Aetna considers transcutaneous electrical nerve stimulators (TENS) medically necessary durable medical equipment (DME) when used as an adjunct or as an alternative to the use of drugs either in the treatment of acute post-operative pain in the first 30 days after surgery, or for certain types of chronic, intractable pain not adequately responsive to other methods of treatment including, as appropriate, physical therapy and pharmacotherapy.

Aetna considers TENS experimental and investigational for acute pain (less than 3 months duration) other than post-operative pain. TENS is also considered experimental and investigational for any of the following (not an all-inclusive list) because there is inadequate scientific evidence to support its efficacy for these specific types of pain:

- Acute and chronic headaches
- Adhesive capsulitis (frozen shoulder)
- Carpal tunnel syndrome pain
- Cervicalgia (e.g., by means of the Quell device)
- Chemotherapy-induced peripheral neuropathy
- Chondromalacia patellae and patella femoral disorders
- Chronic low back pain
- Deep abdominal pain
- Fibromyalgia
- Hip fracture pain
- Migraine
- Musculoskeletal pain in hemophilia
- Neuropathic pain
- Pain management in burn persons
- Pelvic pain
- Peripheral arterial disease
- Phantom pain
- Post-total knee arthroplasty pain
- Rotator cuff disease (e.g., calcific tendinitis, rotator cuff tendinitis, and subacromial impingement syndrome)
- Stump pain
- Temporomandibular joint (TMJ) pain.

Note: When TENS is used for acute post-operative or chronic intractable pain, Aetna considers use of the device medically necessary initially for a trial period of at least 1 month but not to exceed 2 months. The trial period must be monitored by the physician to determine the effectiveness of the TENS unit in modulating the pain. After this 1-month trial period, continued TENS treatment may be considered medically necessary if the treatment significantly alleviates pain and if the attending physician documents that the patient is likely to derive significant therapeutic benefit from continuous use of the unit over a long period of time. The physician's records must document a reevaluation of the member at the end of the trial period, must indicate how often the member used the TENS unit, the typical duration of use each time, and the results. The physician ordering the TENS unit must be the attending physician or a consulting physician for the disease or condition resulting in the need for the TENS unit. If the TENS unit produces incomplete relief, further evaluation with percutaneous electrical nerve stimulation (PENS) may be indicated. This clinical policy is consistent with Medicare DME MAC guidelines.
II. Aetna considers a form-fitting conductive garment medically necessary DME only when it has been approved for marketing by the FDA, has been prescribed by a doctor for delivering TENS for one of the medically necessary indications listed above, and any of the following criteria is met:

- The member cannot manage without the conductive garment due to the large area or the large number of sites to be stimulated, and the stimulation would have to be delivered so frequently that it is not feasible to use conventional electrodes, adhesive tapes, and lead wires; or
- The member has a medical need for rehabilitation strengthening following an injury where the nerve supply to the muscle is intact; or
- The member has a skin problem or other medical conditions that precludes the application of conventional electrodes, adhesive tapes, and lead wires; or
- The member requires electrical stimulation beneath a cast to treat disuse atrophy, where the nerve supply to the muscle is intact.

III. Aetna considers stellate ganglion blockade using TENS experimental and investigational because its clinical value has not been established.

IV. Aetna considers interferential stimulation (e.g., RS-4i Sequential Stimulator) experimental and investigational for the reduction of pain and edema and all other indications because its effectiveness has not been established.

V. Aetna considers percutaneous electrical nerve stimulation (PENS) medically necessary DME for

A. Up to a 30-day period for the treatment of members with chronic low back pain secondary to degenerative disc disease when PENS is used as part of a multi-modality rehabilitation program that includes exercise, and

B. Treatment of members with diabetic neuropathy or neuropathic pain who failed to adequately respond to
conventional treatments including three or more of the following groups of agents: anti-convulsant (e.g., pregabalin), anti-depressants (e.g., amitriptyline, and duloxetine), opioids (e.g., morphine sulphate and tramadol), and other pharmacological agents (e.g., capsaicin and isosorbide dinitrate spray).

Aetna considers PENS experimental and investigational for the management of opioid withdrawal, treatment of chronic neck pain, and all other indications because its effectiveness for these indications has not been established.

Aetna considers IB-Stim experimental and investigational for the treatment of irritable bowel syndrome because its effectiveness has not been established.

VI. Aetna considers peripherally implanted nerve stimulators (e.g., StimRouter System) medically necessary DME for treatment of members with intractable neurogenic pain when all of the following criteria are met:

- Member has chronic intractable pain, refractory to other methods of treatment (e.g., analgesics, physical therapy, local injection, surgery), and
- Member is not addicted to drugs (per American Society of Addiction Medicine guidelines), and
- There is no psychological contraindication to peripheral nerve stimulation, and;
- There is objective evidence of pathology (e.g., electromyography), and;
- Trial of transcutaneous stimulation was successful (resulting in at least a 50 % reduction in pain).

Note: Peripheral nerve stimulation is considered experimental and investigational for post-herpetic neuralgia and all other indications because its effectiveness for these indications has not been established.
VII. Aetna considers H-WAVE type stimulators experimental and investigational for diabetic peripheral neuropathy and for all other indications including any of the following indications because their effectiveness for these indications has not been established.

- To accelerate healing; or
- To reduce edema; or
- To reduce pain from causes other than chronic diabetic peripheral neuropathy; or
- To treat chronic pain due to ischemia.

VIII. Aetna considers intramuscular stimulation experimental and investigational for the management of members with soft-tissue or neuropathic pain and all other indications because its effectiveness has not been established.

IX. Aetna considers sympathetic therapy (Dynatronics Corporation, Salt Lake City, UT) experimental and investigational since its effectiveness has not been established.

X. Aetna considers electroceutical therapy (also known as bioelectric nerve block) experimental and investigational for the treatment of acute pain or chronic pain (e.g., back pain, diabetic pain, joint pain, fibromyalgia, headache, and reflex sympathetic dystrophy) or other indications because there is a lack of scientific evidence regarding the effectiveness of this technology.

**Note:** Other terms used to refer to electroceutical therapy devices include "non-invasive neuron blockade" devices, "electroceutical neuron blockade" devices, and "bioelectric treatment systems."

XI. Aetna considers the Electro-Acuscope Myopulse Therapy System experimental and investigational for the treatment of pain and tissue damage and all other indications because its effectiveness has not been demonstrated in the peer-reviewed scientific literature.
XII. Aetna considers electrical stimulation of the sacral nerve roots or lumbosacral plexus experimental and investigational for the treatment of chronic pelvic or abdominal pain or other indications because the effectiveness of these interventions has not been established.

XIII. Aetna considers microcurrent electrical nerve stimulation (MENS) therapy (including, but not limited to, Algonix, Alpha-Stim 100, Electro-Myopulse 75L, electro-Lyoscope 85P, KFH Energy, MENS 2000-D, MICROCURRENT or Myopulse 75C) experimental and investigational for the treatment of chronic back pain and all other indications because its effectiveness has not been established.

XIV. Aetna considers Scrambler therapy/the Calmare therapy device (also known as transcutaneous electrical modulation pain reprocessing (TEMPRI)) experimental and investigational for the treatment of cancer pain, chronic pain, Dejerine-Roussy syndrome, neuropathic pain associated with chemotherapy-induced peripheral neuropathy, post-mastectomy pain, and other indications because of insufficient evidence regarding its effectiveness.

XV. Aetna considers non-invasive interactive neurostimulation (e.g., the InterX 1000 neurostimulator device experimental and investigational for the treatment of chronic pain and other indications (e.g., ankle fracture, knee osteoarthritis and neck pain) because of insufficient evidence regarding its effectiveness.

XVI. Aetna considers peripherally implanted nerve stimulation (also known as peripheral subcutaneous field stimulation (PSFS) or peripheral nerve field stimulation (PNFS)) experimental and investigational for the treatment of chronic pain, hemiplegic shoulder pain, and other indications (e.g., angina, notalgia paraesthetica) because of insufficient evidence regarding its effectiveness.

XVII. Aetna considers electro-therapeutic point stimulation (also known as microcurrent point stimulation) experimental and investigational for the treatment of chronic pain and other
indications because of insufficient evidence regarding its effectiveness.

XVIII. Aetna considers pulse stimulation (e.g., the P-STIM device) experimental and investigational for the treatment of cervicalgia, cervical radiculopathy, cervical spasm, chronic neck pain, failed back syndrome, lumbago, lumbar muscle spasm, lumbosacral my fasciitis, lumbosacral radiculopathy, osteoarthritis of the knee, post-herpetic neuralgia, or other conditions because its clinical value has not been established.

XIX. Aetna considers TENS with low level laser therapy (LLLT) (e.g., the Neurolumen device) for the treatment of Morton’s neuroma and all other indications experimental and investigational because its clinical value has not been established.

XX. Aetna considers non-invasive/no-incision pain procedure (NIP) device experimental and investigational for the treatment of chronic pain (arthritis, cancer pain, cervical pain, fibromyalgia, joint pain, low back pain, migraines, post-operative pain, and sciatica; not an all-inclusive list) and all other conditions (e.g., anxiety, depression and insomnia; not an all-inclusive list) because its clinical value has not been established.

XXI. Aetna considers Electro-Analgesia Treatment (EAT) using the Synaptic electrical stimulator with or without peripheral nerve blocks experimental and investigational for peripheral neuropathy and all other indications.

XXII. Aetna considers electrotherapy for the treatment of adhesive capsulitis (frozen shoulder) experimental and investigational because its effectiveness of for this indication has not been established.

XXIII. Aetna considers Cefaly transcutaneous electrical stimulator headband experimental and investigational for migraine headache prevention and treatment and all other indications.
XXIV. Aetna considers percutaneous neuromodulation therapy (e.g., Vertis PNT, BiowavePRO) experimental and investigational for pain and other indications.

XXV. Aetna considers the Quell device experimental and investigational for all indications.

XXVI. Aetna considers SENSUS transcutaneous electrical nerve stimulation experimental and investigational for diabetic neuropathy and other indications.

XXVII. Aetna considers transcutaneous electrical joint stimulation devices/pulsed electrical stimulation (PES) (e.g., the BioniCare device, Jstim 1000) experimental and investigational for the treatment of knee osteoarthritis. Aetna considers pulsed electrical stimulator (PES) experimental and investigational for soft-tissue injuries (e.g., ankle sprain) and all other indications because its effectiveness has not been established.

XXVIII. Aetna considers variable muscle stimulators experimental and investigational because their effectiveness has not been established.

XXIX. Aetna considers combined high frequency electrical stimulation and peripheral nerve block (also referred to as combination electrochemical therapy, combination electrochemical treatment, or CET) experimental and investigational for all indications. See CPB 0729 - Diabetic Neuropathy: Selected Treatments (/..700_799/0729.html).

XXX. Aetna considers combined PENS and spinal cord stimulation experimental and investigational for back pain and other indications. See CPB 0194 - Spinal Cord Stimulation (/..100_199/0194.html).

XXXI. Aetna considers galvanic stimulation or other types of electrical stimulation for the treatment of peripheral arterial disease experimental and investigational because their effectiveness for this indication has not been established.
XXXII. Aetna considers combination stimulation devices experimental and investigational for all indications:

A. ICS and muscle stimulator (e.g., RS-4i sequential stimulator, EMSI TENS/EMS-14); or
B. TENS with ICS; or
C. TENS with NMES (e.g., Empi Phoenix, QB1 System); or
D. TENS with ultrasound device; or
E. Transcranial direct current stimulation and breathing-controlled electrical stimulation for the treatment of neuropathic pain after spinal cord injury.

XXXIII. Aetna considers electrical stimulation of the posterior tibial nerve for the treatment of neuropathic pain associated with polyneuropathy experimental and investigational because the effectiveness of this approach has not been established.

XXXIV. Aetna considers intravaginal electrical stimulation, percutaneous tibial nerve stimulation, and respiratory-gated auricular vagal afferent nerve stimulation for the treatment of chronic pelvic pain experimental and investigational because the effectiveness of these approaches has not been established.

XXXV. Aetna considers reduced impedance non-invasive cortical electrostimulation (RINCE) for the treatment of chronic pain experimental and investigational because its effectiveness has not been established.

XXXVI. Aetna considers ultrasound-guided percutaneous stimulation of the femoral nerve for post-operative analgesia following anterior cruciate ligament reconstruction experimental and investigational because the effectiveness of this approach has not been established.

XXXVII. Aetna considers ultrasound-guided percutaneous stimulation of the sciatic nerve for post-operative analgesia following ambulatory foot surgery experimental and investigational because the effectiveness of this approach has not been established.
XXXVIII. Aetna considers auricular electrical stimulation (e.g., DyAnsys auricular electrical nerve stimulator) experimental and investigational for the treatment of headache, low-back pain, neuropathic pain, and all other indications because the effectiveness of this approach has not been established.

XXXIX. Aetna considers Neurogenx 4000PRO device experimental and investigational for the treatment of Achilles tendonitis and all other indications because the effectiveness of this approach has not been established.

XL. Aetna considers Sprint (peripheral subcutaneous field stimulation) for the treatment of low back pain experimental and investigational because the effectiveness of this approach has not been established.

XLI. Aetna considers transcutaneous magnetic stimulation for the treatment of chronic pain experimental and investigational because the effectiveness of this approach has not been established.

Note: Below is a list of CPBs that address other types of electrical stimulation:

- CPB 0175 - High-Frequency Pulsed Electromagnetic Stimulation (./100_199/0175.html)
- CPB 0191 - Vagus Nerve Stimulation (./100_199/0191.html)
- CPB 0194 - Spinal Cord Stimulation (./100_199/0194.html)
- CPB 0208 - Deep Brain Stimulation (./200_299/0208.html)
- CPB 0223 - Urinary Incontinence (./200_299/0223.html)
- CPB 0302 - Xerostomia: Selected Treatments (./300_399/0302.html)
- CPB 0327 - Infertility (./300_399/0327.html) (discusses electroejaculation)
- CPB 0343 - Bone Growth Stimulators (./300_399/0343.html)
- CPB 0398 - Idiopathic Scoliosis (./300_399/0398.html) (discusses surface electrical muscle stimulation)
- CPB 0406 - Tinnitus Treatments (./400_499/0406.html) (discusses the use of TENS)
• CPB 0469 - Transcranial Magnetic Stimulation and Cranial Electrical Stimulation (.../400_499/0469.html)
• CPB 0545 - Electrothermal Arthroscopy (.../500_599/0545.html)
• CPB 0676 - Electrical Stimulation for Nausea, Vomiting, and Motion Sickness (PrimaBella and ReliefBand) and Other Selected Indications (.../600_699/0676.html)
• CPB 0677 - Functional Electrical Stimulation and Neuromuscular Electrical Stimulation (.../600_699/0677.html) (for Bell's palsy, cerebral palsy, diaphragmatic pacing, neurogenic bladder, spinal cord injury, and stroke)
• CPB 0678 - Gastric Pacing / Electrical Stimulation and Gastric Per Oral Endoscopic Myotomy (.../600_699/0678.html)
• CPB 0679 - Levator Syndrome Treatments (.../600_699/0679.html)
• CPB 0680 - Electrical Stimulation for Chronic Ulcers (.../600_699/0680.html)
• CPB0707 - Headaches: Invasive Procedures (.../700_799/0707.html) (discusses electrical stimulation of the occipital nerve for occipital neuralgia)

BACKGROUND

The following are brief descriptions of various types of electrical stimulation discussed in this CPB, and a summary of available evidence:

Transcutaneous Electrical Nerve Stimulator (TENS)

A TENS is a device which utilizes electrical current delivered through electrodes placed on the surface of the skin to decrease the patient's perception of pain by inhibiting the transmission of afferent pain nerve impulses and/or stimulating the release of endorphins. A TENS unit must be distinguished from other electrical stimulators (e.g., neuromuscular stimulators) which are used to directly stimulate muscles and/or motor nerves. Transcutaneous electrical nerve stimulation is characterized by biphasic current and selectable parameters such as pulse rate and pulse width. In theory, TENS stimulates sensory nerves to block pain signals; it
also stimulates endorphin production to help normalize sympathetic function. Most TENS units produce current of 1 to 80 microampere (mA), 9 V (average), 2 to 1000 Hz, with a pulse width of 250 to 400 microseconds (mS).

Transcutaneous electrical nerve stimulation has been widely used in the treatment of various types of pain. It has been shown that TENS is highly effective in alleviating pain and reducing analgesic medications following cesarean section, orthopedic and thoracic operations as well as mixed surgical procedures (AHCPR, 1992). Moreover, TENS has been found to be beneficial also to those who suffer from acute musculoskeletal pain (Long, 1991). On the other hand, the use of TENS in the treatment of chronic malignant pain is sparse and its effectiveness remains unproven. Studies by Ventafridda and colleagues (1979) reported that of the 159 cancer patients who experienced short-term pain relief with TENS therapy, 58 % of them found the treatment ineffective by day 10, and only 35 % of these subjects continued its use after 1 month. In another group of 37 patients, pain was markedly reduced in 96 % of them during the first 10 days of TENS treatment. However, pain reduction was found only in 33 % of the subjects during the second 10 days, and to only 11 % during the third 10 days. Physical mobility was improved initially in 76 % of patients but dropped to 19 % by the end of 1 month (Ventafridda et al, 1979). The Canadian Coordinating Office for Health Technology Assessment evaluated the clinical value of TENS in pain management and concluded that there is little evidence of the effectiveness of TENS in treating chronic pain (1995).

On June 8, 2012, the Centers for Medicare & Medicaid Services (CMS) rendered a decision memo for TENS for chronic low back pain. It states that TENS is not reasonable and necessary for the treatment of chronic low back pain. The CMS will only cover TENS if individuals are enrolled in an approved clinical study meeting specific requirements.

The Centers for Medicare & Medicaid Services (2012) has issued a decision memorandum concluding that TENS not reasonable and necessary for the treatment of chronic low back pain. For purposes of the decision memorandum, chronic low back pain was defined as an episode of low back pain that has persisted for three months or longer; and is not a manifestation of a clearly defined and generally recognizable primary
disease entity. For example, there are cancers that, through metastatic spread to the spine or pelvis, may elicit pain in the lower back as a symptom; and certain systemic diseases such as rheumatoid arthritis and multiple sclerosis manifest many debilitating symptoms of which low back pain is not the primary focus. The CMS decision memorandum stated that the evidence demonstrates that the use of TENS for chronic low back pain as defined within the scope of this analysis does not produce a clinically meaningful improvement in any of the considered health outcomes. The decision memorandum stated that it is apparent that sham (placebo) TENS produces equivalent analgesia as active TENS.

In an evidence-based review, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated the effectiveness of TENS in the treatment of pain in neurological disorders (Dubinsky and Miyasaki, 2010). There are conflicting reports of TENS compared to sham TENS in the treatment of chronic low back pain (LBP), with 2 Class II studies showing benefit, while 2 Class I studies and another Class II study not showing benefit. Because the Class I studies are stronger evidence, TENS is established as ineffective for the treatment of chronic LBP. On the other hand, TENS is probably effective in treating painful diabetic neuropathy (2 Class II studies. The authors concluded that: (i) TENS is not recommended for the treatment of chronic LBP (Level A), and (ii) TENS should be considered in the treatment of painful diabetic neuropathy (Level B). They stated that further research into the mechanism of action of TENS is needed, as well as more rigorous studies for determination of efficacy.

Guidelines on treatment of LBP from the National Collaborating Centre for Primary Care (Savigny et al, 2009) found insufficient evidence for the use of TENS in LBP and recommended against its use for that indication.

In a Cochrane review, Mulvey et al (2010) evaluated the analgesic effectiveness of TENS for the treatment of phantom pain and stump pain following amputation in adults. These investigators searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, AMED, CINAHL, PEDRO and SPORTDiscus (February 2010). Only randomized controlled trials (RCTs) investigating the use of
TENS for the management of phantom pain and stump pain following an amputation in adults were included. Two review authors independently assessed trial quality and extracted data. It was planned that where available and appropriate, data from outcome measures were to be pooled and presented as an overall estimate of the effectiveness of TENS. No RCTs that examined the effectiveness of TENS for the treatment of phantom pain and stump pain in adults were identified by the searches. The authors concluded that there were no RCTs on which to judge the effectiveness of TENS for the management of phantom pain and stump pain. The published literature on TENS for phantom pain and stump pain lacks the methodological rigor and robust reporting needed to confidently assess its effectiveness. They stated that further RCT evidence is needed before such a judgment can be made.

Johnson et al (2015) updated of a Cochrane review published in 2010 on TENS for phantom pain and stump pain following amputation in adults. The authors concluded that there were no RCTs to judge the effectiveness of TENS for the management of phantom pain and stump pain. The published literature on TENS for phantom pain and stump pain lacks the methodological rigor and robust reporting needed to confidently assess its effectiveness. They stated that further RCT evidence is needed before an assessment can be made. Since publication of the original version of this review, these investigators have found no new studies and their conclusions remain unchanged.

Zeng et al (2015) examined the effectiveness of different electrical stimulation (ES) therapies in pain relief of patients with knee osteoarthritis (OA). Electronic databases including MEDLINE, Embase and Cochrane Library were searched through for RCTs comparing any ES therapies with control interventions (sham or blank) or with each other. Bayesian network meta-analysis was used to combine both the direct and indirect evidence on treatment effectiveness. A total of 27 trials and 6 types of ES therapies, including high-frequency TENS (h-TENS), low-frequency TENS (l-TENS), neuromuscular electrical stimulation (NMES), interferential current (IFC), pulsed electrical stimulation (PES), and noninvasive interactive neurostimulation (NIN), were included. Interferential current is the only significantly effective treatment in terms of both pain intensity and change pain score at last follow-up time-point when compared with the control group. Meanwhile, IFC showed the
greatest probability of being the best option among the 6 treatment methods in pain relief. These estimates barely changed in sensitivity analysis. However, the evidence of heterogeneity and the limitation in sample size of some studies could be a potential threat to the validity of results. The authors conclude that IFC seems to be the most promising pain relief treatment for the management of knee OA. However, evidence was limited due to the heterogeneity and small number of included trials. Although the recommendation level of the other ES therapies is either uncertain (h-TENS) or not appropriate (l-TENS, NMES, PES and NIN) for pain relief, it is likely that none of the interventions is dangerous.

Cheing and Luk (2005) examined the clinical effectiveness of high-frequency (HF) TENS for reducing hyper-sensitivity of the hand in patients with neuropathic pain. A total of 19 patients suffering from hand hyper-sensitivity were randomly assigned into either a treatment or a placebo group. A visual analog scale (VAS) and the Downey Hand Center Hand Sensitivity Test were used to measure the tactile tolerance of the hand. Grip strength was assessed by a grip dynamometer. Daily applications of electrical stimulation were provided for 2 weeks. Significantly lower pain scores were found in the treatment group than in the placebo group by day 7 and day 11. The ranking of 10 dowel textures of the Downey Hand Center Hand Sensitivity Test in the treatment group was significantly higher than in the placebo group by day 7 and day 11. However, no significant inter-group difference was found in grip strength.

The Ad hoc Committee of the Croatian Society for Neurovascular Disorders and the Croatian Medical Association's recommendations for neuropathic pain treatment (Demarin et al, 2008) stated that damage to the somatosensory nervous system poses a risk for the development of neuropathic pain. Such an injury to the nervous system results in a series of neurobiological events resulting in sensitization of both the peripheral and central nervous system. The diagnosis of neuropathic pain is based primarily on the history and physical examination finding. Although monotherapy is the ideal approach, rational polypharmacy is often pragmatically used. Several classes of drugs are moderately effective, but complete or near-complete relief is unlikely. Anti-depressants and anti-convulsant are most commonly used. Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs anda
A lidocaine-containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome. TENS was not mentioned as a therapeutic option.

Norrbrink (2009) assessed the short-term effects of HF and low-frequency (LF) TENS for neuropathic pain following spinal cord injury (SCI). A total of 24 patients participated in the study. According to the protocol, 50% of the patients were assigned to HF (80 Hz) and 50% to LF (burst of 2 Hz) TENS. Patients were instructed to treat themselves 3 times daily for 2 weeks. After a 2-week wash-out period, patients switched stimulation frequencies and repeated the procedure. Results were calculated on an intent-to-treat basis. No differences between the 2 modes of stimulation were found. On a group level, no effects on pain intensity ratings or ratings of mood, coping with pain, life satisfaction, sleep quality, or psychosocial consequences of pain were seen. However, 29% of the patients reported a favorable effect from HF and 38% from LF stimulation on a 5-point global pain-relief scale. Six of the patients (25%) were, at their request, prescribed TENS stimulators for further treatment at the end of the study. The authors concluded that TENS merits consideration as a complementary treatment in patients with SCI and neuropathic pain. The mild benefits observed -- 29% of subjects in the HF group and 38% of subjects in the LF group could be a placebo effect.

Moharic and Burger (2010) examined if TENS improves small fiber function diminished because of painful diabetic neuropathy. A total of 46 patients with painful diabetic neuropathy were treated with TENS 3 consecutive hours a day for 3 weeks. Treatment effect was evaluated with cold, warm, cold pain and heat pain thresholds, vibration perception thresholds and touch perception thresholds. In all patients, thermal-specific and thermal pain sensitivity determination showed quantitative and qualitative abnormalities in all the measured spots. After the TENS therapy, no statistically significant changes in cold, warm, cold pain, heat pain, vibratory perception and touch perception thresholds were observed in the stimulated area. TENS did not alter C, Aδ nor Aβ fiber-mediated perception thresholds. The authors noted that the observed changes at thenar were probably because of central mechanisms. In general, analgesic mechanisms of TENS are likely to be complex.
Jin et al (2010) evaluated the effectiveness of TENS on diabetic peripheral neuropathy (DPN). Randomized controlled trials (RCTs) comparing TENS with routine care, pharmacological interventions or placebo devices on patients with symptomatic DPN, were identified by electronic and manual searches. Studies were selected and available data were extracted independently by 2 investigators. Meta-analysis was performed by RevMan 4.2.8 software. A total of 3 RCTs involving 78 patients were included in this study. The reductions in mean pain score were significantly greater in TENS group than in placebo TENS group in 4 weeks and 6 weeks follow-up [4 weeks, standard mean difference (SMD) -5.37, 95 % confidence interval [CI]: -6.97 to -3.77; 6 weeks, SMD-1.01, 95 % CI: -2.01 to -0.01], but not in 12 weeks follow-up [SMD-1.65, 95 % CI: -4.02 to 0.73]. TENS therapy was associated with significantly subjective improvement in overall neuropathic symptoms in 12 weeks follow-up [WMD-0.18, 95 % CI: -0.32 to -0.051]. No TENS-related adverse events were registered in TENS group. The authors concluded that TENS therapy may be an effective and safe strategy in treatment of symptomatic DPN. They stated that due to small sample and short-term treatment duration, large multi-center RCTs are needed to further evaluate the long-term effect of TENS on DPN.

Johnson and Bjordal (2011) stated that the management of neuropathic pain is challenging, with medication being the first-line treatment. Transcutaneous electrical nerve stimulation is a non-invasive, self-administered technique that is used as an adjunct to medication. Clinical experience suggested that TENS is beneficial providing it is administered at a sufficiently strong intensity, close to the site of pain. At present, there are too few RCTs on TENS for neuropathic pain to judge effectiveness. The findings of systematic reviews of TENS for other pain syndromes are inconclusive because trials have a low fidelity associated with inadequate TENS technique and infrequent treatments of insufficient duration. The use of electrode arrays to spatially target stimulation more precisely may improve the efficacy of TENS in the future.

In a systematic review, Abou-Setta (2011) reviewed the benefits and harms of pharmacological and non-pharmacological interventions for managing pain after hip fracture. A total of 25 electronic databases (January 1990 to December 2010), gray literature, trial registries, and reference lists, with no language restrictions were searched. Multiple
reviewers independently and in duplicate screened 9,357 citations to identify RCT); non-RCTs; and cohort studies of pain management techniques in older adults after acute hip fracture. Independent, duplicate data extraction and quality assessment were conducted, with discrepancies resolved by consensus or a third reviewer. Data extracted included study characteristics, inclusion and exclusion criteria, participant characteristics, interventions, and outcomes. A total of 83 unique studies (64 RCTs, 5 non-RCTs, and 14 cohort studies) were included that addressed nerve blockade (n = 32), spinal anesthesia (n = 30), systemic analgesia (n = 3), traction (n = 11), multi-modal pain management (n = 2), neurostimulation (n = 2), rehabilitation (n = 1), and complementary and alternative medicine (n = 2). Overall, moderate evidence suggested that nerve blockades are effective for relieving acute pain and reducing delirium. Low-level evidence suggested that pre-operative traction does not reduce acute pain. Evidence was insufficient on the benefits and harms of most interventions, including spinal anesthesia, systemic analgesia, multi-modal pain management, acupressure, relaxation therapy, TENS, and physical therapy regimens, in managing acute pain. The authors concluded that nerve blockade seems to be effective in reducing acute pain after hip fracture. Sparse data preclude firm conclusions about the relative benefits or harms of many other pain management interventions (including TENS) for patients with hip fracture.

In a Cochrane review, Page et al (2014) examined the available evidence regarding the benefits and harms of electrotherapy modalities, delivered alone or in combination with other interventions, for the treatment of adhesive capsulitis (frozen shoulder). These investigators searched CENTRAL, MEDLINE, EMBASE, CINAHL Plus and the ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) clinical trials registries up to May 2014, unrestricted by language, and reviewed the reference lists of review articles and retrieved trials to identify any other potentially relevant trials. They included RCTs and controlled clinical trials using a quasi-randomized method of allocation that included adults with adhesive capsulitis and compared any electrotherapy modality to placebo, no treatment, a different electrotherapy modality, or any other intervention. The 2 main questions of the review focused on whether electrotherapy modalities are effective compared to placebo or no treatment, or if they are an effective adjunct to manual therapy or exercise (or both). The
main outcomes of interest were participant-reported pain relief of 30% or greater, overall pain, function, global assessment of treatment success, active shoulder abduction, quality of life, and the number of participants experiencing any adverse event. Two review authors independently selected trials for inclusion, extracted the data, performed a risk of bias assessment, and assessed the quality of the body of evidence for the main outcomes using the GRADE approach. A total of 19 trials (1,249 participants) were included in the review; 4 trials reported using an adequate method of allocation concealment and 6 trials blinded participants and personnel. Only 2 electrotherapy modalities (low-level laser therapy (LLLT) and pulsed electromagnetic field therapy (PEMF)) have been compared to placebo. No trial has compared an electrotherapy modality plus manual therapy and exercise to manual therapy and exercise alone. The 2 main questions of the review were investigated in 9 trials. Low-quality evidence from 1 trial (40 participants) indicated that LLLT for 6 days may result in improvement at 6 days; 81% (16/20) of participants reported treatment success with LLLT compared with 10% (2/20) of participants receiving placebo (risk ratio (RR) 8.00, 95% CI: 2.11 to 30.34; absolute risk difference 70%, 95% CI: 48% to 92%). No participants in either group reported adverse events. These researchers were uncertain whether PEMF for 2 weeks improved pain or function more than placebo at 2 weeks because of the very low quality evidence from 1 trial (32 participants); 75% (15/20) of participants reported pain relief of 30% or more with PEMF compared with 0% (0/12) of participants receiving placebo (RR 19.19, 95% CI: 0.91 to 221.75; absolute risk difference 55%, 95% CI: 31 to 79). Moderate quality evidence from 1 trial (63 participants) indicated that LLLT plus exercise for 8 weeks probably resulted in greater improvement when measured at the 4th week of treatment, but a similar number of adverse events, compared with placebo plus exercise. The mean pain score at 4 weeks was 51 points with placebo plus exercise, while with LLLT plus exercise the mean pain score was 32 points on a 100-point scale (mean difference (MD) 19 points, 95% CI: 15 to 23; absolute risk difference 19%, 95% CI: 15% to 23%). The mean function impairment score was 48 points with placebo plus exercise, while with LLLT plus exercise the mean function impairment score was 36 points on a 100-
point scale (MD 12 points, 95% CI: 6 to 18; absolute risk difference 12%, 95% CI: 6 to 18). Mean active abduction was 70 degrees with placebo plus exercise, while with LLLT plus exercise mean active abduction was 79 degrees (MD 9 degrees, 95% CI: 2 to 16; absolute risk difference 5%, 95% CI: 1% to 9%). No participants in either group reported adverse events; LLLT's benefits on function were maintained at 4 months. Based on very low quality evidence from 6 trials, these investigators were uncertain whether therapeutic ultrasound, PEMF, continuous short-wave diathermy, Iodex phonophoresis, a combination of Iodex iontophoresis with continuous short-wave diathermy, or a combination of therapeutic ultrasound with TENS were effective adjuncts to exercise. Based on low or very low quality evidence from 12 trials, these researchers were uncertain whether a diverse range of electrotherapy modalities (delivered alone or in combination with manual therapy, exercise, or other active interventions) were more or less effective than other active interventions (e.g., glucocorticoid injection). The authors concluded that based upon low quality evidence from 1 trial, LLLT for 6 days may be more effective than placebo in terms of global treatment success at 6 days. Based upon moderate quality evidence from 1 trial, LLLT plus exercise for 8 weeks may be more effective than exercise alone in terms of pain up to 4 weeks and function up to 4 months. It is unclear whether PEMF is more or less effective than placebo, or whether other electrotherapy modalities are an effective adjunct to exercise. They stated that further high quality RCTs are needed to establish the benefits and harms of physical therapy interventions (that comprise electrotherapy modalities, manual therapy and exercise, and are reflective of clinical practice) compared to interventions with evidence of benefit (e.g., glucocorticoid injection or arthrographic joint distension).

TENS for Pain Management in Burn Persons

In a pilot study, Perez-Ruvalcaba and colleagues (2015) examined the effect of continuous and intermittent TENS on the perception of pain in patients with burns of different types. This study was conducted in 14 patients (aged 30.9 ± 7.5 years) with 2nd- and 3rd-degree burns of different types. The burn types included electrical, fire/flame, and chemical. All patients received continuous and intermittent TENS sessions 3 times per week for 4 weeks; each session had a duration of 30
minutes. A pair of electrodes were placed around the burn. The primary effectiveness endpoint was the perception of pain assessed by a VAS at baseline and at the 30th day. A significant reduction of pain perception was reported (8.0 ± 1.7 versus 1.0 ± 0.5; p = 0.027) by all patients after TENS therapy. There were no reports of adverse events during the intervention period. The authors concluded that TENS could be a potential non-pharmacological therapeutic option for pain management in burn patients. These preliminary findings need to be validated by well-designed studies.

TENS for Peripheral Arterial Disease

Seeinan and colleagues (2016) examined the effects of 2 types of TENS on walking distance and measures of pain in patients with peripheral arterial disease (PAD) and intermittent claudication (IC). In a phase Ila clinical trial, a total of 40 participants with PAD and IC completed a graded treadmill test on 2 separate testing occasions. Active TENS was applied to the lower limb on the first occasion and placebo TENS on the second occasion. Participants were divided into 2 experimental groups: (i) one group received high-frequency TENS; and (ii) the 2nd group received low-frequency TENS. Measures taken were initial claudication distance, functional claudication distance and absolute claudication distance. The McGill Pain Questionnaire (MPQ) vocabulary was completed at the end of the intervention and the MPQ-Pain Rating Index score was calculated. Four participants were excluded from the final analysis because of non-completion of the experimental procedure. Median walking distance increased with high-frequency TENS for all measures (p < 0.05, Wilcoxon signed rank test, all measures). Only absolute claudication distance increased significantly with low-frequency TENS compared with placebo (median of 179 to 228; Ws = 39; z = 2.025; p = 0.043; r = 0.48). No difference was observed between reported median MPQ-Pain Rating Index scores: 21.5 with placebo TENS and 21.5 with active TENS (p = 0.41). The authors concluded that TENS applied to the lower limb of the patients with PAD and IC was associated with increased walking distance on a treadmill; but not with any reduction in pain. They stated that TENS may be a useful adjunctive intervention to help increase walking performance in patients with IC.

TENS for Post-Total Knee Arthroplasty Pain
Chughtai and associates (2016) noted that despite technological advances in total knee arthroplasty (TKA), management of post-operative muscle weakness and pain continue to pose challenges for both patients and health care providers. Non-pharmacologic therapies, such as neuromodulation in the form of NMES and TENS, and other modalities, such as cryotherapy and pre-habilitation, have been highlighted as possible adjuncts to standard-of-care pharmacologic management to treat post-operative pain and muscle weakness. These researchers discussed existing evidence for neuromodulation in the treatment of pain and muscular weakness following TKA and shed light on other non-invasive and potential future modalities. The review of the literature demonstrated that NMES, pre-habilitation, and some specialized exercises are beneficial for post-operative muscle weakness and TENS, cooling therapies, and compression may help to alleviate post-TKA pain. However, there are no clear guidelines for the use of these modalities. The authors concluded that further studies should be aimed at developing guidelines or delineating indications for neuromodulation and other non-pharmacologic therapies in the management of post-TKA pain and muscle weakness.

TENS for Rotator Cuff Disease

In a Cochrane review, Page and colleagues (2016) synthesized available evidence regarding the benefits and harms of electrotherapy modalities for the treatment of people with rotator cuff disease. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3), Ovid Medline (January 1966 to March 2015), Ovid Embase (January 1980 to March 2015), CINAHL Plus (EBSCOhost, January 1937 to March 2015), ClinicalTrials.gov and the WHO ICTRP clinical trials registries up to March 2015, unrestricted by language, and reviewed the reference lists of review articles and retrieved trials, to identify potentially relevant trials. They included RCTs and quasi-randomized trials, including adults with rotator cuff disease (e.g., calcific tendinitis, rotator cuff tendinitis, and subacromial impingement syndrome), and comparing any electrotherapy modality with placebo, no intervention, a different electrotherapy modality or any other intervention (e.g., glucocorticoid injection). Trials investigating whether electrotherapy modalities were more effective than placebo or no treatment, or were an effective addition to another physical therapy intervention (e.g., manual
therapy or exercise) were the main comparisons of interest. Main outcomes of interest were overall pain, function, pain on motion, patient-reported global assessment of treatment success, quality of life and the number of participants experiencing adverse events. Two review authors independently selected trials for inclusion, extracted the data, performed a risk of bias assessment and assessed the quality of the body of evidence for the main outcomes using the GRADE approach. These researchers included 47 trials (2,388 participants). Most trials (n = 43) included participants with rotator cuff disease without calcification (4 trials included people with calcific tendinitis); 16 (34 %) trials investigated the effect of an electrotherapy modality delivered in isolation. Only 23 % were rated at low risk of allocation bias, and 49 % were rated at low risk of both performance and detection bias (for self-reported outcomes). The trials were heterogeneous in terms of population, intervention and comparator, so none of the data could be combined in a meta-analysis. In 1 trial (61 participants; low quality evidence), pulsed therapeutic ultrasound (US) (3 to 5 times a week for 6 weeks) was compared with placebo (inactive US therapy) for calcific tendinitis. At 6 weeks, the mean reduction in overall pain with placebo was -6.3 points on a 52-point scale, and -14.9 points with US (MD -8.60 points, 95 % CI: -13.48 to -3.72 points; absolute risk difference 17 %, 7 % to 26 % more). Mean improvement in function with placebo was 3.7 points on a 100-point scale, and 17.8 points with US (MD 14.10 points, 95 % CI: 5.39 to 22.81 points; absolute risk difference 14 %, 5 % to 23 % more); 91 % (29/32) of participants reported treatment success with US compared with 52 % (15/29) of participants receiving placebo (RR 1.75, 95 % CI: 1.21 to 2.53; absolute risk difference 39 %, 18 % to 60 % more). Mean improvement in quality of life with placebo was 0.40 points on a 10-point scale, and 2.60 points with US (MD 2.20 points, 95 % CI: 0.91 points to 3.49 points; absolute risk difference 22 %, 9 % to 35 % more). Between-group differences were not important at 9 months. No participant reported adverse events. Therapeutic US produced no clinically important additional benefits when combined with other physical therapy interventions (8 clinically heterogeneous trials, low quality evidence). The authors were uncertain whether there were differences in patient-important outcomes between US and other active interventions (manual therapy, acupuncture, glucocorticoid injection, glucocorticoid injection plus oral tolmetin sodium, or exercise) because the quality of evidence is very low; 2 placebo-controlled trials reported results favoring LLLT up to 3
weeks (low quality evidence), however combining LLLT with other physical therapy interventions produced few additional benefits (10 clinically heterogeneous trials, low quality evidence). These researchers were uncertain whether TENS was more or less effective than glucocorticoid injection with respect to pain, function, global treatment success and active range of motion (ROM) sooner because of the very low quality evidence from a single trial. In other single, small trials, no clinically important benefits of PEMF, MENS, acetic acid iontophoresis and microwave diathermy were observed (low or very low quality evidence). No adverse events of therapeutic US, LLLT, TENS or microwave diathermy were reported by any participants. Adverse events were not measured in any trials investigating the effects of PEMF, MENS or acetic acid iontophoresis. The authors concluded that based on low quality evidence, therapeutic US may have short-term benefits over placebo in people with calcific tendinitis, and LLLT may have short-term benefits over placebo in people with rotator cuff disease. They stated that further high quality placebo-controlled trials are needed to confirm these results. In contrast, based on low quality evidence, PEMF may not provide clinically relevant benefits over placebo, and therapeutic US, LLLT and PEMF may not provide additional benefits when combined with other physical therapy interventions. The authors were uncertain if TENS is superior to placebo, and whether any electrotherapy modality provides benefits over other active interventions (e.g., glucocorticoid injection) because of the very low quality of the evidence. They stated that practitioners should communicate the uncertainty of these effects and consider other approaches or combinations of treatment. The authors stated that further trials of electrotherapy modalities for rotator cuff disease should be based upon a strong rationale and consideration of whether or not they would alter the conclusions of this review.

Desmeules et al (2016) performed a systematic review on the effectiveness of TENS for the treatment of rotator cuff tendinopathy in adults. A literature search was conducted in 4 databases (CINAHL, Embase, PubMed and PeDRO) for RCTs published from date of inception until April 2015, comparing the effectiveness of TENS for the treatment of rotator cuff tendinopathy with placebo or any other intervention. Risk of bias was evaluated using the Cochrane risk of bias tool; results were summarized qualitatively. A total of 6 studies were included in this review. The mean methodological score was 49 % (standard deviation 16
One placebo-controlled trial reported that a single TENS session provided immediate pain reduction for patients with rotator cuff tendinopathy, but did not follow the participants in the short-, medium- or long-term. Two trials that compared US therapy with TENS reported discrepancy and contradictory results in terms of pain reduction and shoulder ROM. Corticosteroid injections were found to be superior to TENS for pain reduction in the short-term, but the differences were not clinically important. Other studies included in this review concluded that TENS was not superior to heat or pulsed radiofrequency. The authors concluded that due to the limited number of studies and the overall high risk of bias of the studies included in this review, no conclusions can be drawn on the effectiveness of TENS for the treatment of rotator cuff tendinopathy. They stated that more methodologically sound studies are needed to document the effectiveness of TENS; until then, clinicians should prefer other evidence-based rehabilitation interventions proven to be effective to treat patients with rotator cuff tendinopathy.

TENS for Chemotherapy-Induced Peripheral Neuropathy

In a double-blind, randomized and placebo-controlled study, Tonegger and associates (2017) examined the effects of TENS for reducing the side effects of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients undergoing chemotherapy with oxaliplatin or paclitaxel. A total of 24 patients were randomly allocated into 2 groups: (i) active or (ii) placebo stimulation. All patients were evaluated for pain, numbness/tingling, frequency of symptoms, and quality of life. The TENS device was applied daily with modulating frequencies ranging between 7-Hz and 65-Hz in distal limb regions during 3 cycles of chemotherapy (45 days). The other stimulation parameters were: pulse duration of 200 μsec, intensity at the highest tolerable level, and increases in intensity when it diminished. The data showed no difference between active or placebo groups in terms of pain, numbness/tingling, frequency of symptoms or impact on daily life activities. The authors concluded that these results suggested that TENS applied in the frequency variation mode was not proven to be effective to improve the symptoms of CIPN during chemotherapy cycles. There was no worsening of symptoms in subsequent cycles of the onset of symptoms of the disease.
TENS for Fibromyalgia

In a Cochrane review, Johnson and colleagues (2017) evaluated the effectiveness and adverse events of TENS alone or added to usual care (including exercise) compared with placebo (sham) TENS; no treatment; exercise alone; or other treatment including medication, electro-acupuncture, warmth therapy, or hydrotherapy for fibromyalgia in adults. These investigators searched the following electronic databases up to January 18, 2017: CENTRAL (CRSO); Medline (Ovid); Embase (Ovid); CINAHL (EBSCO); PsycINFO (Ovid); LILACS; PEDRO; Web of Science (ISI); AMED (Ovid); and SPORTDiscus (EBSCO). They also searched 3 trial registries. There were no language restrictions. These researchers included RCTs or quasi-randomized trials of TENS treatment for pain associated with fibromyalgia in adults. They included cross-over and parallel-group trial designs. They included studies that evaluated TENS administered using non-invasive techniques at intensities that produced perceptible TENS sensations during stimulation at either the site of pain or over nerve bundles proximal (or near) to the site of pain. The authors included TENS administered as a sole treatment or TENS in combination with other treatments, and TENS given as a single treatment or as a course of treatments. Two review authors independently determined study eligibility by assessing each record and reaching agreement by discussion. A 3rd review author acted as arbiter. These researchers did not anonymize the records of studies before assessment. Two review authors independently extracted data and assessed risk of bias of included studies before entering information into a “Characteristics of included studies” table. Primary outcomes were participant-reported pain relief from baseline of 30% or greater or 50% or greater, and Patient Global Impression of Change (PGIC). These investigators assessed the evidence using GRADE and added “Summary of findings” tables. The authors included 8 studies (7 RCTs, 1 quasi-RCT, 315 adults (299 women), aged 18 to 75 years): 6 used a parallel-group design and 2 used a cross-over design. Sample sizes of intervention arms were 5 to 43 subjects. Two studies, 1 of which was a cross-over design, compared TENS with placebo TENS (82 participants), 1 study compared TENS with no treatment (43 subjects), and 4 studies compared TENS with other treatments (medication (2 studies, 74 participants), electro-acupuncture (1 study, 44 participants), superficial warmth (1 cross-over study, 32 subjects), and hydrotherapy (1 study, 10 participants)). Two studies
compared TENS plus exercise with exercise alone (98 participants, 49 per treatment arm). None of the studies measured participant-reported pain relief of 50% or greater or PGIC. Overall, the studies were at unclear or high risk of bias, and in particular all were at high risk of bias for sample size. Only 1 study (14 participants) measured the primary outcome participant-reported pain relief of 30% or greater; 30% achieved 30% or greater reduction in pain with TENS and exercise compared with 13% with exercise alone. One study found 10/28 participants reported pain relief of 25% or greater with TENS compared with 10/24 participants using superficial warmth (42°C). These researchers judged that statistical pooling was not possible because there were insufficient data and outcomes were not homogeneous. There were no data for the primary outcomes participant-reported pain relief from baseline of 50% or greater and PGIC. There was a paucity of data for secondary outcomes. One pilot cross-over study of 43 subjects found that the mean (95% CI) decrease in pain intensity on movement (100-mm VAS) during one 30-min treatment was 11.1 mm (95% CI: 5.9 to 16.3) for TENS and 2.3 mm (95% CI: 2.4 to 7.7) for placebo TENS. There were no significant differences between TENS and placebo for pain at rest. One parallel group study of 39 participants found that mean ± standard deviation (SD) pain intensity (100-mm VAS) decreased from 85 ± 20 mm at baseline to 43 ± 20 mm after 1 week of dual-site TENS; decreased from 85 ± 10 mm at baseline to 60 ± 10 mm after single-site TENS; and decreased from 82 ± 20 mm at baseline to 80 ± 20 mm after 1 week of placebo TENS. The authors of 7 studies concluded that TENS relieved pain but the findings of single small studies are unlikely to be correct. One study found clinically important improvements in Fibromyalgia Impact Questionnaire (FIQ) subscales for work performance, fatigue, stiffness, anxiety, and depression for TENS with exercise compared with exercise alone. One study found no additional improvements in FIQ scores when TENS was added to the first 3 weeks of a 12-week supervised exercise program. No serious adverse events were reported in any of the studies although there were reports of TENS causing minor discomfort in a total of 3 participants. The quality of evidence was very low. These investigators downgraded the GRADE rating mostly due to a lack of data; thus, they had little confidence in the effect estimates where available. The authors concluded that there was insufficient high-quality evidence to support or refute the use of TENS for
fibromyalgia. They found a small number of inadequately powered studies with incomplete reporting of methodologies and treatment interventions.

TENS for Musculoskeletal Pain in Hemophilia

Rodriguez-Merchan (2018) noted that musculoskeletal pain treatment is inadequate in many hemophilic patients. Analgesics are used only by 36% of adult patients. FVIII/FIX intravenous infusion is mainly used to lessen pain, followed in frequency by usage of NSAIDS (primarily COX-2 inhibitors). In about 30% of patients, pain continues after infusion of F VIII/IX. In acute hemarthroses pain treatment must continue until total disappearance (checked by ultrasonography) and include hematologic treatment, short-term rest of the involved joint, cryotherapy, joint aspiration and analgesic medication (paracetamol in mild pain, metamizole for more intense pain, and in a few precise patients, soft opioids such as codeine or tramadol). In the circumstance of intolerable pain these investigators use morphine hydrochloride either by continual infusion or a patient-controlled analgesia (PCA) pump, determined by the age, mental condition and grade of observance of the patient. Epidural blocks utilizing bupivacaine and fentanyl may be very effective as well. Three main strategies to alleviate chronic musculoskeletal pain secondary to hemophilic arthropathy (joint degeneration) exist: (i) pharmacologic management, (ii) physical medicine and rehabilitation, and (iii) intra-articular injections. As for pharmacologic management, NSAIDs (ibuprofen, diclofenac, celecoxib, robecoxib) are better than paracetamol. The advantages of tramadol or tramadol/paracetamol and non-tramadol opioids are scanty. With respect to physical medicine and rehabilitation, there is insufficient confirmation that a brace has supplementary favorable effect compared with isolated pharmacologic management. Land-based curative exercise and watery exercise have at the minimum a tiny short-run benefit. Curative ultrasound can be helpful (poor quality of evidence). The effectiveness of TENS for pain mitigation has not been proven. Electrical stimulation treatment can procure notable ameliorations. With respect to intra-articular injections, viscosupplementation appears to be a useful method for pain alleviation in the short-run (months). The short-run (weeks) advantage of intra-articular corticosteroids in the treatment of joint pain has been shown.
Interferential Stimulation

Interferential stimulation (IFS) is characterized by 2 alternating-current sine waves of differing frequencies that "work" together to produce an interferential current that is also known as a beat pulse or alternating modulation frequency. One of the 2 currents is usually held at 4,000 Hz, and the other can be held constant or varied over a range of 4,001 to 4,100 Hz. Interferential currents reportedly can stimulate sensory, motor, and pain fibers. Because of the frequency, the interferential wave meets low impedance when crossing the skin to enter the underlying tissue. This deep tissue penetration can be adjusted to stimulate parasympathetic nerve fibers for increased blood flow. According to proponents, interferential stimulation differs from TENS because it allows a deeper penetration of the tissue with more comfort (compliance) and increased circulation.

It has been claimed that IFS is highly effective in reducing: (i) pain and use of pain medications, (ii) edema and inflammation, and (iii) healing time, as well as in improving range of motion, and activity levels, and quality of life. However, there are very few well-designed studies such as randomized, double blind, controlled clinical trials that support such claims. Low (1988) stated that in spite of widespread agreement among physiotherapists that IFS has a marked pain relieving effect, there is a paucity of objective investigations into this analgesic effect. He claimed that both the therapeutic and physiological effects of interferential currents require further investigation. This notion is echoed by Goats (1990) who reported that evidence supporting the use of IFS in the control of edema appears mainly anecdotal. Reitman and Esses (1995) noted that there were no controlled studies proving the effectiveness of IFS. Indergand and Morgan (1995) reported that interferential current applied over the stellate ganglion did not change forearm hemodynamics in asymptomatic individuals. The authors stated that these findings challenged the concept that IFS can block sympathetic vasoconstrictor impulses in peripheral nerves. In a randomized placebo controlled study, Van Der Heijden et al (1999) evaluated the effectiveness of bipolar interferential electrotherapy (ET) and pulsed ultrasound (US) as adjuvants to exercise therapy for soft tissue shoulder disorders (n = 180). Patients with shoulder pain and/or restricted shoulder mobility, because of soft tissue impairment without underlying specific or generalized condition,
were randomized to receive: (i) active ET plus active US; (ii) active ET plus dummy US; (iii) dummy ET plus active US; (iv) dummy ET plus dummy US; or (v) no adjuvants. Additionally, they received a maximum of 12 sessions of exercise therapy in 6 weeks. Measurements at baseline, 6 weeks and 3, 6, 9, and 12 months later were blinded for treatment. Outcome measures: recovery, functional status, chief complaint, pain, clinical status, and range of motion. At the 6th-week, 7 patients (20%) without adjuvants reported very large improvement (including complete recovery), 17 (23%) and 16 (22%) with active and dummy ET, and 19 (26%) and 14 (19%) with active and dummy US. These proportions increased to about 40% at the 3rd-months, but remained virtually stable thereafter. The authors concluded that neither ET nor US proved to be effective as adjuvants to exercise therapy for soft tissue shoulder disorders. Jarit et al (2003) concluded that home IFS may help reduce pain, pain medication taken, and swelling while increasing range of motion in patients undergoing knee surgery. This could result in quicker return to activities of daily living and athletic activities. Drawbacks of this study were as follows: (i) while placebo subjects did consume more medications at all time points, the difference was only at some points, and (ii) a functional assessment scale was not used. The findings of this study need to be validated by further investigation. Furthermore, a technology assessment by the California Technology Assessment Forum (CTAF, 2005) concluded that interferential stimulation does not meet CTAF’s assessment criteria.

A review on non-pharmacological therapies (including IFS) for acute and chronic LBP by the American Pain Society and the American College of Physicians (Chou et al, 2007) concluded that therapies with good evidence of moderate efficacy for chronic or sub-acute LBP are cognitive-behavioral therapy, exercise, spinal manipulation, and inter-disciplinary rehabilitation. For acute LBP, the only therapy with good evidence of efficacy is superficial heat.

Guidelines on treatment of LBP from the National Collaborating Centre for Primary Care (Savigny et al, 2009) found insufficient evidence for the use of interferential stimulation in LBP and recommended against its use for that indication.
In a systematic review and meta-analysis, Fuentes et al (2010) analyzed the available information regarding the efficacy of IFS in the management of musculoskeletal pain. Randomized controlled trials were obtained through a computerized search of bibliographic databases (i.e., CINAHL, Cochrane Library, EMBASE, MEDLINE, PEDro, Scopus, and Web of Science) from 1950 to February 8, 2010. Two independent reviewers screened the abstracts found in the databases. Methodological quality was assessed using a compilation of items included in different scales related to rehabilitation research. The mean difference, with 95% confidence interval (CI), was used to quantify the pooled effect. A chi-square test for heterogeneity was performed. A total of 2,235 articles were found. A total of 20 studies fulfilled the inclusion criteria; 7 articles assessed the use of IFS on joint pain; 9 articles evaluated the use of IFS on muscle pain; 3 articles evaluated its use on soft tissue shoulder pain; and 1 article examined its use on post-operative pain. Three of the 20 studies were considered to be of high methodological quality, 14 studies were considered to be of moderate methodological quality, and 3 studies were considered to be of poor methodological quality. Fourteen studies were included in the meta-analysis. The authors concluded that IFS as a supplement to another intervention seems to be more effective for reducing pain than a control treatment at discharge and more effective than a placebo treatment at the 3-month follow-up. However, it is unknown whether the analgesic effect of IFS is superior to that of the concomitant interventions. Interferential current alone was not significantly better than placebo or other therapy at discharge or follow-up. Results must be considered with caution due to the low number of studies that used IFS alone. In addition, the heterogeneity across studies and methodological limitations prevent conclusive statements regarding analgesic efficacy.

Percutaneous Electrical Nerve Stimulation (PENS)

Percutaneous electrical nerve stimulation uses acupuncture-like needles as electrodes. These needles are placed in the soft tissues or muscles at dermatomal levels corresponding to local pathology (needles are usually inserted above and below and into the central area of pain). A 5-Hz frequency with a pulse width of 0.5 mS is usually used. If relief is not attained within 15 minutes, the frequency may be lowered to 1 Hz. According to PENS proponents, the main advantage of PENS over TENS
is that it bypasses the local skin resistance and delivers electrical stimuli at the precisely desired level in close proximity to the nerve endings located in soft tissue, muscle, or periosteum of the involved dermatomes.

Percutaneous electrical nerve stimulation has also been used in the treatment of neck pain; however, there is insufficient evidence to support its effectiveness for this indication. Harris and Susman (2002) stated that the Philadelphia Panel recently formulated evidence-based guidelines for selected rehabilitation interventions in the management of low back, knee, neck, and shoulder pain. The guidelines were developed with the use of a 5-step process: (i) define the intervention, (ii) collect evidence, (iii) synthesize results, (iv) make recommendations based on the research, and (v) grade the strength of the recommendations.

Outpatient adults with low back, knee, neck, or shoulder pain without vertebral disk involvement, scoliosis, cancer, or pulmonary, neurological, cardiac, dermatological, or psychiatric conditions were included in the review. To prepare the data, systematic reviews were performed for low back, knee, neck, and shoulder pain. Therapeutic exercise, massage, transcutaneous electrical nerve stimulation, thermotherapy, ultrasound, electrical stimulation, and combinations of these therapies were included in the literature search. Studies were identified and analyzed based on study type, clinical significance, and statistical significance. The authors concluded that the Philadelphia Panel guidelines recommend continued normal activity for acute, uncomplicated LBP and therapeutic exercise for chronic, subacute, and post-surgical LBP; TENS and exercise for knee osteoarthritis; proprioceptive and therapeutic exercise for chronic neck pain; and the use of therapeutic ultrasound in the treatment of calcific tendonitis of the shoulder.

Weiner and Ernst (2004) reviewed common complementary and alternative treatment modalities for the treatment of persistent musculoskeletal pain in older adults. A critical review of the literature on acupuncture and related modalities, herbal therapies, homeopathy, and spinal manipulation was carried out. Review included 678 cases within 21 randomized trials and 2 systematic reviews of herbal therapies: 798 cases within 2 systematic reviews of homeopathy; 1,059 cases within 1 systematic review of spinal manipulation for LBP, and 419 cases within 4 randomized controlled trials for neck pain. The review of acupuncture
and related modalities was based upon a paucity of well-controlled studies combined with the authors’ clinical experience. Insufficient experimental evidence exists to recommend the use of traditional Chinese acupuncture over other modalities for older adults with persistent musculoskeletal pain. Promising preliminary evidence exists to support the use of percutaneous electrical nerve stimulation for persistent LBP. The authors noted that while the use of complementary and alternative modalities for the treatment of persistent musculoskeletal pain continues to increase, rigorous clinical trials examining their effectiveness are needed before definitive recommendations regarding the application of these modalities can be made.

A Cochrane review on electrotherapy for mechanical neck disorders (Kroeling et al, 2005) evaluated if electrotherapy relieves pain or improves function/disability in adults with mechanical neck disorders (MND). For the pain outcome, there was limited evidence of benefit, i.e., pulsed electromagnetic field (PEMF) therapy resulted in only immediate post-treatment pain relief for chronic MND and acute whiplash (WAD). Other findings included unclear or conflicting evidence (galvanic current for acute or chronic occipital headache; iontophoresis for acute, subacute WAD; TENS for acute WAD, chronic MND; PEMF for medium- or long-term effects in acute WAD, chronic MND); and limited evidence of no benefit (diadynamic current for reduction of trigger point tenderness in chronic MND, cervicogenic headache; permanent magnets for chronic MND; electrical muscle stimulation (EMS) for chronic MND). The authors concluded that in pain as well as other outcomes, the evidence for treatment of acute or chronic MND by different forms of electrotherapy is either lacking, limited, or conflicting.

The National Institute for Health and Clinical Excellence’s assessment on “Percutaneous electrical nerve stimulation for refractory neuropathic pain” (NICE, 2013) stated that “Current evidence on the safety of percutaneous electrical nerve stimulation (PENS) for refractory neuropathic pain raises no major safety concerns and there is evidence of efficacy in the short term. Therefore this procedure may be used with normal arrangements for clinical governance, consent and audit”.

Fraser and Woodbury (2017) stated that fibromyalgia and complex regional pain syndrome (CRPS) are both chronic pain syndromes with
pathophysiologic mechanisms related to autonomic nervous system (ANS) dysregulation and central sensitization. Both syndromes are considered difficult to treat with conventional pain therapies. These investigators described a female veteran with fibromyalgia and a male veteran with CRPS, both of whom failed multiple pharmacologic, physical and psychological therapies for pain, but responded to percutaneous electrical neural field stimulation (PENFS) targeted at the auricular branches of the cranial nerves. The authors concluded that while PENFS applied to the body has been previously described for treatment of localized pain, PENFS effects on cranial nerve branches of the ear was not well-known, particularly when used for regional and full-body pain syndromes such as those described here. They stated that PENFS of the ear is a minimally-invasive, non-pharmacologic therapy that could lead to improved quality of life (QOL) and decreased reliance on medication. However, they stated that further research is needed to guide clinical application, particularly in complex pain patients.

Percutaneous Neuromodulation

Percutaneous neuromodulation therapy (PNT) is a variation of PENS, but utilizes different electrical impulses than PENS; it utilizes an alternating low and high frequency current at varying pulse impulses (Washington State Department of Labor and Industries, 2004). The electrical stimulation is delivered via needle-like electrodes which is purported to allow the stimulation to reach the deep tissue. Examples of this type of device include, but may not be limited to, the Vertis PNT System and the BioWavePRO Neuromodulation Pain Therapy System. The Vertis PNT is for treatment of back pain; the BioWavePRO, however, is not limited to the spine but may also be used in other painful areas in the body. These devices are not for home use, but must be used by a healthcare provider, such as a physician or physical therapist, in a clinic or office setting.

Kang, et al. (2007) reported on a single-blinded pilot randomized controlled trial in 70 patients with knee osteoarthritis who were randomized to a BioWave Deepwave percutaneous neuromodulation device or to sham administered in a clinic over 30 minutes. Seven subjects assigned to sham were lost to follow-up. Pain intensity difference was the primary measure of efficacy in this trial. Pain intensity difference was defined as the difference in visual analog pain scale noted
Electrical Stimulation for Pain

at pretreatment (baseline) versus the visual analog pain scale noted at each post-treatment period. The active group's pain intensity difference was statistically significantly greater than the sham group's pain intensity difference by 9.5 mm immediately after treatment. The active group's pain intensity difference was also greater than the sham group's pain intensity difference by 5.0 mm, 9.0 mm, and 7.0 mm for the 6-, 24-, and 48-hour post-treatment periods, respectively, although the pain intensity difference was not statistically significant at these time points. Additionally, a nonsignificant trend was noted in improvement of the pain intensity difference in the live group as compared to the sham group 48 hours post-treatment. Limitations of this pilot study include single blinding, lack of testing of adequacy of blinding, and lack of intention-to-treat analysis. The authors concluded: "The results from this pilot phase may be used to design a broader multicenter study that will be powered to provide greater data points leading to broader conclusions as to the treatment efficacy of the percutaneous Deepwave device."

Peripherally Implanted Nerve Stimulation

In this particular treatment, an electrical current is transmitted via an electrode that has been implanted around the selected peripheral nerve. This electrical current purports to block or disrupt the normal transmission of pain signals. The electrodes are connected by a wire to the peripherally implanted neurostimulator (also known as an implantable subcutaneous target stimulator). An external generator (similar to a remote control device) controls the degree of stimulation the individual receives.

In an industry funded study, Deer, et al. (2016) reported on a crossover study of 94 patients with pain of peripheral origin were implanted and then randomized to the treatment with peripheral nerve stimulation (45) or the control group (49). The primary efficacy endpoint was response rate, defined as a 30 percent decrease in a numerical rating scale, with no upward titration in the patient's medication regimen, three months after randomization to treatment. The investigators reported that patients receiving active stimulation achieved a statistically significantly higher response rate of 38% versus the 10% rate found in the control group ($p=0.0048$). Improvement in pain was statistically significant between the randomized groups, with the treatment group achieving a mean pain reduction of 27.2% from baseline to month 3 compared to a 2.3%
reduction in the control group (p < 0.0001). During the partial crossover period, patients again demonstrated statistically significant improvement in pain relief with active stimulation compared to baseline. Further, the treatment group had significantly better improvement than the control group in secondary measures including but not limited to quality of life and satisfaction. Safety, assessed throughout the trial and with follow-up to one year, demonstrated no serious adverse events related to the device. The investigators reported that all device-related adverse events were minor and self-limiting. Additional studies confirming these benefits are needed.

Shimada et al (2006) examined the ability to relieve shoulder pain by implanting ceramic-case versions of radiofrequency microstimulators (RFM) in paralyzed shoulder muscles. A 66-year old man, who had left-sided chronic hemiplegia due to a stroke 5 years previously, had developed shoulder subluxation resulting in pain. Two RFM devices were implanted, 1 next to the axillary nerve and 1 at the motor point of the middle deltoid muscle. Electrical stimulation at both sites was commenced 2 weeks after implantation for a 6-month period. Evaluation of the effectiveness of the RFM devices was carried out by measuring pain (using the VAS), ROM at the shoulder, strength of the deltoid muscle, degree of shoulder subluxation, and muscle atrophy. Following commencement of stimulation, follow-up evaluations were performed at 1, 2, 3, 4, and 6 weeks, 3 and 6 months, and after 6 months of no stimulation. During the treatment period of 6 months of stimulation, the patient's pain had reduced from 70 to 0 on the VAS. At 6 months after completion of the treatment, pain relief and effective evoked muscle contraction have remained. The authors concluded that although these results suggested that the feasibility of using RFM devices implanted both epineurally to the axillary nerve and next to the muscle motor point in this 1 patient, to relieve pain and elicit contraction, further investigation is needed to demonstrate the clinical feasibility of using RFMs for treating post-stroke shoulder pain.

In a case-report, Nguyen et al (2015) described the 1st participant treated with a fully implantable, single-lead PNS system for refractory hemiplegic shoulder pain. During the 6-week trial stage, a temporary lead was placed percutaneously near the terminal branches of the axillary nerve to the deltoid. The primary outcome measure was the Brief Pain Inventory-
Short Form Question 3, a 0 to 10 pain numeric rating scale (NRS). The participant experienced 75% pain reduction and proceeded to the implantation stage, where he received a single-lead, implantable pulse generator. After 3 weeks, the participant became pain-free. However, 7 weeks after implantation, the system was turned off because of an unrelated acute medical illness. Hemiplegic shoulder pain re-emerged with a Brief Pain Inventory-Short Form Question 3 score of 9. After 11 weeks of recovery, PNS was re-initiated and the participant became pain-free through the 9-month follow-up. At 12 months, Brief Pain Inventory-Short Form Question 3 score was 1. The authors concluded that this case-report demonstrated the feasibility of a single-lead, fully implantable PNS system for refractory hemiplegic shoulder pain.

Wilson et al (2018) examined the feasibility and safety of a single-lead, fully implantable PNS system for the treatment of chronic shoulder pain in stroke survivors. Subjects had moderate-to-severe shoulder pain not responsive to conservative therapies for 6 months. During the trial phase, which included a blinded sham introductory period, a percutaneous single-lead PNS system was implanted to stimulate the axillary nerve of the affected shoulder. After a 3-week successful trial, subjects received an implantable pulse generator with an electrode placed to stimulate the axillary nerve of the affected shoulder. Outcomes included pain, pain interference, pain-free external rotation ROM, QOL, and safety; subjects were followed-up for 24 months. A total of 28 subjects underwent trial stimulation and 5 participants received an implantable pulse generator. Subjects who received the implantable generator experienced an improvement in pain severity \((p = 0.0002)\). All 5 subjects experienced a 50% or greater pain reduction at 6 and 12 months, and 4 experienced at least a 50% reduction at 24 months. There was an improvement in pain interference \((p < 0.0001)\). There was an improvement in pain-free external ROM \((p = 0.003)\). There were no serious adverse event (AE) related to the device or to the procedure. The authors concluded that this case series demonstrated the safety and efficacy of a fully implantable axillary PNS system for chronic hemiplegic shoulder pain. Subjects experienced reduction in pain, reduction in pain interference, and improved pain-free external rotation ROM. There were no serious AEs associated with the system or the procedure.

Peripheral Subcutaneous Field Stimulation
Subcutaneous stimulation (peripheral nerve field stimulation/PNFS) is a novel neuromodulation modality that has increased in its utilization during the past decade. It consists of introducing a lead in the subdermal level to stimulate the small nerve fibers in that layer. Unlike other neuromodulation techniques including direct peripheral nerve stimulation, spinal cord stimulation (SCS), or deep brain stimulation, the precise target is not identified. Falco et al (2009) stated that relief of regional, non-appendicular pain, particularly LBP, through SCS has proven challenging. Recently, peripheral nerve stimulation (PNS), also known as PNFS depending on the stimulation area, has demonstrated efficacy for the treatment of well-localized, small areas of pain involving the abdomen, inguinal region, pelvis, face, occipital area, and low back. More widespread application of PNFS has been limited by its narrow field of coverage in a larger group of patients with diffuse or poorly localized pain.

McRoberts and Roche (2010) described a novel approach for the treatment of severe, chronic knee joint pain following total knee arthroplasty utilizing peripheral subcutaneous field stimulation (PSFS) and discussed the role of this treatment modality in patients with symptoms that are refractory to conventional pharmacologic, surgical, and physical therapies. These researchers presented 2 case reports of patients with chronic intractable knee pain where PNS via a permanent neurostimulating implant was introduced successfully. Both patients presented with persistent knee pain, for greater than 1 year, after having had total knee arthroplasty. Their symptoms failed to be alleviated by a variety of interventions including NSAIDS, oral anti-depressants, membrane stabilizers, opioids, physical therapy, surgical revisions, manipulation under anesthesia, local anesthetic patches, and TENS. In each case, direct stimulation of the knee was achieved utilizing a peripheral nerve stimulator via a peri-articular approach. Neuromodulation daily has produced both significant pain relief and functional improvement. Significant decreases in VAS pain scores and improvement in functional capacity were observed during the stimulation trial and during the follow-up after permanent implantation. The mean VAS score changed dramatically. The authors concluded that introduction of PSFS directly to the painful knee area is a novel and simple procedure that was extremely effective for the relief of pain and may provide a breakthrough in the treatment of chronic intractable knee pain.
pain following total knee arthroplasty. The peri-articular approach has several advantages, including only small incisions over the lateral and medial knee, proximal thigh and abdomen resulting in minimal strain on the lead array with flexion and extension contributing to overall stability of this system.

Yakovlev and Resch (2010) presented a case report describing application of PSFS to a patient with chronic intractable atypical facial pain (ATFP) that conventional treatment failed to ameliorate. The patient underwent an uneventful PSFS trial with percutaneous placement of 2 temporary 8-electrode leads (Medtronic Inc, Minneapolis, MN) placed subdermally over the left mandible. After experiencing excellent pain relief over the next 2 days, the patient was implanted with permanent leads and rechargeable generator 2 and a half weeks later and reported sustained pain relief at 12-month follow-up visit. Peripheral subcutaneous field stimulation provides an effective treatment option for patients suffering from chronic ATFP who have failed conservative treatment. The authors concluded that PSFS offers an alternative treatment option to select patients with intractable ATFP.

In a retrospective study, Yakovlev et al (2010) evaluated the effectiveness of PSFS for the treatment of chronic hip pain after total hip arthroplasty (THA) and greater trochanteric bursectomy (GTB). A total of 12 patients with chronic post-operative pain after THA and GTB underwent an uneventful PSFS trial with percutaneous placement of 2 temporary 8-electrode leads positioned in the subcutaneous tissue in the area of greatest pain, parallel to post-operative scar over the affected upper lateral thigh. After experiencing excellent pain relief over the next 2 days, the patients were implanted with permanent leads and rechargeable or non-rechargeable generator 2 to 4 weeks later. They reported sustained pain relief at 12-month follow-up visits. The authors concluded that PSFS provided an effective alternative treatment option for select patients with chronic post-operative pain after THA and GTB who have failed conservative treatment.

Ricciardo et al (2010) presented a case study to exemplify the application of PSFS in the treatment of recalcitrant notalgia paraesthetica. The patient was a 60-year old woman with severe and disabling notalgia paraesthetica. The itch persisted despite the use of several medications -
- topical and oral. Following a successful trial of PSFS with a temporary electrode, 2 subcutaneous electrodes were inserted into the affected area with a battery implanted subcutaneously in her right buttock. The patient was reviewed at 5 months post-implantation. She reported a greater than 85% improvement in her itch. She also reported a major improvement in her quality of life, with particular improvement in her ability to sleep through the night. This case illustrated the possible utilization of PSFS in the treatment of notalgia paraesthetica, which is a common yet poorly understood and treated condition. The authors stated that replication and controlled studies are needed to determine the general applicability of this approach.

Goroszeniuk et al. (2012) reported the use of an alternative approach to neuromodulation of anginal pain using subcutaneous leads placed at the site of pain. In this case series, 5 patients with refractory angina received successful treatment with subcutaneous target stimulation -- peripheral subcutaneous field stimulation. This technique was able to provide good analgesia in 2 patients that had had poor pain relief from existing spinal cord stimulators. All 5 patients achieved significant pain relief with a reduction in symptoms and a decrease in the use of pain medication.

Burgher et al. (2012) performed a retrospective review of consecutive patients evaluated from August 2009 to December 2010 who had undergone trial of subcutaneous (SQ) PNS with inter-lead stimulation for axial spine pain. Patients proceeding to implant were followed post-operatively with routine clinical visits and a survey form at last follow-up. Ultrasound was used intra-operatively to ensure placement of electrodes at the appropriate depth in patients with larger body mass index. Primary outcome was patient-reported pain relief at last follow-up. Literature review was conducted by searching MEDLINE (1948 to present) and through an unstructured review by the authors. A total of 10 patients underwent trial of SQ PNS and 6 proceeded to permanent implantation; 3 of the 6 (50%) implanted patients preferred neurostimulation programming that included inter-lead stimulation ("cross-talk"). Average duration of post-operative follow-up was 4.5 months (range of 2 to 9 months). Average patient-reported pain relief at last follow-up was 45% (range of 20 to 80%). One patient required re-operation for migration. Patients not proceeding to implant had paresthesia coverage but no analgesia. The authors concluded that SQ PNS is a promising therapy.
for axial neck and back pain based on a small cohort of patients. Ultrasound was useful to assist with electrode placement at the most appropriate depth beneath the skin. While inter-lead stimulation has been preferred by patients in published reports, these investigators did not find it clearly influenced pain relief. The authors stated that future investigations should include a randomized, controlled study design, as well as defined implantation technique and neurostimulator programming algorithms.

In a retrospective, multi-center, open label, uncontrolled pilot study, Miranda and Taca (2018) examined the effects of the BRIDGE, a non-invasive, percutaneous electrical nerve field stimulator, on withdrawal scores during the induction phase of opioid withdrawal therapy; and the percentage of subjects who successfully transitioned to medication assisted therapy (MAT). Adult patients treated with the BRIDGE during medically supervised withdrawal were included in this study. The clinical opioid withdrawal scale (COWS) scores were prospectively recorded at different intervals (20, 30, and 60 mins) and analyzed; a subset of patients had scores recorded 5-days post-BRIDGE. Participants who returned to the clinic and received their 1st dose of maintenance medication were considered to be successfully transitioned. In this cohort (n = 73; age greater than or equal to 18 years), 65 % were men. The mean COWS score before BRIDGE placement was 20.1 (± 6.1); 20 mins after BRIDGE placement, the mean score was reduced to 7.5 (± 5.9) (62.7 % reduction, p < 0.001). The scores were further reduced after 30 mins 4.0 (± 4.4) and 60 mins 3.1 (± 3.4) (84.6 % reduction, p < 0.001). No rescue medications were given during this period. The mean withdrawal score on day 5 was 0.6 (97.1 % reduction, n = 33; p < 0.001). Overall, 64/73 patients (88.8 %) successfully transitioned to MAT. The authors concluded that neurostimulation with the BRIDGE was associated with a reduction in opioid withdrawal scores; and this effect persisted during the induction period and allowed for effective transition to MAT. These preliminary findings from a pilot study need to be validated by well-designed studies.

The authors stated that drawbacks of this study included the uncontrolled, retrospective study design, and the relatively small sample size (n = 73). While randomized, placebo-controlled trials have the highest level of validity, most participants in this study presented in moderate-to-severely
moderate withdrawal. The concern of using a placebo or sham device in such a vulnerable population must be taken into consideration in future studies. While the data in this study were collected retrospectively, the objective and subjective COWS scores were all recorded prospectively during intervals of clinical care. This eliminated recall bias and helped establish the temporal relationship of the findings. Another drawback of this study was that the potential presence of psychiatric disorders other than opioid dependence and more precise drug use patterns could not be included in the analysis. Studies suggested that perhaps the types of drugs used or the presence of other psychiatric disorders could influence treatment outcomes. Although a large percentage of subjects successfully transitioned to MAT, the study took place in an out-patient setting, therefore, it did not allow the researchers to record withdrawal scores or the use of adjunct medications between day 1 and day 5. Finally, the study design did not allow for long-term follow-up, which was also an important drawback.

H-Wave Stimulation

H-Wave stimulation is a form of electrical stimulation that differs from other forms of electrical stimulation in terms of its waveform. The H-wave produces low frequency muscle stimulation and high frequency pain control. H-wave stimulation has been purported for use in pain control for conditions such as complex regional pain syndrome (reflex sympathetic dystrophy), muscle sprains, temporomandibular joint dysfunctions or treatment of diabetic neuropathy.

H-wave stimulation delivers electrical stimulation in the form of milliamperage. H-wave stimulation is intended to emulate the H waveform found in nerve signals (Hoffman Reflex) and therefore enables greater and deeper penetration of a low frequency current, while using significantly less power than other machines. This allegedly makes H-Wave stimulation much safer, less painful and more effective than other forms of electrotherapy to date. The H-wave signal is a bipolar, exponential decaying waveform that supposedly overcomes the disadvantages of other electrotherapy machines. It allows the therapist to apply 2 treatments at the same time: (i) low-frequency muscle stimulation and (ii) high-frequency deep analgesic pain control (a "TENS" effect). Note: H-wave stimulation must be distinguished from the
H-waves that are a component of electromyography. The H-wave stimulator (Electronic Waveform Lab, Inc., Huntington Beach, CA) is an electrostimulation device that has been used to reduce pain and swelling associated with a variety of diseases and conditions. In a single-blinded clinical study, Kumar and Marshall (1997) evaluated the effectiveness of H-wave stimulation for the treatment of chronic (greater than 2 months) pain associated with diabetic (type 2) peripheral neuropathy (n = 31). Patients were randomly assigned to: (i) H-wave stimulation, or (ii) sham treatment. The authors reported that H-wave treated patients exhibited greater symptomatic relief than their sham-treated counterparts. Moreover, it has also been shown that H-wave stimulation may be a useful adjunctive modality when combined with pharmacotherapy (e.g., amitriptyline) to augment symptomatic relief in patients with diabetic peripheral neuropathy (Julka et al, 1998; McDowell et al, 1999).

On the other hand, H-wave stimulators have not been shown to be effective in reducing pain from causes other than chronic diabetic peripheral neuropathy, or in reducing edema or swelling. In particular, H-wave stimulation has not been demonstrated to be effective in treating chronic pain due to ischemia. In the study by Kumar and Marshall (1997), patients with significant peripheral vascular disease were excluded from the trial. Furthermore, in a randomized controlled study (n = 112), McDowell et al (1995) reported that H-wave stimulation was not effective in reducing experimental ischemic pain.

A systematic evidence review concluded that H-wave stimulation had a moderate to strong effects in relieving pain, reducing pain medication use and increasing functionality in patients with chronic soft tissue inflammation or neuropathic pain (Blum et al, 2008). A critique of this systematic evidence review by the Centre for Reviews and Dissemination (CRD, 2009) concluded that "it is not possible to determine whether the results of this review are reliable" given its significant methodologic limitations. In particular, very limited details of the included studies were given in the review; in particular it was unclear which studies were randomized, no control interventions were detailed, and there were insufficient details on the outcome measures used. Although a validity assessment was performed, the results were not presented. "Given these omissions, it is difficult to assess either the internal or external
validity of the results.” The CRD noted that the authors of the systematic evidence review used meta-analysis to combine the results, but different measures of effect appeared to be combined in a single effect size. Insufficient details on the outcome measures used in the included studies meant that it was not possible to determine if this was appropriate or not. The CRD critique noted that, in addition to four authors of the systematic evidence review being independent consultants for Electronic Waveform Lab (the makers of the H-Wave device), 2 authors were members of the research groups responsible for conducting the primary studies.

**Intramuscular Stimulation**

Intramuscular stimulation can be considered as a variation of acupuncture. It has been claimed to promote long-term relief in chronic neuropathic pain. Intramuscular stimulation utilizes the same sized needles as in acupuncture; they are inserted into the part of a shortened muscle where a nerve may be entrapped. This most often causes some local pain as the needle is re-inserted several times to release the nerve and lengthen the muscle. In general, treatments are administered once or twice weekly for 3 to 6 weeks. However, the clinical value of this invasive procedure has not been validated by randomized controlled studies.

**Sympathetic Therapy (Dynatron)**

Many chronic pain syndromes/conditions (e.g., peripheral neuropathies and reflex sympathetic dystrophy) are "sympathetically biased" and have no identifiable underlying cause(s).

Sympathetic Therapy is a non-invasive treatment protocol advocated for the symptomatic relief of patients with chronic pain. It is a patented method of delivering electrostimulation via peripheral nerves to create a "special" form of stimulation of the sympathetic nervous system. It incorporates dual interfering waveforms with specific electrode placement on the upper and lower extremities (8 electrodes/treatment). Electrodes are placed bilaterally over dermatomes, thus accessing the autonomic nervous system via the peripheral nervous system.
The treatment plan for Sympathetic Therapy includes clinical treatments followed by home therapy. Electrostimulation is administered by means of the Dynatron STS (a clinical unit) or the Dynatron STS Rx (a home unit). A software program is included with the clinical Dynatron unit to help doctors with electrode placement and to record patient progress. According to the manufacturer, electrostimulation delivered by the Dynatron is different from that provided by TENS. The key difference is in its application -- Dynatron applied within the Sympathetic Therapy protocol supposedly treats systemically while TENS treats transcutaneously at or near the primary pain location. Daily therapy sessions are needed to establish effectiveness of the treatment and to ascertain the most effective protocol for individual patients (20 or more sessions may be needed to complete this process). Each treatment session lasts about 60 mins. If the patient responds to treatment and the optimal protocol has been established, a home Dynatron unit may be prescribed to facilitate treatments over an extended period of time and, in most cases, indefinitely. If necessary, the patient may return to the clinic periodically for a follow-up visit to adjust the protocol or receive additional guidance in administering home therapy.

Guido (2002) reported on the effects of Sympathetic Therapy on 20 patients with chronic pain and peripheral neuropathies. Subjects were treated daily with the Dynatron STS for 28 days. At the beginning of the study, 11 of 15 patients reported being in moderate to severe pain, whereas by the end of treatment, 5 of 15 patients defined their pain as being moderate to severe. For these 15 patients, mean cumulative VAS for multiple locations of pain decreased significantly, from 107.8 to 45.3. (The authors stated, without further explanation, that self-reports of pain severity were unavailable for 5 of the 20 patients.) However, because the study did not include a randomized masked control group, placebo effects and other biases could affect results. In addition, the lack of data on pain severity in a quarter of the patients included in this study may have significantly biased the results. There are no published randomized controlled clinical trials of the effectiveness of Sympathetic Therapy in the management of patients with chronic intractable pain. Randomized controlled trials are needed to ascertain the clinical benefits of this treatment protocol in these patients.


Electroceutical Therapy

Electroceutical therapy is a noninvasive device that uses a variety of electrical modalities as a proposed treatment for acute and chronic pain. The device is similar to TENS, except electroceutical treatments use higher electrical frequencies, altering the electric current to mimic the human bioelectric system. This therapy may also be referred to as bioelectric nerve block, noninvasive neuron blockade, electroceutical neuron blockade and bioelectric treatment system. An example of this is the Hako-Med Pro Elect DT 2000.

Electroceutical therapy, also known as bioelectric nerve block, involves blockade of axonal transmissions. Electroceutical therapy has been used in the management of neuropathic pain (non-malignant pain) as well as pain associated with cancer (malignant pain). According to a manufacturer of an electroceutical nerve block device, the electroceutical treatment approach is based on the non-invasive application of controlled, specific parameter bioelectric impulses. Electrical current is altered via special step-down transformers into bioelectric impulses, which are designed to mimic the human bioelectric system. Currently, there are 2 distinctive electroceutical classifications: (i) stimulatory class in which repetitive action potentials are induced in excitable cells
(depolarization and repolarization activity), and (ii) multi-facilitatory class that produces biophysical effects without repetitive action potential propagation. The proper electroceutical class, dosage, regimen duration and anatomical placement of electrodes are determined by the individual patient's diagnosis. Proponents of electroceutical therapy claim that its use has resulted in significant relief of pain and elimination or drastic reductions in patients' pain medication requirements, such that patients are able to resume their daily activities. However, there is a lack of scientific evidence to substantiate these claims. Guidelines from the Work Loss Data Institute (2008) considered, but did not recommend, electroceutical therapy for chronic pain. Well-designed, randomized controlled clinical studies are needed to determine the usefulness of electroceutical therapy in the treatment of patients with acute or chronic pain.

Transcutaneous Electrical Joint Stimulation and Pulsed Electrical Stimulation

Transcutaneous electrical joint stimulation is also known as pulsed electrical stimulation; and the Bionicare device uses this type of electrical stimulation. Zizic et al (1995) evaluated the safety and effectiveness of pulsed electrical stimulation for the treatment of osteoarthritis (OA) of the knee (n = 78). Patients were treated 6 hours/day for 4 weeks. The investigators reported that patients treated with the active devices showed significantly greater improvement than the placebo group for all primary efficacy variables in comparisons of mean change from baseline to the end of treatment. Improvement of greater or equal to 50 % from baseline was shown in at least 1 primary efficacy variable in 50 % of the active device group, in 2 variables in 32 %, and in all 3 variables in 24 %. In the placebo group improvement of greater or equal to 50 % occurred in 36 % for one, 6 % for 2, and 6 % for 3 variables. Mean morning stiffness decreased 20 mins in the active device group and increased 2 mins in the placebo group (p < 0.05). No statistically significant differences were observed for tenderness, swelling, or walking time. The authors concluded that improvements in clinical measures for pain and function found in this study suggest that pulsed electrical stimulation is effective for treating OA of the knee. The investigators noted, however, that studies of the durability of results are warranted.
In a Cochrane review on pulsed electric stimulation for the treatment of OA (Hulme et al, 2002), the authors stated that current evidence suggests that electrical stimulation therapy may provide significant improvements for knee OA, but further studies are required to confirm whether the statistically significant results shown in these trials confer clinically significant and durable benefits.

A systematic evidence review by McCarthy et al (2006) concluded that pulsed electromagnetic field therapy is unlikely to benefit patients with knee osteoarthritis. The systematic evidence review identified 5 RCTs of pulsed electromagnetic field therapy for knee osteoarthritis: 2 RCTs scored 5 points for validity, 1 scored 4 and 2 scored 3. The investigators found that none of the individual studies reported a statistically significant difference between treatments for pain. Only 1 study (n = 83) with a low quality score of 3 reported a statistically significant difference between treatments in function (standardized mean difference -0.58, 95 % CI: -1.02 to -0.14). For all studies combined, there was no significant difference between interventions in pain (weighted mean difference -0.66, 95 % CI: -1.67 to 0.35) or function (weighted mean difference -0.70, 95 % CI: -1.92 to 0.52).

Fary and colleagues (2008) stated that OA of the knee is one of the main causes of musculoskeletal disability in the western world. Current available management options provide symptomatic relief (exercise and self-management, medication and surgery) but do not, in general, address the disease process itself. Moreover, adverse effects and complications with some of these interventions (medication and surgery) and the presence of co-morbidities commonly restrict their use. There is clearly a need to investigate treatments that are more widely applicable for symptom management and which may also directly address the disease process itself. The authors described the protocol of a double-blind, randomized, placebo-controlled, repeated measures trial to examine the effectiveness of pulsed electrical stimulation in providing symptomatic relief for people with OA of the knee over 26 weeks. A total of 70 subjects will be recruited and information regarding age, gender, body mass index and medication use will be recorded. The population will be stratified for age, gender and baseline pain levels. Outcome measures will include pain (100 mm VAS and Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] 3.1), function
In a double-blind, randomized, placebo-controlled, repeated-measures study, Fary et al (2011) determined the effectiveness of subsensory, pulsed electrical stimulation (PES) in the symptomatic management of OA of the knee. A total of 70 participants with clinical and radiographically diagnosed OA of the knee were randomized to either PES or placebo. The primary outcome was change in pain score over 26 weeks measured on a 100-mm VAS. Other measures included pain on the WOMAC, function on the WOMAC, patient's global assessment of disease activity (on a 100-mm VAS), joint stiffness on the WOMAC, quality of life on the SF-36 health survey, physical activity (using the Human Activity Profile and an accelerometer), and global perceived effect (on an 11-point scale). Thirty-four participants were randomized to PES and 36 to placebo. Intent-to-treat analysis showed a statistically significant improvement in VAS pain score over 26 weeks in both groups, but no difference between groups (mean change difference 0.9 mm [95% CI: -11.7 to 13.4]). Similarly, there were no differences between groups for changes in WOMAC pain, function, and stiffness scores (-5.6 [95% CI: -14.9 to 3.6], -1.9 [95% CI: -9.7 to 5.9], and 3.7 [95% CI: -6.0 to 13.5], respectively), SF-36 physical and mental component summary scores (1.7 [95% CI: -1.5 to 4.8] and 1.2 [95% CI: -2.9 to 5.4], respectively), patient's global assessment of disease activity (-2.8 [95% CI: -13.9 to 8.4]), or activity measures; 56% of the PES-treated group achieved a clinically relevant 20-mm improvement in VAS pain score at 26 weeks compared with 44% of controls (12% [95% CI: -11% to 33%]). The authors concluded that in this sample of subjects with mild-to-moderate symptoms and moderate-to-severe radiographic OA of the knee, 26 weeks of PES was no more effective than placebo.

Mendel et al (2010) noted that high-voltage pulsed current (HVPC), a form of electrical stimulation, is known to curb edema formation in laboratory animals and is commonly applied for ankle sprains, but the
clinical effects remain undocumented. In a multi-center, randomized, double-blind, placebo-controlled trial, these investigators examined if, as an adjunct to routine acute and subacute care, subsensory HVPC applied nearly continuously for the first 72 hours after lateral ankle sprains affected time lost to injury. Data were collected at 9 colleges and universities and 1 professional training site. A total of 50 intercollegiate and professional athletes were included in this study. Participants were given near-continuous live or placebo HVPC for 72 hours post-injury in addition to routine acute and subacute care. Main outcome measure was time lost to injury measured from time of injury until declared fit to play. Overall, time lost to injury was not different between treated and control groups (p = 0.55). However, grade of injury was a significant factor. Time lost to injury after grade I lateral ankle sprains was greater for athletes receiving live HVPC than for those receiving placebo HVPC (p = 0.049), but no differences were found between groups for grade II sprains (p = 0.079). The authors concluded that application of subsensory HVPC had no clinically meaningful effect on return to play after lateral ankle sprain.

Electro-Acuscope Myopulse

The Electro-Acuscope Myopulse Therapy System is an electronic device that has been used for a wide range of neuromuscular conditions. The Acuscope uses electricity to treat pain by stimulating the nervous system without puncturing the skin. The Myopulse, a companion instrument to the Acuscope, stimulates muscles, tendons and ligaments, reducing spasm, inflammation and strengthening tissue damaged by traumatic injury. This form of therapy purportedly helps the body heal itself by stimulating the supply of blood and oxygen to the involved area. The Electro-Acuscope Myopulse Therapy System has been used in the treatment of pain and many types of tissue damage including swelling, inflammation, and soreness. However there is insufficient scientific evidence to support its effectiveness.

Sacral Nerve Root and Lumbosacral Plexus Stimulation

Electrical stimulation of the sacral nerves (sacral neuromodulation) or lumbosacral plexus has been used for painful conditions resulting from chronic abdominal, pelvic, genital, and anal pain syndromes (Kim, 2004).
Specific conditions that have been treated include pain from interstitial cystitis, coccydynia, pyelonephritis, pancreatitis, rectal fugax, and vulvodynia.

Procedures allowing access to sacral and lumbosacral nerves include a retrograde (cephalocaudad) epidural approach and a sacral transforaminal approach. The transforaminal approach is mainly used for the treatment of urge urinary incontinence and urinary retention, while the retrograde approach has been used primarily for the treatment of pelvic pain.

Evidence for sacral nerve root and lumbosacral plexus stimulation is limited to case reports and small case series. Alo and colleagues (1999) reported that lumbar and sacral nerve root stimulation through the retrograde approach resulted in adequate paresthesia and effective pain relief as reflected by VAS scores in 5 patients with chronic pain (e.g., ilioinguinal neuralgia, discogenic LBP, failed back syndrome, and vulvodynia). These investigators concluded that further clinical trials are needed to assess the safety and long-term success rates of lumbar/sacral nerve root stimulation in the management of patients with chronic pain.

Anterograde sacral nerve root stimulation (SNRS) through the sacral hiatus is another method that has been tried for the treatment of pelvic pain. In a case report study, Falco et al (2003) found that anterograde SNRS provided good pain relief (as indexed by VAS scores) in a patient with chronic pelvic (rectal, coccygeal, and perineal) pain. The authors concluded that further investigation is needed before any conclusions can be rendered regarding the reliability of SNRS in the treatment of these disorders.

Siegel and colleagues (2001) examined the effectiveness of transforaminal sacral nerve stimulation in patients with chronic intractable pelvic pain. After successful percutaneous trial stimulation, a neuroprosthetic sacral nerve stimulation device was surgically implanted in 10 patients with chronic intractable pelvic pain. Leads were placed in the S3 and S4 foramen in 8 and 2 cases, respectively. Patients were evaluated throughout the study using a patient pain assessment questionnaire on a scale of 0 (absence of pain) to 5 (excruciating pain). Pain was assessed at baseline, during test stimulation, and 1, 3 and 6
months after implantation of surgical lead. An additional long-term assessment was done at a median follow-up of 19 months. Of the 10 patients with the implant, 9 had a decrease in the severity of the worst pain compared to baseline at a median follow-up of 19 months. The number of hours of pain decreased from 13.1 to 6.9 at the same follow-up interval. There was also an average decrease in the rate of pain from 9.7 at baseline to 4.4 on a scale of 10 (always having pain) to 0 (never having pain). At a median of 19 months, 6 of 10 patients reported significant improvement in pelvic pain symptomatology. The authors concluded that these data imply that transforaminal sacral nerve stimulation can have beneficial effects on the severity and frequency of chronic intractable pelvic pain. They further stated that future clinical studies are necessary to determine the long-term effectiveness of this therapy.

The available evidence on sacral nerve root and lumbosacral plexus stimulation is insufficient to draw reliable conclusions about the effect of these interventions on chronic pelvic and abdominal pain.

**Microcurrent Therapy**

Microcurrent electrical nerve stimulation (MENS) devices are also non-invasive devices in which precise, tightly controlled electrical current is applied to specific points on the body. These specific points correspond with classical acupuncture points. MENS is also referred to as microelectrical therapy (MET) or microelectrical neuro-stimulation. Examples of this type of device include, but may not be limited to, Algonix, Alpha-Stim 100, Electro-Lyoscope 85P, Electro-Myopulse 75L, KFH Energy, MENS 2000-D, MICROCURRENT and Myopulse 75C.

Microcurrent therapy (MCT), also known as low-voltage microampere stimulation, is characterized by sub-sensory current that acts on the body’s naturally occurring electrical impulses to decrease pain and facilitate the healing process. It uses microamperage instead of milliamperage to drive its current into the injured site. Microcurrent therapy uses current between 1 and 1,000 microA at a voltage of 10 to 60 V, and a frequency of 0.5 to 100 Hz. It differs from TENS in that it uses a significantly reduced electrical stimulation. While TENS blocks pain, MCT acts on the naturally occurring electrical impulses to decrease pain by stimulating the healing process.
Koopman et al (2009) stated that MCT is a novel treatment for pain syndromes. The MCT patch is hypothesized to produce stimuli that promote tissue healing by facilitating physiologic currents. Solid evidence from randomized clinical trials is lacking. To assess the effectiveness of MCT in treating non-specific, chronic LBP, these researchers conducted a double-blind, randomized, cross-over, pilot trial. A total of 10 succeeding patients presenting with non-specific, chronic LBP were included. Patients started with 2, 9-day baseline period followed by a 5-day treatment periods. During the treatment periods, either a placebo or MCT (verum) patch was randomly assigned. Mean and worst pain scores were evaluated daily by a VAS. Furthermore, analgesic use, side effects, and quality of life were assessed after each period. Differences between the last 4 days of a treatment period and the baseline period were calculated. Differences between verum and placebo periods per patient were compared using paired-t tests. A 20-mm VAS score reduction was considered clinically relevant. The VAS score was lower during verum treatment, with a reduction (95 % CI) of -0.43 (-1.74; 0.89) in mean and -1.07 (-2.85; 0.71) in worst pain. Analgesic use decreased during verum treatment, except for non-steroid anti-inflammatory drug use, which increased. Quality of life improved during verum treatment. However, none of the findings was statistically significant. A positive trend in MCT use for a specific, chronic LBP was reported. The authors stated that further investigations are needed to evaluate the significance and relevance of these findings.

Furthermore, the American Pain Society's clinical practice guideline on non-surgical interventional therapies for LBP (Chou et al, 2009) concluded that few non-surgical interventional therapies for LBP have been shown to be effective in randomized, placebo-controlled trials.

Zuim et al (2006) evaluated the effect of microcurrent electrical nerve stimulation (MENS) and compared with occlusal splint therapy in temporo-mandibular disorders (TMD) patients with muscle pain. A total of 20 TMD patients were divided into 4 groups. One received occlusal splint therapy and MENS (I); other received splints and placebo MENS (II); the third, only MENS (III) and the last group, placebo MENS (IV). Sensitivity derived from muscle palpation was evaluated using a VAS. Results were submitted to analysis of variance (p < 0.05). There was reduction of pain level in all groups: group I (occlusal splint and MENS) had a 47.7 %
Electrical Stimulation for Pain

reduction rate; group II (occlusal splint and placebo MENS), 66.7 %; group III (MENS), 49.7 % and group IV (placebo MENS), 16.5 %. In spite of that, there was no statistical difference (analysis of variance/p < 0.05) between MENS and occlusal splint therapy regarding muscle pain reduction in TMD patients after 4 weeks.

In a placebo-controlled, single-blinded, and randomized study, Gossrau et al (2011) evaluated the effect of micro-TENS in reducing neuropathic pain in patients with painful diabetic neuropathy (PDN). A total of 22 diabetic patients have been treated with a micro-TENS therapy and 19 patients have been treated with a placebo therapy. Treatment duration was 4 weeks with 3 therapeutic settings per week. Standardized questionnaires (Pain Disability Index [PDI], neuropathic pain score [NPS], Center for Epidemiologic Studies Depression Scale [CES-D]) were used to assess pain intensity, pain disability, as well as quality of life at baseline at the end of the treatment period and 4 weeks after treatment termination. Patients with a minimum of 30 % reduction in NPS were defined as therapy responders. After 4 weeks of treatment, 6/21 (28.6 %) patients in the verum group versus 10/19 (52.6 %) patients in the placebo group responded to therapy. The median PDI score after 4 weeks of treatment showed a reduction of 23 % in the verum versus 25 % in the placebo group. The differences did not reach statistical significance. The authors concluded that the pain reduction with the applied transcutaneous electrotherapy regimen is not superior to a placebo treatment.

Scrambler Therapy/The Calmare Therapy Device

Scrambler therapy (also known as transcutaneous electrical modulation pain reprocessing) is an electro-cutaneous nerve stimulation device that interferes with pain signal transmission by mixing a "non-pain" information into the nerve fibers. It consists of a multi-processor apparatus capable of simulating 5 artificial neurons that send out signals identified by the central nervous system as "no pain" via the application of surface electrodes on skin in the pain areas.

Marineo (2003) examined the effects of the Scrambler therapy in the treatment of drug-resistant oncological pain of the visceral/neuropathic type. A total of 11 terminal cancer patients (3 pancreas, 4 colon, 4 gastric) suffering from elevated drug resistant visceral pain were included
in this study. The trial program was related to the first 10 treatment sessions. Subsequently, each patient continued to receive treatment until death. Pain measures were performed using the VAS before and after each treatment session and accompanied by diary recordings of the duration of analgesia in the hours following each single application. Any variation in pain-killing drug consumption was also recorded. All patients reacted positively to the treatment throughout the whole reference period. Pain intensity showed a significant decrease (p < 0.001), accompanied by a gradual rise both in the pain threshold and the duration of analgesia; 9 (81.8 %) of the patients suspended pain-killers within the first 5 applications, while the remaining 2 (18.2 %) considerably reduced the dosage taken prior to Scrambler therapy. No undesirable side effects were observed. Compliance was found to be optimal. The authors concluded that these preliminary results obtained using Scrambler therapy were extremely encouraging, both in terms of enhanced pain control after each treatment session and in view of the possible maintenance of effectiveness over time.

Sabato et al (2005) assessed the effectiveness of the Scrambler therapy in the treatment of neuropathic pain. A total of 226 patients, all suffering from intense drug-resistant neuropathic pain, were recruited for this trial. Inclusion criteria included neuropathic pain, very high baseline VAS. Exclusion criteria included pacemaker users, neurolithic blocks or neurolesive pain control treatment. The treated neuropathic pain syndromes were: failed back surgery syndrome (FBSS), post-herpetic neuralgia (PHN), trigeminal neuralgia, post-surgery nerve lesion neuropathy, pudendal neuropathy, brachial plexus neuropathy, LBP, and others. The trial program entailed 1 to 6 therapy sessions of 5 treatments, each one lasting 30 mins. Pain intensity was evaluated using VAS before and after each treatment. The statistical significance of VAS was measured using the paired t-test. The total results showed 80.09 % of responders (pain relief greater than 50 %), 10.18 % of partially responders (pain relief from 25 % to 49 %) and 9.73 % of no responders (patients with pain relief less than 24 % or VAS greater than 3). The authors concluded that the Scrambler therapy produced a statistically significant (p < 0.0001) pain relief in all treated neuropathies.
In a pilot study, Marineo et al (2012) compared guideline-based drug management with Scrambler therapy. A clinical trial with patients randomized to either guideline-based pharmacological treatment or Scrambler therapy for a cycle of 10 daily sessions was performed. Patients were matched by type of pain including post-surgical neuropathic pain, PHN, or spinal canal stenosis. Primary outcome was change in VAS pain scores at 1 month; secondary outcomes included VAS pain scores at 2 and 3 months, pain medication use, and allodynia. A total of 52 patients were randomized. The mean VAS pain score before treatment was 8.1 points (control) and 8.0 points (Scrambler). At 1 month, the mean VAS score was reduced from 8.1 to 5.8 (-28 %) in the control group, and from 8 to 0.7 points (-91 %) in the Scrambler group (p < 0.0001). At 2 and 3 months, the mean pain scores in the control group were 5.7 and 5.9 points, respectively, and 1.4 and 2 points in the Scrambler group, respectively (p < 0.0001). More relapses were seen in polyradicular pain than monoradicular pain, but re-treatment and maintenance therapy gave relief. No adverse effects were observed. The authors concluded that in this pilot randomized trial, Scrambler therapy appeared to relieve chronic neuropathic pain better than guideline-based drug management.

In a pilot study, Smith et al (2010) evaluated the impact on chemotherapy-induced peripheral neuropathy (CIPN) associated with the MC5-A Calmare therapy device. A total of 18 patients from 1 center received 1-hour interventions daily over 10 working days. Of 18 patients, 16 were evaluable. The mean age of the patients (4 men and 14 women) was 58.6 years and the duration of CIPN was 3 months to 8 years. The most common drugs used by these subjects were taxanes, platinum, and bortezomib. At the end of the study (day 10), a 20 % reduction in numeric pain scores was achieved in 15 of 16 patients. The pain score fell 59 % from 5.81 +/- 1.11 before treatment to 2.38 +/- 1.82 at the end of 10 days (p < 0.0001 by paired t-test). A daily treatment benefit was seen with a strong statistically significant difference between the pre- and post-daily pain scores (p < 0.001). Four patients had their CIPN reduced to zero. A repeated-measures analysis using the scores from all 10 days confirmed these results. No toxicity was seen. Some responses have been durable without maintenance. The authors concluded that patient-specific cutaneous electro-stimulation with the MC5-A Calmare device appears to dramatically reduce pain in refractory CIPN patients with no toxicity. They
stated that further studies (determining effectiveness compared with sham or placebo treatment, and the need for maintenance therapy) are underway to define the benefit, mechanisms of action, and optimal schedule. The preliminary findings of this pilot study need to be validated by well-designed studies. There is a phase II clinical trial that examines the effectiveness of the MC5-A Scrambler therapy in reducing peripheral neuropathy caused by chemotherapy.

Ricci et al (2012) evaluated the effectiveness of an innovative neuromodulative approach to the treatment of chronic pain using electrical stimulus integrated with pharmacological support. The MC5-A Calmare is a new device for patient-specific cutaneous electro-stimulation which, by "scrambling" pain information with "no pain" information, aims to reduce the perception of pain intensity. These researchers prospectively treated 73 patients with cancer-related (n = 40) and non-cancer-related (n = 33) pain whose pain management was unsatisfactory. The primary objective of the study was to assess efficacy and tolerability of the device. Pain intensity was assessed daily with a NRS for the duration of treatment (2 weeks) and then on a weekly basis for the 2 weeks of follow-up. Mean pain value at T0 (pre-treatment value) was 6.2 [+/- 2.5 SD], 1.6 (+/- 2.0) (p < 0.0001) at T2 (after the 10th day of treatment), and 2.9 (+/- 2.6) (p < 0.0001) at T4 (after the second week of follow-up, i.e., 1 month after the beginning of treatment). Response after the second week of treatment showed a clear reduction in pain for both cancer (mean absolute delta of the reduction in NRS value = 4.0) and non-cancer (mean delta = 5.2) patients. The pain score had decreased by 74 % at T2. On the basis of pre-established response criteria, there were 78 % of responders at T2 and 81 % at T4. No side effects were reported. The authors concluded that these preliminary results suggested that cutaneous electro-stimulation with the MC5-A Calmare can be hypothesized as part of a multi-modality approach to the treatment of chronic pain. They stated that further studies on larger numbers of patients are needed to assess its efficacy, to quantify the effects of inter-operator variability, and to compare results obtained from the active device versus those from a sham machine.

Smith and Marineo (2018) noted that post-herpetic neuropathy (PHN) is common, severe, and often refractory to treatment. These investigators treated 10 patients with refractory PHN using Scrambler therapy, a
neurocutaneous stimulation device that delivers "non-pain" information with surface electrodes. Scrambler therapy was given as 30-minute sessions daily for 10 days. Pain was recorded before and after treatment. The average pain score rapidly diminished from 7.64 ± 1.46 at baseline to 0.42 ± 0.89 at 1 month, a 95% reduction, with continued relief at 2 and 3 months. Patients achieved maximum pain relief with less than 5 treatments. The authors concluded that the Scrambler therapy appeared to have a promising effect on PHN, with prompt and continued relief and no side effects. They stated that further research is warranted.

Pachman et al (2014) stated that chemotherapy-induced peripheral neuropathy (CIPN) is a common toxicity associated with multiple chemotherapeutic agents. CIPN may have a detrimental impact on patients' quality of life and functional ability, as well as result in chemotherapy dose reductions. Although symptoms of CIPN can improve with treatment completion, symptoms may persist. Currently, the treatment options for CIPN are quite limited. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has the most evidence supporting its use in the treatment of CIPN. Other agents with potential benefit for the treatment of established CIPN include gabapentinoids, venlafaxine, tricyclic antidepressants, and a topical gel consisting of the combination of amitriptyline, ketamine, and baclofen; none of these, however, has been proven to be helpful and ongoing/future studies may well show that they are not beneficial. The use of these agents is often based on their efficacy in the treatment of non-CIPN neuropathic pain, but this does not necessarily mean that they will be helpful for CIPN-related symptoms. Other non-pharmacologic interventions including acupuncture and Scrambler therapy are supported by positive preliminary data; however, further larger, placebo-controlled trial data are needed to confirm or refute their effectiveness.

In a double-blinded, randomized controlled trial, Starkweather et al (2015) evaluated the effects of Calmare, a non-invasive neurocutaneous electrical pain intervention, on lower back pain intensity as measured by the "worst" pain score and on pain interference using the Brief Pain Inventory-Short Form, on measures of pain sensitivity assessed by quantitative sensory testing, and on mRNA expression of pain sensitivity genes. A total of 30 participants were randomized to receive up to 10 sessions of Calmare® treatment (n = 15) or a sham treatment (n = 15)
using the same device at a non-therapeutic threshold. At 3 weeks after conclusion of treatment, compared with the sham group, the Calmare® group reported a significant decrease in the "worst" pain and interference scores. There were also significant differences in pain sensitivity and differential mRNA expression of 17 pain genes, suggesting that Calmare® can be effective in reducing pain intensity and interference in individuals with persistent low back pain by altering the mechanisms of enhanced pain sensitivity. The authors stated that further study of long-term pain outcomes, particularly functional status, analgesic use and health care utilization, is warranted.

Pachman et al (2015) stated that CIPN, a common side effect of chemotherapy, needs better effective treatments. Preliminary data support the use of Scrambler therapy, a device which treats pain via noninvasive cutaneous electrostimulation, for the treatment of CIPN. The current manuscript reported data from a pilot trial, performed to investigate the effect of Scrambler therapy for the treatment of established CIPN. Eligible patients had CIPN symptoms of greater than or equal to 1 month duration with tingling and/or pain greater than or equal to 4/10 during the prior week. Patients were treated with Scrambler therapy to the affected area(s) for up to 10 daily 30-min sessions. Symptoms were monitored using a neuropathy questionnaire consisting of numerical analog scales ranging from 0 to 10, daily before therapy as well as weekly for 10 weeks after therapy. Descriptive summary statistics formed the basis of data analysis. A total of 37 patients were enrolled; 25 patients were treated primarily on their lower extremities while 12 were treated primarily on their upper extremities. There was a 53 % reduction in pain score from baseline to day 10; a 44 % reduction in tingling; and a 37 % reduction in numbness. Benefit appeared to last throughout 10 weeks of follow-up. There were no substantial adverse events. The authors concluded that preliminary data support that Scrambler therapy may be effective for the treatment of CIPN; they stated that a prospective placebo-controlled clinical trial should be performed.

In a single-center, case-series study, Notaro et al (2016) examined the effectiveness of Scrambler therapy in reducing cancer pain induced by skeletal and visceral metastases after failure of standard treatments, including pharmacological therapies and radiation therapy. A total of 25 consecutive patients underwent Scrambler therapy individually delivered
by MC5-A Calmare for 10 daily sessions each of 30 to 40 mins. Pain was measured by a numeric rating scale at baseline, as well as before and after each treatment session; 100 % of patients reached a pain relief of greater than or equal to 50 %. Pain score was reduced from 8.4 at baseline to 2.9 after treatment, with a mean pain relief of 89 %. The sleeping hours improved from 4.4 ± 1.2 to 7.5 ± 1.1. The duration of pain control by Scrambler therapy was 7.7 ± 5.3 weeks. No adverse events were observed. The authors concluded that Scrambler therapy did not present toxicity and allowed opioids dosage reduction, and it is also a repeatable treatment. They stated that present novel data support that Scrambler therapy appeared to be effective for the treatment of cancer pain; further evaluation in RCTs is needed to confirm these findings.

Majithia et al (2016) evaluated what is known regarding the mechanisms and mechanics of Scrambler therapy and investigated the preliminary data pertaining to the effectiveness of this treatment modality. The PubMed/Medline, SCOPUS, Embase, and Google Scholar databases were searched for all articles published on Scrambler therapy prior to November 2015. All case studies and clinical trials were evaluated and reported in a descriptive manner. To-date, 20 reports, of varying scientific quality, have been published regarding this device; all but 1 small study, published only as an abstract, provided results that appeared positive. The authors concluded that the positive findings from preliminary studies with Scrambler therapy support that this device provides benefit for patients with refractory pain syndromes. Moreover, they stated that larger, randomized studies are needed to further evaluate the effectiveness of this approach.

Smith and colleagues (2017) stated that chronic post-mastectomy pain (cPMP), including post-lumpectomy pain, is common with no established ways of treatment. These researchers treated 3 consecutive patients referred with cPMP with Scrambler therapy. Treatment was given across the area of pain following the dermatomes for 45 minutes daily, for several consecutive days until relief, and then was repeated as needed. The Scrambler therapy MC5A device synthesized 16 different waveforms that resemble action potentials, delivered to the surface receptors of the c-fibers, to send "non-pain" information along the damaged pathways to reduce central sensitization. All 3 had marked (over 75 %) and sustained (months) reduction of allodynia, hyperalgesia, and pain. All reported
marked improvements in their quality of life and normal function. One woman was able to stop chronic opioid use. No side effects were observed. The authors concluded that Scrambler therapy is a promising way to relieve cancer and other types of neuropathic pain, and may be helpful in cPMP. They stated that further prospective clinical trials are needed.

In a randomized, single-blind, sham-controlled trial, Mealy and colleagues (2020) examined if Scrambler therapy is an effective and feasible treatment of persistent central neuropathic pain in patients with neuromyelitis optica spectrum disorder (NMOSD) and examined the effect of Scrambler therapy on co-occurring symptoms. This trial entailed patients with NMOSD who had central neuropathic pain using Scrambler therapy for 10 consecutive week-days. Pain severity, pain interference, anxiety, depression, and sleep disturbance were assessed at baseline, at the end of treatment, and at the 30- and 60-day follow-up. A total of 22 patients (11 each in the treatment and sham groups) were enrolled in and completed this trial. The median baseline NRS pain score decreased from 5.0 to 1.5 after 10 days of treatment with Scrambler therapy, whereas the median NRS score did not significantly decrease in the sham arm. Depression was also reduced in the treatment arm, and anxiety was decreased in a subset of patients who responded to treatment. These symptoms were not affected in the sham arm. The safety profiles were similar between groups. The authors concluded that the Scrambler therapy was a safe and effective intervention for central neuropathic pain in patients with NMOSD. These researchers stated that decreasing pain with Scrambler therapy may additionally improve depression and anxiety.

The authors stated that this study had several drawbacks. First, the design of this study was single-blinded due to the fact that the technician knew whether treatment or sham was being delivered by necessity. To mitigate the bias this potentially introduced, measurement tools and survey data were collected by an unrelated study coordinator. Second, although patients were recruited with the use of a randomized block design to mitigate the risk of confounding effects from pain medication class on the basis of previous data that reported that the type of medication may be predictive of response to Scrambler therapy, this trial was not powered to sufficiently compare efficacy results across classes of pain medications because patients were often on multiple medications.
The effect that modifying pain through Scrambler therapy had on co-occurring symptoms was also limited by the sample size. Lastly, while it was encouraging that a difference was detected between the Scrambler-treated and sham arms, this study was not powered to effectively examine sustainability of treatment through the 60-day follow-up period. The practicality of using Scrambler increases if the effect is sustained. The trend toward significance at 60 days suggested that a larger study that includes 29 patients per arm may uncover sustained effect. Furthermore, re-emergence of pain in treatment of both central and peripheral pain conditions has been described, and pain has been shown to be amenable to subsequent booster treatments, often with fewer Scrambler treatment sessions needed. Anecdotally, 1 complete responder from the current study was subsequently treated when pain began to re-emerge after study completion and remained pain-free months later. Therefore, adapting the protocol to include subsequent booster treatments when pain emerges should be considered for future studies. Overall, the safety and effectiveness profiles these investigators reported support the need for a larger, phase-III clinical trial to further examine the effect of Scrambler on pain, reduction of analgesic medication use, co-occurring symptoms, and QOL in a larger NMOSD patient cohort.

Christo and associates (2020) stated that Dejerine-Roussy syndrome or central thalamic pain can be devastating, and treatment with drugs and even DBS can be unsatisfactory. Scrambler therapy is a form of neuromodulation that uses external skin electrodes to send a “non-pain” signal to the brain, with some success in difficult-to-treat syndromes such as NMOSD. These researchers used Scrambler therapy to treat a patient with 6 years of disabling Dejerine-Roussy syndrome pain. A 56-year old man received multiple daily then monthly treatments with electrode pairs placed just above the area of distal pain. Each treatment was for 40 mins. His allodynia and hyperalgesia resolved within 10 mins, and his pain score fell to almost 0 after 30 mins. Months later, he resumed normal activity and was off all his pain medications. No side effects were noted. The authors concluded that Scrambler therapy appeared to reverse 6 years of disabling pain safely and economically, and continued to be effective. These researchers stated that further multi-institutional trials are needed for this rare syndrome.
Non-Invasive Interactive Neurostimulation (e.g., the InterX 1000 Neurostimulator Device)

The InterX 1000 neurostimulator appears to be a hand-held, personal device for home use. It delivers interactive, high amplitude, high density stimulation to the cutaneous nerves, activating the body's natural pain relieving mechanisms (segmental and descending inhibition). However, there is insufficient evidence regarding its effectiveness for the treatment of chronic pain.

In a randomized, sham-controlled, pilot study, Selfe et al (2008) examined the effects of non-invasive interactive neurostimulation used as an adjunct to usual care, on pain and other symptoms in adults with OA of the knee. A total of 37 adults with knee OA (based on American College of Rheumatology diagnostic criteria) were included in this study. Subjects received 17 non-invasive interactive neurostimulation (active or sham) sessions over 8 weeks with a week 12 follow-up. Outcome measures included 11-point numeric rating scale for weekly pain; WOMAC, patient global assessment, and SF-36 completed at baseline and weeks 4, 8, and 12. For the main outcome, pain, the differences between the groups over time did not reach statistical significance (all p > 0.05). However, a clinically important reduction in pain (defined as a 2-point or 30% reduction on an 11-point numeric rating scale) was maintained at week 12 by the active non-invasive interactive neurostimulation group (2.17 points, 34.55% reduction) but not the sham group (1.63, 26.04% reduction). Pain improved over time in participants regardless of group membership (numeric rating scale average pain, p = 0.002; numeric rating scale worst pain, p < 0.001; and WOMAC pain, p < 0.001), as did WOMAC function, WOMAC stiffness, and WOMAC total score (all p < 0.001). Repeated measures ANOVA revealed a statistically significant difference between the groups over time for the SF-36 Vitality scale, F (3, 105) = 3.54, p = 0.017. In addition, the active device group improved on the patient global assessment from baseline to week 8 compared to the sham device group, F (1, 35) = 4.025, p = 0.053. The authors concluded that in this pilot study, clinically important reductions in knee pain were maintained at week 12 in the active, but not the sham, non-invasive interactive neurostimulation group. They stated that further study of this non-invasive therapy is needed.
Gorodetskyi et al (2010) undertook a trial with 60 patients who had undergone operative reduction and internal fixation of bimalleolar, AO type B2 ankle fractures with comminution. Patients were randomized into 2 groups, one of which received post-operative treatment using a non-invasive interactive neurostimulation device (InterX) and the other with a sham device. The trial was designed to test the hypothesis that incorporation of non-invasive interactive neurostimulation into the rehabilitation protocol would result in reduced pain, increased range of motion (ROM), reduced edema, and reduced consumption of pain medication, in comparison with the sham therapy group. Outcome measurements included the patient's subjective assessment of level of pain, ROM, and the extent of edema in the involved ankle, and the use of ketorolac for post-operative control of pain. The authors concluded that these results showed significantly better results in the patients receiving treatment with active neurostimulation (repeated measures analysis of variance, p < 0.001).

In a Cochrane review, Lin and colleagues (2012) evaluated the effects of rehabilitation interventions following conservative or surgical treatment of ankle fractures in adults. The authors concluded that there is limited evidence supporting early commencement of weight-bearing and the use of a removable type of immobilization to allow exercise during the immobilization period after surgical fixation. Because of the potential increased risk of adverse events, the patient's ability to comply with the use of a removable type of immobilization to enable controlled exercise is essential. There is little evidence for rehabilitation interventions during the immobilization period after conservative orthopedic management and no evidence for stretching, manual therapy or exercise compared to usual care following the immobilization period. Furthermore, they stated that small, single studies showed that some electrotherapy modalities may be beneficial. They stated that more clinical trials that are well-designed and adequately-powered are needed to strengthen current evidence.

Teodorczyk-Injeyan et al (2015) evaluated the effect of treatment with a novel non-invasive interactive neurostimulation device (InterX5000) on the production of inflammatory biomarkers in chronic and recurrent mechanical neck pain (NP) syndrome. This study represented pilot biological data from a RCT. A total of 25 NP patients and 14 asymptomatic subjects included for baseline comparison only completed
the study. The patients received 6 InterX5000 or placebo treatments within 2 weeks, and pre-treatment and post-treatment blood samples were collected for in-vitro determination of biomarker production. Whole blood cell cultures were activated by lipopolysaccharide or by the combination of lipopolysaccharide and phytohemagglutinin for 24 to 48 hours. The levels of tumor necrosis factor-alpha (TNFα) and its soluble type II receptor (sTNFR II), interleukin (IL) 1, IL-1 receptor antagonist (IL-1RA), IL-6, IL-10, and monocyte chemotactic protein (CCL2/MCP-1) were determined by specific immunoassays. Compared with asymptomatic subjects, baseline production levels of all pro-inflammatory mediators (TNFα, IL-1β, IL-6, and CCL2/MCP-1) were significantly augmented or trended higher (p = 0.000 to 0.008) in patients with NP. Of the anti-inflammatory markers, only IL-1RA was significantly elevated (p = 0.004). The increase in IL-10 and TNF receptor II levels did not reach statistical significance. Neither InterX5000 nor placebo therapy had any significant effect on the production of the inflammatory mediators over the study period. The authors concluded that this investigation determined that inflammatory cytokine pathways are activated in NP patients but found no evidence that a short course of InterX5000 treatment normalized the production of inflammatory biomarkers.

Electro Therapeutic Point Stimulation

Electro-therapeutic point stimulation (ETPS), also known as microcurrent point stimulation (MPS), employs a non-invasive device to administer low-frequency direct current to acupuncture points, motor/trigger points, and contracted muscle bands. The device (known as called the ETPS 1000) has an enhanced point finder that detects treatment points on the skin and applies brief, concentrated electrical microstimulation in short bursts. This modality/approach combines the principles of acupuncture, massage, physical therapy and microcurrent stimulation. The treatment can be self-administered by the patient at home. There is insufficient peer-reviewed evidence to support the safety and effectiveness of ETPS/MPS.

Aliyev and Geiger (2012) examined the effects of cell-stimulation therapy of lateral epicondylitis with frequency-modulated low-intensity electric current. Patients with lateral epicondylitis were subjected to a 12-week cell-stimulation therapy with low-intensity frequency-modulated electric
current in addition to routine therapy. Patients in the control group received the same routine therapy and sham stimulation (the therapeutic apparatus was not energized). The effectiveness of MPS was estimated by comparing medical indices before therapy and at the end of a 12-week therapeutic course using a 10-point pain severity numeric rating scale (NRS) and Roles-Maudsley pain score. The study revealed high therapeutic efficiency of cell-stimulation with low-intensity electric current resulting probably from up-regulation of intracellular transmitters, interleukins, and prostaglandins playing the key role in the regulation of inflammation. The findings of this study need to be validated by well-designed studies with long-term follow-up.

Pulsed Stimulation (e.g., P-Stim)

In a pilot study, Sator-Katzenschlager et al (2003) tested the hypothesis that auricular electro-acupuncture (EA) relieves pain more effectively than conventional manual auricular acupuncture. These researchers studied 21 chronic cervical pain patients without radicular symptoms with insufficient pain relief (VAS greater than 5) treated with standardized analgesic therapy. All patients received disposable acupuncture needles on the dominant side on the following acupuncture points: cervical spine, shen men, and cushion. In 10 patients, needles were continuously stimulated (2-mA constant current, 1 Hz monophasic) by using the electrical point stimulation device P-STIM. In 11 control patients, no electrical stimulation was administered. All needles were withdrawn 48 hours after insertion. Acupuncture was performed once a week for 6 weeks. Patients had to complete a questionnaire assessing pain intensity, psychological well-being, activity, sleep, and demand for rescue medication (lornoxicam and tramadol). The reduction in pain scores was significant in the EA group. Similarly, psychological well-being, activity, and sleep were significantly improved in patients receiving EA, and consumption of rescue medication was significantly less. These results demonstrated that continuous electrical stimulation of auricular acupuncture points by using the new point stimulation device P-STIM improves the treatment of chronic cervical pain in an outpatient population. The authors concluded that continuous electrical stimulation of auricular acupuncture points by using the new point stimulation device P-STIM significantly decreases pain intensity and significantly improves
psychological well-being, activity, and sleep in chronic cervical pain patients. This was a pilot study with small number of subjects with short-term follow-up.

In a prospective, randomized, double-blind, controlled study, Sator-Katzenschlager et al (2004) tested the hypothesis that auricular EA relieves pain more effectively than conventional manual auricular acupuncture (CO) in chronic LBP patients with insufficient pain relief (VAS greater than or equal to 5) treated with standardized analgesic therapy. Disposable acupuncture needles were inserted in the auricular acupuncture points 29, 40, and 55 of the dominant side and connected to a newly developed battery-powered miniaturized stimulator worn behind the ear. Patients were randomized into group EA (n = 31) with continuous low-frequency auricular EA (1 Hz biphasic constant current of 2 mA) and group CO (n = 30) without electrical stimulation (sham-EA). Treatment was performed once-weekly for 6 weeks, and in each group needles were withdrawn 48 hours after insertion. During the study period and a 3-month follow-up, patients were asked to complete the McGill questionnaire. Psychological well-being, activity level, quality of sleep, and pain intensity were assessed by means of VAS; moreover, analgesic drug consumption was documented. Pain relief was significantly better in group EA during the study and the follow-up period as compared with group CO. Similarly, psychological well-being, activity, and sleep were significantly improved in group EA versus group CO, the consumption of analgesic rescue medication was less, and more patients returned to full-time employment. Neuropathic pain in particular improved in patients treated with EA. There were no adverse side effects. These results were the first to demonstrate that continuous EA stimulation of auricular acupuncture points improves the treatment of chronic LBP in an outpatient population. The authors concluded that continuous electrical stimulation of auricular acupuncture points using the new point stimulation device P-Stim significantly decreases pain intensity and improves psychological well-being, activity, and sleep in chronic LBP patients. This was a small study with a short-term follow-up.

Sator-Katzenschlager and Michalek-Sauberer (2007) stated that acupuncture is now accepted as a complementary analgesic treatment. Auricular acupuncture is a distinct form of acupuncture. Electrical stimulation of acupoints (EA) increases the effects of acupuncture.
Recently, an auricular EA device, the P-Stim, has become available. Clinical studies in outpatients have investigated the P-Stim in chronic musculo-skeletal pain and its use for minor surgery. In chronic cervical or LBP, auricular EA was more effective than conventional auricular acupuncture. The results in acute pain were controversial. Auricular EA reduced pain and remifentanil consumption during oocyte aspiration when compared with conventional auricular acupuncture or a sham treatment. However, after third molar tooth extraction, auricular EA and auricular acupuncture failed to reduce either postoperative pain or analgesic consumption. The authors concluded that further large-scale studies are needed to evaluate the analgesic efficacy of auricular EA.

Michalek-Sauberer et al (2007) examined the effects of auricular EA on pain and analgesic drug consumption in the first 48 hours after unilateral mandibular third molar tooth extraction under local anesthesia in a prospective, randomized, double-blind, placebo-controlled study in 149 patients. Patients received either auricular acupuncture with electrical stimulation (AE, n = 76) or without (AA, n = 37) electrical stimulation at an alternating frequency of 2/100 Hz or a sham AE with metal plates instead of needles and no electrical stimulation, no-needle (NN, n = 36) at the AA points 1 (tooth), 55 (Shen men) and 84 (mouth) during the entire study period. Regularly rated pain intensity (5-point verbal rating scale), consumption of acetaminophen 500-mg tablets and additional rescue medication with 500-mg mefenamic acid were assessed. The median fraction of time when pain was rated as moderate or worse (upper and lower quartile): AE: 33 % (12 %, 64 %), AA: 22 % (6 %, 56 %), NN: 30 % (7 %, 53 %) did not differ significantly among the treatment groups. There were no significant differences in mean number of acetaminophen 500-mg tablets (range): AE: 5.2 (0 to 12), AA: 4.6 (0 to 11), NN: 5.4 (0 to 10) or percentage of patients requiring additional mefenamic acid: AE: 19 %, AA: 18 %, NN: 19 %. The authors concluded that neither AE nor AA alone reduce either pain intensity or analgesic consumption in a molar tooth extraction model of acute pain.

Wang (2007) reported the successful treatment of a patient with post-herpetic neuralgia (PHN) using traditional pharmacology in combination with acupuncture. A 13-year old girl developed PHN following a severe attack of varicella zoster. Despite a 1-week course of intravenous acyclovir initiated at the onset of symptoms, the patient developed
persistent left facial pain and constant nausea after lesions were healed. A comprehensive pain treatment regimen, consisting of a stellate ganglia block, medications, transcutaneous electrical nerve stimulation and hypnosis, was administered, but the patient did not gain any incremental pain relief. The acupuncture service was consulted to provide assistance with this patient's pain management. A combination of body and auricular acupuncture as well as related techniques, including acupressure and transcutaneous acupoint electrical stimulation, was added to the pain treatment regimen. After 10 complementary acupuncture treatments over a 2-month period, the patient's nausea disappeared. Her left facial pain continued to decline from a maximum of 10 to 0 as assessed by a VAS over a period of 4 months following self-administered treatments of acupressure and transcutaneous acupoint electrical stimulation. The patient was then gradually weaned off all her medications and the complementary acupuncture treatment. She was discharged from the pediatric pain clinic after 5 months of the combined therapy. The author concluded that acupuncture and its related techniques may be an effective adjunctive treatment for symptoms associated with PHN and deserved further study.

Holzer et al (2011) examined the effects of electrical auricular acupuncture (AA) on post-operative pain in patients undergoing laparoscopy with an emphasis on patient-blinding and the exclusion of therapist-patient interactions. With institutional review board approval and written informed consent, these investigators included 40 female patients undergoing laparoscopy. Patients were randomly assigned to receive AA (shen men, thalamus and 1 segmental organ-specific point) or electrodes only and an electrical stimulation device. All patients received this intervention under general anesthesia guaranteeing patient blinding and excluding therapist-patient interactions. Needles and devices were removed 72 hours post-operatively. Post-operatively, patients received 1,000-mg paracetamol every 6 hours. Additional piritramide was given on demand. A blinded observer obtained the VAS scores at 0, 2, 24, 48, and 72 hours as well as the post-operatively administered doses of piritramide. There was no difference in VAS scores or the consumption of piritramide during the first 72 hours post-operatively between groups (acupuncture versus placebo: 2.32 [1.40 to 3.25] versus 2.62 [1.89 to 3.36] average pain on VAS 0-10; 15.3 [12.0 to 18.6] mg versus 13.9 [10.5 to 17.3] mg piritramide). Values are expressed as mean CI. The authors
concluded that the findings of this study showed no reduction in postoperative pain or an opioid sparing effect of auricular acupuncture in women undergoing laparoscopic procedures. Because the authors emphasized blinding of the patients and the exclusion of therapist-patient interactions, this study suggested that electrical auricular acupuncture has no effect on post-operative pain.

In a double-blind, randomized, placebo-controlled, repeated-measures trial, Fary and colleagues (2011) examined the effectiveness of sub-sensory, pulsed electrical stimulation (PES) in the symptomatic management of osteoarthritis (OA) of the knee. A total of 70 participants with clinical and radiographically diagnosed OA of the knee were randomized to either PES or placebo. The primary outcome was change in pain score over 26 weeks measured on a 100-mm VAS. Other measures included pain on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), function on the WOMAC, patient's global assessment of disease activity (on a 100-mm VAS), joint stiffness on the WOMAC, quality of life on the Medical Outcomes SF-36 health survey, physical activity (using the Human Activity Profile and an accelerometer), and global perceived effect (on an 11-point scale). Thirty-four participants were randomized to PES and 36 to placebo. Intent-to-treat analysis showed a statistically significant improvement in VAS pain score over 26 weeks in both groups, but no difference between groups (mean change difference 0.9 mm [95 % CI: -11.7 to 13.4]). Similarly, there were no differences between groups for changes in WOMAC pain, function, and stiffness scores (-5.6 [95 % CI: -14.9 to 3.6], -1.9 [95 % CI: -9.7 to 5.9], and 3.7 [95 % CI: -6.0 to 13.5], respectively), SF-36 physical and mental component summary scores (1.7 [95 % CI: -1.5 to 4.8] and 1.2 [95 % CI: -2.9 to 5.4], respectively), patient's global assessment of disease activity (-2.8 [95 % CI: -13.9 to 8.4]), or activity measures; 56 % of the PES-treated group achieved a clinically relevant 20-mm improvement in VAS pain score at 26 weeks compared with 44 % of controls (12 % [95 % CI: -11.5 to 33 %]). The authors concluded that in this sample of subjects with mild-to-moderate symptoms and moderate-to-severe radiographic OA of the knee, 26 weeks of PES was no more effective than placebo.

Neurolumen Device
The Neurolumen is a portable machine that consists of a control unit, 4 wrap assemblies and a battery charger. Each wrap contains 2 laser diodes, 4 light emitting diodes and 1 or 2 electrolytic nerve stimulation gel pads. Once the wraps are in place, the control unit provides up to 30 mins of simultaneous TENS, low-level laser (LLLT) and light-emitting diode (LED) therapy.

However, there is a lack of evidence regarding the effectiveness of the Neurolumen device for the treatment of Morton’s neuroma or any other indications. An UpToDate review on “on Peripheral Nerve Tumors” (Gilchrist and Donahue, 2013) states that “Morton neuroma is a subject of controversy regarding its nomenclature, pathology, and appropriate treatment. Abnormalities ascribed to Morton neuroma are typically located between the metatarsals of the third and fourth toes or at the bifurcation of the fourth plantar digital nerve. The lesions look like a traumatic neuroma grossly, and are comprised of degenerated and/or demyelinated axons, vascular hyalinization, and fibrosis. Clinical manifestations can include pain and tenderness, but similar lesions are common in patients who are asymptomatic. Surgical removal is advocated by some authors for those who fail conservative measures, but data are limited regarding the effectiveness of surgical and nonsurgical interventions for Morton neuroma”. Furthermore, an UpToDate review on “Overview of running injuries of the lower extremity (Callahan, 2013) does not mention the use of electrical stimulation or laser therapy as therapeutic options for Morton’s neuroma.

Non-Invasive/No-Incision Pain Procedure (NIP) Device

According to the FixPain website, the NIP Procedure refers to “Non-Invasive, or No-Incision Pain” Procedure. It is FDA-cleared/certified for various types of chronic pain (arthritis, cancer pain, cervical pain, fibromyalgia, joint pain, low back pain, migraines, post-operative pain, and sciatica) and other conditions (e.g., anxiety, depression and insomnia). The microchip NIP Procedure™ device is placed behind the ear of the patient, the acupuncture in corresponding points and the pulses are transmitted through the stimulating needle. With the help of the NIP Procedure™ device, the patients are receiving continuous treatment for 4 to 5 days. It is recommended that therapies be applied for up to 9 weeks.
However, there is a lack of evidence regarding the effectiveness of the NIP Procedure device for the treatment of chronic pain or any other indications.

Electro-Analgesia Treatment (EAT)

Electro-Analgesia Treatment (EAT) has been described as nerve block injections followed by electrical stimulation administered with the Synaptic device, and has been used as a treatment for diabetic peripheral neuropathy. The combination of nerve block therapy and electrical stimulation is referred to as Electro-Analgesia Treatment or EAT. The manufacturer states that the Synaptic 4000 treatment is controlled by the patient using a joystick.

According to the manufacturer, electrical stimulation with the Synaptic device is different from other forms of electrical stimulation: “The Synaptic technology is unique and stands apart from all other electrical neuro-stimulation devices such as TENS, EMS, functional electrical stimulation (FES), sacral nerve stimulation (SNS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), spinal cord stimulation (SCS) and cochlear and ocular implants.” The manufacturer explains: “The frequency range is from 40,000 to 400 Hertz. Conventional modalities have a frequency range of only 500-180 Hertz and begin their activity at the low end of the range increasing to their maximum as controls are elevated. In contrast, Synaptic begins its frequency sweep at the maximum (40,000 Hertz) and as the remote is advanced the frequency decreases to the minimum (400 Hertz). This cycle may be repeated during each of the ten intensity levels.”

The manufacturer states that the waveform of the Synaptic is also unique. “Also protected are the A-waveform, the unique mechanism for SEA energy delivery as well as the method of patient-controlled treatment using a joystick. The waveform developed for SEA technology mimics a biological process. It simulates the action potential responsible for producing electrical activity in the neuron using a fast rise time and a slow decay, reproducing the action potential in humans.”

There are a lack of peer-reviewed published studies of Electro-Analgesia Treatment or of the Synaptic electrical stimulation device.
Variable Muscle Stimulators (VMS)

Variable muscle stimulators (VMS), like TENS units, produce bi-phasic waves. However, TENS units produce asymmetric bi-phasic waves, whereas VMS units produce symmetrical bi-phasic waves. Unlike TENS, VMS is used to do FES. However, there is a lack of evidence regarding the clinical effectiveness of VMS.

Cefaly

The Cefaly transcutaneous supraorbital nerve stimulator, classified as a transcutaneous electrical nerve stimulator, has an FDA approved indication which is limited to the prophylactic treatment of episodic migraine in individuals 18 years of age or older. Cefaly is a plastic, battery-powered transcutaneous electrical nerve stimulator worn like a headband with reusable self-adhesive electrodes placed on the forehead to cover the supratrochlear and supraorbital nerves (branches of the trigeminal nerve). The device purportedly works through neuromodulatory effects on those nerves, thereby blocking pain signals.

Piquet et al (2011) stated that transcutaneous neurostimulation (TNS) at extra-cephalic sites is a well-known treatment of pain. Thanks to recent technical progress, the Cefaly device now also allows supraorbital TNS. During observational clinical studies, several patients reported decreased vigilance or even sleepiness during a session of supraorbital TNS. These researchers examined in more detail the potential sedative effect of supraorbital TNS, using standardized psychophysical tests in healthy volunteers. They performed a double-blind, cross-over, sham-controlled study on 30 healthy subjects. Subjects underwent a series of 4 vigilance tests (Psychomotor Vigilance Task, Critical Flicker Fusion Frequency, Fatigue Visual Numeric Scale, d2 test). Each subject was tested under 4 different experimental conditions: without the neurostimulation device, with sham supraorbital TNS, with low frequency supraorbital TNS and with high frequency supraorbital TNS. As judged by the results of 3 tests (Psychomotor Vigilance Task, Critical Flicker Fusion Frequency, Fatigue Visual Numeric Scale) there was a statistically significant (p < 0.001) decrease in vigilance and attention during high frequency TNS, while there were no changes during the other experimental conditions. Similarly, performance on the d2 test was impaired during high frequency
TNS, but this change was not statistically significant. The authors concluded that supraorbital high frequency TNS applied with the Cefaly device decreased vigilance in healthy volunteers. They stated that additional studies are needed to determine the duration of this effect, the underlying mechanisms and the possible relation with the stimulation parameters. Meanwhile, this effect opened interesting perspectives for the treatment of hyperarousal states and, possibly, insomnia.

In a double-blinded, randomized controlled trial (RCT), Schoenen et al (2013) examined the safety and efficacy of trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) in migraine prevention. This trial was conducted at 5 Belgian tertiary headache clinics. After a 1-month run-in, patients with at least 2 migraine attacks/month were randomized 1:1 to verum (n = 34) or sham (n = 33) stimulation, and applied the stimulator daily for 20 mins during 3 months. Primary outcome measures were change in monthly migraine days and 50 % responder rate. A total of 67 patients were randomized and included in the intention-to-treat analysis. Between run-in and third month of treatment, the mean number of migraine days decreased significantly in the verum (6.94 versus 4.88; p = 0.023), but not in the sham group (6.54 versus 6.22; p = 0.608). The 50 % responder rate was significantly greater (p = 0.023) in the verum (38.1 %) than in the sham group (12.1 %). Monthly migraine attacks (p = 0.044), monthly headache days (p = 0.041), and monthly acute anti-migraine drug intake (p = 0.007) were also significantly reduced in the verum but not in the sham group. There were no AEs in either group. The authors concluded that supraorbital transcutaneous stimulation with the device used in this trial was safe and effective as a preventive therapy for migraine. The therapeutic gain (26 %) was within the range of those reported for other preventive drug and non-drug anti-migraine treatments. Moreover, they stated that adequate studies are needed to disentangle the precise mode of action. This study provided Class III evidence that treatment with a supraorbital transcutaneous stimulator was safe and effective as a preventive therapy for migraine.

The authors noted that despite methodologic precautions including concealed allocation, partial un-blinding may have occurred in this trial. It was difficult to blind peripheral neurostimulation trials because the effective electrical stimulation produces intense paresthesia. These
investigators doubted, however, that un-blinding markedly influenced their results for the following reasons. The sham response was within the range of that found in other trials with neurostimulation devices. Compared to the ONSTIM trial of occipital nerve stimulation, it was even higher for the 50 % responder rate: 6 % in ONSTIM, 12.8 % in PREMICE. Un-blinding could thus have been twice more pronounced in ONSTIM than in PREMICE, if one assumed that it was inversely proportional to the percentage of responders in a sham group. The rather small difference (7.3 %) in compliance rates between verum and sham groups also did not favor massive un-blinding. If this were the case, one would expect a much lower compliance in the sham group. Another possible weakness of this trial appeared when data from the different centers were analyzed: patients in the verum group were on average younger than those in the sham group and the duration of their migraine was somewhat shorter. On post-hoc statistical analyses these researchers were unable, however, to detect an influence of age or of disease duration on treatment outcome. In the ONSTIM trial, the difference in mean age between the effectively stimulated patients and the smaller “ancillary” group was 9 years.

Overall, both patient groups in PREMICE were well in the age range of migraine patients included in other trials. These researchers stated that beyond statistics, the question whether the results of the PREMICE trial were clinically relevant merits consideration. Besides the therapeutic gain for 50 % responders, other outcome measures suggested that STS could be of benefit to migraine patients. It decreased significantly consumption of acute anti-migraine drugs, which is a pharmaco-economical advantage. In addition, more than 70 % of effectively stimulated patients were satisfied with the treatment. The patients recruited for PREMICE were not the most disabled migraineurs. Having 4 migraine attacks or 7 migraine days per month, they were similar, however, to those included in topiramate trials and representative of the majority of migraine patients in the general population who are in need of preventive treatment according to international recommendations. Whether STS treatment is effective in patients with more frequent attacks or with chronic migraine remains to be determined.

Russo and Tessitore (2015) noted that transcutaneous supraorbital neurostimulation (tSNS) has been recently found superior to sham stimulation for episodic migraine prevention in a randomized trial. These researchers evaluated both the safety and efficacy of a brief period of
tSNS in a group of patients with migraine without aura (MwoA). They enrolled 24 consecutive patients with MwoA experiencing a low frequency of attacks, which had never taken migraine preventive drugs in the course of their life. Patients performed a high frequency tSNS and were considered “compliant” if they used the tSNS for greater than or equal to 2/3 of the total time expected. For this reason, 4 patients were excluded from the final statistical analysis. Primary outcome measures were the reduction migraine attacks and migraine days per month (p < 0.05). Furthermore, these investigators evaluated the percentage of patients having at least 50 % reduction of monthly migraine attacks and migraine days. Secondary outcome measures were the reduction of headache severity during migraine attacks and HIT-6 (Headache Impact Test) rating as well as in monthly intake of rescue medication (p < 0.05). Finally, compliance and satisfaction to treatment and potential adverse effects related to tSNS have been evaluated. Between run-in and 2nd month of tSNS treatment, both primary and secondary end-points were met. Indeed, these researchers observed a statistically significant decrease in the frequency of migraine attacks (p < 0.001) and migraine days (p < 0.001) per month. They also demonstrated at least 50 % reduction of monthly migraine attacks and migraine days in respectively 81 % and 75 % of patients. Furthermore, a statistically significant reduction in average of pain intensity during migraine attacks (p = 0.002) and HIT-6 rating (p < 0.001) and intake of rescue medication (p < 0.001) has been shown. All patients showed good compliance levels and no relevant AEs. The authors concluded that in patients experiencing a low frequency of attacks, significant improvements in multiple migraine severity parameters were observed following a brief period of high frequency tSNS. Thus, tSNS may be considered a valid option for the preventive treatment of migraine attacks in patients who cannot or are not willing to take daily medications, or in whom low migraine frequency and/or intensity would not require pharmacological preventive therapies.

The authors stated that this study had several drawbacks. First, these researchers did not use a tSNS sham device and, therefore, they could not rule-out the possible role of a placebo-effect on primary and secondary outcomes in this study. In particular, several factors may contribute to the remedial efficacy of tSNS in these patients such as alternative form of medical therapy, patients naïve to preventive treatment and observation period limited to no more than 2 months. However, the
placebo-effect appeared to have a lower impact in the prophylactic treatment than in the acute treatment of migraine attacks. This could be due to the inherent variability in response measured over a period of months compared with one measured over a period of hours. Moreover, the effective tSNS superiority respect to sham stimulation for the prevention of migraine headaches has been extensively demonstrated in a previous RCT in a large cohort of patients with migraine. Nevertheless, in partial disagreement with these findings, Schoenen and colleagues (2013) did not show statistically significant effect on migraine attacks at 2 months, although ameliorating effect on migraine severity vanished in sham treated patients and amplified in effectively treated patients at this time of the study. These investigators suggested that a greater migraine severity (i.e., frequency of migraine per month and disease duration) and, probably, previous pharmacological anti-migraine preventive therapies may cause a different impact on pain pathways in the 2 migraine populations and consequent different response to the tSNS treatment. Second, the lack of blinding may weaken the results of the present study. However, empirical evidence showed that although double-blind RCTs are the gold standard for proving efficacy of a therapeutic procedure, they often suffer from lack of generalizability. Therefore, the authors believed that these data, in addition to the previous effectiveness and safety results of double-blind RCTs (Schoenen and colleagues, 2013) could provide additional information which may be useful in everyday clinical practice. Finally, although these findings were consistent with previous studies, the sample size was relatively small (n = 20 available for final analysis). Thys, they stated that further studies are needed to corroborate these findings and to explore tSNS efficacy and tolerability in patients with migraine compared with preventive treatments used in clinical practice.

Magis et al (2017) noted that a recent sham-controlled trial showed that external trigeminal nerve stimulation (eTNS) is effective in episodic migraine (MO) prevention. However, its mechanism of action remains unknown. These researchers performed 18-fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate brain metabolic changes before and after eTNS in episodic migraineurs. A total of 28 individuals were recruited: 14 with MO and 20 healthy volunteers (HVs). HVs underwent a single FDG-PET, whereas patients were scanned at baseline, directly after a first prolonged session of eTNS (Cefaly) and
after 3 months of treatment (uncontrolled study). The frequency of migraine attacks significantly decreased in compliant patients (n = 10). Baseline FDG-PET revealed a significant hypo-metabolism in fronto-temporal areas, especially in the orbito-frontal (OFC) and rostral anterior cingulate cortices (rACC) in MO patients. This hypo-metabolism was reduced after 3 months of eTNS treatment. The authors concluded that the findings of this study suggested that OFC and rACC are hypo-metabolic in MO patients at rest. After a 3-month treatment with eTNS, this hypo-metabolism was reduced and the changes were associated with a significant decrease of migraine attack frequency. It is known that neurostimulation can modulate OFC and rACC activity. Like cluster and medication overuse headache, MO appeared to be associated with dysfunction of medial frontal cortex areas involved in affective and cognitive dimensions of pain control. Because this study was under-powered and had no sham arm, these researchers were unable to formally attribute the metabolic changes to the non-invasive neurostimulation treatment. Nonetheless, the observed effect was likely similar to that found with invasive neurostimulation of peri-cranial nerves, such as pONS. These researchers stated that further trials are needed to confirm these findings.

The authors stated that this study had several drawbacks. Because of the small number of evaluable patients (n = 14), the results must be taken with caution. As discussed, the study design did not allow assessing a direct causal effect of eTNS on brain metabolism since a sham condition is missing. These investigators found sham stimulation for 3 months would be unethical knowing that there is evidence for eTNS efficacy from an RCT. The compliance rate with eTNS therapy was rather low. For preventive drug treatments, adherence varies from 48 % to 94 % between studies. Neurostimulation was more time consuming (20 mins daily in this study), which provoked lower compliance. In the PREMICE trial, patients had a compliance rate of 62 %, while participants renting the eTNS Cefaly device via the internet used it on average 58 % of the recommended time. In this study, the authors considered patients who performed at least 30 % of the sessions as “compliant”; this threshold was chosen on an empirical basis and experience from clinical practice showing that patients may benefit from eTNS with non-daily use of the device. However, the minimal time of use to obtain a clinical improvement in migraine is unknown, and may vary between patients.
Although the headache diaries allowed monitoring global intake of acute medications for each patient, they did not allow these researchers to determine the precise proportion of drugs taken within each of the pharmacological classes, analgesics, NSAIDs, triptans, nor its possible change after eTNS. It is unlikely, however, that such a change would have influenced brain metabolism.

Russo et al (2017) examined the functional re-organization of the pain processing network during trigeminal heat stimulation (THS) after 60 days of eTNS in migraine without aura (MwoA) patients between attacks. Using whole-brain BOLD-fMRI, functional response to THS at 2 different intensities (41 and 51°C) was investigated interictally in 16 adults MwoA patients before and after eTNS with the Cefaly device. These researchers calculated the percentage of patients having at least a 50% reduction of monthly migraine attacks and migraine days between baseline and the last month of eTNS. Secondary analyses evaluated associations between BOLD signal changes and clinical features of migraine. Before eTNS treatment, there was no difference in BOLD response between MwoA patients and healthy controls (HC) during low-innocuous THS at 41°C, whereas the perigenual part of the right anterior cingulate cortex (ACC) revealed a greater BOLD response to noxious THS at 51°C in MwoA patients when compared to HC. The same area demonstrated a significant reduced BOLD response induced by the noxious THS in MwoA patients after eTNS (p = 0.008). Correlation analyses showed a significant positive correlation between ACC BOLD response to noxious THS before eTNS treatment and the decrease of ACC BOLD response to noxious THS after eTNS. Moreover, a significant negative correlation in the migraine group after eTNS treatment between ACC functional activity changes and both the perceived pain ratings during noxious THS and pre-treatment migraine attack frequency has been found. The authors concluded that the findings of this study suggested that eTNS treatment with the Cefaly® device induced a functional anti-nociceptive modulation in the ACC that is involved in the mechanisms underlying its preventive anti-migraine efficacy.

Nevertheless, these researchers stated that further observations to confirm whether the observed fMRI effects of eTNS are both related to clinical improvement and specific to anti-nociceptive modulation in migraine patients are mandatory.
The authors noted that this study had several drawbacks. First, these investigators did not use an eTNS sham device and, therefore, they could not rule out the possible role of a placebo effect in imaging and clinical data. However, the superiority of effective eTNS respect to sham stimulation for the prevention of migraine headaches has already been demonstrated in a randomized, sham-controlled trial. Second, the HC did not undergo eTNS treatment, thus, the authors could not determine if the eTNS-induced changes in ACC activation by THS were specific to migraineurs. By corollary, these researchers could not exclude that these changes could be due to the clinical improvement of patients after eTNS, rather than to the neurostimulation treatment itself.

An UpToDate review on "Preventive treatment of migraine in adults" (Bajwa and Smith, 2018) states that “Transcutaneous nerve stimulation -- Although data are limited, the findings of a controlled trial conducted at 5 tertiary headache centers in Belgium suggest that treatment with a supraorbital transcutaneous electrical nerve stimulator is beneficial for patients with episodic migraine. The trial randomly assigned 69 adults with migraine (with or without aura) to active or sham stimulation for 20 minutes daily for three months. Exclusion criteria included the use of preventive treatment for migraine in the 3 months prior to enrollment. At 3 months of treatment, the responder rate, defined as the percentage of subjects with a ≥ 50 % reduction in migraine days per month, was significantly higher for the active stimulation compared with the sham stimulation group (38.2 versus 12.1 %), as was the mean reduction in monthly migraine days (-2.1 versus +0.3 days). There were no adverse events in either group. Limitations to this trial include small effect size, low patient numbers, and uncertainty in concealing treatment allocation, given that active stimulation causes intense paresthesia. The device used in this trial is approved for marketing in the United States, Canada, Europe, and several additional countries … Non-pharmacologic measures that may be beneficial for migraine headache prevention include aerobic exercise, biofeedback, other forms of relaxation training, cognitive-behavioral therapies, acupuncture, and transcutaneous electrical nerve stimulation”.

Furthermore, an UpToDate review on “Preventive treatment of migraine in children” (Mack, 2018) does not mention “Cefaly / supraorbital transcutaneous electrical nerve stimulation” as a management option.
Quell Device

A recently FDA-cleared device, the Quell device, is the first electrical stimulator to receive approval for use during sleep. The device consists of a band worn around the upper calf to theoretically provide systemic relief of chronic pain and is controlled by an individual’s smartphone or tablet. Like a TENS unit, the electrode strip sends electrical signals that trigger one’s body’s own pain relief mechanisms. The Quell is an FDA-approved Class II medical device for symptomatic relief and management of chronic pain. It is available without a prescription.

An UpToDate review on “Management of non-radicular neck pain in adults” (Isaac, 2020) states that “Transcutaneous electrical nerve stimulation -- Although transcutaneous electrical nerve stimulation (TENS) is widely used in the management of musculoskeletal pain syndromes, the evidence of its efficacy is uncertain. In a systematic review including 7 trials of TENS in the treatment of chronic neck pain, no definitive conclusions could be drawn due to the heterogeneity in study interventions and measured outcomes. Even when including only the 2 trials comparing TENS with placebo (sham TENS treatment) for neck pain, there was very low certainty evidence for similar short-term pain outcomes … We do not routinely recommend the use of cervical collars, low-level laser light therapy (LLLT), cervical traction, botulinum toxin injections, transcutaneous electrical nerve stimulation (TENS), electromagnetic therapy, or surgery for the treatment of non-radicular neck pain”.

Combination Therapies

A more recent approach to electrical stimulation has been development of devices that may use a combination of different stimulation modalities, such as combining TENS with ICS, TENS with ultrasound, TENS with low-level laser therapy (LLLT) or TENS with neuromuscular stimulation (NMES). Examples of combination devices include, but may not be limited to, the Neurolumen device (combines TENS with LLLT and light-emitting diode (LED) therapy) or the Empi Phoenix and QB1 System (combination TENS with NMES devices).
Additionally, combined ICS and muscle stimulation utilize ICS for pain and muscle stimulation to treat underlying muscle conditions. Examples of this type of device are the RS-4i sequential stimulator and the EMSI TENS/EMS-14.

In combined therapy which consists of high frequency electrical stimulation and peripheral nerve block (also referred to as combination electrochemical therapy, combination electrochemical treatment, or CET), it is purported to treat peripheral neuropathy by first injecting the peripheral nerve with a local anesthetic, followed by a high frequency electrical stimulation.

In a sham-controlled, single-blinded, single-center, cross-over study, Li and co-workers (2018) examined if transcranial direct current stimulation (tDCS) augments the analgesic effect of breathing-controlled electrical stimulation (BCES) in patients with spinal cord injury (SCI) who have chronic neuropathic pain. This trial included 12 participants with incomplete SCI. The treatment protocol included a 20-min tDCS (sham or active), followed by a 20-min BCES to the median nerve on the dominant side. The treatment session with sham or control tDCS was given on different days in a randomized order; VAS was used to assess neuropathic pain at baseline, 10 mins after tDCS, and 10 mins after BCES. Subjects were blinded to the status of tDCS. Of the 12 subjects, 10 completed sessions of both sham and active tDCS, while the other 2 completed only active tDCS and BCES treatment. Of the 12 subjects, 7 showed analgesic effects after active tDCS, while sham tDCS produced some analgesic effects in 4 of 10 subjects. At the group level, there was no difference between active and sham tDCS treatment. All except 1 subject responded positively to BCES in all sessions; VAS score for pain decreased significantly after BCES combined with either active tDCS or sham tDCS treatment. The authors concluded that the immediate analgesic effect of BCES was confirmed. However, this effect was not augmented after 1 session of tDCS treatment.

SENSUS Device

The SENSUS device uses transcutaneous electromagnetic nerve stimulation to purportedly treat individuals with diabetic peripheral neuropathy.
Galvanic Stimulation for Peripheral Arterial Disease

Williams et al (2017) noted that PAD is common and symptoms can be debilitating and lethal. Risk management, exercise, radiological and surgical intervention are all valuable therapies, but morbidity and mortality rates from this disease are increasing. Circulatory enhancement can be achieved using simple medical electronic devices, with claims of minimal adverse side effects. The evidence for these is variable, prompting a review of the available literature. Embase and Medline were interrogated for full text articles in humans and written in English. Any external medical devices used in the management of PAD were included if they had objective outcome data. A total of 31 papers met inclusion criteria, but protocols were heterogeneous. The medical devices reported were intermittent pneumatic compression (IPC), NMES or EMS, and galvanic electrical dressings. In patients with intermittent claudication, IPC devices increase popliteal artery velocity (49 to 70 %) and flow (49 to 84 %). Gastrocnemius EMS increased superficial femoral artery flow by 140 %. Over 4.5 to 6 months IPC increased intermittent claudication distance (ICD) (97 to 150 %) and absolute walking distance (AWD) (84 to 112 %), with an associated increase in quality of life; NMES of the calf increased ICD and AWD by 82 % and 61 to 150 % at 4 weeks, and 26 % and 34 % at 8 weeks. In patients with critical limb ischemia (CLI), IPC reduced rest pain in 40 to 100 % and was associated with ulcer healing rates of 26 %; IPC had an early limb salvage rate of 58 to 83 % at 1 to 3 months, and 58 to 94 % at 1.5 to 3.5 years. No studies have reported the use of EMS or NMES in the management of CLI. The authors concluded that there is evidence to support the use of IPC in the management of claudication and CLI. There is a building body of literature to support the use of electrical stimulators in PAD, but this is low level to date. Devices may be of special benefit to those with limited exercise capacity, and in non-reconstructable CLI. Moreover, they stated that galvanic stimulation is not recommended.

Electrical Stimulation for the Treatment of Chronic Pelvic Pain

Fuentes-Marquez and colleagues (2018) summarized the available scientific evidence on physiotherapy interventions in the management of chronic pelvic pain (CPP). These researchers carried out a systematic review of RCTs. An electronic search of Medline, CINAHL, and Web of
Science databases was performed to identify relevant randomized trials from 2010 to 2016. Manuscripts were included if at least 1 of the comparison groups received a physiotherapy intervention. Studies were assessed in duplicate for data extraction and risk of bias using the Physiotherapy Evidence Database scale PEDro; 8 of the studies screened met the inclusion criteria -- 4 manuscripts studied the effects of electrotherapy including intravaginal electrical stimulation, short wave diathermy, respiratory-gated auricular vagal afferent nerve stimulation, percutaneous tibial nerve stimulation, and sono-electro-magnetic therapy with positive results; 3 studies focused on manual assessing the efficacy of myofascial versus massage therapy in 2 of them and ischemic compression for trigger points. The authors concluded that although physiotherapy interventions showed some beneficial effects, evidence could not support the results. They stated that heterogeneity in terms of population phenotype, methodological quality, interpretation of results, and operational definition resulted in little overall evidence to guide treatment.

Electrical Stimulation of the Posterior Tibial Nerve for the Treatment of Neuropathic Pain associated with Polyneuropathy

Dabby and associates (2018) stated that peripheral neuropathic pain (PNP) is caused by neuronal damage to the peripheral nervous system (PNS) and usually affects the distal extremities. In an open-label study, these researchers examined the effect of short-term PNS on individuals with PNP due to polyneuropathy. A total of 12 patients (mean age of 63.0 ± 10.0 years, 41.7 % men) with daily bilateral PNP for at least 6 months (mean duration of neuropathic pain of 7.4 ± 7.8 years) received a total of 6 direct electrical stimulation therapies to the posterior tibial nerve at 3 to 4-day intervals; 8 patients completed the study and were included in the efficacy analysis. The average pain at baseline was 36.6 ± 3.80 estimated by the Short-Form McGill Pain Questionnaire. After the last stimulation, pain was significantly reduced by 85.5 % to 4.88 ± 3.1 (p = 0.008); 6 patients (75 %) had over 50 % decrease in pain after the first stimulation therapy and 99.2 % after the final stimulation therapy. The patients also reported statistically significant decreases in pain level (measured by VAS), ranging from 54.85 % to 87.50 % after each of the stimulations as compared to the pain experienced prior to the stimulations. The authors concluded that the procedure was safe without
any serious AEs; PNS has shown excellent efficacy and improvement of PNP symptoms. Moreover, they stated that further studies in larger patient populations and longer duration are needed.

The authors stated that this study’s drawbacks included its small sample size (n = 8), short duration of treatment (6 months), and 33% patient drop-out.

Reduced Impedance Non-Invasive Cortical Electrostimulation (RINCE) for the Treatment of Chronic Pain

O’Connell and colleagues (2018) provided an update on the original Cochrane Review published in 2010, Issue 9, and last updated in 2014, Issue 4. Non-invasive brain stimulation techniques aim to induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity. They include repetitive transcranial magnetic stimulation (rTMS), cranial electrotherapy stimulation (CES), tDCS, transcranial random noise stimulation (tRNS) and reduced impedance non-invasive cortical electrostimulation (RINCE). These investigators evaluated the efficacy of non-invasive cortical stimulation techniques in the treatment of chronic pain. For this update, they searched CENTRAL, Medline, Embase, CINAHL, PsycINFO, LILACS and clinical trials registers from July 2013 to October 2017. Randomized and quasi-randomized studies of rTMS, CES, tDCS, RINCE and tRNS if they employed a sham stimulation control group, recruited patients over the age of 18 years with pain of 3 months’ duration or more, and measured pain as an outcome were selected for analysis. Outcomes of interest were pain intensity measured using VAS or NRS, disability, QOL and adverse events (AEs). These investigators included an additional 38 trials (involving 1,225 randomized participants) in this update, making a total of 94 trials in the review (involving 2,983 randomized participants). This update included a total of 42 rTMS studies, 11 CES, 36 tDCS, 2 RINCE and 2 tRNS; 1 study evaluated both rTMS and tDCS. These investigators judged only 4 studies as low-risk of bias across all key criteria. The authors concluded that there is very low-quality evidence that single doses of high-frequency rTMS of the motor cortex and tDCS may have short-term effects on chronic pain and QOL; but multiple sources of bias existed that may have influenced the observed effects. These researchers did not find evidence that low-frequency rTMS, rTMS
applied to the dorsolateral prefrontal cortex and CES were effective for reducing pain intensity in chronic pain. They noted that the broad conclusions of this review have not changed substantially for this update. There remains a need for substantially larger, rigorously designed studies, particularly of longer courses of stimulation.

Scrambler Therapy for Neuropathic Pain Associated with Chemotherapy-Induced Peripheral Neuropathy

Tomasello and colleagues (2018) noted that chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy in need of effective treatment. Preliminary data supported the efficacy of scrambler therapy (ST), a non-invasive cutaneous electrostimulation device, in adults with CIPN. These researchers examined the safety, efficacy, and durability of ST for neuropathic pain in adolescents with CIPN. They studied 9 pediatric patients with cancer and CIPN who received ST for pain control. Each patient received 45-min daily sessions for 10 consecutive days as a first step, but some of them required additional treatment. Pain significantly improved comparing NRS after 10 days of ST (9.22 ± 0.83 versus 2.33 ± 2.34; p < 0.001) and at the end of the optimized cycle (EOC) (9.22 ± 0.83 versus 0.11 ± 0.33, p < 0.001). The improvement in QOL was significantly reached on pain interference with general activity (8.67 ± 1.66 versus 3.33 ± 2.12, p < 0.0001), mood (8.33 ± 3.32 versus 2.78 ± 2.82, p < 0.0005), walking ability (10.00 versus 2.78 ± 1.22, p < 0.0001), sleep (7.56 ± 2.24 versus 2.67 ± 1.41, p < 0.001), and relations with people (7.89 ± 2.03 versus 2.11 ± 2.03, p < 0.0002; Lansky score 26.7 ± 13.2 versus 10 days of ST 57.8 ± 13.9, p < 0.001; 26.7 ± 13.2 versus EOC 71.1 ± 16.2, p < 0.001). The authors concluded that based on these preliminary data, ST could be a good choice for adolescents with CIPN for whom pain control is difficult; ST caused total relief or dramatic reduction in CIPN pain and an improvement in QOL, durable in follow-up. It resulted in no detected side effects, and could be re-trained successfully. Moreover, these researchers stated that further larger studies are needed to confirm these promising preliminary data in pediatric patients with cancer.

Transcutaneous Electrical Nerve Stimulation for the Treatment of Migraine
Tao and colleagues (2018) stated that migraine is now ranked as the 2nd most disabling disorder worldwide reported by the Global Burden of Disease Study 2016. As a non-invasive neuro-stimulation technique, TENS has been applied as an abortive and prophylactic treatment for migraine recently. These investigators conducted this meta-analysis to analyze the safety and effectiveness of TENS on migraineurs. They searched Medline (via PubMed), Embase, the Cochrane Library and the Cochrane Central Register of Controlled Trials to identify RCTs, which compared the effect of TENS with sham TENS on migraineurs. Data were extracted and methodological quality assessed independently by 2 reviewers. Change in the number of monthly headache days, responder rate, painkiller intake, adverse events and satisfaction were extracted as outcome. A total of 4 studies were included in the quantitative analysis with 161 migraine patients in real TENS group and 115 in sham TENS group. These researchers found significant reduction of monthly headache days (SMD: -0.48; 95 % CI: -0.73 to - 0.23; p < 0.001) and painkiller intake (SMD: -0.78; 95 % CI: -1.14 to - 0.42; p < 0.001). Responder rate (RR: 4.05; 95 % CI: 2.06 to 7.97; p < 0.001) and satisfaction (RR: 1.85; 95 % CI: 1.31 to 2.61; p < 0.001) were significantly increased compared with sham TENS. The authors concluded that the findings of this meta-analysis suggested that TENS may serve as an effective and well-tolerated alternative for migraineurs. However, they stated that the low quality of evidence prevented them from reaching definitive conclusions; future well-designed RCTs are needed to confirm and update the findings of this analysis.

Transcutaneous Electrical Nerve Stimulation for the Treatment of Chronic Pain Following Ankylosing Spondylitis

Chen and colleagues (2018) examined the effect of TENS for the treatment of patients with chronic pain after ankylosing spondylitis (AS). A total of 72 eligible patients with chronic pain following AS were included. All included patients received exercise and were assigned to a treatment group and a control group equally. In addition, patients in the treatment group also underwent TENS therapy. All patients were treated for a total of 6 weeks. The primary outcome of pain intensity was measured by VAS. The secondary outcomes included degree of functional limitation, as assessed by Bath Ankylosing Spondylitis Functional Index (BASFI); and QOL, as evaluated by Ankylosing
Spondylitis Quality of Life (ASQOL) questionnaire. All outcomes were assessed before and after 6 weeks treatment. Furthermore, adverse events were also recorded. After 6-week treatment, patients in the treatment group did not show more promising outcomes in pain reduction, as measured by VAS (p=0.08); functional evaluation, as evaluated by BASFI (p=0.19); as well as QOL, as assessed by ASQOL (p=0.18), compared with patients in the control group; no AEs occurred in both groups. The authors concluded that this study did not exert encouraging outcomes in patients with chronic pain following AS after 6-week treatment.

**Transcutaneous Electrical Nerve Stimulation (TENS) for the Treatment of Carpal Tunnel Syndrome Pain**

In a randomized, pilot study, Casale et al (2013) compared laser versus TENS in reducing pain and paresthesia; and in improving motor and sensory median nerve conduction parameters in mild-to-moderate carpal tunnel syndrome (CTS). Patients and staff administered treatments and outcome measures were blinded. A total of 20 symptomatic CTS patients were included in this trial; 15 sessions of 100-Hz TENS (30 mins; rectangular waves; 80 ms width, intensity below muscle contraction); combined 830 to 1,064 nm laser (radiating dose: 250 J cm-2 delivered to the skin overlying the course of the median nerve at the wrist for 100 s at 25 W (18 W [1,064 nm] + 7 W [830 nm]) via a fiber-optic probe with a spot size of approximately 1 cm2). Outcome measures were VAS for pain and paresthesia; median nerve motor distal latency (mMDL) and median sensory nerve conduction velocity (mSNCV). Laser improved both positive and negative sensory symptoms; TENS induced clinical improvement but this was not statistically significant and was limited to pain reduction. Laser, but not TENS, favorably modified the neurophysiological parameters. The authors concluded that high-intensity combined laser wavelengths of 830 nm and 1,064 nm, which produced a better transparency with less scattering and a high energy transfer, were better than TENS in improving both pain and paresthesia as well as neurophysiological parameters in CTS.

In a RCT, Koca et al (2014) examined the effectiveness of interferential current (IFC) and TENS therapies in the management of CTS compared with splint therapy. This was a prospective, single-blinded, single-center,
randomized, 3-group parallel intervention study of 3 weeks duration.
Efficacy was examined in the 3rd week after the end of treatments.
Subjects were randomly assigned to 1 of the 3 groups: group I patients
received splint therapy, group II patients received TENS applied on the
palmar surface of the hand and the carpal tunnel, and group III patients
underwent IFC therapy applied on the palmar surface of the hand and the
volar surface of the forearm. TENS and ICF treatments were applied 5
times weekly for a total of 15 sessions. Group 1 patients were stabilized
with volar wrist splints for 3 weeks. The efficacy of the therapies was
assessed before initiation of therapy and at 3 weeks after completion of
therapy using a VAS, a symptom severity scale, the functional capacity
scale of the BCTQ, and measurements of mMDL and mSNCV. Groups
were compared pair-wise using the Mann-Whitney U test to identify the
source of differences between groups. The Wilcoxon test was used to
analyze changes in variables over time within a group. In the VAS,
BCTQ, mMDL, and mSNCV, no significant difference was observed
between the groups (p > 0.05). In the VAS, BCTQ, and mSNCV,
statistically significant improvements were detected in all groups (p <
0.05). There was no statistically significant difference between TENS and
splint therapy with respect to improvement in clinical scores, whereas IFC
therapy provided a significantly greater improvement in VAS, mMDL, and
mSNCV values than splint therapy (VAS: 4.80 ± 1.18 and 6.37 ± 1.18; p =
0.001, mMDL: 3.89 ± 0.88 and 4.06 ± 0.61; p = 0.001, mSNCV: 41.80 ±
1.76 and 40.75 ± 1.48; p = 0.010). IFC therapy provided a significantly
greater improvement in VAS, symptom severity, functional capacity, and
mMDL and mSNCV values than TENS therapy (VAS: 4.80 ± 1.18 and
6.68 ± 1.42; p < 0.001, symptom severity: 2.70 ± 1.03 and 3.37 ± 1.21; p
= 0.015, functional capacity: 1.90 ± 1.21 and 2.50 ± 0.78; p = 0.039,
mMDL: 3.89 ± 0.88 and 4.06 ± 0.88; p = 0.003, and mSNCV: 41.80 ± 1.76
and 41.38 ± 1.78; p = 0.021). The authors concluded that IFC may be
considered a new and safe therapeutic option for the treatment of CTS.

In a systematic review, Huisstede et al (2018) examined scientific
literature studying the effectiveness of physical therapy and
electrophysical modalities for the treatment of CTS. Data sources
included the Cochrane Library, PubMed, Embase, CINAHL, and
Physiotherapy Evidence Database; 2 reviewers independently applied the
inclusion criteria to select potential eligible studies; and 2 reviewers
independently extracted the data and assessed the methodologic quality
using the Cochrane Risk of Bias Tool. A best-evidence synthesis was carried out to summarize the results of the included studies (2 reviews and 22 RCTs). For physical therapy, moderate evidence was found for myofascial massage therapy versus ischemic compression on latent, or active, trigger points or LLLT in the short-term. For several electrophysical modalities, moderate evidence was found in the short-term (ultrasound [US] versus placebo, US as single intervention versus other non-surgical interventions, US versus corticosteroid injection plus a neutral wrist splint, local microwave hyperthermia versus placebo, iontophoresis versus phonophoresis, pulsed radiofrequency (PRF) added to wrist splint, continuous versus pulsed versus placebo shortwave diathermy, and IFC versus TENS versus a night-only wrist splint). In the mid-term, moderate evidence was found in favor of radial extracorporeal shockwave therapy (ESWT) added to a neutral wrist splint, in favor of ESWT versus US, or cryo-US, and in favor of US versus placebo. For all other interventions studied, only limited, conflicting, or no evidence was found. No RCTs investigating the long-term effects of physical therapy and electrophysical modalities were found. Because of heterogeneity in the treatment parameters used in the included RCTs, optimal treatment parameters could not be identified. The authors concluded that moderate evidence was found for several physical therapy and electrophysical modalities for CTS in the short-term and mid-term. Moreover, these researchers stated that future studies should concentrate on long-term effects and which treatment parameters of physical therapy and electrophysical modalities are most effective for CTS.

Ultrasound-Guided Percutaneous Stimulation off the Sciatic Nerve for Post-Operative Analgesia Following Ambulatory Foot Surgery

Ilfeld and colleagues (2018) noted that percutaneous PNS is an analgesic modality involving the insertion of a lead through an introducing needle followed by the delivery of electric current. This modality has been reported to treat chronic pain as well as post-operative pain the day following knee surgery. However, it remains unknown if this analgesic technique may be used in ambulatory subjects following foot procedures beginning within the recovery room immediately following surgery, and with only short series of patients reported to-date, the only available data are derived from strictly observational studies. In a proof-of-concept study, these researchers examined the feasibility of using percutaneous
sciatric nerve PNS to treat post-operative pain following ambulatory foot surgery in the immediate post-operative period and provided the first available data from a randomized controlled study design to provide evidence of analgesic effect. Pre-operatively, an electrical lead (SPRINT; SPR Therapeutics, Inc., Cleveland, OH) was percutaneously inserted posterior to the sciatric nerve between the sub-gluteal region and bifurcation with US-guidance. Following hallux valgus osteotomy, subjects received 5 mins of either stimulation or sham in a randomized, double-masked fashion followed by a 5-min cross-over period and then continuous stimulation until lead removal on post-operative days 14 to 28. During the initial 5-min treatment period, subjects randomized to stimulation (n = 4) experienced a down-ward trajectory in their pain over the 5 mins of treatment, whereas those receiving sham (n = 3) reported no such change until their subsequent 5-min stimulation cross-over. During the subsequent 30 mins of stimulation, pain scores decreased to 52 % of baseline (n = 7); 3 subjects (43 %) used a continuous popliteal nerve block for rescue analgesia during post-operative days 0 to 3. Overall, resting and dynamic pain scores averaged less than 1 on the NRS, and opioid use averaged less than 1 tablet daily with active stimulation. One lead dislodged, 2 fractured during use, and 1 fractured during intentional withdrawal. The authors concluded that this small, pilot, proof-of-concept study demonstrated that percutaneous sciatric nerve PNS was feasible for ambulatory foot surgery and suggested that this modality provided analgesia and decreased opioid requirements following hallux valgus osteotomy procedures. However, lead dislodgement and fracture were concerns. Moreover, they stated that the findings of this pilot study indicated that a subsequent clinical trial is needed.

The authors stated that this study had several drawbacks. Prior experience with percutaneous PNS in post-operative subjects 6 to 97 days following knee arthroplasty suggested that analgesia onset and peak were nearly instantaneous following the introduction of electrical current. Thus, these researchers designed the current randomized, sham-controlled, cross-over portion of this study with only 5-min treatment periods so that subjects randomized to sham initially would have a minimal duration without supplemental analgesia. However, the results of this trial suggested that for acute pain in the immediate post-operative period maximum PNS-induced analgesia requires far longer than 5 mins: pain scores continued to decrease even as subjects
emerged from general anesthesia through the 40-min time-point. Unfortunately, no subsequent pain data were collected until the following day, so the duration for maximum analgesic effect remains to be determined. In contrast, these investigators were aware of a “carryover” effect following PNS so that subjects continued to receive a variable duration and degree of analgesia following electrical current discontinuation, possibly due to sustained modification of supra-spinal pain processing. These researchers knew that this carryover effect would make the data of the 5-min sham period for the group who initially received active current difficult or impossible to interpret. However, to keep the double-masked study design, the authors had no choice but to collect the measurements from this 5-min period. Thus, they included the collected data; but presented them in ghost to indicate the uncertainty of its interpretation.

Ultrasound-Guided Percutaneous Stimulation off the Femoral Nerve for Post-Operative Analgesia Following Anterior Cruciate Ligament Reconstruction

In a prospective, proof-of-concept study, Ilfeld and associates (2019) examined the feasibility of using percutaneous PNS of the femoral nerve to treat pain in the immediate post-operative period following ambulatory anterior cruciate ligament (ACL) reconstruction with a patellar autograft. Pre-operatively, an electrical lead (SPRINT, SPR Therapeutics, Inc., Cleveland, OH) was percutaneously implanted with US-guidance anterior to the femoral nerve caudad to the inguinal crease. Within the recovery room, subjects received 5 mins of either stimulation or sham in a randomized, double-masked fashion followed by a 5-min cross-over period, and then continuous active stimulation until lead removal post-operative day 14 to 28. Statistics were not applied to the data due to the small sample size of this feasibility study. During the initial 5-min treatment period, subjects randomized to stimulation (n = 5) experienced a slight down-ward trajectory (decrease of 7 %) in their pain over the 5 mins of treatment, while those receiving sham (n = 5) reported a slight up-ward trajectory (increase of 4 %) until their subsequent 5-min stimulation cross-over, during which time they also experienced a slight down-ward trajectory (decrease of 11 % from baseline). A majority of subjects (80 %) used a continuous adductor canal nerve block for rescue analgesia (in addition to stimulation) during post-operative days 1 to 3, after which the
median resting and dynamic pain scores remained equal or less than 1.5 on the NRS, respectively, and the median daily opioid consumption was less than 1.0 tablet. The authors concluded that the findings of this proof-of-concept study demonstrated that percutaneous femoral nerve stimulation was feasible for ambulatory knee surgery; and suggested that this modality may be effective in providing analgesia and decreasing opioid requirements following ACL reconstruction. These researchers stated that the results of this pilot study indicated that a subsequent clinical trial is needed.

The authors stated that this study had several drawbacks. First, this proof-of-concept study lacked a control group following the initial 10-min treatment period within the recovery room; and, thus documentation and quantification of analgesia delivery and opioid sparing require additional investigation. Second, the needle could not be withdrawn without deploying the lead. Therefore, instead of withdrawing and re-positioning the needle/lead combination if a first attempt passed the femoral nerve without the desired response, an entirely new lead had to be implanted at a different trajectory. This obviously added greatly to both the required attempts and overall procedure duration since multiple implantation kits and leads had to be prepared. Lastly, these researchers were aware of a “carryover” effect following PNS so that subjects continued to receive a variable duration and degree of analgesia following electrical current discontinuation, possibly due to sustained modification of supra-spinal pain processing. They knew that this carryover effect would make the data of the 5-min sham period for the group which initially received active current difficult or impossible to interpret. However, to keep the double-masked study design, the authors had no choice but to collect the measurements from this 5-min period. Thus, they included the collected data but presented them in ghost to indicate the uncertainty of its interpretation.

Neurogenx 4000PRO Device for the Treatment of Achilles Tendonitis

The Neurogenx 4000PRO (400 to 40,00 Hz) is a FDA-cleared electromedical device used for the treatment of various types of neuropathies and chronic pain conditions including CRPS, fibromyalgia,
Electrical Stimulation for Pain

migraines, neuritis, phantom limb pain, plantar fasciitis, radiculopathy and restless leg syndrome. However, there is a lack of evidence regarding its clinical effectiveness.

Sprint (Peripheral Subcutaneous Field Stimulation) for the Treatment of Low Back Pain

Gilmore et al (2020) stated that percutaneous PNS provides an opportunity to relieve chronic LBP and reduce opioid analgesic consumption as an alternative to radiofrequency ablation (RFA) and permanently implanted neurostimulation systems. Traditionally, the use of neurostimulation earlier in the treatment continuum has been limited by its associated risk, invasiveness, and cost. Percutaneous PNS leads (SPRINT MicroLead) were placed bilaterally to target the medial branches of the dorsal rami nerves under image guidance. The percutaneous leads were connected to miniature wearable stimulators (SPRINT PNS System) for the 1-month therapy period, after which the leads were removed. Pain and disability were assessed long-term up to 12 months after lead removal. Substantial, clinically significant reductions in average pain intensity (greater than or equal to 50 % reduction as measured by the Brief Pain Inventory Short Form) were experienced by a majority of subjects (67 %) at end of treatment compared to baseline (average 80 % reduction among responders; p < 0.05, analysis of variance; n = 9).

Twelve months after the end of PNS treatment, a majority of subjects who completed the long-term follow-up visits experienced sustained, clinically significant reductions in pain and/or disability (67 %, n = 6; average 63 % reduction in pain intensity and 32-point reduction in disability among responders). No serious or unanticipated AEs were reported. The authors concluded that the findings of this study challenged the long-held notion that a positive trial of PNS should be followed by a permanent implant in responders. These researchers stated that percutaneous PNS may serve as an effective neurostimulation therapy for patients with chronic LBP, and should be considered earlier in the treatment continuum as a motor-sparing means of avoiding opioids, denervation, and permanently implanted neurostimulation systems. They stated that this approach has the potential to significantly influence the care continuum for chronic LBP by providing the benefits of an effective neurostimulation therapy to patients earlier than has been previously possible. These researchers stated that additional studies are needed to confirm these
findings in a larger population of patients, including studies that compare the effects of percutaneous PNS to other standard interventional approaches used for patients with chronic LBP.

The authors stated that this study had 2 main drawbacks. First, the sample size was small (n = 9) and did not include a control group or examine the placebo effect. Second, because chronic LBP could include a heterogeneous population (e.g., facetogenic, discogenic, arthritic, or myofascial pain) and the selection criteria for inclusion in this study were broad, additional studies and analyses of larger populations, including larger, prospective, multi-center, case-series studies, may determine LBP subtypes or characteristics that are more likely to benefit from percutaneous PNS, as well as if specific types of diagnostic tests or imaging are predictive of success.

Transcutaneous Magnetic Stimulation for the Treatment of Chronic Pain

Leung and colleagues (2014) stated peripheral nerve injury can result in the formation of neuroma/nerve entrapment, a persistent peripheral neuropathic pain state that is often refractory to invasive interventions or medications; thus; there is a need to develop innovative non-invasive therapy in treating post-traumatic peripheral neuropathic pain states. A new intervention, transcutaneous magnetic stimulation (tMS), is derived from the use of transcranial magnetic stimulation in which a rapid discharge of electric current is converted into dynamic magnetic flux for modulating neuronal functions. In a case-series study, low-frequency (0.5 Hz) tMS was developed over the site of neuroma/nerve entrapment in 5 patients who have failed both steroid injection and conventional pain medications; 400 pulses of stimulation were delivered per treatment session. Each patient received 3 to 4 sessions of treatment over a period of 2 months. Pre- and post-intervention spontaneous pain levels were evaluated with NRS; 5 patients with post-traumatic neuroma/nerve entrapment pain received the treatment. Average pre- and post-scores (± SD) on the NRS were 5.00 (± 1.41) and 0.80 (± 1.10), respectively, with an average pain reduction of 84 (± 21.91) % in the NRS after 3 to 4 treatments within 2 months. This analgesic effect appeared to be sustainable with repeated treatment delivered at a 6- to 8-week duration. Pre-treatment tactile allodynia found in 3 patients resolved after the initial
2-month treatment sessions. The authors concluded that tMS offered a non-invasive therapeutic option for neuroma-related neuropathic pain conditions. Moreover, these researchers stated that RCTs are needed to validate the efficacy of this treatment modality; additional studies are also needed to examine the underlying electrophysiological mechanisms of the observed analgesic benefit.

**IB-Stim for the Treatment of Irritable Bowel Syndrome**

Babygirija et al (2017) noted that a non-invasive, auricular percutaneous electrical nerve field stimulation (PENFS) has been suggested to modulate central pain pathways. These investigators examined the effects of BRIDGE device on the responses of amygdala and lumbar spinal neurons and the development of post-colitis hyperalgesia. Male Sprague-Dawley rats received intra-colonic trinitrobenzene sulfonic acid (TNBS) and PENFS on the same day. Control rats had sham devices. The visceromotor response (VMR) to colon distension and paw withdrawal threshold (PWT) was recorded after 7 days. A different group of rats had VMR and PWT at baseline, after TNBS and following PENFS. Extracellular recordings were made from neurons in central nucleus of the amygdala (CeA) or lumbar spinal cord. Baseline firing and responses to compression of the paw were recorded before and after PENFS. Sham-treated rats exhibited a much higher VMR (greater than 30 mmHg) and lower PWT compared to PENFS-treated rats (p < 0.05). PENFS decreased the VMR to colon distension and increased the PWT compared to pre-stimulation (p < 0.05). PENFS resulted in a 57% decrease in spontaneous firing of the CeA neurons (0.59 ± 0.16 versus control: 1.71 ± 0.32 imp/s). Similarly, the response to somatic stimulation was decreased by 56% (3.6 ± 0.52 versus control: 1.71 ± 0.32 imp/s, p < 0.05). Spinal neurons showed a 47% decrease in mean spontaneous firing (4.05 ± 0.65 versus control: 7.7 ± 0.87 imp/s) and response to somatic stimulation (7.62 ± 1.7 versus control: 14.8 ± 2.28 imp/s, p < 0.05). The authors concluded that PENFS attenuated baseline firing of CeA and spinal neurons, which may account for the modulation of pain responses in this model of post-inflammatory visceral and somatic hyperalgesia. This was an animal study.

Kovacic et al (2017) stated that development of safe and effective
therapies for pediatric abdominal pain-related functional gastro-intestinal (GI) disorders is needed. A non-invasive, Food and Drug Administration (FDA)-cleared device (Neuro-Stim, Innovative Health Solutions, IN, USA) delivers PENFS in the external ear to modulate central pain pathways. In randomized, double-blind, sham-controlled trial, these researchers examined the efficacy of PENFS in adolescents with abdominal pain-related functional GI disorders. They enrolled adolescents (aged 11 to 18 years) who met Rome III criteria for abdominal pain-related functional GI disorders from a single U.S. outpatient gastroenterology clinic. Patients were randomly assigned (1:1) with a computer-generated randomization scheme to active treatment or sham (no electrical charge) for 4 weeks. Patients were stratified by sex and presence or absence of nausea. Allocation was concealed from participants, caregivers, and the research team. The primary efficacy endpoint was change in abdominal pain scores. These investigators measured improvement in worst abdominal pain and composite pain score using the Pain Frequency-Severity-Duration (PFSD) scale. Participants with less than 1 week of data and those with organic disease identified after enrolment were excluded from the modified intention-to-treat (ITT) population. Between June 18, 2015 and November 17, 2016, a total of 115 children with abdominal pain-related functional GI disorders were enrolled and assigned to either PENFS (n = 60) with an active device or sham (n = 55). After exclusion of patients who discontinued treatment (n = 1 in the PENFS group; n = 7 in the sham group) and those who were excluded after randomization because they had organic disease (n = 2 in the PENFS group; n = 1 in the sham group), 57 patients in the PENFS group and 47 patients in the sham group were included in the primary analysis. Patients in the PENFS group had greater reduction in worst pain compared with sham after 3 weeks of treatment (PENFS: median score 5.0 [inter-quartile range [IQR] 4.0 to 7.0]; sham: 7.0 [5.0 to 9.0]; least square means estimate of change in worse pain 2.15 [95 % CI: 1.37 to 2.93], p < 0·0001). Effects were sustained for an extended period (median follow-up 9.2 weeks [IQR 6.4 to 13.4]) in the PENFS group: median 8.0 (IQR 7.0 to 9.0) at baseline to 6.0 (5.0 to 8.0) at follow-up versus sham: 7.5 (6.0 to 9.0) at baseline to 7.0 (5.0 to 8.0) at follow-up (p < 0.0001). Median PFSD composite scores also decreased significantly in the PENFS group (from 24.5 [IQR 16.8 to 33.3] to 8.4 [3.2 to 16.2]) compared with sham (from 22.8 [IQR 8.4 to 38.2] to 15.2 [4.4 to 36.8]) with a mean decrease of 11.48 (95 % CI: 6.63 to 16.32; p < 0.0001) after 3 weeks. These effects were sustained at
extended follow-up in the PENFS group: median 24.5 (IQR 16.8 to 33.3) at baseline to 12 (3.6 to 22.5) at follow-up, compared with sham: 22.8 (8.4 to 38.2) at baseline to 16.8 (4.8 to 33.6) at follow-up (p = 0.018); 10 patients reported side-effects (3 of whom discontinued the study): ear discomfort (n = 6; 3 in the PENFS group, 3 in the sham group), adhesive allergy (n = 3; 1 in the PENFS group, 2 in the sham group), and syncope due to needle phobia (n = 1; in the sham group). There were no serious adverse events (AEs). The authors concluded that the findings of this study suggested that non-invasive PENFS was a safe and effective therapeutic option for adolescents with abdominal pain-related functional GI disorders. These researchers stated that further studies should focus on finding the optimal duration of therapy and establishing the specific patient characteristics that are predictive of clinical response.

In an editorial, van Tilburg (2017) stated that the study by Kovacic et al (2017) offered a new direction for treating visceral hypersensitivity via central pathways. PENFS targets the auricular branches of the vagal nerve, and evidence showed that it modulates the pain matrix in the CNS, such as the amygdala. Findings from Kovacic et al showed that a 4-week treatment of PENFS reduced pain and disability compared with sham, and these effects were sustained 2 to 3 months following treatment. A major benefit of PENFS was that it is non-invasive -- PENFS is administered via the ear and electrical stimulation is below the sensation threshold. As a safe and efficacious treatment, PENFS could be an important addition to the therapeutic options for abdominal pain-related functional GI disorders. However, before recommending PENFS widely, the study results need to be replicated. Kovacic et al found only a small placebo response (29 % versus 41 % on average in other trials). Many treatment trials of abdominal pain-related functional GI disorders have not shown significant differences because of a robust placebo response in patients. Investigation of whether PENFS will remain superior to placebo or sham in the long-term should be scrutinized more closely. Secondly, Kovacic et al did not examine if PENFS changed visceral hypersensitivity, central pain pathways, or both. Nor did they indicate whether pain reduction was more robust in patients with pre-existing visceral hypersensitivity. Data on the mechanism of PENFS in pain reduction would strengthen the findings and ease the worries around a possible low placebo response. Furthermore, such findings would provide important information to target PENFS treatment to the right patient. It is hoped that
in the future clinicians could confidently explain why children have abdominal pain-related functional GI disorders and that they will have access to safe and effective therapeutic options. The study by Kovacic et al is a major step in this direction. The editorialist concluded that although more studies are needed, their findings suggested that PENFS is a novel treatment targeting visceral hypersensitivity, which can safely reduce pain and disability in these disorders.

In a retrospective study, Wang et al (2018) examined the safety and effectiveness of neuromuscular electrical stimulation (NMES) as an adjunctive therapy to drotaverine hydrochloride (DHC) in patients with diarrhea-predominant IBS (BP-IBS). A total of 108 patient cases with BP-IBS were included in this study. Of these, 54 cases were assigned to a treatment group and received NMES and DHC, whereas the other 54 subjects were assigned to a control group and underwent DHC alone. All patients were treated for a total of 4 weeks. Primary outcomes were measured by the VAS, and average weekly stool frequency. Secondary outcome was measured by the Bristol scale. In addition, adverse events (AEs) were documented. All outcome measurements were analyzed before and after 4-week treatment. Patients in the treatment group did not show better effectiveness in VAS (p = 0.14), and average weekly stool frequency (p = 0.42), as well as the Bristol scale (p = 0.71), compared with the patients in the control group. Moreover, no significant differences in AEs were found between 2 groups. The authors concluded that the findings of this study showed that NMES as an adjunctive therapy to DHC may be not effective for patients with BP-IBS after 4-week treatment.

Krasaelap et al (2020) noted that pre-clinical studies showed that PENFS modulates central pain pathways and attenuates visceral hyperalgesia. In a randomized, double-blind study, these researchers examined the efficacy of PENFS in adolescents with irritable bowel syndrome (IBS). They analyzed data from pediatric patients with IBS who participated in a double-blind trial at a tertiary care gastroenterology clinic from June 2015 through November 2016. Patients were randomly assigned to groups that received PENFS (n = 27; median age of 15.3 years; 24 female) or a sham stimulation (n = 23; median age of 15.6 years; 21 female), 5 days/week for 4 weeks. The primary endpoint was number of patients with a reduction of 30% or more in worst abdominal pain severity after 3 weeks. Secondary endpoints were reduction in composite abdominal
pain severity score, reduction in usual abdominal pain severity, and improvement in global symptom based on a symptom response scale (-7 to +7; 0 = no change) after 3 weeks. Reductions of 30% or more in worst abdominal pain were observed in 59% of patients who received PENFS versus 26% of patients who received the sham stimulation (p = 0.024). The patients who received PENFS had a composite pain median score of 7.5 (IQR, 3.6 to 14.4) versus 14.4 for the sham group (IQR, 4.5 to 39.2) (p = 0.026) and a usual pain median score of 3.0 (IQR, 3.0 to 5.0) versus 5.0 in the sham group (IQR, 3.0 to 7.0) (p = 0.029). A symptom response scale score of 2 or more was observed in 82% of patients who received PENFS versus 26% of patients in the sham group (p ≤ 0.001). No significant side effects were reported. The authors concluded that PENFS is a promising, and now FDA-approved, novel therapy for adolescents with IBS. This study confirmed that auricular neurostimulation via PENFS significantly improved abdominal pain and global symptoms in affected adolescents. Traditionally, therapies targeting FAPDs are approved in adults but used off-label in children. Given the safety profile and the likely mechanisms, it appeared reasonable to also consider its use in adults. Future studies should focus on characterizing short- and long-term responses to PENFS in different IBS subtypes and other functional GI disorders, finding the optimal duration of therapy while also assessing changes in stool pattern. Further mechanistic studies are also needed to help target this therapy to the most appropriate patient population, including adults. Moreover, these researchers stated that although future studies are needed to define appropriate thresholds, its utility for identifying treatment responders, low cost, and ease of administration with an ECG device makes vagal efficiency (VE) a promising neurophysiological biomarker. Identification of patients with reduced VE may ultimately help individualize and target therapy for functional GI disorders, findings not previously described.

The authors stated that drawbacks of this study included short-term study duration and outcome assessment and the lower number of measures available at follow-up, resulting in decrease in power and difficulties assessing long-term impact. Notably, VE did not predict long-term treatment response. This may be due to medications or disease status alterations that were not controlled for long-term. Alternatively, the auricle may provide a portal for vagal stimulation to reduce pain short-term, but a longer treatment course may be necessary for sustained effects. Slight
group differences such as longer pain duration and higher rates of depression along with temporary stressors may have influenced results. Furthermore, the small number of males prohibited assessment of sex interactions.

In a RCT, Kovacic et al (2020) examined if pre-treatment vagal efficiency (VE), respiratory sinus arrhythmia, and heart period could predict pain improvement with auricular neurostimulation in pediatric functional abdominal pain disorders (FAPDs). A total of 92 adolescents with FAPDs underwent a 4-week randomized, double-blinded, sham-controlled auricular neurostimulation trial. Electrocardiogram-derived variables at baseline were used to predict pain using mixed effects modeling. A 3-way interaction (95% confidence intervals [CI]: 0.004 to 0.494) showed that the treatment group subjects with low baseline VE had lower pain scores at week 3. There was no substantial change in the placebo or high VE treatment group subjects. This effect was supported by a significant correlation between baseline VE and degree of pain reduction only in the treatment group. The authors concluded that impaired cardiac vagal regulation measured by VE predicted pain improvement with auricular neurostimulation. Moreover, these researchers stated that although future studies are needed to define appropriate thresholds, its utility for identifying treatment responders, low cost, and ease of administration with an ECG device made VE a promising neurophysiological biomarker. Identification of patients with reduced VE may help individualize and target therapy for functional gastro-intestinal (GI) disorders, findings not previously described. This study did not examine the effectiveness of IB-Stim for the treatment of IBS.

The authors stated that drawbacks of this study included short-term study duration and outcome assessment and the lower number of measures available at follow-up, resulting in decrease in power and difficulties evaluating long-term impact. Notably, VE did not predict long-term treatment response. This may be due to medications or disease status alterations that were not controlled for long-term. Alternatively, the auricle may provide a portal for vagal stimulation to reduce pain short-term, but a longer treatment course may be necessary for sustained effects. Slight group differences such as longer pain duration and higher rates of depression along with temporary stressors may have influenced results. Furthermore, the small number of males prohibited assessment of sex
interactions.

Furthermore, an UpToDate review on “Treatment of irritable bowel syndrome in adults” (Wald, 2021) does not mention electrical stimulation as a therapeutic option.

**Auricular Electrical Stimulation**

Liao et al (2019) examined the effect of auricular electrical stimulation (ES) on migraine. Migraine was induced in rats by intra-peritoneal administration of nitroglycerin (NTG, 10 mg/kg) 3 times. Auricular ES pre-treatment was carried out for 5 consecutive days. Migraine behaviors were observed by a video recording. Auricular ES pre-treatment could reverse the decrease of the total time spent on exploratory (2,619.0 ± 113.0 s versus 1,581.7 ± 217.6 s, p = 0.0029) and locomotor behaviors (271.3 ± 21.4 s versus 114.3 ± 19.7 s, p = 0.0135) and also could reverse the increase of the total time spent on resting (19.0 ± 10.6 s versus 154.3 ± 46.5 s, p = 0.0398) and grooming (369.9 ± 66.8 s versus 1302.0 ± 244.5 s, p = 0.0324) behaviors. Auricular ES pre-treatment could increase the frequency of rearing behaviors (38.0 ± 1.8 versus 7.7 ± 3.5, p < 0.0001) and total distance traveled (1,372.0 ± 157.9 cm versus 285.3 ± 85.6 cm, p < 0.0001) and also could increase the percentage of inner zone time (6.0 ± 1.6 % versus 0.4 ± 0.2 %, p = 0.0472). The CGRP, COX-2, TRPV1, and TRPA1 immunoreactive cells in the trigeminal ganglion increased in the NTG group compared with the control group (all p < 0.0001); this increase could, however, be reduced by auricular ES pre-treatment (27.8 ± 2.6 versus 63.0 ± 4.2, p < 0.0001; 21.7 ± 1.2 versus 61.8 ± 4.0, p < 0.0001; 24.3 ± 1.0 versus 36.5 ± 1.7, p = 0.0003; and 20.7 ± 1.9 versus 90.8 ± 6.5, p < 0.0001, respectively). The authors suggested that auricular ES pre-treatment was beneficial for the treatment of migraine and this effect was partly related to CGRP/COX-2/TRPV1/TRPA1 signaling pathways.

The authors stated that this study had several drawbacks. First, more objective methods to examine nociceptive pain are needed, such as von Frey test for nociceptive peri-orbital pain threshold; thus, more evaluations need to be carried out for assessment of migraine except video recordings for associated behavior of migraine in the future.
Second, more objective methods to examine emotional behavior is needed, such as forced-swim or tail suspension tests except locomotor activity of open-field test in the future. Third, one experiment was inadequate to conclude the signaling pathway; another genetic modification or molecular technique to examine the signaling is needed in the future. Fourth, the study must be concerning with the emotional data that can be interrupted by physical factor, which is a locomotor behavior in the future.

APPENDIX

TENS Unit Supplies

- A 4-lead TENS unit may be used with either 2 leads or 4 leads, depending on the characteristics of the member's pain. If it is ordered for use with 4 leads, the medical record must document why 2 leads are insufficient to meet the member's needs.
- If 2 TENS leads are medically necessary, then a maximum of 1 unit of a TENS supply allowance (HCPCS Code A4595) would be considered medically necessary per month; if 4 TENS leads are necessary, a maximum of 2 units per month would be considered medically necessary. If the use of the TENS unit is less than daily, medical necessity of the TENS supply allowance is reduced proportionally. **Note:** A TENS supply allowance (HCPCS code A4595) includes electrodes (any type), conductive paste or gel (if needed, depending on the type of electrode), tape or other adhesive (if needed, depending on the type of electrode), adhesive remover, skin preparation materials, batteries (9 volt or AA, single use or rechargeable), and a battery charger (if rechargeable batteries are used).
- Replacement of lead wires more often than every 12 months is rarely medically necessary.

For ongoing supplies and rental DME items, in addition to information described above that justifies the initial provision of the item(s) and/or supplies, there must be information in the member's medical record to support that the item continues to be used by the member and remains medically necessary.
CPT Codes/ HCPCS Codes/ICD-10 Codes
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Transcutaneous Electrical Nerve Stimulators (TENS):</strong></td>
</tr>
<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
<tr>
<td>97014</td>
<td>Application of a modality to 1 or more areas; electrical stimulation (unattended)</td>
</tr>
<tr>
<td>97032</td>
<td>Application of a modality to one or more areas; electrical stimulation, (manual), each 15 minutes</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>A4556</td>
<td>Electrodes (e.g., apnea monitor), per pair</td>
</tr>
<tr>
<td>A4557</td>
<td>Lead wires (e.g., apnea monitor), per pair</td>
</tr>
<tr>
<td>A4558</td>
<td>Conductive gel or paste, for use with electrical device (e.g., TENS, NMES), per oz.</td>
</tr>
<tr>
<td>A4595</td>
<td>Electrical stimulator supplies, 2 lead, per month, (e.g. TENS, NMES)</td>
</tr>
<tr>
<td>E0720</td>
<td>Transcutaneous electrical nerve stimulation (TENS) device, 2 lead, localized stimulation [not covered for Sensus]</td>
</tr>
<tr>
<td>E0730</td>
<td>Transcutaneous electrical nerve stimulation (TENS) device, 4 or more leads, for multiple nerve stimulation [not covered for Sensus]</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>G89.18</td>
<td>Other acute postprocedural pain [not covered for post-total knee arthroplasty pain]</td>
</tr>
<tr>
<td>G89.21 - G89.29</td>
<td>Chronic pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G89.4</td>
<td>Chronic pain syndrome</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
</tr>
<tr>
<td>E08.40 - E08.42</td>
<td>Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified, mononeuropathy, and polyneuropathy [not covered for SENSUS]</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>E09.40 - E09.42</td>
<td>Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy unspecified, mononeuropathy, and polyneuropathy [not covered for SENSUS]</td>
</tr>
<tr>
<td>E10.40 - E10.42</td>
<td>Type 1 diabetes mellitus with diabetic neuropathy, unspecified, mononeuropathy, and polyneuropathy [not covered for SENSUS]</td>
</tr>
<tr>
<td>E11.40 - E11.42</td>
<td>Type 2 diabetes mellitus with diabetic neuropathy, unspecified, mononeuropathy, and polyneuropathy [not covered for SENSUS]</td>
</tr>
<tr>
<td>E13.40 - E13.42</td>
<td>Other specified diabetes mellitus with diabetic neuropathy, unspecified, mononeuropathy, and polyneuropathy [not covered for SENSUS]</td>
</tr>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraine</td>
</tr>
<tr>
<td>G44.001 - G44.89</td>
<td>Other headache syndromes</td>
</tr>
<tr>
<td>G62.0</td>
<td>Drug-induced polyneuropathy [chemotherapy-induced peripheral neuropathy]</td>
</tr>
<tr>
<td>G54.6</td>
<td>Phantom limb syndrome with pain</td>
</tr>
<tr>
<td>G56.00 - G56.03</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>G89.11</td>
<td>Acute pain due to trauma [hip fractures]</td>
</tr>
<tr>
<td>I73.9</td>
<td>Peripheral vascular disease, unspecified</td>
</tr>
<tr>
<td>M22.2X1 - M22.2X9</td>
<td>Patellofemoral disorders</td>
</tr>
<tr>
<td>M22.40 - M22.42</td>
<td>Chondromalacia patellae</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>M26.602 -</td>
<td>Temporomandibular joint disorders</td>
</tr>
<tr>
<td>M26.609</td>
<td></td>
</tr>
<tr>
<td>M54.40 -</td>
<td>Lumbago</td>
</tr>
<tr>
<td>M54.5</td>
<td></td>
</tr>
<tr>
<td>M75.00 -</td>
<td>Adhesive capsulitis of shoulder</td>
</tr>
<tr>
<td>M75.02</td>
<td></td>
</tr>
<tr>
<td>M75.30 -</td>
<td>Calcific tendinitis of shoulder</td>
</tr>
<tr>
<td>M75.32</td>
<td></td>
</tr>
<tr>
<td>M75.40 -</td>
<td>Impingement syndrome of shoulder</td>
</tr>
<tr>
<td>M75.42</td>
<td></td>
</tr>
<tr>
<td>M75.50 -</td>
<td>Bursitis of shoulder [rotator cuff tendinitis]</td>
</tr>
<tr>
<td>M75.52</td>
<td></td>
</tr>
<tr>
<td>M79.7</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>N94.0 -</td>
<td>Pain and other conditions associated with female genital organs and menstrual cycle</td>
</tr>
<tr>
<td>N94.9</td>
<td></td>
</tr>
<tr>
<td>R10.0 -</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>R10.13</td>
<td></td>
</tr>
<tr>
<td>R10.30 -</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>R10.33</td>
<td></td>
</tr>
<tr>
<td>R51</td>
<td>Headache</td>
</tr>
<tr>
<td>T20.00xA –</td>
<td>Burns and corrosions</td>
</tr>
<tr>
<td>T32.99</td>
<td></td>
</tr>
<tr>
<td>T87.9</td>
<td>Unspecified complications of amputation stump [stump pain]</td>
</tr>
</tbody>
</table>

**Form-fitting Conductive Garment:**

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0731</td>
<td>Form-fitting conductive garment for delivery of TENS or NMES (with conductive fibers separated from the patient's skin by layers of fabric)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M62.50 -</td>
<td>Muscular wasting and atrophy, not elsewhere classified</td>
</tr>
<tr>
<td>M62.59</td>
<td></td>
</tr>
<tr>
<td>M62.84</td>
<td>Sarcopenia</td>
</tr>
</tbody>
</table>

**Interferential Stimulation:**

No specific codes

HCPCS codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S8130</td>
<td>Interferential current stimulator, 2 channel</td>
</tr>
<tr>
<td>S8131</td>
<td>Interferential current stimulator, 4 channel</td>
</tr>
</tbody>
</table>

**Percutaneous Electrical Nerve Stimulation (PENS):**

CPT codes covered if selection criteria are met:

**Percutaneous Electrical Nerve Stimulation (PENS) - no specific code:**

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76942</td>
<td>Ultrasonic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device), imaging supervision and interpretation</td>
</tr>
<tr>
<td>76998</td>
<td>Ultrasonic guidance, intraoperative</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S8930</td>
<td>Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G56.00</td>
<td>Mononeuropathies of upper and lower limbs</td>
</tr>
<tr>
<td>G56.9</td>
<td>Mononeuropathies of upper and lower limbs</td>
</tr>
<tr>
<td>M51.04</td>
<td>Thoracic, thoracolumbar and lumbosacral intervertebral disc disorders with myelopathy</td>
</tr>
<tr>
<td>M51.06</td>
<td>Thoracic, thoracolumbar and lumbosacral intervertebral disc disorders with myelopathy</td>
</tr>
<tr>
<td>M51.24</td>
<td>Other thoracic, thoracolumbar and lumbosacral intervertebral disc displacement and degeneration</td>
</tr>
<tr>
<td>M51.37</td>
<td>Other thoracic, thoracolumbar and lumbosacral intervertebral disc displacement and degeneration</td>
</tr>
<tr>
<td>M54.10</td>
<td>Radiculopathy</td>
</tr>
<tr>
<td>M54.18</td>
<td>Radiculopathy</td>
</tr>
<tr>
<td>M54.30</td>
<td>Sciatica</td>
</tr>
<tr>
<td>M54.32</td>
<td>Sciatica</td>
</tr>
<tr>
<td>M54.40</td>
<td>Lumbago with sciatica</td>
</tr>
<tr>
<td>M54.42</td>
<td>Lumbago with sciatica</td>
</tr>
<tr>
<td>M54.5</td>
<td>Low back pain [lumbago]</td>
</tr>
<tr>
<td>M54.6</td>
<td>Pain in thoracic spine</td>
</tr>
<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified [neuropathic pain]</td>
</tr>
<tr>
<td>M96.1</td>
<td>Post laminectomy syndrome, lumbar region</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F11.13</td>
<td>Opioid abuse, dependence, unspecified use with withdrawal</td>
</tr>
<tr>
<td>F11.23</td>
<td>Opioid abuse, dependence, unspecified use with withdrawal</td>
</tr>
<tr>
<td>F11.93</td>
<td>Opioid abuse, dependence, unspecified use with withdrawal</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>G89.18</td>
<td>Other acute postprocedural pain</td>
</tr>
<tr>
<td>M47.11</td>
<td>Cervical spondylosis [with or without myelopathy]</td>
</tr>
<tr>
<td>M47.13</td>
<td></td>
</tr>
<tr>
<td>M47.811</td>
<td></td>
</tr>
<tr>
<td>M47.813</td>
<td></td>
</tr>
<tr>
<td>M48.01</td>
<td>Spinal stenosis [cervical region]</td>
</tr>
<tr>
<td>M48.03</td>
<td></td>
</tr>
<tr>
<td>M50.00</td>
<td>Cervical disc disorder with myelopathy</td>
</tr>
<tr>
<td>M50.03</td>
<td></td>
</tr>
<tr>
<td>M50.20</td>
<td>Other cervical disc displacement</td>
</tr>
<tr>
<td>M50.23</td>
<td></td>
</tr>
<tr>
<td>M50.30</td>
<td>Other cervical disc degeneration</td>
</tr>
<tr>
<td>M50.33</td>
<td></td>
</tr>
<tr>
<td>M50.80</td>
<td>Other cervical disc disorders</td>
</tr>
<tr>
<td>M50.83</td>
<td></td>
</tr>
<tr>
<td>M50.90</td>
<td>Cervical disc disorder, unspecified</td>
</tr>
<tr>
<td>M50.93</td>
<td></td>
</tr>
<tr>
<td>M96.1</td>
<td>Post laminectomy syndrome, not elsewhere classified [cervical region]</td>
</tr>
</tbody>
</table>

**Scrambler Therapy/Calmare Therapy Device:**

CPT codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0278T</td>
<td>Transcutaneous electrical modulation pain reprocessing (e.g., scrambler therapy), each treatment session (includes placement of electrodes) [Calmare therapy device]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G62.0</td>
<td>Drug-induced polyneuropathy [chemotherapy-induced peripheral neuropathy]</td>
</tr>
<tr>
<td>G89.0</td>
<td>Central pain syndrome [Dejerine-Roussy syndrome]</td>
</tr>
<tr>
<td>G89.21</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>G89.29</td>
<td></td>
</tr>
<tr>
<td>G89.3</td>
<td>Neoplasm related pain (acute) (chronic)</td>
</tr>
<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified [neuropathic pain]</td>
</tr>
</tbody>
</table>

**Non-Invasive Interactive Neurostimulation:**
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>M17.0</td>
<td>Osteoarthritis of knee</td>
</tr>
<tr>
<td>M54.2</td>
<td>Cervicalgia</td>
</tr>
<tr>
<td>M84.471</td>
<td>Pathological fracture, left, right, or unspecified ankle</td>
</tr>
<tr>
<td></td>
<td><strong>Peripheral Subcutaneous Field Stimulation:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>0282T</td>
<td>Percutaneous or open implantation of neurostimulator electrode array(s), subcutaneous (peripheral subcutaneous filed stimulation), including imaging guidance, when performed, cervical, thoracic or lumbar; for trial, including removal at the conclusion of trial period</td>
</tr>
<tr>
<td>0283T</td>
<td>permanent, with implantation of a pulse generator</td>
</tr>
<tr>
<td>0284T</td>
<td>Revision or removal of pulse generator or electrodes, including imaging guidance, when performed, including addition of new electrodes, when performed</td>
</tr>
<tr>
<td>0285T</td>
<td>Electronic analysis of implanted peripheral subcutaneous field stimulation pulse generator, with reprogramming when performed</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>I20.0</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>I20.1</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>R20.0</td>
<td>Disturbances of skin sensation</td>
</tr>
<tr>
<td></td>
<td><strong>Peripherally Implanted Nerve Stimulators:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>64555</td>
<td>Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)</td>
</tr>
<tr>
<td>64568</td>
<td>Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator</td>
</tr>
<tr>
<td>64575</td>
<td>peripheral nerve (excludes sacral nerve)</td>
</tr>
<tr>
<td>64585</td>
<td>Revision or removal of peripheral neurostimulator electrodes</td>
</tr>
<tr>
<td>64590</td>
<td>Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>64595</td>
<td>Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

- 95860 - 95872 Electromyography
- 95937 Neuromuscular junction testing (repetitive stimulation, paired stimuli), each nerve, any 1 method

HCPCS codes covered if selection criteria are met:

- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
- L8686 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
- L8695 External recharging system for battery (external) for use with implantable neurostimulator, replacement only

ICD-10 codes covered if selection criteria are met:

- G56.00 - G59 Mononeuropathies
- G90.50 - G90.59 Complex regional pain syndrome I (CRPS I)
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S14.101S - S14.159S</td>
<td>Spinal cord injury, injury to nerve root(s), spinal plexus(s), and other nerves of trunk, injury to peripheral nerve of shoulder and girdle and upper limb, or injury to peripheral nerve of pelvic girdle and lower limb, sequela</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>S14.2xx+</td>
<td>Injury to nerve roots and spinal plexus, injury to other nerve(s) of trunk, excluding shoulder and pelvic girdles, injury to peripheral nerve(s) of shoulder girdle and upper limb, or injury to peripheral nerve(s) of pelvic girdle and lower limb</td>
</tr>
<tr>
<td>S14.9xx+</td>
<td></td>
</tr>
<tr>
<td>S24.101+</td>
<td></td>
</tr>
<tr>
<td>S24.159+</td>
<td></td>
</tr>
<tr>
<td>S24.2xx+</td>
<td></td>
</tr>
<tr>
<td>S24.9xx+</td>
<td></td>
</tr>
<tr>
<td>S34.101+</td>
<td></td>
</tr>
<tr>
<td>S34.139+</td>
<td></td>
</tr>
<tr>
<td>S34.21x+</td>
<td></td>
</tr>
<tr>
<td>S34.9xx+</td>
<td></td>
</tr>
<tr>
<td>S44.8x1+</td>
<td></td>
</tr>
<tr>
<td>S44.92x+</td>
<td></td>
</tr>
<tr>
<td>S54.8x1+</td>
<td></td>
</tr>
<tr>
<td>S54.92x+</td>
<td></td>
</tr>
<tr>
<td>S64.8x1+</td>
<td></td>
</tr>
<tr>
<td>S64.92x+</td>
<td></td>
</tr>
<tr>
<td>S74.8x1+</td>
<td></td>
</tr>
<tr>
<td>S74.92x+</td>
<td></td>
</tr>
<tr>
<td>S84.801+</td>
<td></td>
</tr>
<tr>
<td>S84.92x+</td>
<td></td>
</tr>
<tr>
<td>S94.8x1+</td>
<td></td>
</tr>
<tr>
<td>S94.92x+</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

- **B02.23** Postherpetic polyneuropathy
- **F11.90** - **F19.99** Drug dependence disorders
- **G81.00** - **G81.94** Hemiplegia and hemiparesis [shoulder pain]
- **R10.2** Pelvic and perineal pain

**H-Wave Type Stimulators:**

HCPCS codes not covered for indications listed in the CPB:

- **E0745** Neuromuscular stimulator; electronic shock unit [ H-Wave stimulator]

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.49, E09.49, E10.49, E11.49, E13.49</td>
<td>Diabetes mellitus with other diabetic neurological complication</td>
</tr>
</tbody>
</table>

**Intramuscular stimulation:**

CPT codes not covered for indications listed in the CPB:

- **64565**
  - Percutaneous implantation of neurostimulator electrodes; neuromuscular

- **64580**
  - Incision for implantation of neurostimulator electrodes; neuromuscular

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **M25.50 - M25.579**
  - Pain in joint

- **M54.10**
  - Radiculopathy [radiculitis]

- **M60.80 - M60.9**
  - Other and unspecified myositis

- **M79.10 - M79.18**
  - Myalgia

- **M79.2**
  - Neuralgia and neuritis, unspecified

**Sympathetic Therapy:**

No specific codes

**Electroceutical Therapy:**

No specific codes

**Transcutaneous electrical joint stimulation devices (BioniCore):**

HCPCS codes not covered for indications listed in the CPB:

- **E0762**
  - Transcutaneous electrical joint stimulation device system, includes all accessories

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **S93.401+ - S93.499+**
  - Sprain of ankle

**Electro-Acuscope Myopulse Therapy:**

No specific codes

**Electrical stimulation of sacral roots or lumbosacral plexus:**

CPT codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64555</td>
<td>Percutaneous implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve)</td>
</tr>
<tr>
<td>64561</td>
<td>Sacral nerve (transforaminal placement) including image guidance, if performed</td>
</tr>
<tr>
<td>64575</td>
<td>Incision for implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve)</td>
</tr>
<tr>
<td>64581</td>
<td>Sacral nerve (transforaminal placement)</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>R10.0 - R10.13</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>R10.30 - R10.33</td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td>R19.8</td>
<td>Other specified symptoms and signs involving the digestive system and abdomen</td>
</tr>
</tbody>
</table>

**Microcurrent Therapy:**

No specific codes

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M54.5</td>
<td>Low back pain [lumbago]</td>
</tr>
<tr>
<td>M54.9</td>
<td>Dorsalgia, unspecified</td>
</tr>
</tbody>
</table>

**Pulse Stimulation [P-Stim]:**

HCPCS codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S8930</td>
<td>Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient [P-STIM device]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B02.21 - B02.29</td>
<td>Zoster with other nervous system involvement</td>
</tr>
<tr>
<td>M17.0 - M17.9</td>
<td>Osteoarthritis of knee</td>
</tr>
<tr>
<td>M51.14 - M54.17</td>
<td>Thoracic, thoracolumbar and lumbosacral intervertebral disc disorders with radiculopathy</td>
</tr>
<tr>
<td>M54.10 - M54.2</td>
<td>Radiculopathy</td>
</tr>
<tr>
<td>M54.5</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>M62.830</td>
<td>Muscle spasm of back [cervical, lumbar]</td>
</tr>
<tr>
<td>M96.1</td>
<td>Post laminectomy syndrome [failed back]</td>
</tr>
</tbody>
</table>

**Neurolumen device:**
No specific code

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.40,</td>
<td>Polyneuropathy in diabetes</td>
</tr>
<tr>
<td>E08.42,</td>
<td></td>
</tr>
<tr>
<td>E09.40,</td>
<td></td>
</tr>
<tr>
<td>E09.42,</td>
<td></td>
</tr>
<tr>
<td>E10.40,</td>
<td></td>
</tr>
<tr>
<td>E10.42,</td>
<td></td>
</tr>
<tr>
<td>E11.40,</td>
<td></td>
</tr>
<tr>
<td>E11.42,</td>
<td></td>
</tr>
<tr>
<td>E13.40,</td>
<td></td>
</tr>
<tr>
<td>E13.42</td>
<td></td>
</tr>
<tr>
<td>G57.60 -</td>
<td>Lesion of plantar nerve [Morton's neuroma]</td>
</tr>
<tr>
<td>G57.63</td>
<td></td>
</tr>
<tr>
<td>G60.0 - G60.9</td>
<td>Hereditary and idiopathic neuropathy</td>
</tr>
</tbody>
</table>

**Non-invasive/no-incision pain procedure (NIP) device:**
No specific code

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F32.9</td>
<td>Major depressive disorder, single episode, unspecified</td>
</tr>
<tr>
<td>F41.9</td>
<td>Anxiety disorder, unspecified</td>
</tr>
<tr>
<td>G43.001 -</td>
<td>Migraine</td>
</tr>
<tr>
<td>G43.919</td>
<td></td>
</tr>
<tr>
<td>G47.00 -</td>
<td>Insomnia</td>
</tr>
<tr>
<td>G47.09</td>
<td></td>
</tr>
<tr>
<td>G89.18</td>
<td>Other acute postprocedural pain</td>
</tr>
<tr>
<td>G89.3</td>
<td>Neoplasm related pain (acute) (chronic)</td>
</tr>
<tr>
<td>M12.00 -</td>
<td>Other and unspecified arthropathy</td>
</tr>
<tr>
<td>M12.9</td>
<td></td>
</tr>
<tr>
<td>M25.50 -</td>
<td>Pain in joint</td>
</tr>
<tr>
<td>M25.579</td>
<td></td>
</tr>
<tr>
<td>M54.2</td>
<td>Cervicalgia</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------</td>
<td>-----------------</td>
</tr>
<tr>
<td>M54.30 - M54.5</td>
<td>Sciatica and low back pain</td>
</tr>
<tr>
<td>M60.80 - M60.9</td>
<td>Myositis</td>
</tr>
<tr>
<td>M79.10 - M78.18</td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

Electro-Analgesia Treatment (EAT) using the Synaptic electrical stimulator:

No specific code

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64450</td>
<td>Injection, anesthetic agent, other peripheral nerve or branch</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G60.0</td>
<td>Hereditary motor and sensory neuropathy</td>
</tr>
<tr>
<td>G60.8</td>
<td>Other hereditary and idiopathic neuropathies</td>
</tr>
</tbody>
</table>

Cefaly transcutaneous electrical stimulator headband:

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraines</td>
</tr>
</tbody>
</table>

Percutaneous neuromodulation therapy:

No specific code

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G89.0 - G89.4</td>
<td>Pain, not elsewhere classified</td>
</tr>
</tbody>
</table>

Variable Neuromuscular Stimulation - see CPB 677:

The Quell device:

No specific code

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M54.2</td>
<td>Cervicalgia</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>Combination electrochemical therapy/treatment (CET):</strong></td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td><strong>Galvanic stimulation and other types of electrical stimulation:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>97014</td>
<td>Application of a modality to 1 or more areas; electrical stimulation (unattended)</td>
</tr>
<tr>
<td>97032</td>
<td>Application of a modality to one or more areas; electrical stimulation, (manual), each 15 minutes</td>
</tr>
<tr>
<td></td>
<td><strong>HCPCS codes not covered for indications listed in the CPB (not all-inclusive):</strong></td>
</tr>
<tr>
<td>E0745</td>
<td>Neuromuscular stimulator, electronic shock unit</td>
</tr>
<tr>
<td></td>
<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all inclusive):</strong></td>
</tr>
<tr>
<td>I73.9</td>
<td>Peripheral vascular disease, unspecified</td>
</tr>
<tr>
<td></td>
<td><strong>Combined transcranial direct current stimulation and breathing-controlled electrical stimulation:</strong></td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all inclusive):</strong></td>
</tr>
<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified</td>
</tr>
<tr>
<td></td>
<td><strong>Electrical stimulation of posterior tibial nerve:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>0587T</td>
<td>Percutaneous implantation or replacement of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve</td>
</tr>
<tr>
<td>0588T</td>
<td>Revision or removal of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>0589T</td>
<td>Electronic analysis with simple programming of implanted integrated neurostimulation system (e.g., electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, posterior tibial nerve, 1-3 parameters</td>
</tr>
<tr>
<td>0590T</td>
<td>Electronic analysis with complex programming of implanted integrated neurostimulation system (e.g., electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, posterior tibial nerve, 4 or more parameters</td>
</tr>
<tr>
<td>64566</td>
<td>Posterior tibial neurostimulation, percutaneous needle electrode, single treatment, includes programming</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

- **G61.0 - G63**: Inflammatory polyneuropathy
- **M79.2**: Neuralgia and neuritis, unspecified [neuropathic pain associated with polyneuropathy]
- **R10.2**: Pelvic and perineal pain

*Intravaginal electrical stimulation:*  
No specific code

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

- **R10.2**: Pelvic and perineal pain

*Reduced impedance non-invasive cortical electrostimulation (RINCE):*  
No specific code

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **G89.21** - **G89.29**: Chronic pain
- **G89.4**: Chronic pain syndrome

*Auricular electrical stimulation:*
Code | Code Description
--- | ---
| HCPCS codes not covered for indications listed in the CPB (not all-inclusive):
| S8930 | Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with patient
| ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
| M54.5 | Low back pain
| M79.2 | Neuralgia and neuritis, unspecified
| Neurogenx 4000PRO device:
| CPT codes not covered for indications listed in the CPB (not all-inclusive):
| Neurogenx 4000PRO device – No specific code
| ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
| M76.60 – M76.62 | Achilles tendonitis
| Sprint (peripheral subcutaneous field stimulation):
| CPT codes not covered for indications listed in the CPB (not all-inclusive):
| Sprint (peripheral subcutaneous field stimulation) – No specific code
| ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
| M54.5 | Low back pain
| Transcutaneous magnetic stimulation:
| CPT codes not covered for indications listed in the CPB (not all-inclusive):
| Transcutaneous magnetic stimulation – No specific code
| ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
| G89.21 – G89.29 | Chronic pain
| G89.4 | Chronic pain syndrome

The above policy is based on the following references:

TENS/PENS


26. Forster EL, Kramer JF, Lucy SD, et al. Effect of TENS on pain, medications, and pulmonary function following coronary artery
Electrical Stimulation for Pain


38. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized


42. Kaye V, Brandstater ME. Transcutaneous electrical nerve stimulation. eMedicine J. 2002;3(1).


64. Proctor ML, Smith CA, Farquhar CM, Stones RW. Transcutaneous electrical nerve stimulation and acupuncture for primary
Electrical Stimulation for Pain - Medical Clinical Policy Bulletins | Aetna


65. Reeve J, Corabian P. Transcutaneous electrical nerve stimulation (TENS) and pain management. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); April 1995.


76. van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain: A systematic review of randomized controlled trials of the most common interventions.


Percutaneous Neuromodulation


Interferential Current Therapy


4. Fuentes JP, Armijo Olivo S, Magee DJ, Gross DP. Effectiveness of interferential current therapy in the management of


H-W AVE Type Stimulators


Peripheral Nerve Stimulation


treatment of patients with chronic pain of peripheral nerve origin.


Intramuscular Stimulation


Sympathetic Therapy (Dynatron)


Electroceutical Therapy

1. Benchmark Integrative Medicine, LLC. Clinical electroceutical medicine [website]. Fayetteville, GA: Benchmark; 2002. Available at:
Transcutaneous Electrical Joint Stimulation and Pulsed Electrical Stimulation


3. Fary RE, Carroll GJ, Briffa TG, et al. The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of
Electrical Stimulation for Pain


Lumbosacral Plexus and Sacral Nerve Root Stimulation


Microcurrent Therapy


Scrambler Therapy/The Calmare Therapy Device


7. Pachman DR, Watson JC, Loprinzi CL. Therapeutic strategies for

Peripheral Subcutaneous Field Stimulation


Electro Therapeutic Point Stimulation


Pulsed Stimulation (e.g., P-Stim)


Neurolumen Device

1. Callahan LR. Overview of running injuries of the lower extremity. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2013.

2. Gilchrist JM, Donahue JE. Peripheral nerve tumors. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2013.

Synaptic Device


Electrotherapy for the Treatment of Adhesive Capsulitis (Frozen Shoulder)


Non-Invasive Interactive Neurostimulation (InterX 1000 Neurostimulator Device)


Cefaly


trigeminal neurostimulation in migraine patients. Front Neurol. 2017;8:282.


Galvanic Stimulation


Experimental and Investigational Indications


6. Ilfeld BM, Gabriel RA, Said ET, et al. Ultrasound-guided percutaneous peripheral nerve stimulation: Neuromodulation of


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0011 Electrical Stimulation for Pain

There are no amendments for Medicaid.

revised 10/28/2021