham device.

Roy and colleagues (2023) reported results of a 24-week extension study of the RESTFUL trial. All study completers were invited to participate. Study completers had received either 8 weeks of active TOMAC treatment or 4 weeks of sham treatment followed by 4 weeks of active treatment. The extension study did not differentiate between individuals who had originally been in the sham or active treatment group. Fifty-nine of the first 75 RESTFUL study participants consented to the extension study and they received usual care without TOMAC for 24 weeks. Forty-four of the final 51 RESTFUL participants consented to the extension study and they received 24

weeks of open-label TOMAC treatment. At the end of 24 weeks, the CGI-I response rate was 74% in the group that received TOMAC in the extension study and 13.5% in the group that received usual care without TOMAC; the difference between groups was statistically significant, p<0.0001. The PGI-I response rate was 75.0% in the group that received TOMAC and 20.3% in the group that received usual care without TOMAC, p<0.0001. Outcomes in the extension study may have been impacted by the prior treatment that participants had received in the initial study and may have differed from those in TOMAC-naïve populations; all participants in the extension study had previously received TOMAC and the treatment was taken away for some of the participants.

In 2023, Buchfuhrer and colleagues published findings of a case series with 20 individuals with opioid-refractory RLS to evaluate the impact of TOMAC on opioid utilization. Study participants were recruited from online advertising. It included adults aged 18–89 years with primary RLS taking prescription opioids for refractory RLS and a baseline opioid dose ≤ 60 morphine milligram equivalents (MMEs) per day. Key exclusion criteria were other primary sleep disorders that were inadequately treated, unstable doses of sleep medications or antidepressants, severe peripheral neuropathy affecting the lower legs and severe RLS symptoms during the day (i.e., between 10 am and 6 pm). Individuals were required to maintain a stable dose of their RLS medications for the 30 days prior to study entry and a stable dose of non-opioid RLS medications during study participation. During the study, there were 3 step-downs of opioid dose, each of which included a 1-to-2-week run-in period and a 1-week assessment period. The opioid dose was reduced by 20% of the baseline dose in the first step-down, by 33% of the baseline dose in the second step-down and the dose reduction in the third step-down was at the discretion of the investigator. Participants were allowed to take rescue doses of opioids on nights with RLS symptoms. Individuals recorded daily opioid use and opioid withdrawal symptoms were assessed on a weekly basis.

The primary efficacy endpoint was the proportion of individuals with a CGI-I score of 5 or less (minimally worse to very much improved) in individuals who completed the first step-down and had an opioid dose reduction of at least 20%. A total of 14 (70%) of the 20 participants successfully reduced their opioid dose by at least 20% with a CGI-I score of 5 or less. For the other 6 participants, 2 reduced opioid dose but had a CGI-I score of 6, 3 withdrew during step 1 due to increased RLS symptoms and 1 withdrew due to personal reasons. The study lacked a comparison group that received the clinician-led opioid reduction process without TOMAC.

*H-Wave Electrical Stimulation Devices*

H-Wave electrical stimulation devices have been investigated as a treatment for a variety of conditions including pain from diabetic peripheral neuropathy, muscle spasms, temporomandibular joint (TMJ) dysfunction, reflex sympathetic dystrophy, and healing of wounds such as diabetic peripheral ulcers.

Several RCTs have been published. The early medical literature describes two trials (Kumar and Marshall, 1997; Kumar, 1998) comparing active H-Wave electrical stimulation for the treatment of painful diabetic peripheral neuropathy. Both studies included small numbers of participants (n=31 and 14, respectively). In the first study by Kumar and Marshall (1997), outcomes were assessed using a pain-grading scale ranging from 0 to 5. Both study groups experienced significant declines in pain and the post-treatment mean grade for the active group was significantly lower than the mean grade for the sham group. This study did not state if the participants, investigators, or both were blinded or if any participant withdrew from the study. The second study by Kumar and

colleagues (1998) compared H-Wave electrical stimulation with sham stimulation among individuals who did not adequately respond to an initial 4-week trial of a tricyclic antidepressant for pain from diabetic peripheral neuropathy. Stimulation therapy lasted 12 weeks, with outcomes assessed by an investigator blinded to group assignment at 4 weeks after the end of treatment. As in the earlier study, mean pain grade in both groups improved significantly, but the difference between groups after treatment significantly favored active H-Wave stimulation (p=0.03). It is unclear, however, if the participants were blinded to the type of device, and, the report does not include if any participants withdrew from the study.

The effect of H-Wave electrical stimulation on range of motion and strength testing was assessed in a randomized double-blind, placebo-controlled study of 22 individuals who underwent rotator cuff reconstruction (Blum, 2009). Both groups received the same device treatment instructions. Group I was given the H-Wave device to utilize for 1 hour twice a day for 90 days postoperatively. Group II was given the same instructions with a placebo device. Strength testing and range of motion were assessed between the groups preoperatively, 45 days postoperatively, and 90 days postoperatively by using an active/passive scale for five basic ranges of motion. The authors reported that individuals who received H-Wave electrical stimulation compared to placebo demonstrated, on average, significantly improved active range of motion at 45 and 90 days postoperatively (p=0.007 and p=0.007, respectively). Active internal rotation also demonstrated significant improvement compared to placebo at 45 days and 90 days postoperatively (p=0.007 and p=0.006, respectively). There was no significant difference between the two groups for strength testing. Interpretation of study results is preliminary and warrants further confirmation in a larger randomized, double-blind, placebo-controlled study.

Blum and colleagues (2006a; 2006b) reported on the results of a large observational study. The study consisted of a 10-item survey that assessed the therapeutic response to the H-Wave device in 6774 individuals with chronic soft-tissue injury or neuropathic pain. The H-Wave Customer Service Questionnaire measured each individual's subjective assessment of the device's effectiveness regarding decreased or eliminated need for pain medication, increased functioning and activity, and 25% or greater overall improvement. On a 10-unit visual analog scale (VAS) ranging from 0% to 100%, 75% of the study participants reported a reduced or eliminated need for pain medication; 79% reported improved functional capacity or activity; and 78% reported 25% or greater reduction of pain. The study results suggest that the use of H-Wave electrical stimulation may provide an alternative to standard pharmacologic treatment of chronic soft tissue and neuropathic pain. However, limitations of this study include lack of randomization and placebo control and the use of self-reported data. A subsequent meta-analysis by Blum and colleagues (2008) included five studies; two of them were RCTs. The authors concluded that their findings "are encouraging and support the H-Wave device as a potential non-pharmacological alternative in the management of chronic inflammatory and neuropathic pain conditions" and suggest the need for more rigorous controlled studies.

There is insufficient evidence in the peer-reviewed medical literature to support the efficacy of H-Wave electrical stimulation for any other indication.

*Interferential Stimulation (IFS) Therapy Devices*

IFS for Low Back Pain

A few studies have compared IFS for low back pain to sham or placebo control groups and have not found a significant benefit of IFS. Most recently, Franco and colleagues (2017) conducted an RCT with 6 months of follow-up to determine whether IFS therapy before Pilates exercises was more effective than placebo in individuals with chronic nonspecific low back pain. A total of 148 participants between the ages of 18 and 80 years with chronic nonspecific low back pain were allocated into 2 groups: active IFS plus Pilates or placebo IFS plus Pilates. In the first 2 weeks, participants were treated for 30 minutes with active or placebo IFS. In the following 4 weeks, 40 minutes of Pilates exercises were added after the application of the active or placebo IFS. A total of 18 sessions were offered during 6 weeks. The primary outcome measures were pain intensity, pressure pain threshold, and disability measured at 6 weeks after randomization. No significant differences were found between the groups for pain (0.1 points; 95% CI, -0.9 to 1.0 points), pressure pain threshold (25.3 kPa; 95% CI, -4.4 to 55.0 kPa), and disability (0.4 points; 95% CI, -1.3 to 2.2). The investigators concluded that active IFS before Pilates exercise was not more effective than placebo IFS in individuals with chronic nonspecific low back pain.

A 2007 double-blind RCT by Zambito and colleagues comparing IFS therapy or horizontal therapy (HT) with sham stimulation in 105 women with chronic low back pain due to multiple vertebral fractures did not find a significant difference in outcomes between groups. In addition, several early studies (Taylor, 1987; van Heijden, 1999) failed to show a significant effect of IFS compared with placebo.

Several RCTs (Albornoz-Cabello, 2017; Facci, 2011; Hurley, 2001; Hou, 2002) have found some benefit associated with IFS in individuals with low back pain; however, the lack of a placebo or control group in these studies limits the ability to draw conclusions about the efficacy of IFS. For example, Facci and colleagues (2011) published the results of an RCT comparing IFS (n=50) and TENS (n=50) to a no-treatment control group (n=40) in persons with chronic low back pain. Participants were assessed by a blinded evaluator before and after completing 10, 30-minute treatment sessions over 2 weeks; participants in the control group were reassessed after 2 weeks. A total of 137 of 150 (91%) participants completed the intervention; analysis was intention-to-treat. The mean pain intensity, as measured by a 10-point VAS, decreased 4.48 cm in the IFS group, 3.91 cm in the TENS group, and 0.85 cm in the control group. There was no statistically significant difference in pain reduction in the active treatment groups. Both groups experienced significantly greater pain reduction than the control group. Since a sham treatment was not used, a placebo effect cannot be ruled out when comparing active to control treatments. In addition, findings from this study do not demonstrate equivalence between IFS and TENS; studies with larger numbers of participants that are designed as equivalence or non-inferiority trials would be needed before drawing this conclusion.

Albornoz-Cabello and colleagues (2017) performed a single-blind RCT which compared IFS to a 'usual care' control group in 64 individuals. Participants were recruited from a private physiotherapy research clinic and had low back pain of more than 3 months, with or without pain radiating to the lower extremities above the knee. Transregional IFS was performed for participants in the experimental group, while the usual care consisted of massage, mobilization and soft-tissue techniques. All participants received up to 10 treatment sessions of 25 minutes over a 2-week period. The primary outcome measure was self-perceived pain assessed with a VAS score; secondary outcomes were measured with the Oswestry Low Back Disability Index. Evaluations were collected at baseline and after the intervention protocol. Significant between-group differences were reported for interferential current therapy on pain perception (p=0.032) and disability level (p=0.002). Limitations of this study

include the lack of a sham control, the single-blinded study design, small number of participants, and short-term outcome measurements.

Clinical practice guidelines from the American College of Physicians and the American Pain Society concluded that there was insufficient evidence to recommend IFS therapy for the treatment of low back pain (Chou, 2007).

In 2016, the Agency for Healthcare Research and Quality (AHRQ) (Chou, 2016) published a comparative effectiveness review on noninvasive treatments for acute or subacute low back pain. A total of 156 studies were included with most trials enrolling individuals with pain symptoms of at least moderate intensity (for example, > 5 on a 0- to 10-point numeric rating scale (NRS) for pain). The review evaluated pharmacotherapy and physical modalities including interferential therapy, PENS, and TENS. Four studies investigated interferential therapy for subacute to chronic low back pain. No study evaluated harms of interferential therapy. The review concluded there was insufficient evidence due to methodological limitations and study imprecision to determine the treatment effects of interferential therapy versus other interventions, or interferential therapy plus another intervention versus the other interventions alone. Additional research was recommended "…to understand optimal selection of treatments, effective combinations and sequencing of treatments, and effectiveness of treatments for radicular low back pain."

IFS for Musculoskeletal Pain

Fuentes and colleagues (2010) published a systematic review and meta-analysis of studies evaluating the efficacy of IFS therapy for the management of musculoskeletal pain. A total of 20 RCTs met the inclusion criteria; 14 of the trials reported data that could be included in the pooled meta-analysis. IFS therapy as a stand-alone intervention was not found to be more effective than placebo or an alternative intervention. A pooled analysis of 2 studies comparing IFS therapy alone and placebo did not find a statistically significant difference in pain intensity on completion of the treatment; the pooled mean difference (MD) was 1.17 (95% confidence interval [CI]: 1.70 to 4.05). In addition, a pooled analysis of two studies comparing IFS therapy alone and an alternative intervention (for example, traction or massage) did not find a significant difference in pain intensity at discharge; the pooled MD was -0.16; 95% CI: -0.62 to 0.31. In a pooled analysis of five studies comparing IFS therapy as a co-intervention to a placebo group, there was a non-significant finding (MD=1.60; 95% CI: -0.13 to 3.34). The meta-analysis found IFS therapy plus another intervention to be superior to a control group (that is, no-treatment). A pooled analysis of three studies found an MD of 2.45 (95% CI: 1.69 to 3.22). The latter analysis was limited in that the specific effects of IFS therapy versus the co-intervention could not be determined, and it did not control for potential placebo effects. The authors concluded that the results must be considered with caution due to the low number of studies that used IFS therapy alone. In addition, the heterogeneity across studies and methodological limitations prevent conclusive statements regarding analgesic efficacy.

A more recent systematic review and meta-analysis on IFS for musculoskeletal pain (Hussein, 2022) identified a total of 35 RCTs that met inclusion criteria (conducted with adults, randomized comparison, reported pain using one of several validated pain-rating measures). Seven trials compared IFS and placebo. Only 2 placebo-controlled trials were included in a pooled analysis, and the difference between groups significantly favored pain relief using IFS versus placebo, $p<0.0001$. Seven trials compared IFS to another intervention such as TENS or cryotherapy. In a

pooled analysis, the difference between IFS and other treatments on pain scores was not statistically significant, p=0.65.

Acedo and colleagues (2014) compared the muscle relaxation of the upper trapezius induced by the application of TENS and IFS in individuals with chronic nonspecific neck discomfort. A total of 64 individuals randomly assigned to a TENS or IFS received 3 consecutive days of treatment. Efficacy was assessed by electromyography (EMG) in the third week and after the end of treatments. Pain was assessed using a VAS at baseline (before TENS or IFS application) and at the end of the study. EMG assessment data were similar between groups. Those in the IFS group had a significant trapezius relaxation after 3 IFS applications when compared to baseline and intermediate evaluations ($p<0.05$). Both groups showed an improvement at the end of the study when compared to baseline ($p<0.05$). Limitations of this study include the small sample size, short duration of treatment, and lack of long-term measurement of outcomes demonstrating durability of the treatment effect.

Suriya-amarit and colleagues (2014) studied the immediate effects of IFS on shoulder pain and pain-free passive range of motion (PROM) of the shoulder in a double-blind, placebo-controlled clinical trial of individuals (n=30) with hemiplegic shoulder pain. In the IFS group, participants received treatment for 20 minutes with an amplitude-modulated frequency at 100 Hz with an increase in current intensity until the participants felt a strong tingling sensation. The primary outcome measurements were pain intensity and pain-free PROM of the shoulder until the onset of pain, measured at baseline and immediately after treatment. Participants reported a greater reduction in pain during the most painful movement after treatment with IFS than with placebo ($p<0.05$). The IFS group showed a greater improvement in post treatment pain-free PROM than the placebo group in shoulder flexion ($p<0.01$), abduction ($p<0.01$), internal rotation ($p<0.01$), and external rotation ($p<0.01$). Limitations of this study include the small sample size, an inability to generalize the results to the stroke population as a whole, and short-term effects of IFS treatment; therefore, the long-term effects of IFS treatment in individuals with hemiplegic shoulder pain is unknown.

Dissanayaka and colleagues (2016) compared the effectiveness of TENS and IFS both in combination with hot pack, myofascial release, active range of motion exercise, and a home exercise program on subjects with myofascial pain syndrome. A total of 105 subjects with an upper trapezius myofascial trigger point were randomized to one of three therapeutic regimens (n=35 each group): 1) control group: "standard care" with hot pack, active range of motion exercises, myofascial release, and a home exercise program with postural advice; 2) TENS with standard care; or, 3) IFS with standard care. All interventions were administered 8 times during 4 weeks at regular intervals. Pain intensity and cervical range of motion were measured at baseline, immediately after the first treatment, before the eighth treatment, and 1 week after the eighth treatment. The IFS group showed significant improvement in the outcome measurements when compared to the standard care group ($p<0.05$); however, significant immediate and short-term improvements were reported with TENS and standard care compared to IFS and standard care with respect to pain intensity and cervical range of motion ($p<0.05$).

IFS for OA and other Knee Pain

Several sham-controlled RCTs have been published evaluating IFS for treatment of knee pain (Atamaz, 2012; Defrin, 2015; Gundog, 2011; Jarit, 2003; Kadı, 2019). For example, Atamaz and colleagues (2012) conducted a

double-blind RCT comparing the efficacy of IFS, TENS, and shortwave diathermy in 203 individuals with knee OA. Participants were randomized to 1 of 6 groups, 3 with active treatment and 3 with sham treatment. The primary outcome was a 0 to 100 VAS assessing knee pain. Other outcomes included range of motion, time to walk 15 meters, paracetamol intake, the Nottingham Health Profile (NHP) and WOMAC scores. At 1-, 3-, and 6-month follow-up, a statistically significant difference was not reported among the 6 groups in the VAS pain score, the WOMAC pain score, or the NHP pain score. The WOMAC function score, time to walk 15 meters, and the NHP physical mobility score did not differ significantly among groups at any of the follow-up assessments. At the 1-month follow-up, paracetamol intake was significantly lower in the IFS group than the TENS group.

Gundog and colleagues (2011) compared the effectiveness of different amplitude-modulated frequencies of IFS and sham IFS on knee OA. Participants (n=60) were randomly assigned to 1 of 4 groups: 3 IFS groups at frequencies of 40 Hz, 100 Hz, and 180 Hz, or sham IFS. Treatments were performed 5 times a week for 3 weeks on both groups. During the sham treatment, placement of the pads was the same and duration was the same without the application of electrical stimulation. The primary outcome measurement was pain intensity assessed by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Mean WOMAC scores 1 month after treatment were 7.2, 6.7, and 7.8 in the 40 Hz, 100 Hz, and 180 Hz groups, respectively, and 16.1 in the sham IFS group ($p<0.05$ compared to the active treatment groups). A secondary outcome reported as pain on movement showed significantly higher benefit in the active treatment groups compared to the sham IFS group. Using a 100-point VAS score 1 month after treatment, the mean VAS score was 16.0, 17.0 and 22.5 in the 40 Hz, 100 Hz, and 180 Hz groups, respectively, and 58.5 in the sham group. There were no significant differences in outcomes among the 3 active treatment groups. Limitations of this study include small study size, the lack of reporting the number of participants assigned to each study group and follow-up rates that were not measured beyond 1 month after treatment.

In 2019, Kadı and colleagues evaluated IFS for treating pain after total knee arthroplasty surgery. A total of 113 individuals were randomized to IFS (n=57) or sham treatment (n=56). There were 98 individuals (87%) who completed the study. After 30 days, there was no significant difference between groups in pain assessed by a VAS, 0.278. Pain medication use (paracetamol) also did not differ significantly between groups after treatment and neither did outcome measures assessing range of motion or edema. In this study, IFS was not beneficial at improving outcomes after total knee arthroplasty.

IFS for Other Conditions

There is insufficient evidence on IFS for other conditions. Several RCTs have been published on IFS in individuals with soft tissue shoulder disorders (van der Heijden, 1999), TMJ syndrome or myofascial pain syndrome (Taylor, 1987), carpal tunnel syndrome (Koca, 2014) and chronic stroke plantar flexor spasticity (Suh, 2014). Studies did not find a significant treatment effect (Taylor, 1987; van der Heijden, 1999) or were limited by small sample sizes (Koca, 2014; Suh, 2014)), high drop-out rates (Koca, 2014) and short term outcome assessment (Suh, 2014).

Summary: Evidence on IFS

A substantial number of RCTs using IFS for musculoskeletal conditions vary in the adjunct treatments that are used, comparison groups, types of controls, and outcome measures. Other methodological limitations in these trials include use of multiple treatment modalities without the ability to isolate the effect of IFS or inadequate placebo control. At this time, there is insufficient or limited evidence in the peer-reviewed medical literature to draw conclusions regarding the efficacy of IFS therapy to decrease pain and facilitate healing for any condition.

*Microcurrent Electrical Nerve Stimulation (MENS) Devices*

Bertolucci and Grey (1995) compared the efficacy of MENS therapy to mid-laser and laser placebo treatment of 48 individuals with TMJ pain. There was a difference in pain and functional outcomes between laser and MENS therapy with laser being slightly higher; however, the difference was not statistically significant. There was no data to suggest whether the effect was durable and whether the effects continued with repeated use.

There has been interest in using MENS therapy in the treatment of migraine headaches. However, there are no double-blind, randomized controlled clinical trials of MENS therapy in the treatment of migraine. MENS therapy has been addressed in a few small randomized controlled trials and case series for conditions such as age-dependent muscle weakness (Kwon, 2017), chronic nonspecific back pain (Koopman, 2009), delayed onset muscle soreness (Curtis, 2010), diabetes mellitus (Gossrau, 2011; Lee, 2009), fibromyalgia (Moretti, 2012), generalized pain, hypertension (Lee, 2009), multiple sclerosis, and unhealed wounds (Lee, 2009). None of these studies are large controlled clinical trials designed to test the effectiveness of MENS therapy against a placebo device. Therefore, based on the lack of available evidence, conclusions cannot be reached about the effectiveness of MENS therapy on pain management.

*Non-implantable Percutaneous Neuromodulation Therapy (PNT) Devices*

PNT is described as a variation of PENS developed as a treatment for chronic or intractable pain. Four cross-over RCTs were conducted by one group of investigators (two studies by Ghoname, 1999; Hamza, 1999; White, 2001). Results of these studies suggest that PNT reduces low back pain and disability due to this pain; however, the randomized crossover studies also provided evidence that these benefits were temporary since pain reoccurred between treatment sessions and during 1-week periods in which treatment was stopped before a change in treatment conditions.

In a single-blinded study, Kang and colleagues (2007) randomized 70 individuals with knee OA to PNT stimulation (at the highest tolerable intensity) or placement of electrodes without stimulation (sham intervention). Individuals in the sham group were informed that they would not perceive the normal “pins and needles” with this new device. Individuals received a single treatment and were followed up for 1 week. The neuromodulation group had 100% follow-up; 7 of 35 (20%) individuals from the sham group dropped out. VAS pain scores improved immediately after active (from 5.4 to 3.2) but not sham (5.6 to 4.9) treatments. VAS scores (4.6 vs. 5.2) were not significantly different for the 2 groups at 48 hours after treatment. Changes in the WOMAC scale were significantly better for the category of stiffness (1 point change vs. 0 point change) but not for pain or function at 48 hours. Measures of satisfaction in the study participants were significantly higher in the neuromodulation group (77% vs. 11% good to excellent) at up to 1-week follow-up. Interpretation is limited by the discrepancy between participant satisfaction

ratings and 48-hour VAS pain scores, and the differential loss to follow-up in the 2 groups. These results raise questions about the effectiveness of the blinding and the contribution of short-term pain relief and placebo effects to these results. Questions also remain about the duration of the treatment effects since the study reported only short-term follow-up.

*Percutaneous electrical nerve field stimulation (PENFS)*

PENFS to Treat Chronic Abdominal Pain

PENFS has been evaluated in a single double-blind sham-controlled RCT (Kovacic, 2017). The study enrolled 115 adolescents aged 11 to 18 years with chronic abdominal pain who met ROME III criteria for a functional abdominal disorder (irritable bowel syndrome [IBS], functional dyspepsia, abdominal migraine, functional abdominal pain or functional abdominal pain syndrome). In addition, individuals needed to have an average abdominal pain score of 3 or higher (on a 10-point scale) and a minimum of 2 days per week of pain. Participants received either active (n=60) or sham (n=55) stimulation with the Neuro-Stim device (now known as the IB-Stim device, Innovative Health Solutions). The device was placed behind the ear each week for 4 weeks during clinic visits, and individuals were instructed to keep the device on for 5 days and then remove it for the last 2 days of the week. The sham devices were manufactured identically to the active devices, but without electrical charge. While the investigators claimed that both active stimulation and sham were below sensation threshold, they noted that some individuals could potentially experience an auricular sensation after device placement. At the end of week 3, 75% of individuals in the PENFS group thought they had the active device and 46% of individuals in the sham group thought they had the active device. Participants completed Pain Frequency-Severity-Duration (PFSD) questionnaires (maximum possible score=70) at visits after the first 3 weeks of treatment and at a follow-up visit at 8 to 12 weeks. The primary outcome was change in abdominal pain scores (change in worst pain intensity and a composite PFSD score). Global symptom improvement was assessed as a secondary endpoint using the Symptom Response Scale (SRS). Individuals were followed for a median of 9.2 weeks after the last week of treatment.

A total of 104 of the 115 participants (90%) were included in the primary analysis: 57 in the active PENFS group, and 47 in the sham group. One participant in the PENFS group and 7 in the sham group discontinued treatment. Between baseline and week 3, the worst pain score showed statistically significantly greater improvement in the PENFS group compared with the sham group (difference between groups 2.15 points, $p<0.0001$). However, there was no significant difference between the PENFS group and sham group in the proportion of participants who had an improvement of 30% of more in worst pain ($p=0.47$) or usual pain ($p=0.11$) from baseline to extended follow-up. The median PFSD composite scores decreased significantly more in the PENFS versus sham treatment group (difference between groups, 11.48 points, $p<0.0001$) at week 3. At extended follow-up, both the median worst pain score ($p=0.019$) and the composite PFSD score ($p=0.018$) improved significantly more in the PENFS group compared with the sham treatment group. SRS scores reflected improvements in the PENFS group at 3 weeks versus the sham group ($p=0.0003$), no significant difference between groups was observed at the extended follow-up. The authors noted that the study did not assess changes in bowel habits, considered the most bothersome IBS symptom, and only focused on pain reduction. Reported side effects were similar in the 2 groups and there were no serious adverse events (SAEs).

Several secondary analyses of the Kovacic (2017) RCT have been published. Krasaelap and colleagues (2020) reported on 50 participants with IBS (27 from the PENFS group and 23 in the sham group). They found that significantly more individuals in the active treatment group had at least a 30% or more reduction in worst abdominal pain than individuals in the sham group at 3 weeks (59% versus 26%, p=0.024). Kovacic (2020) examined the association between treatment efficacy and a pre-treatment physiological measure known as vagal efficiency (VE), which was defined as the change in heart rate per unit change in respiratory sinus arrhythmia). The authors found a statistically significant association between low VE and pain reduction in the treatment group and no significant associations in the sham or high-VE groups.

In 2024, Chogle and colleagues reported on data from an open-label registry of children aged 8 to 18 years undergoing PENFS for abdominal pain related to disorders of gut-brain interaction. Up to 12 weeks of data were available per participant. Each week, trained professionals placed the PENFS device on participants, who wore them for 5 days, at which point the family removed the device. A total of 371 individuals were included in the database, and 292 had sufficient data available for the analysis. Compared with child-reported median API scores at baseline (2.68, n=288), scores were significantly improved at 3 weeks (1.99, n=209) and at 3 and 6 months ($p<0.001$ for each comparison). Sample size was only 75 at 3 months and 60 at 6 months. Parent-reported API scores were similar to the child reports. This study lacked a comparison group and had inconsistent follow-up.

While initial findings of the Kovacic (2017) RCT are promising, additional controlled studies are necessary to confirm the results of the study. Given the chronic nature of abdominal pain-related functional gastrointestinal disorders, a longer assessment period is also needed to establish the durability of efficacy. Furthermore, the clinical significance of the purported effects of the PENFS is difficult to assess based on current findings.

PENFS to Reduce Symptoms of Opioid Withdrawal

Results of a retrospective analysis of 73 individuals who were voluntarily treated with the Bridge device was published in 2018 by Miranda and Taca. Eligibility criteria included age at least 18 years old, meeting DSM-IV criteria for opioid dependence and voluntary presentation at an outpatient drug treatment clinic. The primary outcome measure was reduction in Clinical Opioid Withdrawal Scale (COWS) scores. The COWS scale ranges from 0 to 48 and symptoms are categorized as follows: 5-12, mild; 13-24, moderate; 25-36 moderately severe; >36, severe. Most individuals received Bridge placement in the clinic and were sent home within approximately the first hour, when symptoms of withdrawal were relieved. They were instructed to leave the device on for 5-days. Prior to Bridge placement, the mean COWS score was 20.1 (SD, 6.1). By 60 minutes after placement, the mean score was 3.1 (SD, 3.4). No rescue medication was used during the first 60 minutes after device placement and no antipsychotic narcotic or benzodiazepine medications were given during the 5 days of device use. A total of 28 of 73 individuals (38%) used an antiemetic. A total of 33 of 73 individuals (45%) had data available after 5 days of treatment. In this group, the mean COWS score before receiving the first dose of naltrexone was 0.6. No adverse events were reported in any participant. Limitations of the study are the lack of a comparison group, a large amount of missing data at 5 days, and no long-term data to evaluate health outcomes such as sustained abstinence.

PENFS to Reduce Post-Surgical Opioid Use

In 2021, Ahmed and colleagues published data on use of the Bridge device to reduce post-surgical opioid use after Roux-en-Y gastric bypass. The analysis included 8 individuals who received the Bridge device and 10 individuals who underwent similar surgery and did not receive the Bridge device. For those using the Bridge device, it was placed on the individual's ear in the post-anesthesia care unit. The device remained in place and active for 5 days. The primary study outcome was opioid requirement (oral morphine equivalent [OME], in milligrams), 24 hours after surgery. At 24 hours, the OME was 15.19 (SD, 15.02) in the Bridge group and 38.15 (SD, 38.32) in the comparison group. Although use in the Bridge group was lower, the difference between groups was not statistically significant (p=0.063). The difference between groups in OME was also not statistically significant at 24-48 hours post-operatively. In addition, there were no statistically significant differences in the rate of post-operative nausea and vomiting, time to oral intake or time to hospital discharge.

Another study on use of the Bridge device to reduce post-surgical opioid use (Chelly, 2021) was a prospective non-randomized comparison of 10 individuals receiving the Bridge device and 10 control individuals, all of whom underwent donor kidney laparoscopic surgery. For individuals who received the Bridge device, the device remained active for 5 days. The primary study outcome was opioid consumption during the first 24 hours after surgery measured in OME. In the first 24 hours, the mg OME was 8.3 (SD, 9.6) in the Bridge group and 33.5 (SD, 37.3) in the control group; the difference between groups was statistically significant (p=0.03). At 48 hours, the mean pain rating on a 10-point VAS scale was significantly lower in the Bridge group (1.6) versus the comparison group (6.0) and opioid consumption between the groups did not differ significantly (p=0.33). The study did not address long-term outcomes.

Two similarly designed double-blind RCTs evaluating PENFS with the NSS-2 Bridge device for reducing post-surgical opioid use were published by Ilfeld and colleagues in 2024. Both studies involved the randomization of participants who were in the recovery room to 5 days of active stimulation with the NSS-2 Bridge device or sham stimulation. Participants were contacted by telephone for data collection for 5 days. Pain scores were measured using a 10-point NRS score. Each study included 30 participants, 15 randomized to active treatment and 15 to sham treatment. Studies addressed different surgical procedures, cholecystectomy and hernia repair (Ilfeld, 2024a) and knee arthroplasty (Ilfeld, 2024b). In the cholecystectomy and hernia repair study, there was no difference between groups in the median oxycodone use during the first 5 days (0 mg in both groups, p=0.524). The median reported pain level on the NRS scale was 0.6 (IQR [interquartile range] 0.3 to 2.4) in the active stimulation group and 2.6 (IQR, 1.1 to 3.7) in the sham group, p=0.041. In the knee arthroplasty study, there was significantly lower oxycodone consumption in the active treatment group (median, 4mg; IQR, 2 to 12mg) than the sham group (median, 13mg, IQR, 5 to 23mg), p=0.039. The average pain intensity was lower in the active treatment group (median NRS 2.5, IQR, 1.5 to 3.3) than the sham group (median NRS 4.0, IQR, 3.6 to 4.8), p=0.014.

In 2022, Tirado and colleagues published an RCT evaluating the Sparrow device for reducing symptoms related to opioid withdrawal. Eligibility included age 18 to 65 years old seeking treatment for opioid withdrawal symptoms, current opioid physical dependence, use of prescription or non-prescription opioids and a Clinical Opiate Withdrawal Scale (COWS) of at least 13 at baseline (moderate withdrawal symptoms), or in moderate to severe withdrawal according to the investigators, Mean duration from last opioid use to initiation of Sparrow therapy was 2.5 days. A total of 31 individuals were randomized to 30 minutes of blinded active or sham Sparrow stimulation, followed by active stimulation in the group assigned to sham and then a 5-day open-label follow-up period. The

primary outcome measure, COWS from baseline to 60-minutes, was assessed for all participants after both groups received active stimulation. The finding was that the COWS was significantly reduced from baseline by a mean of 7.0 points (SD, 4.7), p<0.001. A comparison of COWS at 30 minutes, following the blinded comparison, was a secondary outcome. Mean (SD) reduction in COWS was 6.3 (3.2) in the active treatment group and 3.7 (3.8) in the sham group; the difference was significantly significant, p=0.036. The study was limited by a relatively small sample size and a one-time brief 30-minute randomized comparison period.

*Pulsed Electrical Stimulation (PES) or Pulsed Electromagnetic Field Stimulation (PEMF) Devices*

A number of RCTs have been published evaluating PES and/or pulsed short-wave electromagnetic field stimulation (PEMF) and these have been summarized in systematic reviews. Several Cochrane reviews have addressed PES and/or PEMF stimulation for treatment of pain and related conditions: Kroeling (2013) on neck pain, Li (2013) on osteoarthritis and Page (2016) on rotator cuff disease. The Cochrane reviews by Page and colleagues and by Kroeling and colleagues (which identified four relevant trials each on PEMF) did not pool study findings due to heterogeneity among trials.

A systematic review by Negm and colleagues (2013) included seven small sham controlled RCTs examining PES or PEMF for the treatment of knee OA. The total sample size was 459 individuals. Five of the trials were conducted outside of the United States, and only one trial was considered to be at low risk of bias. There was no significant difference between the active and sham groups for the outcome of pain. Physical function was significantly higher with PES or PEMF stimulation, with a standardized mean difference of 0.22. The internal validity of the included studies is limited due to a number of factors, including a high risk of bias and inconsistency in the reported results. All of the studies had small sample sizes with wide confidence intervals around outcomes, leading to imprecise estimates of the treatment effect.

Li and colleagues (2013) performed a meta-analysis of nine studies (n=636 participants) evaluating the use of PES and PEMF stimulation for treating OA. The meta-analysis found that participants who were randomized to PES or PEMF stimulation rated their pain relief as greater than sham-treated participants by 15.10 more on a scale of 0 to 100; however, no statistically significant effect was found on function or quality of life. In three studies, a high risk of bias was identified for incomplete outcome data. For all nine studies, the authors noted there were inadequacies in reporting of study design and conduct, making it unclear whether there was bias due to selective outcome reporting.

Additional RCTs or quasi-randomized trials were published after the systematic reviews. Wuschech and colleagues (2015) evaluated 10-minute daily treatment with the MAGCELL® ARTHRO (Physiomed® Elektromedizin, Germany) in a semi-randomized, double-blind, sham-controlled study of 57 subjects with OA. Due to efficacy at the interim analysis, only the first 26 subjects underwent randomization; the remainder were assigned to the active treatment group, although subjects and assessors remained blinded to treatment. Treatment was performed for 5 minutes, twice daily over 18 days. In the sham group, WOMAC total score was 56.9 at baseline and 56.2 at follow-up. In the active PEMF group, WOMAC total score decreased from 65.4 to 42.9. Intention-to-treat analysis showed that the active PEMF group had a clinically and statistically significant reduction in pain (p<0.001) on the WOMAC score compared to the sham group. Stiffness (p=0.032) and disability in daily activities (p=0.005) on the

WOMAC score were also significantly reduced in the active PEMF group. Limitations of this study include the small sample size and whether it was sufficiently powered to draw meaningful conclusions, as the power analysis indicated that 28 participants would be needed per group. To date, the MAGCELL ARTHRO device has not received FDA 510(k) clearance for use in the treatment of any condition.

Bagnato and colleagues (2016) evaluated the effectiveness of a wearable PEMF device in the management of pain in knee OA. In this randomized, double-blind, sham-controlled trial, 60 subjects were treated with 12 hours of nightly ActiPatch® therapy (BioElectronics Corporation, Frederick, MD). After 1 month of treatment, there was a clinically significant decrease (25.5%) in VAS pain scores in the PEMF group compared with a 3.6% reduction in the sham group (effect size, -0.73; 95% CI, -1.24 to -0.19). WOMAC total score was reduced by 18.4% in the active treatment group compared to 2.3% for controls (effect size, -0.34; 95% CI, -0.85 to 0.17). SF-36 Physical Component Summary scores also improved significantly with nightly PEMF. Limitations of this study include the small number of subjects and lack of long-term efficacy outcomes.

Dundar and colleagues (2016) performed a sham-controlled double-blind RCT of 40 subjects who received either conventional physical therapy or physical therapy and PEMF therapy for knee OA pain. The investigators reported there was no additional treatment benefit after 20 minutes of adjuvant PEMF therapy on pain reduction as measured by either the VAS or WOMAC pain scales.

Multanen and colleagues (2018) conducted a double-blind cross-over RCT in which 108 women with fibromyalgia received 12 weeks of PEMF therapy and 12 weeks of sham (inactive) treatment, in random order. There was a 3-week washout period between treatments. The primary outcomes were pain on a 100-point VAS and a validated symptom and function questionnaire, the Fibromyalgia Impact Questionnaire (FIQ). No significant differences were found between groups in the primary outcome measures at any time. Study findings suggest that PEMF is not effective for reducing pain or improving symptoms in individuals with fibromyalgia.

The Shoulder Pacemaker™ is a type of pulsed electrical stimulation; with the device, various muscle stimulation protocols are available to assist shoulder rehabilitation. One proof of concept case series evaluating electrical muscle stimulation (EMS), the basis for the Shoulder Pacemaker, was published (Moroder, 2020). The study included 16 individuals with non-controllable posterior positional functional shoulder instability (PP-FSI). Two individuals were excluded from the analysis due to non-adherence. The intervention consisted of three 1-hour treatment sessions per week for 3 weeks and involved 30 minutes of motion exercises while EMS was applied, followed by 30 minutes physical therapy without EMS application. The study used various types of EMS devices. Participants underwent regular assessment up to 24 months after treatment ended. All clinical outcome measures, which included the Western Ontario Shoulder Instability Index (WOSI), Subjective Shoulder Value and Rowe Score, improved significantly after treatment compared with before treatment, at all follow-up time points. The study combined treatment with an EMS device with physical therapy, and did not include a comparison group.

In 2021, the American Academy of Orthopaedic Surgeons (AAOS) published updated guidelines on the treatment of OA of the knee. The guideline noted that PEMF is a modality that that may be used to improve pain and/or function in patients with knee OA. It states that evidence is limited and cited the Bagnato (2016) study, discussed above.

In summary, there is insufficient evidence in the peer-reviewed published literature to support the efficacy of PES and PEMF devices for decreasing pain and improving function in individuals with OA and RA. The conclusions drawn from the available studies are limited by methodological limitations and inconsistency of the study results. No published studies for RA were identified. Methodologically sound, well-designed randomized, double-blind, controlled trials with larger populations are required before any clinical benefits can be suggested from the use of PES when compared to other established treatment modalities.

*Remote electrical neuromodulation (REN) Devices*

A double-blind RCT by Yarnitsky and colleagues (2019) evaluated the Nerivio™ REN device for treatment of acute migraine. The trial included 252 adults who met International Classification of Headache Disorders (ICHD-3-beta) criteria for migraine, had 2-8 migraines per month and less than 12 headache days per year. Participants needed to either be on no preventive migraine medication or be stable on medication. Individuals were randomized to receive either active or sham stimulation devices. A total of 202 participants (99 in the active group and 103 in the sham group) who completed a test treatment session within 1 hour of symptom onset and reported pain at 2 hours formed the modified intention-to-treat population. The treatment session lasted 45 minutes and outcomes were reported at 2 hours. Significantly more individuals in the active treatment group (66 of 99, 66.7%) than the sham group (40/103, 38.8%) ($p<0.001$) reported pain relief at 2 hours. Rescue medication use at 2 hours was reported by 1% of the active treatment group and 3.8% of the sham group; the difference was not statistically significant, $p=0.190$. Additional RCTs are needed that seek to replicate positive findings in other groups of individuals and that evaluate REN use over longer periods of time.

An open-label extension of the Yarnitsky RCT included 160 of the 252 (63%) randomized participants (Marmura, 2020). A total of 139 individuals used the REN device at least once during the extension study and the analysis focused on the 117 of these individuals who had treated at least 1 migraine attack with REN and reported pain intensity 2 hours post-treatment. Of the 117 individuals, 57 had been in the active group during the double-blind treatment phase and 60 had been in the sham group. The mean number of reported migraine attacks per person was 3.21 (SD, 2.27) in the extension study compared with 3.44 (SD, 1.25) during the run-in phase of the RCT. A total of 105 of the 117 (89.7%) individuals included in the extension study analysis treated their migraine attacks solely with REN and avoided medication. Medication was avoided by 18 of 117 (15.4%) of individuals during the run-in phase of the RCT. In the extension study, 67 of 117 (57.3%) individuals reported pain relief at 2 hours post-treatment for at least 50% of their attacks, compared with 68 of 117 (58.1%) in the run-in phase ($p=0.999$).

In 2023, Tepper and colleagues reported on a double-blind sham-controlled RCT evaluating the Nerivio REN device for migraine prevention. The study included 248 individuals aged 18-75 who had a 6-month history of headaches meeting ICHD-3 criteria for chronic or episodic migraine, had 6 to 24 headache days per 28-day period in each of the 3 months preceding study participation and either did not use preventive medication or were on a stable dose. In an initial 4-week baseline phase, individuals completed daily headache diaries and continued using medication, if applicable. If eligible for participation in the 8-week experimental phase based on number of headache days, individuals were randomized to receive either active (n=128) or sham (n=120) stimulation devices, and were instructed to conduct a 45-minute session every other day. At baseline, a total of 36% of individuals in the

active group and 47% in the sham group were on preventive medication; the proportion did not differ significantly between groups (p=0.094). A total of 179 of the 248 randomized individuals (72%) were included in the analysis (95 in the active group and 84 in the placebo group). Individuals were excluded from the analysis who did not complete at least 22 daily reports, did not complete at least 12 treatments or who dropped out of the study. In weeks 9-12 of the study (the second 4 weeks of the experimental phase), 23 (9.3%) participants did not complete a sufficient number of daily reports, 19 (7.7%) did not perform at least 12 treatments and 19 (7.7%) did not do both. The primary study endpoint was the difference between groups in the number of migraine days per month in the baseline phase (weeks 1-4) versus during study weeks 9-12. Mean change in number of migraine days was -4.0 (SD, 4.0) in the REN group and -1.3 (SD, 4.0) in the sham group, a mean difference of 2.76 days (p<0.001). Among the secondary outcomes, 51.6% in the REN group and 35.7% in the sham group had at least a 50% reduction in moderate/severe headache days per month (p=0.033). At the end of the intervention period, 41 of 95 (43.2%) of the participants in the REN group and 29 of 84 (34.5%) of participants in the sham group correctly guessed their group assignment; the difference between groups was not statistically significant. A safety analysis was performed that included all randomized individuals. There were 2 SAEs in the REN group, a suicide attempt and appendicitis surgery. The study investigators deemed these SAEs unrelated to the device or study procedures. There were no SAEs in the sham group. A limitation of this study is that nearly 30% of the randomized individuals were excluded from the primary efficacy analysis and thus the benefits of randomization may not have been maintained, making it more difficult to conclude that the groups were similar other than the intervention. Moreover, 15% of the randomized individuals did not perform the recommended number of treatments which brings into question compliance outside of the experimental setting.

A number of uncontrolled studies have also been published (Ailani, 2022; Grosberg, 2021; Hershey 2021a; Hershey, 2020b; Nierenburg, 2020; Nierenburg, 2021; Tepper, 2020). A prospective uncontrolled study reporting on REN to treat adolescents with migraine, was published by Hershey (2021a). Eligibility criteria included age 12 to 17 years old, meeting ICHD-3 criteria for migraine with or without aura, history of at least 3 migraine episodes per month for each of the previous 3 months, with typical headache duration of at least 3 hours. A total of 60 individuals were enrolled in the study, 45 continued in the treatment phase that followed a 4-week run-in phase, and 39 were included in the final analysis set. An evaluation of the efficacy of REN was conducted at the time of each individual's first-treated qualifying migraine headache. During this test treatment, 28 of 39 individuals (71%) reported pain relief at 2 hours post-treatment and 14 of 39 (35%) reported being pain-free at 2 hours. At 24 hours after treatment, 20 of 22 (90%) individuals who had initially reported pain relief and had data available reported continued pain relief. The authors did not report pre and post pain scores. At baseline during test treatment, 56%, 79% and 64% of individuals reported nausea and/or vomiting, photophobia and phonophobia, respectively, and after 2 hours, 54% of these reported disappearance of nausea and/or vomiting, 41% reported disappearance of photophobia and 40% reported disappearance of phonophobia. This study lacked a control or comparison group.

In a post-hoc analysis of data on 35 of the participants in the Hershey (2021a) study, Hershey and colleagues (2021b) compared outcomes during the run-in phase of the study, during which time individuals were treated with medication, to outcomes during the intervention phase when REN was used. Pain relief 2 hours after initiating treatment of a migraine episode occurred in 25 of 35 (71.4%) of participants in the REN phrase and 20 of 35 (57.1%) participants in the medication phase; the difference between groups was not statistically significant, p=0.225. Freedom from pain 2 hours after treatment initiation occurred in 13 of 35 (37.1%) participants in the REN

phase compared with 3 of 35 (8.6%) in the medication phase, a statistically significant difference between groups (p=0.004). Limitations of this analysis are that it was not blinded and severity of migraine episodes are variable.

A number of studies reporting on individuals' experiences using the Nerivio app have been published (Ailani, 2022; Esparham, 2023; Monteith, 2023; Tepper, 2020; Synowiec, 2024). In 2020, Tepper and colleagues reported on the experiences of 4725 individuals in the United States who installed the Nerivio app and used the device between October 1, 2019 and March 31, 2020. An efficacy analysis included 1384 individuals who used REN during at least one episode in which no medication was taken, and recorded pain data using the Nerivio app. In the sub-group treated by headache specialists, 662 of 1123 (58.9%) individuals reported pain relief at 2 hours for at least 50% of their treated attacks, compared with 23 of 31 (74.2%) individuals treated virtually by non-headache specialists. Moreover, 268 of 1139 (20%) individuals treated by headache specialists reported pain freedom (i.e. no pain) at 2 hours in at least 50% of treated attacks, compared with 16 of 45 (35.6%) of those treated virtually by non-headache specialists. Safety analysis included all 4725 individuals enrolled in the study. A total of 23 individuals (0.5%) experienced at least one device-related adverse event. None of the adverse events were considered to be serious and all resolved within 24 hours of treatment.

Ailani and colleagues (2022) reported on data collected from the Nervio app from 5805 users who reported symptoms and medication intake. There were data on 23,151 treatments and medication reports on 22,329 of these (n=822 had no medication report). Efficacy outcomes were calculated for each treatment session based on user reports at baseline and 2 hours after the session. Pain relief was defined as a decrease from moderate or severe headache at baseline to mild or no pain at the 2-hour follow-up. Pain freedom was defined as a decrease from mild, moderate or severe headache at baseline to no pain 2 hours after treatment. Data from 2514 users (12.734 treatments) who used REN as a standalone treatment were available for the efficacy analysis. A total of 66.5% of users reported pain relief after at least 50% of their treatments, 22.6% reported pain freedom in at least 50% of the episodes, 61.3% reported reduction in functional disability in at least 50% of the episodes and 29.8% reported returning to normal function in at least 50% of the episodes. Out of a total of 121,947 treatments by 12,368 users in the analyzed time periods, adverse events were reported by 59 (0.48%) users, none of which were severe adverse events. The analysis lacked data from a comparable control group.

Synowiec and colleagues reported on users who had used REN for 12 consecutive months. The analysis included 409 individuals with a mean age of 45.8 (SD, 15.9) years who received a total of 39,531 treatments. The monthly average number of treatments per user was 8.05 (SD, 115). Efficacy endpoints were calculated using data from all treatments in which users provided information both at the beginning of treatment and at 2 hours after initiating treatment about headache intensity, functional disability, and headache symptoms. An average efficacy of at least 50% of all treatments was reported by 74.1% (180 of 243) for pain relief, 26.0% (67 of 258) for pain freedom, 70.2% (177 of 252) for functional disability relief and by 33.7% (85 of 252) for functional disability freedom. A total of 409 users reported 9 adverse events; 8 were device-related and none of these were severe.

The American Headache Society published a consensus statement in 2021 (Ailani, 2021) that addressed REN. The document stated, "All patients with a confirmed diagnosis of migraine may be offered treatment with a neuromodulatory device, which modulates pain mechanisms involved in headache by stimulating the nervous

system centrally or peripherally with an electric current or a magnetic field". REN was one of four devices mentioned as neuromodulation devices that have been cleared by the FDA.

*Supraorbital Transcutaneous Neurostimulation*

Prophylactic Treatment of Migraine Headache

Schoenen and colleagues (2013) evaluated the safety and effectiveness of trigeminal neurostimulation in migraine headache prevention using the supraorbital transcutaneous stimulator, the Cefaly® device (STX-Med., Herstal, Belgium). The multicenter double-blind, sham-controlled RCT (PREMICE study) included 67 adults (18-65 years) who experienced two or more migraine headache attacks (with or without aura) per month and had not taken any preventive antimigraine medications in the previous 3 months. After a 1-month run-in, participants were randomized 1:1 to active or sham stimulation applied 20 minutes daily for 3 months. Primary outcomes measures included a change in migraine days and at least 50% reduction in migraine days. A total of 59 of the 67 randomized participants were included in the intent-to-treat analysis. The primary outcome measure was reported as a non-significant greater decrease in migraine days per month (active: 6.94 vs. 4.88 [-2.06]; sham: 6.54 vs. 6.22 [-0.32]; p=0.054); however, the 50% responder rate was significantly greater in the active treatment group than in the sham group (38% vs. 12.1%; p=0.023). Monthly migraine attacks (p=0.044), monthly headache days (p=0.041), and monthly acute antimigraine drug intake (p=0.007) were also significantly reduced in the treatment group but not in the sham group. The investigators reported no adverse events in either group. A greater proportion of participants in the active treatment group were moderately or very satisfied with the Cefaly device (71% vs. 39%). Limitations of this study include the small number of participants and the likelihood of bias as potential unblinding to treatment may have occurred during the trial. The investigators noted that the stimulation electrodes of the active device could be painful to finger touch while the sham device electrodes would not be painful. In addition, there were apparent differences between the two groups at baseline, as participants randomized to the treatment group were of younger (average) age and had a shorter duration of migraine attacks.

Treatment of Acute Migraine Headache

Data collected from a satisfaction survey described the observational experience of 2313 individuals with migraine headaches from France, Belgium, and Switzerland who used the Cefaly device for 40 days (Magis, 2013). The rate of reported AEs was 4.3%, and 2% (n=46) of users stopped treatment with the device due to AEs. The most common AE reported was intolerance to the paresthesias felt during electrical stimulation (1.3% of users). Other common AEs included sleepiness (0.5%), headache following treatment (0.5%), and forehead skin irritation (0.2%). A total of 53% of users elected to purchase the device after the trial period; the remainder returned the device. For those individuals who returned the device, 59% used it for the recommended length of time during the rental period, similar to the utilization duration observed in the randomized trial.

Chou and colleagues (2017) performed a prospective, open-label pilot study of 30 individuals who experienced acute migraine attacks with or without aura. Participants at a single clinic site were treated with a 1 hour session of trigeminal nerve stimulation with the Cefaly device. Pain intensity was scored using a VAS before the treatment, after the treatment session, and at 2 hours after treatment initiation. Participants were allowed to take rescue

migraine medication with treatment recorded at 2 and 24 hours. The primary outcome was the mean change in pain intensity after the 1-hour treatment compared to baseline, which was reported as significantly reduced by 57.1% after the 1-hour Cefaly treatment (-3.22 ± 2.40; p<0.001) and by 52.8% at 2 hours (-2.98 ± 2.31; p<0.001). No participants took rescue medication within the 2-hour observation phase; however, 34.6% of participants used a rescue mediation within the 24-hour follow-up. No adverse events were reported. A limitation of drawing conclusions from this pilot study was the small sample size, open-label design, lack of blinding to treatment, and no control group.

In September 2017, the FDA cleared the Cefaly Acute device, a substantially equivalent device to the predicate Cefaly device, as an external trigeminal nerve stimulator for use in the treatment of adults ≥ 18 years of age with migraine attacks, with or without aura. The FDA 510(k) clearance was based on results from a multicenter, randomized, double-blind, placebo-controlled Acute Treatment of Migraine With e-TNS trial (ACME; NCT02590939), completed in March 2017. According the clinicaltrial.gov website, eligible participants were 18 to 65 years (mean age, approximately 40 years), had a history of episodic or chronic migraine with or without aura meeting the diagnostic criteria of the International Classification of Headache Disorders (ICHD-3-beta) with the exception of "complicated migraine", experienced a migraine attack lasting for at least 3 hours with migraine pain intensity stabilized for at least 1 hour, and not have taken an acute migraine medication within the past 3 hours. Study participants were randomly assigned 1:1 to a single treatment with active or sham stimulation. The primary endpoint was the mean change in VAS pain score at 1 hour compared to baseline. Secondary endpoints included change in VAS pain scores at 2 and 24 hours from baseline, and the proportion of participants who did not use pain medications at these time points. To date, the ACME trial results have not been published in the peer-reviewed medical literature.

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) and American Headache Society (AHS) updated their evidence-based recommendations for use of pharmacologic treatment for episodic migraine prevention in adults. The guidelines do not address the use of any type of Cefaly device for prevention of episodic migraines or the treatment of acute migraine headache (Silberstein, 2012).

In summary, there is insufficient evidence in the peer-reviewed published medical literature demonstrating a significant net health benefit on the use of any type of Cefaly device for the prevention of migraine headaches or the treatment of acute migraine headaches, with or without aura. Outcomes from peer-reviewed published randomized controlled trials of large sample populations with blinding of participants are needed to determine if supraorbital transcutaneous neurostimulation with any Cefaly device improves health outcomes when compared to existing therapies for prevention of episodic migraine headaches or the treatment of acute migraine headaches, and to assess longer-term safety and adverse effects.

*Sympathetic Therapy*

Sympathetic therapy is a patented method of delivering electrostimulation via peripheral nerves to create a unique form of stimulation of the sympathetic nervous system. It incorporates dual interfering waveforms with specific electrode placement on the upper and lower extremities (eight electrodes per treatment). Electrodes are placed bilaterally over dermatomes, thus accessing the autonomic nervous system via the peripheral nervous system.

A literature search identified only one small, non-randomized study by Guido and colleagues (2002). A total of 20 individuals with chronic pain and peripheral neuropathies were treated daily with the Dynatron STS™ (Dynatron Corporation, Salt Lake City, UT) for 28 days. Pain was reported as moderate to severe by 11 of 15 individuals prior to treatment, with a decrease in pain reported by 6 of the individuals at conclusion of the treatment. For these 15 individuals who remained in the study (5 dropped out), the authors reported the mean cumulative VAS scores for multiple locations of pain decreased from 107.8 to 45.3. However, drawing conclusions concerning the efficacy of Dynatron STS for the management of chronic, intractable pain is limited due to the small participant population, lack of a randomized control group, placebo effects and lack of data on pain severity in a quarter of the subjects in this study. There is a lack of additional peer-reviewed literature concerning the efficacy of sympathetic therapy in terms of pain relief or for any other indication. Consequently, no conclusions can be drawn regarding the usefulness of this modality in terms of improving health outcomes or quality of life in individuals with moderate to severe pain.

*Transcutaneous electrical modulation pain reprocessing*

Transcutaneous electrical modulation pain reprocessing (also known as Scrambler Therapy® or Calmare pain therapy) using an MC-5A TENS device, has been evaluated in several RCTs. Two were double-blind and sham-controlled (Nayback-Beebe, 2020; Starkweather 2015). In both studies, the sham intervention was use of a device with a sub-therapeutic level of stimulation. Nayback-Beebe and colleagues included 57 individuals who had at least 3 months of chronic neuropathic pain, 97% of whom had low-back pain. At the 1-month follow-up, there were no significant differences between groups in pain intensity, use of analgesic medication or quality of life. For example, the mean score on the 11-point numerical rating scale (NRS-11) for pain was 3.1 (standard deviation [SD]: 2.0) in the active treatment group and 3.2 (SD: 2.1) in the sham group, p=0.494. The other sham-controlled study, by Starkweather and colleagues, included 30 individuals with persistent non-specific low-back pain. At the 3-week follow-up, the primary outcome, "worst" pain over the past week as measured on a 10-point scale, was significantly less in the active treatment group. Mean "worst pain" scores at 3 weeks were 3.23 (SD: 1.27) in the active treatment group and 5.81 (SD: 1.75) in the sham group, p<0.01. The authors did not report average pain over the last week.

Marineo and colleagues (2012), compared Scrambler therapy with guideline-recommended medication management. The trial included 52 individuals with at least 3 months of chronic neuropathic pain. At the 1- and 3-month follow-ups, mean scores on a 10-point VAS were significantly lower in the Scrambler group than the medication-only control group. Mean scores at 1 month were 0.78 (SD: 1.78) in the Scrambler group and 5.84 (SD 1.34) in the control group, p<0.001. At 3 months, scores were 2.03 (SD: 3.14) and 5.91 (SD: 1.44), respectively, p<0.001. The study was not blinded which could have affected participants' perceptions of their pain at follow-up.

A 2021 open-label RCT by Kashyap and colleagues compared medication management with Scrambler therapy to medication management alone in 80 individuals with head and neck or thoracic cancer who had pain of oncologic origin. The Scrambler group received 40 minutes of treatment per day for 10 days. Pain was measured on a numeric rating scale (NRS) ranging from 0 to 10, with higher numbers referring to higher levels of pain. At baseline, mean pain scores were 6.65 (SD, 0.83) in the Scrambler group and 6.57 (SD, 0.75) in the control group. Pain levels and medication use were assessed each day. On days 3 through 10, mean pain was significantly lower in the Scrambler

group than the control group. For example, on day 10, the mean NRS score was 0.74 (SD, 0.75) in the Scrambler arm and 3.15 (SD, 1.00) in the control arm, p<0.01. Morphine use was similar in the two groups at baseline. Beginning on day 7, morphine use was significantly lower in the Scrambler group compared with the control group. The study assessed multiple outcomes and did not adjust p-values for multiple comparisons.

All RCTs had relatively small sample sizes and 3 out of 4 had 1 month or less of follow-up. The two double-blind sham-controlled studies had contradictory findings. Additional randomized trials with larger sample sizes and longer follow-up are needed.

A meta-analysis of RCTs on Scrambler therapy was published by Jin and colleagues in 2022. The authors identified 7 RCTs, the ones described above and several others with small sample sizes of less than 20 individuals each. The authors assessed the included studies as "generally of low quality", including due to lack of blinding of participants and lack of blinding of outcome assessment. The authors stated that they could not rule out publication bias. In a pooled analysis of study findings, the Scambler device, compared to control, decreased pain at the end of treatment (s=SMD, -0.85, 95% CI, -1.56 to -0.03). The difference between groups was statistically significant, but the clinical significance of this degree of difference is unclear. The analysis is limited by the small size and generally low methodological quality of the included studies, as well as follow-up periods that varied among studies from the end of treatment to 3 months after treatment.

There are also several case series (Lee, 2016; Ricci, 2011; Smith, 2018), which are limited by lack of blinding and control or comparison groups.

## Background/Overview

*Auricular Electrostimulation Devices*

Auricular electrostimulation, or electroacupuncture, is a type of ambulatory electrical stimulation of acupuncture points on the ear over several days. Point stimulation by P-Stim is proposed for use in the treatment of: 1) preoperative, intraoperative and postoperative acute pain therapy (including dental procedures); 2) chronic pain syndromes associated with back pain, cervical syndrome, fibromyalgia, migraine headaches, sciatic-related pain; and, 3) pain associated with OA and RA. Other proposed uses include treatment of anxiety, depression, and special fields of anesthesia. P-Stim is generally well tolerated and can be combined with other forms of therapy.

According to the manufacturer and the U.S. Food and Drug Administration (FDA) 510(k) clearance summary (March 30, 2006), P-Stim is a single-use miniaturized, battery-powered, low frequency transcutaneous electrical nerve stimulator with a pre-programmed frequency, pulse, and duration for the stimulation of auricular acupuncture points. The device is worn behind the ear with a self-adhesive electrode patch. A selection stylus that measures electrical resistance is used to identify three auricular acupuncture points. The P-Stim device connects to the three acupuncture needles with caps and stainless steel wires. The device is powered by three zinc air batteries, each with a voltage of 1.4 V, and is preprogrammed to be on for 180 minutes, then off for 180 minutes, with a maximum battery life of up to 96 hours. The indications for use of P-Stim (and the FDA 510(k) cleared, substantially equivalent devices) are in the practice of acupuncture by qualified practitioners of acupuncture. All three devices

have similar operating principles as electrical nerve stimulators including a single output channel and mode with similar pulse width and frequencies.

*CES Devices*

Cranial Electrical Stimulation (CES), also known as electrosleep, cranial electrotherapy, and transcranial electrotherapy, involves transcutaneous delivery of low-level electrical stimulation (<1000 *u*A) to the head via electrodes. CES devices vary in terms of the location of electrode placement which can include the earlobes, mastoid processes and the zygomatic arches. maxilla-occipital junction. The mechanism of action of CES remains unclear and has been hypothesized to include deactivating cortical brain activity and altering brain connectivity to the default mode network (DMN) (Feusner, 2012).

The first CES device was approved by the FDA in the late 1970s for treatment of anxiety, insomnia and depression and a number of devices have subsequently been cleared by the FDA through the 510(k) process as substantially equivalent. Most recently, Cervella (Innovative Neurological Devices, LLC, Carmel, IN) was cleared by the FDA in March 2019 for treatment of anxiety, depression and insomnia. The device, which provides a very low level of electric current to the individual's brain, includes electrodes integrated into the ear pads of noise-cancelling Bluetooth-enabled headphones. The device is controlled by an app on the individual's smart device. Using the app, the person can control the intensity level and duration of the treatment. The manufacturer recommends 30 minute treatment sessions.

The Alpha-Stim®AID device (Electromedical Products International, Mineral Wells, TX) was cleared by the FDA in 1992 as a treatment of anxiety, insomnia and depression. Electrical stimulation is delivered via electrodes attached to earclips. The Alpha-Stim®M pain treatment device, listed below under MENS devices, can also be used to deliver CES to treat anxiety, insomnia and/or depression associated with pain.

In 2024, the Modius Stress device (Neurovalens Ltd., Ballymena, UK) was cleared by the FDA to treat generalized anxiety disorder in adults aged 22 and older. FDA materials note that the device is indicated for approximately 4 weeks and that the efficacy beyond 4 weeks has not been established.

*External Lower Extremity Nerve Stimulation Devices*

According to the FDA, this type of device "uses external electrical stimulators and cutaneous electrodes to stimulate nerves in the lower extremity (e.g., peroneal nerves) and evoke tonic, sustained muscle activation in the legs to reduce the symptoms of Restless Legs Syndrome". RLS is a neurological disorder that causes uncomfortable sensations in the legs and involves a strong urge to move them. The symptoms commonly occur later in the day and at night, and while sitting or lying down, and can severely disrupt sleep. Moving the legs tends to temporarily relieve the discomfort.

In 2023, the FDA received De Novo approval of the NTX100 Tonic Motor Activation (NTX100 ToMAc) System (Noctrix Health, Inc., Washington, DC) for the indication of "reduc[ing] symptoms of primary moderate-severe Restless Leg Syndrome and to improve sleep quality in adults refractory to medications".

*H-Wave Electrical Stimulation Devices*

H-Wave devices are classified by the FDA as a powered muscle stimulator "intended for medical purposes that repeatedly contracts muscles by passing electrical currents through electrodes contacting the affected body area." H-Wave is used in both low frequency and high frequency settings. The H-Wave Muscle Stimulator device (Electronic Waveform Lab, Inc., Huntington Beach, CA) received FDA 510(k) clearance in 2011.

*IFS Therapy Devices*

IFS therapy, also referred to as interferential therapy (IF/IFT), is a type of electrical stimulation that uses paired electrodes of two independent circuits carrying high-frequency (4,000 Hz) and medium-frequency (150 Hz) alternating currents. The superficial electrodes are aligned on the skin. It is believed that IFS permeates the tissues more effectively, with less unwanted stimulation of cutaneous nerves, and is more comfortable than TENS. IFS therapy devices are regulated by the FDA as Class II devices, with more than 50 instruments receiving 510(k) clearance.

*MENS Devices*

MENS therapy involves the application of a very precise, low, tightly controlled electrical current to specific points on the body. These points of low electrical resistance correspond with classical acupuncture points. Proposed uses include chronic and acute pain, swelling, TMJ dysfunctions, post-operative care, sports injuries and arthritis. The MICROCURRENT (Precision MICROCURRENT, Inc., Newberg, OR) has received FDA 510(k) clearance as a Class II device.

In 2021, Prelivia (Rehabtronics, Edmonton, AB, Canada) received FDA 510(k) clearance as a Class II device. The system delivers electrical stimulation to at-risk areas of skin. The level of stimulation does not fatigue muscles and thus can be used continuously. It is being marketed for the prevention of bedsores or pressure ulcers in individuals who are bedridden or chair-bound.

*PES and PEMF Devices*

PES and PEMF devices, including pulsed electromagnetic stimulation, have been used to decrease pain and joint damage and improve function in individuals with OA or RA. Several devices have been cleared by the FDA, including but not limited to, the following:

In 2003, the FDA cleared the BioniCare Stimulator BIO-1000™ (BioniCare Medical Technologies, Inc., Sparks, MD), for use as an adjunctive therapy in reducing the level of pain and symptoms associated with OA of the knee that has not adequately responded to NSAID therapy. The BioniCare BIO-1000 device is applied to the knee and can be worn under clothing and during sleep. The device should be used at least 6 hours per day. A low-amplitude pulsed electric field is delivered to the area surrounding the knee, which is purported to provide improvement in knee pain and function. The device is currently called the BioniCare Knee System and is offered by VQ OrthoCare.

The neoGEN-Series® system (RST Sanexas, Las Vegas, NV) uses electrical cell signaling, the use of electronic signal energy waves, to treat pain and other conditions. The manufacturer's website states that FDA clinical indications for the neoGEN-Series includes treatment of acute and chronic pain, but no approval or clearance documents were identified on the FDA website.

The SofPulse® (Models: 912-M10, and Roma3™, Torino II™; Ivivi Health Sciences, LLC, Montvale, NJ) received 510(k) marketing clearance (K070541) in 2008 as short-wave diathermy devices that apply electromagnetic energy at a radiofrequency of 27.12 MHz. The devices are indicated for adjunctive use in the palliative treatment of postoperative pain and edema in superficial soft tissue.

The OrthoCor™ Active Knee System™ (OrthoCor Medical, Arden Hills, MN) uses PEMF energy at a radiofrequency of 27.12 MHz to treat pain. The OrthoCor Knee System received 510(k) marketing clearance (K091996, K092044) from the FDA in 2009 and is classified as a shortwave diathermy device for use other than applying therapeutic deep heat. It is indicated for adjunctive use in the palliative treatment of postoperative pain and edema in superficial soft tissue and for the treatment of muscle and joint aches and pain associated with overexertion, strains, sprains, and arthritis. The system includes single-use packs (pods) that deliver hot or cold and are supplied in packets of 15. The predicate devices are the OrthoCor (K091640) and Ivivi Torino II™ (K070541).

*PENFS Devices*

The IB-Stim device (Innovative Health Solutions (IHS), Inc. Versailles, IN) received de novo FDA approval in 2018. According to the FDA, the device is "intended to be used in patients 11-18 years of age with functional abdominal pain associated with irritable bowel syndrome (IBS)". It is intended for use for up to 120 hours per week for up to 3 consecutive weeks; no safety data are available for longer-term use. The disposable, battery-powered device involves a stimulator that is placed behind the ear and percutaneous electrodes that are placed near the nerve branches in the ear. A pen light is used to aid in the placement of the electrodes. Electrical stimulation is delivered to branches of the cranial nerves V, VII, IX and X and the occipital nerves.

IHS also markets the NSS-2 Bridge Device, which received de novo approval by the FDA in 2017 "as an aid to reduce the symptoms of opioid withdrawal, through application to branches of Cranial Nerves V, VII, IX and X, and the occipital nerves identified by transillumination". Device use is limited to 120 hours, after which it is disposable.

S.T. Genesis, Sperenza Therapeutics (Boca Raton, FL) is also described as a device that applies stimulation to branches of cranial nerves V, VII, IX, and X and the occipital nerve, and that aids in the reduction of opioid withdrawal symptoms.

The FDA cleared the Drug Relief® device, DyAnsys, Inc.(San Mateo, CA) through the 510(k) process in 2018. The FDA stated that the device can be "used as an aid to reduce the symptoms of opioid withdrawal, through application to branches of cranial nerves V, VII, IX and X, and the occipital nerves identified by transillumination." DyAnsys, Inc. also has FDA 510(k) clearance for the PENFS device under the name First Relief® v.1 that is

intended 'to be used up to 120 hours per week up to 3 consecutive weeks, through application to cranial nerves V, VII, IX and X and the occipital nerves identified to trans-illumination, as an aid in the reduction of pain when combined with other treatments for IBS."

Another PENFS device, the Sparrow Ascent®, was cleared by the FDA under the 510(k) process in 2023. It was originally cleared under the name the Sparrow Therapy System and cited the NSS-2 Bridge as a predicate device. According to FDA documents, the Sparrow Ascent, "is intended to be used in patients experiencing opioid withdrawal in conjunction with standard symptomatic medications and other therapies for opioid withdrawal symptoms under the supervision of trained clinical personnel".

*Non-Implantable PNT Devices*

An electrical stimulation device identified as Percutaneous Neuromodulation Therapy™ Nerve Stimulation System (Vertis Neuroscience, Inc, Vancouver, WA) received FDA 510(k) clearance in 2002. The clearance order stated that the therapy is "indicated for symptomatic relief and management of chronic or intractable pain and/or as an adjunctive treatment for the management of post-surgical pain and post-trauma pain." Its primary indication is for low back pain and spinal pain. The procedure involves the insertion of pairs of electrodes into the skin of the lower back area with the intent of stimulating nerve fibers that lie in the deep tissues. Treatments may be given several times a week, typically for about 30 minutes at a time.

The Axon Therapy® Peripheral Nerve Stimulation System For Chronic Pain Relief (NeuraLace Medical, San Diego, CA).) received FDA 510k clearance in 2021. The device is indicated for pain relief in adults with chronic, intractable, post-traumatic or post-surgical pain. The system targets sensory nerve fibers with focused magnetic pulses. It is intended to be used in a clinical setting (e.g. pain management clinic or physical therapy clinic) and involves a series of 15-20 minute sessions.

*REN Devices*

The FDA approved a de novo application for a REN device (Nerivio Migra®, Theranica Bio-Electronics Ltd., Israel) in May, 2019. The Nerivio Migra system delivers low energy electrical pulses to the individual's upper arm via an armband. The device is battery-powered and controlled by software installed on a user's personal mobile device. The FDA stated that the device is indicated for acute treatment of migraine with or without aura in adults who do not have chronic migraine. In 2021, the FDA expanded use of the Nerivio to individuals age 12 older.

*Supraorbital Transcutaneous Neurostimulation Devices*

The Cefaly device was cleared by the FDA in March 2014 as a Class II "transcutaneous electrical nerve stimulator (TENS)" *de novo* device for prophylactic (preventive) treatment of episodic migraine headaches (that is, migraine headaches occurring less than 15 times a month) in adults 18 years of age or older. On September 15, 2017, the FDA cleared the Cefaly Acute device as substantially equivalent to the predicate device (Cefaly) for use during an acute migraine attack with or without aura.

The externally worn nerve stimulator is applied to the forehead using a self-adhesive electrode positioned bilaterally over the upper branches of the trigeminal nerve. The battery-powered headband device is intended to stimulate the upper branches of the trigeminal nerve in order to reduce the frequency of migraine attacks. The device consists of two distinct components: an electrical pulse generator (EPG) and a self-adhesive electrode. The Cefaly EPG is made of ABS plastic and consists of electrical circuits controlled by firmware and powered by two 1.5V batteries. The front of the Cefaly EPG has a single button that is used to turn the device on/off and adjust the intensity of the electrical stimulus during a treatment session. Visual and auditory indicators inform the user when the device is on or off and assists in troubleshooting if the device it is not working properly (for example, the device indicates if batteries need replacement and if electrical connection between device and skin is unacceptable). The back side of the Cefaly EPG has two metal blades that serve to electrically connect it to the Cefaly electrode.

A treatment session begins by attaching the Cefaly electrode to the middle of the forehead and fastening the Cefaly EPG to the electrode. When the on/off button is depressed, a pulsatile electrical stimulus is applied for 20 minutes. During the first 14 minutes, the intensity of the stimulus gradually increases until it reaches a maximum. At any time while the stimulus intensity is increasing, the user can press the button on the front of the device to select an intensity that is lower than the maximum, and it will remain constant at this lower value for the remainder of the treatment session. The device turns the stimulus off automatically after 20 minutes, or alternatively, the user can stop a treatment session by pressing the button twice or simply removing the device from their forehead.

According to the manufacturer, the following are limitations of use of the device:

- The Cefaly device cannot be used by an individual who has a cardiac pacemaker or an implanted or wearable defibrillator.
- The Cefaly device cannot be used by an individual who has an implanted metallic or electronic device in their head.
- The Cefaly device should not be used by an individual with chronic migraine, refractory migraine, medication overuse headache, or chronic tension-type headaches. The safety and effectiveness of the device has not been demonstrated for individuals with these conditions.
- The Cefaly device should not be applied on the neck or chest, and it should not be used in the presence of electronic monitoring equipment (for example, cardiac monitors), in the bath or shower, while sleeping, while driving, or while operating machinery.
- The long-term effects of using the Cefaly device are unknown.

*Sympathetic Therapy*

Sympathetic therapy describes a type of electrical stimulation of the peripheral nerves that is designed to stimulate the sympathetic nervous system in an effort to normalize the autonomic nervous system and alleviate chronic pain. Unlike TENS or IFS therapy, sympathetic therapy is not designed to treat local pain, but is designed to induce a systemic effect on sympathetically induced pain. Sympathetic therapy uses four intersecting channels of various frequencies with bilateral electrode placement on the feet, legs, arms, and hands. Electrical current is then induced with beat frequencies between 0-1000Hz. Treatment may include 1 hour of daily treatments in the physician's office followed by home treatments if the initial treatment was effective. The Dynatron STS device (Dynatronics

Corporation, Salt Lake City, UT) and companion home device, Dynatron STS Rx, are devices that deliver sympathetic therapy and have received FDA 510(k) clearance.

*Transcutaneous electrical modulation pain reprocessing*

This treatment is a transcutaneous therapy involving a rapidly changing electrical impulse that is intended to interfere with the transmission of pain signals. Treatment is delivered with a device such as the FDA-cleared Scrambler Therapy MC-5A TENS device, also known as a Calmare device, a multichannel TENS device that uses five artificial neurons. In contrast to transcutaneous electrical nerve stimulation (TENS), which generates linear waveforms to produce paresthesia and/or block the conduction of nerve fibers to produce an analgesic effect, the Scrambler/Calmare device generates nonlinear waveforms with the aim of "scrambling" pain information, with the aim of reducing the perception of pain. In 2008, the FDA cleared the Scambler device for symptomatic relief of chronic, intractable pain, acute pain and post-operative pain.

*Wearable electrical muscle stimulator*

The Shoulder Pacemaker is a wearable electrical muscle stimulator that consists of a device and electrodes placed in the shoulder area. It is designed to enhance rehabilitation by stimulating the periscapular muscles in individuals with a variety of shoulder pathologies. The device is operated via an app that can be downloaded to a personal phone or tablet. The Shoulder Pacemaker (NCS Lab SRL, Carpi, Italy) received 510k clearance from the FDA in April 2021. According to the FDA, the device is indicated for “prevention or retardation of disuse atrophy”, “muscle re-education” and “maintaining or increasing range of motion”. Use of the device is limited to adults.

**Types of Devices Used for Treatment**

*Auricular Electrical Stimulation Devices*

- AcuStim™ (S.H.P. International PTY., LTD., Fullarton, S.A., Australia)
- E-pulse (AMM Marketing LLC, Coral Springs, FL)
- P-Stim device (Octus Spine Laguna Hills, CA)

*CES Devices*

- Alpha-Stim AID (Electromedical Products International, Mineral Wells, TX)
- Cervella (Innovative Neurological Devices, LLC, Carmel, IN)
- Modius Stress (Neurovalens Ltd., Ballymena, UK)
- Transcranial direct current stimulation (tDCS): Not FDA cleared or approved. FDA approval being sought for MINDD-STIM+ device
- High-definition cathodal transcranial direct current stimulation (HD C-tDCS): Not FDA cleared or approved

*External Lower Extremity Nerve Stimulation Devices*

- NTX100 Tonic Motor Activation System (Noctrix Health, Inc., Washington, DC)

*H-Wave Electrical Stimulation Devices*

- H-Wave Muscle Simulator (Electronic Waveform Lab, Inc., Huntington Beach, CA)

*IFS Therapy Devices*

- BioStim® INF, INF Plus™ (BioMedical Life Systems, Inc., Vista, CA)
- Endomed Interferential Stimulators (Enraf Nonius B.V., Rotterdam, The Netherlands)
- Flex-IT™ (EMSI, Alexander, VA)
- Soleo Galva Electrotherapy System (Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany)
- IF 4000 (ProMed Specialties, Huntingdon Valley, PA)
- IF 8000 (Biomotion, Madison, AL)
- FastStart® IF, OrthoStim4™, SurgiStim4™, VQ™ Vector (VQ OrthoCareSM, Irvine, CA)
- RSJ, RS JC, RS-4i® Sequential Stimulator; RS-2i® Interferential Stimulator (RS Medical, Vancouver, WA)
- Stereodynator® (Gbo Medizintechnik AG, Rimbach, Germany)
- PRO ElecDT® 2000 (Hako-Med, Las Vegas, NV)
- Vectorsurge 5 Model 470 (Metron Medical-Australia PL, Victoria, Australia)

*MENS Devices*

- Algonix® (Medilab GmbH & Co., Germany)
- Alpha-Stim®M (Electromedical Products International, Inc., Mineral Wells, TX,)
- Electro-Myopulse 75 L, Electro-Myoscope 85P, Myopulse 75C (Biomedical Design Instruments, U.S.A.)
- Micro Plus™ Microcurrent Electrical Nerve Stimulator (BioMedical Life Systems, Inc. Vista, CA)
- Prelivia (Rehabtronics, Edmonton, AB, Canada)

*PENFS Devices*

- First Relief® (DyAnsys, San Mateo, CA)
- Drug Relief® (DyAnsys, San Mateo, CA)
- IB-Stim (Innovative Health Solutions, Inc. Versailles, IN)
- NSS-2 Stim BRIDGE device (Innovative Health Solutions Versailles, IN)
- Sparrow Ascent® (Spark Biomedical, San Diego, CA)
- S.T. Genesis (Sperenza Therapeutics, Boca Raton, FL)

*PES and PEMF Stimulation Devices*

- AmpCoil System (AmpCoil, Nevada City, CA)
- BioniCare Knee System (includes the OActive Knee Brace), formerly known as the BIO-1000™ System (BioniCare Medical Technologies, Inc., Sparks, MD)
- Diatermed II (Carci, São Paulo, Brazil)
- neoGEN-Series® system (RST Sanexas, Las Vegas, NV)
- OrthoCor™ Active Knee System™ (OrthoCor Medical, Arden Hills, MN)
- Oska Pulse (Oska Wellness, Carlsbad, CA)
- Shoulder Pacemaker™ (NCS America Inc., Dover, DE)

- SofPulse®, SofPulse® (Models: 912-M10, and Roma3™, Torino II™; Ivivi Health Sciences, LLC, Montvale, NJ)

*Non-Implantable PNT Devices*

- Axon Therapy® Peripheral Nerve Stimulation System For Chronic Pain Relief (NeuraLace Medical, San Diego, CA).
- BioWave PRO® Neuromodulation Pain Therapy Relief, Deepwave® Percutaneous Neuromodulation Pain Therapy System (Biowave Corporation, Norwalk, CT)
- Vertis PNT System (Vertis Neuroscience, Inc., Vancouver, WA)

*REN Devices*

- Nerivio Migra®, (Theranica Bio-Electronics Ltd., Israel)

*Supraorbital Transcutaneous Neurostimulation*

- Cefaly (STX-MED SPRL, Belgium)
- Cefaly Acute (STX-MED SPRL, Belgium)

*Sympathetic Therapy*

- Dynatron STS and Dynatron STS Rx (Companion Home Device) (Dynatronics Corporation, Salt Lake City, UT)

*Transcutaneous electrical modulation pain reprocessing*

- Scrambler Therapy, also known as Calmare® device (Calmare Therapeutics Incorporated, Fairfield, CT)

*Wearable electrical muscle stimulator*

- Shoulder Pacemaker™ (NCS Lab SRL, Carpi, Italy)

## Definitions

Clinical Global Impressions (CGI) score:
1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse

Visual analog scale (VAS): A pain assessment tool that helps an individual describe the intensity of their pain by marking on a line their level of discomfort; a VAS is a straight line with the left end of the line representing no pain and the right end of the line representing the worst pain.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider*

*reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**When services are Investigational and Not Medically Necessary:**
For the codes listed below for all indications, or when the code describes a procedure or device indicated in the Position Statement section as investigational and not medically necessary.

| | |
|---|---|
| **CPT** | |
| 64999 | Unlisted procedure, nervous system [when specified as percutaneous neuromodulation therapy] |
| 0278T | Transcutaneous electrical modulation pain reprocessing (eg, scrambler therapy), each treatment session (includes placement of electrodes) |
| 0720T | Percutaneous electrical nerve field stimulation, cranial nerves, without implantation |
| 0766T | Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve |
| 0767T | Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve |
| 0783T | Transcutaneous auricular neurostimulation, set-up, calibration, and patient education on use of equipment |
| **HCPCS** | |
| A4540 | Distal transcutaneous electrical nerve stimulator, stimulates peripheral nerves of the upper arm |
| A4543 | Supplies for transcutaneous electrical nerve stimulator, for nerves in the auricular region, per month |
| A4544 | Electrode for external lower extremity nerve stimulator for restless legs syndrome |
| A4596 | Cranial electrotherapy stimulation (CES) system supplies and accessories, per month |
| E0721 | Transcutaneous electrical nerve stimulator, stimulates nerves in the auricular region |
| E0732 | Cranial electrotherapy stimulation (CES) system, any type |
| E0743 | External lower extremity nerve stimulator for restless legs syndrome, each |
| E0761 | Non-thermal pulsed high frequency radiowaves, high peak power electromagnetic energy treatment device |
| E0762 | Transcutaneous electrical joint stimulation device system, includes all accessories [PES] |
| E0769 | Electrical stimulation or electromagnetic wound treatment device, not otherwise classified |
| E1399 | Durable medical equipment, miscellaneous [when specified as any of the types of non-implantable devices listed, including but not limited to auricular electrostimulation, H-Wave, microcurrent stimulation, PENFS, PNT, REN or sympathetic therapy devices, or headband device for trigeminal nerve stimulation for migraines] |
| S8130 | Interferential current stimulator, 2 channel |

| | |
|---|---|
| S8131 | Interferential current stimulator, 4 channel |
| S8930 | Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient |

**ICD-10 Diagnosis**

All diagnoses

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**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

## Document History

| Status | Date | Action |
|---|---|---|
| Revised | 08/08/2024 | Medical Policy & Technology Assessment Committee (MPTAC) review. Revised INV/NMN statement, adding external lower extremity nerve stimulator. Updated Description/Scope, Rationale, Background/Overview, References and Index sections. Updated Coding section with 10/01/2024 HCPCS changes; added A4543, A4544, E0721, E0743. |
| | 12/28/2023 | Updated Coding section with 01/01/2024 CPT and HCPCS changes; revised descriptors for 0766T, 0767T and removed 0768T, 0769T deleted as of 01/01/2024, added A4540, E0732 replacing K1002, K1023 deleted as of 01/01/2024. |
| Revised | 08/10/2023 | MPTAC review. Reformatted bullet points to letters. Added lines to INV/NMN statement on electrical stimulation wound treatment device, electromagnetic wound treatment devices and pulsed electromagnetic field stimulation. Updated Rationale, Background/Overview, References and Index sections. Updated Coding section to add HCPCS code E0769. |
| Reviewed | 05/11/2023 | MPTAC review. Updated Rationale, Background/Overview, References and Index sections. Updated Coding section, added HCPCS E0761. |
| | 12/28/2022 | Updated Coding section with 01/01/2023 CPT changes; added 0766T, 0767T, 0768T, 0769T and 0783T. |
| | 09/28/2022 | Updated Coding section with 10/01/2022 HCPCS changes; revised descriptor for K1002 and added A4596. |

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|---|---|---|
| | 08/29/2022 | Added transcranial direct current stimulation (tDCS) to Background/Overview section. |
| Reviewed | 05/12/2022 | MPTAC review. Updated Rationale, Background, References and Index sections. Updated Coding section with 07/01/2022 CPT changes; added 0720T. |
| Reviewed | 11/11/2021 | MPTAC review. Updated Rationale, Background, References and Index sections. |
| | 10/01/2021 | Updated Coding section with 10/01/2021 HCPCS changes; added K1023. |
| Revised | 11/05/2020 | MPTAC review. Reformatted Position Statement section to a single bulleted list of INV/NMN devices and added Note. Added "non-implantable" to bullet point on percutaneous neuromodulation therapy. Added bullet point on percutaneous electrical nerve field stimulation (PENFS) to INV/NMN statement. Updated Rationale, Background, References and Index sections. |
| Revised | 05/14/2020 | MPTAC review. Added statement that transcutaneous electrical modulation pain reprocessing is considered investigational and not medically necessary for all indications including, but not limited to, treatment of acute and chronic pain. Statements reordered in alphabetical order. Updated Rationale, Background, References and Index sections. Updated Coding section; added CPT 0278T. |
| Revised | 02/20/2020 | MPTAC review. In title, changed "related" to "other". Added statement that cranial electrical stimulation (CES) is considered investigational and not medically necessary for all indications, including but not limited to, treatment of pain, anxiety, insomnia and depression. Added statement that remote electrical neuromodulation (REN) is considered investigational and not medically necessary for all indications, including but not limited to, treatment of acute migraine headaches, with or without aura. Updated Rationale, Background, References and Index sections. Updated Coding section; added K1002. |
| Reviewed | 08/22/2019 | MPTAC review. Updated Rationale, Background and References sections. |
| Reviewed | 09/13/2018 | MPTAC review. Updated Rationale and References sections. |
| Revised | 11/02/2017 | MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Revised INV & NMN statement for supraorbital transcutaneous neurostimulation. Updated Rationale, Background, References, and Websites for Additional Information sections. |
| Reviewed | 11/03/2016 | MPTAC review. Updated formatting in Position Statement section. Updated Description, Rationale, Background, References, Websites for Additional Information and Index sections. |
| Reviewed | 11/05/2015 | MPTAC review. Updated Description, Rationale, Discussion, Device tables, References, Websites for Additional Information, and Index sections. Removed ICD-9 codes from Coding section. |
| Revised | 11/13/2014 | MPTAC review. Added investigational and not medically necessary statement for supraorbital transcutaneous neurostimulation for all indications. Updated Rationale, Background, Coding, References, Index and Websites for Additional Information sections. |

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|---|---|---|
| Revised | 08/14/2014 | MPTAC review. Added investigational and not medically necessary statement for auricular electrostimulation for all indications. Minor format changes throughout document. Updated Rationale, Background, Coding, References, Index and Websites for Additional Information sections. |
| Reviewed | 05/15/2014 | MPTAC review. Updated Rationale, References and Websites for Additional Information sections. |
| Reviewed | 05/09/2013 | MPTAC review. Updated Rationale, Background, References, and Websites for Additional Information. |
| Reviewed | 05/10/2012 | MPTAC review. Updated Description, Rationale, Background tables, References, Websites for Additional Information, and Index. |
| Reviewed | 05/19/2011 | MPTAC review. Updated Description, Rationale, Background, References, Websites for Additional Information, and Index. |
| Reviewed | 05/13/2010 | MPTAC review. Updated Discussion, Rationale, Coding, References, and Index. |
| Reviewed | 05/21/2009 | MPTAC review. Updated and clarified Description/scope of document. Updated Rationale, Background/Overview, product tables, Definitions, and References. |
| Reviewed | 05/15/2008 | MPTAC review. Updated Rationale, Background, Definitions, and References. |
| | 02/21/2008 | The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting. |
| Reviewed | 05/17/2007 | MPTAC review. Position Statements clarified. Rationale, Background, Index, and References updated. Product tables added. |
| Reviewed | 06/08/2006 | MPTAC annual review. Updated References. |
| | 01/01/2006 | Updated Coding section with 01/01/2006 CPT/HCPCS changes. |
| | 11/22/2005 | Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD). |
| Revised | 07/14/2005 | Medical review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization. |

| **Pre-Merger Organizations** | **Last Review Date** | **Document Number** | **Title** |
|---|---|---|---|
| Anthem, Inc. | 10/28/2004 | DME.00011 | Electrical Stimulation as a Treatment for Pain and Related Conditions: Surface and Percutaneous Devices |
| WellPoint Health Networks, Inc. | 09/25/2004 | 2.07.12 | Pulsed Electrical Stimulation in the Treatment of Osteoarthritis |
| | 12/2/2004 | 2.10.14 | Sympathetic Therapy as a Treatment of Chronic Pain |
| | 04/28/2005 | 5.01.01 | Inferential Current Stimulation |