Electrical Stimulation for the Treatment of Pain and Muscle Rehabilitation (for Louisiana Only)

Policy Number: CS036LA.O~~N~~
Effective Date: ~~January 1, 2021~~**TBD**

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

Transcutaneous electrical nerve stimulator (TENS) is proven and medically necessary in certain circumstances; for medical necessity clinical coverage criteria, refer to InterQual® CP:Durable Medical Equipment Transcutaneous Electrical Nerve Stimulation (TENS).

Click here to view the InterQual® criteria.

Functional electrical stimulation (FES) is proven and medically necessary as a component of a comprehensive ambulation rehabilitation program in members with lower limb paralysis due to spinal cord injury (SCI) when all of the following criteria are met:

- Demonstration of intact lower motor units (L1 and below) (both muscle and peripheral nerves)
- Muscle and joint stability for weight bearing at upper and lower extremities that can demonstrate balance and control to maintain an upright support posture independently
- Demonstration of brisk muscle contraction
- Demonstration of sensory perception sufficient for muscle contraction
- Demonstration of a high level of motivation, commitment and cognitive ability for device use

- Ability to transfer independently
- Demonstration of independent standing tolerance for at least 3 minutes
- Demonstration of hand and finger function to manipulate controls
- Post-recovery from SCI and restorative surgery of at least 6 months
- Absence of hip and knee degenerative disease
- Absence of history of long bone fracture secondary to osteoporosis

Neuromuscular electrical stimulation (NMES) is proven and medically necessary for treating the following indications:

- Disuse muscle atrophy if:
  - The nerve supply to the muscle is intact; and
  - The disuse muscle atrophy is not of neurological origin but results from other conditions including but not limited to casting, splinting or contractures
- **When used as part of a comprehensive lower limb rehabilitation program following total knee arthroplasty; and**
- **To improve upper extremity function in persons with partial paralysis following stroke when used as part of a comprehensive rehabilitation program**
- ~~To improve wrist and finger function and prevent or correct shoulder subluxation in persons with partial paralysis following stroke~~

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- ~~Dorsal root ganglion (DRG) stimulation~~
- FES for treating **any** other indication not listed above
- Interferential therapy (IFT) for treating musculoskeletal disorders/injuries, or to facilitate healing of nonsurgical soft tissue injuries or bone fractures
- Microcurrent electrical nerve stimulation (MENS)
- NMES for treating **any** other indication not listed above
- Percutaneous electrical nerve stimulation (PENS), percutaneous electrical nerve field stimulation (PENFS) or percutaneous neuromodulation therapy (PNT)
- **Percutaneous peripheral nerve stimulation (PNS)***
- Peripheral subcutaneous field stimulation (PSFS) or peripheral nerve field stimulation (PNFS)
- Pulsed electrical stimulation (PES)
- Scrambler Therapy (ST)
- **Translingual Stimulation for gait rehabilitation (TS)**

***For information regarding percutaneous peripheral nerve stimulation for occipital neuralgia and headache, refer to the Medical Policy titled Occipital Neuralgia and Headache Treatment (for Louisiana Only)**

Note: For information regarding dorsal root ganglion (DRG) stimulation, refer to the Medical Policy titled Implanted Electrical Stimulator for Spinal Cord (for Louisiana Only)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
*0278T	Transcutaneous electrical modulation pain reprocessing (e.g., scrambler therapy), each treatment session (includes placement of electrodes)
*0720T	Percutaneous electrical nerve field stimulation, cranial nerves, without implantation
63650	Percutaneous implantation of neurostimulator electrode array, epidural
63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
*64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
64999	Unlisted procedure, nervous system

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Coding Clarification: Transcutaneous electrical joint stimulation devices (E0762) are noninvasive devices that deliver low-amplitude pulsed electrical stimulation.

*† **Note:** The following are the only FES devices verified by the Centers for Medicare & Medicaid Services (CMS) Pricing, Data Analysis, and Coding (PDAC) to be reported with HCPCS E0770:

- NESS L300 and H200 devices (Bioness)
- Odstock ODFS Pace FES System (Odstock Medical/Boston Brace)
- WalkAide (Innovative Neurotronics)
- Deluxe Digital Electronic Muscle Stimulator (Drive medical)

HCPCS Code	Description
A4556	Electrodes (e.g., apnea monitor), per pair
A4557	Lead wires (e.g., apnea monitor), per pair
*A4558	Conductive gel or paste, for use with electrical device (e.g., TENS, NMES), per oz
*A4595	Electrical stimulator supplies, 2 lead, per month, (e.g., TENS, NMES)

HCPCS Code	Description
*A4630	Replacement batteries, medically necessary, transcutaneous electrical stimulator, owned by patient
*E0720	Transcutaneous electrical nerve stimulation (TENS) device, two-lead, localized stimulation
*E0730	Transcutaneous electrical nerve stimulation (TENS) device, four or more leads, for multiple nerve stimulation
*E0731	Form-fitting conductive garment for delivery of TENS or NMES (with conductive fibers separated from the patient's skin by layers of fabric)
*E0744	Neuromuscular stimulator for scoliosis
*E0745	Neuromuscular stimulator, electronic shock unit
*E0762	Transcutaneous electrical joint stimulation device system, includes all accessories
*E0764	Functional neuromuscular stimulation, transcutaneous stimulation of sequential muscle groups of ambulation with computer control, used for walking by spinal cord injured, entire system, after completion of training program
†E0770 *	Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified
E1399	Durable medical equipment, miscellaneous
*K1023	Distal transcutaneous electrical nerve stimulator, stimulates peripheral nerves of the upper arm
*L8679	Implantable neurostimulator, pulse generator, any type
*L8680	Implantable neurostimulator electrode, each
*L8682	Implantable neurostimulator radiofrequency receiver
*L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
*L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
*L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
*L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
*S8130	Interferential current stimulator, 2 channel
*S8131	Interferential current stimulator, 4 channel

Codes labeled with an asterisk(*) are not on the state of Louisiana Fee Schedule and therefore not covered by the State of Louisiana Medicaid Program.

Description of Services

Electrical stimulators provide direct, alternating, pulsating and/or pulsed waveform forms of energy. The devices are used to exercise muscles, demonstrate a muscular response to stimulation of a nerve, relieve pain, relieve incontinence, and provide test measurements. Electrical stimulators may have controls for setting the pulse length, pulse repetition frequency, pulse amplitude, and triggering modes. Electrodes for such devices may be indwelling, implanted transcutaneously, or surface.

Functional Electrical Stimulation (FES)

FES is the direct application of electric current to intact nerve fibers in a coordinated fashion to cause involuntary but purposeful contraction. FES bypasses the central nervous system and targets motor neurons innervating either skeletal muscle or other organ systems. Electrodes may be on the surface of the skin or may be surgically implanted along with a stimulator. FES is categorized as therapeutic and functional. Therapeutic FES enables typically resistive exercise, with the goal of preventing muscular atrophy and promoting cardiovascular conditioning. Functional FES enables or enhances standing, ambulation, grasping, pinching, reaching, respiration, bowel or bladder voiding, or ejaculation. The two goals of FES are mutually supportive (Hayes, 2017).

Neuromuscular Electrical Stimulation (NMES)

NMES involves the use of transcutaneous application of electrical currents to cause muscle contractions. The goal of NMES is to promote reinnervation, to prevent or retard disuse atrophy, to relax muscle spasms, and to promote voluntary control of muscles in individuals who have lost muscle function due to surgery, neurological injury, or disabling condition.

Interferential Therapy (IFT)

IFT is a treatment modality that is proposed to relieve musculoskeletal pain and increase healing in soft tissue injuries and bone fractures. Two medium-frequency, pulsed currents are delivered via electrodes placed on the skin over the targeted area producing a low-frequency current. IFT delivers a crisscross current resulting in deeper muscle penetration. It is theorized that IFT prompts the body to secrete endorphins and other natural painkillers and stimulates parasympathetic nerve fibers to increase blood flow and reduce edema.

Pulsed Electrical Stimulation (PES)

PES is hypothesized to facilitate bone formation, cartilage repair, and alter inflammatory cell function. Some chondrocyte and osteoblast functions are mediated by electrical fields induced in the extracellular matrix by mechanical stresses. Electrostatic and electrodynamic fields may also alter cyclic adenosine monophosphate or DNA synthesis in cartilage and bone cells.

Percutaneous Peripheral Nerve Stimulation (PNS)

PNS is a type of neuromodulation therapy where an electrode(s) is implanted near a peripheral nerve (i.e., nerve located outside of the brain and spinal cord) that subserves the painful dermatome. The electrode(s) deliver electrical impulses to the affected nerve to disrupt the transmission of pain signals thereby reducing the level of pain (International Neuromodulation Society, 2019). Implanted peripheral nerve stimulators include systems such as the ReActiv8 Implantable Neurostimulation System, StimRouter Neuromodulation System, SPRINT PNS System, and StimQ Peripheral Nerve Stimulator System.

Peripheral Subcutaneous Field Stimulation (PSFS)

PSFS, also known as peripheral nerve field stimulation (PNFS), is a technique used when the field to be stimulated is not well defined or does not fit exactly within the area served by any one or two peripheral nerves. Different from spinal cord stimulation (SCS)

or peripheral nerve stimulation (PNS), the electrode arrays are implanted within the subcutaneous tissue of the painful area, not on or around identified neural structures, but most probably in or around cutaneous nerve endings of the intended nerve to stimulate (Abejon and Krames, 2009).

Microcurrent Electrical Nerve Stimulation Therapy (MENS)

MENS is intended for pain relief and to facilitate wound healing, delivering current in the microampere range. One micro amp (µA) equals 1/1000th of a milliamp (mA). By comparison, TENS therapy delivers currents in the milliamp range causing muscle contraction, pulsing and tingling sensations. The microcurrent stimulus is subsensorial, so users cannot not detect it. Although microcurrent devices are approved in the category of TENS for regulatory convenience, in practical use they are in no way similar and cannot be compared to TENS in their effect (Curtis, et al. 2010; Zuim, et al. 2006). MENS is also referred to as microelectrical therapy (MET) or microelectrical neuro-stimulation. **Examples of MENS devices currently in use include, but are not limited to, Algonix®, Alpha-Stim®100, Electro-Myopulse 75L, electro-Lyoscope 85P, KFH Energy, MENS 2000-D, MICROCURRENT, Myopulse 75C, and Micro Plus™.**
~~Examples of MENS devices currently in use include, but are not limited to, Algonix®, Alpha-Stim®100, Microcurrent, and Micro Plus™.~~

Percutaneous Electrical Nerve Stimulation (PENS)

PENS, also known as percutaneous electrical nerve field stimulation (PENFS), is a conservative, minimally invasive treatment for pain in which acupuncture-like needles connected through a cable to an external power source are inserted into the skin. Needle placement is near the area of pain and is percutaneous instead of cutaneous (e.g., TENS). PENS electrodes are not permanently implanted as in SCS. The mechanism of action of PENS is theorized to modulate the hypersensitivity of nerves from which the persistent pain arises, potentially involving endogenous opioid-like substances. Examples of PENS/PENFS devices include, but are not limited to, IB-Stim and Neuro-Stim. The term percutaneous neuromodulation therapy (PNT) is sometimes used interchangeably with PENS. However, reports indicate PNT is a variant of PENS in which electrodes are placed in patterns that are uniquely different than placement in PENS (Hayes, 2019).

~~Dorsal Root Ganglion Stimulation~~

~~DRG stimulation therapy may be prescribed for pain that is limited to a specific area of the body that starts in a lower part of the body (e.g., foot, knee, hip and groin) following an injury or surgical procedure and grows worse over time. DRGs are spinal structures densely populated with sensory nerves that transmit information to the brain via the spinal column. Through the use of a neurostimulator system, (for example, Axium™ or the next-generation implantable pulse generator Proclaim™), physicians are able to directly treat targeted areas of the body where pain occurs (St. Jude Medical, 2018).~~

Scrambler Therapy

Scrambler Therapy (ST) (also referred to as Calmare Pain Therapy [Calmare Therapeutics Inc.] or transcutaneous electronic modulation pain reprocessing), is a noninvasive, transdermal treatment designed for the symptomatic relief of chronic pain. Treatment is performed by applying electrodes corresponding to the dermatome on the skin just above and below the area of pain. The device provides electrical signals via the electrodes presenting nonpain information to the painful area using continuously changing, variable, nonlinear waveforms (Hayes, 2021~~18~~).

Translingual Stimulation

Translingual Stimulation (TLS) is a noninvasive method used to elicit neural changes by stimulating the trigeminal and facial cranial nerves. Input from neurostimulation and physical therapy are thought to enhance neuroplasticity and enable the brain to restructure and relearn motor skills (ECRI, 2021).

Clinical Evidence

Functional Electrical Stimulation (FES)

FES has been proposed for improving ambulation in individuals with gait disorders such as drop foot, hemiplegia due to stroke, cerebral injury, or incomplete SCI. Randomized controlled trials (RCTs) and case series **for the use of FES in these other indications** have primarily included small patient populations with short-term follow-ups.

Nervous System Conditions

Spinal Cord Injury

Hayes published a Health Technology Assessment on FES for rehabilitation following spinal cord injury. Their review of the literature found 15 prospective studies consisting of 9 RCTs and 6 pretest/posttest studies, that included 9 to 70 participants. Hayes noted that there was substantial variability across the included studies in treatment parameters such as the FES device used, the use of orthoses, the area of body targeted by FES, and the goal of FES. The studies included adult and pediatric populations with complete and incomplete motor spinal cord injuries (SCI). The report found that there is a large body of low-quality evidence indicating FES may lead to improved health outcomes in adult patients with complete SCI, but the data are mixed in incomplete SCI and in pediatric populations. The report concluded that well-designed studies reporting the effectiveness and safety of long-term use of FES are still needed (2021).

Sadowsky et al. (2013) conducted a single-center cohort study to examine the effect of long-term lower extremity FES cycling on the physical integrity and functional recovery in people with chronic SCI. Twenty-five individuals with chronic SCI (at least 16 months following injury) who received FES during cycling were matched by age, gender, injury level, severity, and duration of injury to 20 people with SCI who received range of motion and stretching. The main outcome measure was change in neurological function, which comprised motor, sensory, and combined motor-sensory scores (CMSS) assessed by the American Spinal Injury Association Impairment scale. Response was defined as ≥1 point improvement. FES was associated with an 80% CMSS responder rate compared to 40% in controls. An average 9.6 CMSS point loss among controls was offset by an average 20-point gain among FES subjects. Quadriceps muscle mass was on average 36% higher and intra/inter-muscular fat 44% lower, in the FES group. Hamstring and quadriceps muscle strength was 30 and 35% greater, respectively, in the FES group. Quality of life and daily function measures were significantly higher in FES group. The authors concluded that FES during cycling in chronic SCI may provide substantial physical integrity benefits, including enhanced neurological and functional performance, increased muscle size and force-generation potential, reduced spasticity, and improved quality of life.

Harvey et al. (2010) conducted an RCT to determine the effectiveness of electrical stimulation (ES)-evoked muscle contractions superimposed on progressive resistance training (PRT) for increasing voluntary strength in the quadriceps muscles of people with SCI. A total of 20 individuals with established SCI (more than 6 months post injury) and neurologically induced weakness of the quadriceps muscles participated in the trial.

Additional inclusion criteria were at least 90 degrees passive knee range of motion and moderate neurologically induced weakness in their quadriceps muscles of one leg responsive to ES. Patients with a recent history of trauma to the lower extremity, currently participating in a lower limb strength or ES training program or limited ability to comply were excluded. Participants were randomized to experimental or control groups. The experimental group received ES superimposed on PRT to the quadriceps muscles of one leg three times weekly for 8 weeks. The control group received no intervention. Assessments occurred at the beginning and at the end of the 8-week period. The four primary outcomes were voluntary strength (muscle torque in Newton meters [Nm]), endurance (fatigue ratio), and performance and satisfaction items of the Canadian Occupational Performance Measure (COPM; points). The between-group mean differences (95% confidence interval [CI]) for voluntary strength and endurance were 14 Nm (1 to 27; p=0.034) and 0.1 (-0.1 to 0.3; p=0.221), respectively. The between-group median differences (95% CI) for the performance and satisfaction items of the COPM were 1.7 points (-0.2 to 3.2; p=0.103) and 1.4 points (-0.1 to 4.6; p=0.058), respectively. The authors concluded the results provide initial support for the use of ES superimposed on PRT for increasing voluntary strength in the paretic quadriceps muscles of individuals with SCI however, there is uncertainty about whether the size of the treatment effect is clinically important. They also stated that it is not clear whether ES was the critical component of the training program or whether the same results could have been attained with PRT alone.

Griffin et al. (2009) conducted a single-center case series study to evaluate body composition as well as metabolic and neurological profiles before and after 10 weeks of FES cycling in individuals with paralysis from SCI. Eighteen individuals with SCI received FES cycling 2–3 times per week for 10 weeks. Body composition was analyzed by dual X-ray absorptiometry. The American Spinal Injury Association (ASIA) neurological classification of SCI test battery was used to assess motor and sensory function. An oral glucose tolerance (OGTT) and insulin-response test was performed to assess blood glucose control. Additional metabolic variables including plasma cholesterol (total-C, HDL-C, LDL-C), triglyceride, and inflammatory markers (IL-6, TNF-α, and CRP) were also measured. Total FES cycling power and work done increased with training. Lean muscle mass also increased however, bone and adipose mass did not change. The ASIA motor and sensory scores for the lower extremity significantly increased with training. Blood glucose and insulin levels were lower following the OGTT after 10 weeks of training. Triglyceride levels did not change following training. However, levels of IL-6, TNF-α, and CRP were all significantly reduced. The authors concluded that significant improvements in blood glucose control and inflammatory markers occurred in conjunction with an increase in lean muscle mass and motor and sensory ability following 10 weeks of FES cycling in persons with paralysis from SCI. They also stated that it is expected that continuous use would be required to maintain the observed health benefits across the life span.

Thrasher et al. (2006) conducted a single-center case series study to determine if direct muscle stimulation would have greater rehabilitative potential than the stimulation of reflexes. A convenience sample of five subjects with chronic, incomplete SCI trained for 12–18 weeks using a new multichannel neuroprosthesis for walking. The outcome measures, which were recorded throughout the training period, included walking speed, step frequency and average stride length based on a 2-min walk test. Also identified were which walking aids and orthoses subjects preferred to use, and whether they employed a step-to or step-through gait strategy. Follow-up measurements of three subjects were made up to 10 weeks after treatment. All subjects demonstrated significant improvements in walking function over the training period. Four of the subjects achieved significantly increased walking speeds, which were due to increases in both stride length and step frequency. The fifth subject experienced a significant reduction in preferred assistive

devices. Follow-up measurements revealed that two subjects walked slightly slower several weeks after treatment, but they still walked significantly faster than at the start of treatment. The authors concluded that the gait training regimen was effective for improving voluntary walking function in a population for whom significant functional changes are not expected and therefore, this application of functional electrical therapy is viable for rehabilitation of gait in incomplete SCI. Limitations of this study include its design and small sample size and therefore, further study is still needed to compare the effects of FES to conventional physiotherapy.

Additional evidence indicates that paraplegics can benefit from FES that exercises muscles without providing locomotion. In one study, electrically stimulated use of an exercise cycle by paraplegics restored muscle mass (Baldi, 1998). In another study, bone mineral density improved in some bones of patients with SCI after use of the FES bicycle (Chen, 2005). While most studies involved patients with many years of muscular atrophy, Baldi et al. utilized patients with less than 4 months of atrophy. Moreover, electrically stimulated isometric exercise stimulated bone remineralization that was not observed with electrically stimulated walking (Needham-Shropshire, 1997). Even if the ambulation provided by devices such as the Parastep significantly improves, it will still only be usable by a subset of paraplegic patients such as those with T4-T11 SCIs (Klose, 1997). Stationary electrically stimulated exercise can be performed by a much larger group of patients including quadriplegics. To summarize, electrically stimulated ambulation cannot be considered safer or more beneficial than electrically stimulated stationary exercise unless the benefits of ambulation are shown to be superior in large-scale trials in which paraplegic patients are randomized to these 2 therapies. Further studies also need to be performed to confirm the benefits of electrically stimulated stationary exercise since the controlled trials conducted to date have used very small study populations and have assessed a limited set of outcome measures.

Cerebral Palsy

Moll et al. (2017~~8~~) conducted a systematic review to assess the effect of functional electrical stimulation (FES) of ankle dorsiflexors in children and adolescents with spastic cerebral palsy (CP) during walking. A search, using predetermined terms, was conducted using PubMed/MEDLINE, Embase, the Physiotherapy Evidence Database (PEDro), Web of Science, CINAHL, and the Cochrane Library. Outcomes were reported according to the International Classification of Functioning, Disability and Health (ICF). The ICF domains are classified by body, individual and societal perspectives by means of two lists: a list of structure and function and a list of domains of participation and activity. A total of 780 articles were identified and after review, 14 articles were included, including two small randomized controlled trials. In total, 127 patients received FES of the ankle dorsiflexors (14 bilaterally affected and 113 unilaterally affected). The participants' ages ranged from 5 to 19 years and the Gross Motor Function Classification System (GMFCS) level ranged from I to III. The authors concluded that: At the ICF participation and activity level, there is limited evidence for a decrease in self-reported frequency of toe-drag and falls; At the ICF body structure and function level, there is clear evidence (level I to III studies) that FES increased (active) ankle dorsiflexion angle, strength, and improved selective motor control, balance, and gait kinematics, but decreased walking speed. Adverse events included skin irritation and acceptance issues. The authors further stated that it cannot be concluded that FES (of the ankle dorsiflexors) improves functioning at the activity and participation level however, current evidence supports the potential role of FES as an alternative to classic orthotic treatment. The authors recommend that future studies should focus on the domain

of activity and participation. The findings are limited by the study design of most of the included studies.

A~~n~~ 2016 RCT by El-Shamy and Abdelaal conducted an RCT to investigate the effects of the WalkAide FES on gait pattern and energy expenditure in children with hemiplegic CP. Seventeen children were assigned to the study group, whose members received FES (pulse width, 300 µs; frequency, 33 Hz, 2 hours/d, 3 days/week for 3 consecutive months). Seventeen other children were assigned to the control group, whose members participated in a conventional physical therapy exercise program for 3 successive months. Baseline and post-treatment assessments were performed using the GAITRite system to evaluate gait parameters and using an open-circuit indirect calorimeter to evaluate energy expenditure. Children in the study group showed a significant improvement when compared with those in the control group ($p < 0.005$). The gait parameters (stride length, cadence, speed, cycle time, and stance phase percentage) after treatment were (0.74 m,119 steps/min, 0.75 m/s, 0.65 s, 55.9%) and (0.5 m,125 steps/min, 0.6 m/s, 0.49 s, 50.4%) for the study group and control group, respectively. The mean energy expenditures after treatment were 8.18 ± 0.88 and 9.16 ± 0.65 mL/kg per minute for the study and control groups, respectively. The authors concluded that WalkAide FES may be a useful tool for improving gait pattern and energy expenditure in children with hemiplegic CP. The study was limited to a small sample size.

Chiu and Ada (2014) conducted a systematic review to determine the effectiveness of FES versus activity training alone in children with cerebral palsy (CP). Five RCTs met inclusion criteria. The experimental group had to receive FES while performing an activity such as walking. The studies used outcome measures of activity that best reflected the activity used in the study. When continuous data (e.g., walking speed) were not available, ordinal data (e.g., Gross Motor Function Measurement) were used. A statistically significant between-group difference in activity in the FES groups was reported for the 3 studies that compared FES with no FES. Improvements were seen immediately after the intervention period, but long-term follow-up was not reported. The 2 studies investigating the effects of FES vs. activity training reported no significant differences between the groups. The results reported that FES is better than no FES, but that FES is not more effective than activity training. The authors stated that they may be fairly confident that FES is effective given that all 3 trials reported between-group differences in favor of FES, but with no meta-analysis providing an effect size it is not possible to judge the clinical significance of the benefit. Limitations of the studies included the heterogeneous patient populations and the variations in the frequency, intensity and duration of the interventions.

Cerebrovascular Accident

Hayes published a Comparative Effectiveness Review that focused on the use of FES in addition to conventional occupational and physical therapy (COPT) compared with COPT alone for upper extremity (UE) rehabilitation post stroke. The review found that the addition of FES to COPT is at least as effective as COPT alone for improving some outcomes in post-stroke patients undergoing UE rehabilitation with some studies showing improvement in activities of daily living, motor function and shoulder subluxation. The results were mixed, and the overall body of evidence was of low-quality and there was a lack of clarity regarding clinically meaningful changes. The report also noted that the efficacy of FES with COPT is similar to COPT alone regarding spasticity outcomes. The report concluded that additional information is needed to determine whether FES effectiveness varies by the type, location or chronicity of the stroke, that long-term

(>18 months) efficacy is needed, and that optimal parameters for FES treatment have yet to be established (2021).

A systematic review and meta-analysis by Jaqueline da Cunha et al. (2021) evaluated the effectiveness of FES applied to the paretic peroneal nerve and its influence on gait speed, active ankle dorsiflexion mobility, balance, and functional mobility. Electronic databases were searched for RCTs or crossover trials that focused on the effectiveness of FES with or without other therapies on individuals with foot drop after stroke. The review included 14 studies that provided data for 1115 participants who had sustained a stroke between <1 month and 108 months prior to their study participation. The study demonstrated that FES alone did not enhance gait speed when compared to conventional treatments although when FES was combined with supervised exercises, gait speed was better than supervised exercises alone. It also showed that FES had no effect when combined with unsupervised exercises on gait speed and that the data was inconclusive when FES was combined with regular activities at home. When FES was compared with conventional treatments, the analysis determined that it improved ankle dorsiflexion, balance and functional mobility. The authors concluded that the meta-analysis showed the quality of evidence was low for positive effects of FES on gait speed when combined with physical therapy and that FES can improve ankle dorsiflexion, balance and functional mobility. They stated that the results of the systematic review and meta-analysis should be interpreted carefully considering the low quality of evidence and high heterogeneity of the data.

~~A systematic and meta-analysis by Eraifej et al. aimed to evaluate the effectiveness of post-stroke upper limb FES on ADL and motor outcomes. Systematic review of randomized controlled trials from MEDLINE, PsychINFO, EMBASE, CENTRAL, ISRCTN, ICTRP and ClinicalTrials.gov. Twenty studies met inclusion criteria. Outcomes were ADL (primary), functional motor ability (secondary) and other motor outcomes (tertiary). Quality assessment was determined using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. In 6 studies, no significant benefit of FES was found for objective ADL measures (FES group participants = 67). A significant benefit on ADLs was demonstrated in an analysis of three studies where FES was initiated on average within 2 months post-stroke (n=32). No significant ADL improvements were seen in 3 studies where FES was initiated more than 1 year after stroke (n=35). Quality assessment using GRADE found very low quality evidence in all analyses due to heterogeneity, low participant numbers and lack of blinding. Meta-analyses gave rise to certain limitations. including but not limited to the utilization of many different measurement instruments and only a minority were employed by more than a few studies, as well as inadequate participant blinding in most studies. The authors concluded that FES is a promising therapy which could play a part in future stroke rehabilitation. There is a need for high quality large-scale randomized controlled trials of upper limb FES after stroke in order to draw firm conclusions regarding its efficacy or its optimum therapeutic window (2017).~~

ECRI published a Clinical Evidence Assessment on the MyndMove FES device that has been developed to voluntary hand and arm movement in patients with paralysis after a stroke or spinal cord injury. The focus of the ECRI report, however, was on the device's safety and efficacy in adults post-stroke. The report determined that the evidence is inconclusive due to limited available published evidence that included two very small single center, unblinded RCTs and one pre-post study. ECRI concluded that the studies are too high risk of bias to be conclusive and that larger, multicenter RCTs are needed to demonstrate improvement in pain, spasticity, or quality of life and to demonstrate that the benefits of the device are sustainable after therapy completion (2020).

Nascimento et al. (2020) conducted a systematic review and meta-analysis to evaluate the efficacy of ankle-foot orthoses (AFOs) and FES to the pre-tibialis muscle applied throughout the day to reduce footdrop after stroke. The review included 11 parallel RCTs that assessed the use of AFOs and FES on walking speed and balance in ambulatory adults who were moderately disabled following their stroke. The RCTs included 1135 participants between 47 and 65 years of age who were in both acute and chronic phases of recovery. The authors reported that AFO with FES significantly increased walking speed, compared with no intervention/placebo; however, the results regarding the efficacy of AFO with FES on balance were inconclusive. The meta-analysis also found that AFOs alone were not superior to FES for improving walking speed or balance after stroke. The authors concluded that the systematic review provided moderate-quality evidence that both AFOs and FES improve walking speed after stroke, but the effects on balance remain unclear. The limitations of the review identified by the authors include lack of blinding of the therapists, patients, and assessors, lack of description of whether an intention-to-treat analysis was done, the small number of included studies and the number of participants per group varied across trials. There was also a lack of evaluation of the maintenance of effects beyond the intervention period. The authors recommend future RCTs investigate the effects on clinical outcomes related to social participation and adverse events in people with stroke.

A systematic and meta-analysis by Eraifej et al. aimed to evaluate the effectiveness of post-stroke upper limb FES on ADL and motor outcomes. Systematic review of randomized controlled trials from MEDLINE, PsychINFO, EMBASE, CENTRAL, ISRCTN, ICTRP and ClinicalTrials.gov. Twenty studies met inclusion criteria. Outcomes were ADL (primary), functional motor ability (secondary) and other motor outcomes (tertiary). Quality assessment was determined using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. In 6 studies, no significant benefit of FES was found for objective ADL measures (FES group participants = 67). A significant benefit on ADLs was demonstrated in an analysis of three studies where FES was initiated on average within 2 months post-stroke (n=32). No significant ADL improvements were seen in 3 studies where FES was initiated more than 1 year after stroke (n=35). Quality assessment using GRADE found very low-quality evidence in all analyses due to heterogeneity, low participant numbers and lack of blinding. Meta-analyses gave rise to certain limitations. including but not limited to the utilization of many different measurement instruments and only a minority were employed by more than a few studies, as well as inadequate participant blinding in most studies. The authors concluded that FES is a promising therapy which could play a part in future stroke rehabilitation. There is a need for high quality large-scale randomized controlled trials of upper limb FES after stroke to draw firm conclusions regarding its efficacy or its optimum therapeutic window (2017).

Jonsdottir et al. (2017) conducted a RCT assessing the efficacy of myoelectric continuous control FES (MeCFES) when used as a part of task-oriented therapy (TOT) in persons who are post-stroke. Eighty-two acute and chronic stroke victims were recruited and randomized to receive either the experimental (MeCFES assisted TOT (M-TOT) or conventional rehabilitation care including TOT (C-TOT). Both groups received 45 minutes of rehabilitation over 25 sessions. Outcomes were Action Research Arm Test (ARAT), Upper Extremity Fugl-Meyer Assessment (FMA-UE) scores and Disability of the Arm Shoulder and Hand questionnaire. Sixty-eight individuals completed the protocol, and 45 were seen at follow up 5 weeks later. There were significant improvements in both groups on ARAT (median improvement: MeCFES TOT group 3.0; C-TOT group 2.0) and FMA-UE (median improvement: M-TOT 4.5; C-TOT 3.5). Considering subacute subjects (time since stroke < 6 months), there was a trend for a larger proportion of improved patients in the M-TOT group following rehabilitation (57.9%) than in the C-TOT group (33.2%). This is the first

large multicenter RCT to compare MeCFES assisted TOT with conventional care TOT for the UE. No AEs or negative outcomes were encountered. The authors concluded that MeCFES can be a safe adjunct to rehabilitation and could promote recovery of upper limb function in persons after stroke, particularly when applied in the subacute phase. Several study limitations were identified for example, the predicted sample size needed to make a definitive conclusion as to the efficacy of the MeCFES was not reached, there may have been differences in use of the device between centers, and missing data where 14 of 82 enrolled patients failing to provide follow-up data and of those 9 had a baseline assessment. Additional studies are still needed to clarify the utility of meCFES for patients who experience a stroke.

de Sousa et al. (2016) conducted a blinded, multi-institutional, RCT to determine whether active FES cycling as a supplement to standard care would improve mobility and strength more than standard care alone in individuals with a sub-acute acquired brain injury caused by stroke or trauma. The control group (n=20) received standard care, which consisted of a minimum of one-on-one therapy with a physiotherapist at least 1 hour per day. In addition, participants could join group exercise classes or have another hour of one-on-one therapy, if available. The study group (n=20) received an incremental progressive, individualized FES cycling program 5 times a week for 4 weeks, along with standard therapy. The primary outcomes measured were mobility and strength of the knee extensors of the affected lower limb. The secondary outcomes were strength of key muscles of the affected lower limb, strength of the knee extensors of the unaffected lower limb, and spasticity of the affected plantar flexors. On admission to the study, most participants could not walk or required a high level of assistance to walk/transfer. Only 2 individuals could ambulate without assistance at the end of 4 weeks. The mean composite score for affected lower limb strength was 7 out of 20 points, reflecting severe weakness. The authors concluded that 4 weeks of FES cycling in addition to standard therapy does not improve mobility in people with a sub-acute acquired brain injury. Further studies could clarify the effects of FES cycling on strength, although the clinical significance may be limited without its accompanying impact on mobility.

Tan et al. (2016) performed an observational randomized study on 58 patients recovering from stroke to assess the effects of FES on walking function based on normal gait pattern. Participants were randomly divided into 3 groups: four-channel FES group (group A, n=29), single-channel FES group (group B, n=15) and placebo electrical group (group C, n=14) at the rate of 2:1:1. All received the standardized rehabilitation program. The four-channel and single-channel FES groups received treatment based on normal gait pattern. The placebo electrical group received the same ES as the four-channel FES group, but without current output when stimulating. After 3 weeks of treatment and statistically significant improvement in all 3 groups, the authors concluded FES based on normal gait pattern could improve walking function in individuals recovering from stroke.

~~The National Institute for Health and Clinical Excellence (NICE) published a guidance document for the use of FES for foot drop of central neurological origin. NICE concluded that the evidence on safety and efficacy appears adequate to support the use of FES for foot drop in terms of improving gait, but further publication on the efficacy of FES would be useful regarding patient-reported outcomes, such as QOL and ADL (2009, updated 2012).~~

In 2010, Weber et al. conducted a RCT to assess whether Onabotulinum toxin A injections and occupational therapy with or without FES improved upper limb motor function in 23 stroke patients with chronic spastic hemiparesis. The primary outcome was progression in

upper limb motor function as measured by improvement in the Motor Activity Log instrument after 12 weeks of therapy. Although improvements in motor activity were seen among all patients after 6 and 12 weeks, no additional benefit was observed among patients treated with functional FES versus the comparison group, potentially due to small sample size.

Alon et al. (2007) conducted a randomized pilot study to evaluate if FES can enhance the recovery of upper extremity function during early stroke rehabilitation. The study included 15 individuals who survived a stroke and had mild-moderate upper extremity paresis during inpatient rehabilitation, which was continued at home. Participants were assigned to either FES combined with task-specific upper extremity rehabilitation (n=7) or task-specific therapy alone (control group, n=8) over 12 weeks. Outcomes were assessed via video recording on both upper extremities at baseline, 4, 8, and 12 weeks. Results demonstrated the study group experienced better functional recovery than the control group. Limitations include small study size and no long-term outcomes data post-therapy.

An RCT was conducted by Ring and Rosenthal to assess the effects of daily neuroprosthetic (NESS Handmaster) FES in 22 patients with moderate to severe upper limb paresis persisting 3-6 months post-stroke. Patients were clinically stratified to 'no' and 'partial' active finger movement groups, then randomized to the standard rehabilitation protocol (control) or standard rehabilitation plus neuroprosthesis at home (study) groups. Observer blinded evaluations occurred at baseline and at completion (6 weeks). The use of the Handmaster system plus daily therapy showed significantly improved outcomes versus the control group. Because this treatment is performed by the patient at home, it may well be continued as needed to maintain the benefits. The intensive daily use of this therapy at home in patients receiving sub-acute stroke rehabilitation has proved to be safe and resulted in significantly improved outcomes with no AEs. Limitations include small study size and no long-term outcomes data post-therapy (2005).

Multiple Sclerosis **(MS)**

Hayes (2021) published a Health Technology Assessment focusing on the use of FES for treatment of foot drop in patients with MS. In the 8 studies reviewed, the goals were to improve gait, walking speed, quality of life (QOL) and overall functional mobility. The studies consisted of three RCTs, two randomized crossover trials, two case-control studies and one pretest-posttest study. Six of the studies used the Odstock FES device and three studies used the WalkAide FES device. The assessment stated that FES poses little risk of serious adverse events because it is noninvasive and involves low levels of electrical stimulation. Minor complications included pain, muscle spasms, weakness and pain, temporary paresthesia, light-headedness, increased falls, skin irritation and knee hyperextension. The authors noted that the body of evidence for FES and its efficacy to treat foot drop in patients with MS was low in quality due to the individual study limitations, use of different FES devices and limited number of studies for comparisons. The studies individually were found to be of low quality due to small size, observational design, high dropout rates, incomplete statistical analysis, potential bias from previous experience with the therapy being evaluated and short follow-up times. The report concluded that a low-quality body of evidence shows FES improves walking speed and duration with reduced exertion at about the same benefit level as AFOs and that FES improves psychological outcomes and perceived but not actual exertion. The authors recommend additional RCTs of FES versus AFOs to validate the psychological and perceived exertion benefits and to determine the durability of benefits over time.

In a systematic review investigating the effect of FES used for foot drop on health-related quality of life (HRQOL) in adults with MS, Miller et al. (2019) evaluated the

results of eight studies that included one RCT, one randomized crossover trial, three experimental nonrandomized studies, and three observational studies. The total number of participants was 168 with 63% female and the sample sizes in the study groups varied from 2 to 64. Participants in these studies were older than 18 years, had a diagnosis of MS, presented with foot drop (unilateral or bilateral), and had used FES. Selected studies required at least one validated HRQOL outcome measure that assessed the effect of FES to be reported. The authors found that 7 of the studies demonstrated significant positive effects of FES on different aspects of HRQOL as measured by the 29-item Multiple Sclerosis Impact Scale, 36-item Short Form Health Status Survey, Canadian Occupational Performance Measure, and Psychosocial Impact of Assistive Devices Scale. The authors concluded that the review showed that FES had a positive effect on aspects of HRQOL in people with MS; however, the variety of HRQOL outcomes used made it difficult to determine definitive conclusions. Future larger-scale RCTs with long-term follow-up are recommended to better understand the effect of FES on HRQOL. Limitations that the authors noted include the small number of studies, small number of participants, lack of control comparators and the broad variety of HRQOL outcomes used in the studies made it difficult to determine definitive conclusions from this review. They recommend further qualitative studies to understand how FES affects HRQOL, before the most appropriate HRQOL measures can be identified to determine the effectiveness of FES on HRQOL in people with MS and that future high-quality research should aim to capture the effect of FES on clinically meaningful aspects of HRQOL in longer-term studies.

Broekmans et al. (2011) conducted an RCT involving 36 persons with MS to examine the effect(s) of unilateral long-term (20 weeks) standardized resistance training with and without simultaneous ES on leg muscle strength and overall functional mobility. The authors found that long-term light to moderately intense resistance training improves muscle strength in persons with MS, but simultaneous ES does not further improve training outcome.

A pilot study by Ratchford et al. (2010) evaluated the safety and preliminary efficacy of home FES cycling in 5 patients with chronic progressive MS (CPMS) to explore how it changes cerebrospinal fluid (CSF) cytokine levels. Outcomes were measured by: 2-Minute Walk Test, Timed 25-foot Walk, Timed Up and Go Test, leg strength, Expanded Disability Status Scale (EDSS) score, and MS Functional Composite (MSFC) score. QOL was measured using the Short-Form 36 (SF-36). Cytokines and growth factors were measured in the CSF before and after FES cycling. Improvements were seen in the 2-Minute Walk Test, Timed 25-foot Walk, and Timed Up and Go tests. Strength improved in muscles stimulated by the FES cycle, but not in other muscles. No change was seen in the EDSS score, but the MSFC score improved. The physical and mental health subscores and the total SF-36 score improved. The authors concluded that FES cycling was reasonably well tolerated by CPMS patients and encouraging improvements were seen in walking and QOL. The study is limited by small sample and lack of a comparison group. Larger studies are needed to evaluate the effects of FES for patients with MS.

Circulatory System Conditions

Kadoglou et al. (2017) performed a randomized, placebo-controlled study to investigate the effects of FES on the lower limbs as an alternative method of training in patients with chronic heart failure (HF). Participants deemed stable (n=120) (defined by New York Heart Association (NYHA) class II/III and mean left ventricular ejection fraction (LVEF) of 28 ± 5%), were randomly selected for either a 6-week FES training program or placebo. Patients were followed for up to 19 months for death and/or hospitalization due to HF decompensation. At baseline, there were no significant differences in demographic

parameters, HF severity, or medications between groups. During a median follow-up of 383 days, 14 patients died (11 cardiac, three non-cardiac deaths), while 40 patients were hospitalized for HF decompensation. Mortality did not differ between groups, although the HF-related hospitalization rate was significantly lower in the FES group. The latter difference remained significant after adjustment for prognostic factors: age, gender, baseline NYHA class and LVEF. Compared to placebo, FES training was associated with a lower occurrence of the composite endpoint (death or HF-related hospitalization) after adjustment for the above-mentioned prognostic factors. The authors concluded that 6 weeks of FES training in individuals with chronic HF reduced the risk of HF-related hospitalizations without affecting the mortality rate. The beneficial long-term effects of this alternative method of training require further investigation.

Miscellaneous Conditions

In a prospective, assessor-blinded RCT evaluating FES-assisted cycle therapy for mechanically ventilated adults in an intensive care unit (ICU), Waldauf et al (2021) randomized 150 patients to either receive functional electrical stimulation-assisted cycle ergometry (FESCE) or standard therapy. The first rehabilitation occurred 63 versus 68 hours after ICU admission in the intervention versus control groups, respectively. Follow-up through 6 months was completed for 42 (56%) of the patients in the intervention group and 46 (61%) of patients in the control group. The authors reported that FESCE did not improve physical disability 6 months after surviving critical illness for mechanically ventilated patients with anticipated long ICU stays. They noted that, at ICU discharge, there were no differences in the ICU length of stay or functional performance. The authors stated that limitations to their study included a higher-than-expected mortality (41% were not alive at 6 months), the single-center design and their standard protocol for intensive rehabilitation therapy in the control group. The authors recommended future trials emphasize progressive mobility elements in the interventional group, enroll more homogeneous patient populations and involve patients in multiple centers.

Fossat et al. (2018) investigated whether early in-bed leg cycling plus ES of the quadriceps muscles added to standardized early rehabilitation would result in greater muscle strength at discharge from the ICU in a single center blinded RCT enrolling 314 critically ill adult patients. Patients were randomized to early in-bed leg cycling plus ES of the quadriceps muscles added to standardized early rehabilitation (n=159) or standardized early rehabilitation alone (usual care, n=155). The primary outcome was muscle strength at discharge from the ICU assessed by physiotherapists blinded to treatment group using the Medical Research Council grading system (score range, 0-60 points; a higher score reflects better muscle strength). Functional autonomy and health-related QOL were assessed at 6 months. Of the 314 participants, 312 completed the study and were included in the analysis. The median global Medical Research Council score at ICU discharge was higher in the usual care group than in the intervention group, scoring 51 and 48, respectively. There were no significant differences between the groups at 6 months. The authors concluded that adding early in-bed leg cycling exercises and ES of the quadriceps muscles to a standardized early rehabilitation program did not improve global muscle strength at discharge from the ICU.

~~*Professional Societies*~~*Clinical Practice Guidelines*

American Occupational Therapy Association (AOTA)

The AOTA practice guidelines for adults with stroke state that for improved occupational performance of individuals with motor impairments, there is high certainty based on

evidence that the use of ES has a moderate net benefit. The guidelines also state that the evidence is weak regarding whether or not this therapy improves patient outcomes (Wolf and Nilsen, 2015).

National Institute for Health and Clinical Excellence (NICE)

NICE published a guidance document for the use of FES for foot drop of central neurological origin. NICE concluded that the evidence on safety and efficacy appears adequate to support the use of FES for foot drop in terms of improving gait, but further publication on the efficacy of FES would be useful regarding patient-reported outcomes, such as QOL and ADL (2009, updated 2012).

Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation

Although the evidence is limited, NMES for the treatment of disuse atrophy in individuals where the nerve supply to the muscle is intact is supported by evidence. There is some evidence that the use of NMES may be an effective rehabilitative regimen **for swallowing disorders or** to prevent muscle atrophy associated with **intensive care unit acquired weakness and** prolonged knee immobilization following ligament reconstruction surgery or injury; however, controlled clinical trials are necessary to determine if the addition of NMES to the **current standard** rehabilitation program**s** will improve health outcomes.

Musculoskeletal System Conditions

Talbot et al. (2017) conducted a pilot RCT (NCT00942890) to compare the effects of a home-based NMES rehabilitation program plus the traditional military amputee rehabilitation program (TMARP) vs. the effects of TMARP alone on quadriceps muscle strength, functional mobility, and pain in military service members after a combat-related lower extremity amputation. In total, 44 participants with a unilateral transtibial amputation were randomly assigned to the TMARP plus NMES (n=23) or to TMARP alone (n=21). Both groups received 12 weeks of the traditional amputee rehabilitation, including pre- and post-prosthetic training. Those in the NMES group also received 12 weeks of NMES. Participants were tested at 3-week intervals during the study for muscle strength and pain. For functional measures, they were tested after receiving their prosthesis and at study completion (weeks 6 and 12). In both groups, residual limb quadriceps muscle strength and pain severity improved from baseline to 12 weeks. The NMES plus TMARP group showed greater strength than the TMARP alone group at 3 weeks, before receiving the prosthesis. However, 6 weeks post-prosthesis, there was no group difference in the residual limb strength. Functional mobility improved in both groups between weeks 6 and 12 with no difference between the 2 treatment groups. The authors concluded that a home-based NMES intervention with TMARP worked at improving residual limb strength, pain, and mobility. While NMES seemed most effective in minimizing strength loss in the amputated leg pre-prosthesis, further research on amputation rehabilitation is warranted, as NMES may accelerate recovery.

De Oliveira Melo et al. (2013) conducted a systematic review to identify the evidence for NMES for strengthening quadriceps muscles in elderly patients with knee osteoarthritis (OA). Six RCTs met inclusion criteria. Four studies included ≤ 50 patients. Study designs and outcome measures were heterogeneous and comparators varied. NMES parameters were poorly reported. The trials scored extremely low on the allocation concealment and blinding items. In most of the trials, the randomization methods were not described. Due to the poor methodology of the studies and poor description of the strength measurement methods, no or insufficient evidence was found to support NMES alone or combined with

other modalities for the treatment of elderly patients with OA. Due to the study limitations, no meta-analysis was performed.

In a prospective, longitudinal RCT, 66 patients, aged 50 to 85 years and planning a primary unilateral total knee arthroplasty (TKA), were randomly assigned to receive either standard rehabilitation (control) or standard rehabilitation plus NMES applied to the quadriceps muscle (initiated 48 hours after surgery). The NMES was applied twice daily at the maximum tolerable intensity for 15 contractions. Data for muscle strength, functional performance, and self-report measures were obtained before surgery and 3.5, 6.5, 13, 26, and 52 weeks after TKA. At 3.5 weeks after TKA, significant improvements with NMES were found for quadriceps and hamstring muscle strength, functional performance, and knee extension AROM. At 52 weeks, the differences between groups were attenuated, but improvements with NMES were still significant for quadriceps and hamstring muscle strength, functional performance, and some self-report measures. The authors concluded that the early addition of NMES effectively attenuated loss of quadriceps muscle strength and improved functional performance following TKA. The effects were most pronounced and clinically meaningful within the first month after surgery but persisted through 1 year after surgery. Further research focused on early intervention after TKA is warranted to continue to optimize patient outcomes (Stevens-Lapsley et al., 2012).

There are also studies that NMES can be effective when used for quadriceps strength training following anterior cruciate ligament (ACL) reconstruction or prior to TKA. In a small RCT of NMES for quadriceps strength training following ACL reconstruction, the group that received NMES demonstrated moderately greater quadriceps strength at 12 weeks and moderately higher levels of knee function at both 12 and 16 weeks of rehabilitation compared to the control group (Fitzgerald, 2003). Another small study by Walls et al. (2010) evaluated the effects of preoperative NMES for 9 patients undergoing TKA. Five patients served as a control group. Preoperative quadriceps muscle strength increased by 28% in the NMES group. Early postoperative strength loss was similar in both groups; however, the NMES group had a faster recovery with greater strength over the control group at 12 weeks postoperatively.

Nervous System Conditions

Cerebral Palsy

Cobo-Vicente et al (2021) performed a systematic review and meta-analysis to analyze the effect of NMES on skeletal muscle and on biomechanics of movement, functional mobility, strength, spasticity, muscle architecture and body composition of children and adolescents with chronic neurological disorders (CNDs) and chronic diseases. Their review consisted of 18 studies (including the Pool et al. study below) of which 15 were RCTs, two were non-RCTs, and one was a cross-sectional study. There were 595 participants between 3 and 14 years of age, of which 49% were female. Most of the studies (88.9%) included in the review were about cerebral palsy (16 articles). There was also one study on spinal muscular atrophy and one study about obstetric brachial plexus injury. All the studies used NMES as their main intervention with the NMES programs lasting from 4 t~~o~~o 48 weeks in duration with an average application of 14 weeks. Half of the programs were home-based programs and half of the cases indicated the NMES was applied by professionals. The authors concluded that the use of NMES programs for children with CNDs, specifically cerebral palsy, appears to be effective in improving strength, biomechanics of movement, and functional mobility; however, they noted that there were not enough studies to confirm that NMES produces benefits on spasticity, muscle architecture, and body composition. This study noted that there was little agreement in

the variables analyzed in the different studies which made it hard to compare results and perform the statistical analysis of some variables. It also identified that there were small sample sizes in most of the studies and that, since most of the studies were focused on cerebral palsy, the conclusions would be difficult to expand to other types of CNDs. The authors recommend future RCTs focusing on analysis of the effect of NMES on spasticity, muscle architecture and body composition in children with CNDs and that further research is needed to evaluate the effectiveness of NMES in pediatric patients with other chronic diseases.

A RCT by Pool et al. (2016) evaluated whether NMES applied to the ankle dorsiflexors during gait improves muscle volume and strength in children with unilateral spastic CP. The study involved 32 children (mean age of 10.5 years) and a Gross Motor Function Classification System of I or II. Participants were randomly assigned to either the 8-week daily NMES treatment group or control group (usual or conventional treatments). Outcomes at week 8 (post-NMES) and week 14 (carryover) included magnetic resonance imaging for muscle volumes (tibialis anterior, anterior compartment, and gastrocnemius), strength (hand-held dynamometry for isometric dorsiflexion strength and heel raises for functional strength), and clinical measures for lower limb selective motor control. At week 8, the treatment group demonstrated significantly increased muscle volumes and dorsiflexion strength not only when compared to their baseline values but also when compared to the control group at week 8. At week 14, both tibialis anterior and lateral gastrocnemius volumes in the treatment group remained significantly increased when compared to their baseline values. However, only lateral gastrocnemius volumes had significantly greater values when compared to the control group at week 14. There were no between group differences in the clinical measures for lower limb selective motor control at weeks 8 and 14. The authors concluded that 8 weeks of daily NMES-assisted gait increases muscle volume and strength of the stimulated ankle dorsiflexors in children with unilateral spastic CP. These changes are use-dependent and do not carry over after the 8-week treatment period. Gastrocnemius volume also increased post-treatment with carryover at week 14.

Cerebral Vascular Accident

In a systematic review of RCTs, Alamer et al (2020) evaluated the efficacy of NMES on swallowing function in dysphagic stroke patients. The authors analyzed 11 RCTs that included studies that examined NMES, and/or NMES combined with conventional swallowing therapy irrespective of the duration of the intervention was provided or the outcome(s) measured. The studies included a total of 784 patients with a mean age of 54 to 66.2 in the treatment groups and 55.8 to 66.1 in the control groups. The mean duration since stroke was 15.7 hours to 35.4 weeks in the treatment groups and 16.0 hours to 36.0 weeks in the control groups. The RCTs compared the effectiveness of NMES, and/or conventional swallowing therapy with controlled group; conventional swallowing therapies, and/or placebo/sham stimulations were considered. The reviewers used the Physiotherapy Evidence Database (PEDro) scale and determined that the overall methodological quality of the evidence was ranged from moderate to high. The authors concluded that NMES along with traditional swallowing therapy could be an optional intervention to improve swallowing after stroke; however, they noted that great attention is needed regarding the course of disease duration and its severity when NMES is used for post-stroke dysphagia. The authors were not able to perform a meta-analysis due to the heterogeneity of the interventions. They recommended future research be conducted on NMES efficacy on chronic stroke patients with swallowing dysfunction.

Knutson et al. (2016) evaluated whether contralaterally controlled FES (CCFES) or cyclic NMES (cNMES) was more effective for post-stroke upper limb rehabilitation in an interventional, phase II, randomized trial conducted at a single institution (NCT00891319). Stroke patients (n=80) with chronic (> 6 months) moderate to severe upper extremity (UE) hemiparesis were randomized into 2 groups, receiving 10 sessions/week of CCFES- or cNMES-assisted hand opening exercise at home plus 20 sessions of functional task practice in the lab over 12 weeks. The primary outcome was improvement in Box and Blocks Test (BBT) score at 6-months post-treatment, with UE Fugl-Meyer motor assessment (UEFMA) and Arm Motor Abilities Test (AMAT) also being measured. Evaluation of participants occurred at baseline, every 3 weeks during the treatment period, at end-of-treatment, and 2, 4, and 6 months post-treatment by a blinded assessor. At 6-months post-treatment, the CCFES group had greater improvement than the cNMES group on the BBT, 4.6 versus 1.8, respectively, and a between-group difference of 2.8. No significant between-group difference was found for the UEFMA or AMAT. The authors concluded that 12 weeks of CCFES therapy resulted in improved manual dexterity compared to cNMES in stroke survivors experiencing chronic moderate to severe hand impairment, with advantage given to those whose impairment was moderate and were < 2 years post-stroke. The translatability of CCFES therapy to other research sites and to clinical practice still has not been established.

In a RCT by Shen et al. (2015), CCFES was compared to NMES as an innovative method to improve UE functions after stroke. Sixty-six patients were also treated with conventional medical treatment and rehabilitation training and were equally randomized into 2 groups. The treatments were administered in 20-minute sessions, 5 times per week for 3 weeks. Tools to assess results included the FMA, motricity index (MI), the Hong Kong version of functional test for the hemiplegic UE (FTHUE-HK) and active range of motion (AROM) of wrist extension. Patient status was measured before and after 3 weeks of treatment. Both groups showed significant improvements in all the measurements after treatment. Patients in CCFES group showed significantly higher UE FMA, FTHUE-HK scores and AROM of wrist extension than those in NMES group. The authors concluded that compared with the conventional NMES, CCFES provides better recovery of UE function in patients with stroke.

Lin et al. (2011) completed a single-blinded, RCT to investigate the long-term efficacy of NMES in enhancing motor recovery in the UEs of stroke patients. A total of 46 patients with stroke were assigned to a NMES group or a control group. Patients in the NMES group received the treatment for 30 min, 5 days a week for 3 weeks. Measurements were recorded before treatment, at the 2nd and 3rd week of treatment and 1, 3 and 6 months after treatment ended. The Modified Ashworth Scale for spasticity, the UE section of the FMA, and the Modified Barthel Index were used to assess the results. Significant improvements were found in both groups in terms of FMA and Modified Ashworth Scale scores after the 3rd week of treatment. The significant improvements persisted 1 month after treatment had been discontinued. At 3 and 6 months post-treatment, the average scores in the NMES group were significantly better than those in the control group. The authors concluded that 3 weeks of NMES to the affected UE of patients with stroke improves motor recovery. One limitation of this study was the absence of a sham stimulation group. Future studies using similar stimulation protocols with a larger sample are needed to gain further insight into the potential to induce functionally beneficial neuroplasticity in stroke patients.

Hsu et al. (2010) conducted a RCT to investigate the effects of different doses of NMES on UE function in acute stroke patients with severe motor deficit. Sixty-six acute stroke patients were equally randomized to 3 groups: high NMES, low NMES, or control. The treatment groups received NMES 5 days per week with the high-NMES group receiving 60

minutes of stimulation per day, and low-NMES group receiving 30 minutes per day for 4 weeks. The FMA, Action Research Arm Test, and Motor Activity Log (MAL) were used to assess the patients at baseline, 4 and 12 weeks. Twelve subjects were lost to follow-up. Both NMES groups showed significant improvement on FMA and Action Research Arm Test scales compared with the control group at weeks 4 and 12. The high-NMES group showed treatment effects ~~similar to~~like those of the low-NMES group. The authors concluded that both higher and lower doses of NMES led to similar improvements in motor function.

~~Professional Societies~~

~~American Heart Association/American Stroke Association (AHA/ASA)~~

~~In its Guidelines for Adult Stroke Rehabilitation and Recovery, the AHA/ASA state that NMES combined with therapy may improve spasticity, but there is insufficient evidence that the addition of NMES improves functional gait or hand use. The AHA/ASA guidelines are endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Society of Neurorehabilitation (Winstein et al., 2016).~~

Respiratory System Conditions

Wu et al. (2020) conducted a systematic review and meta-analysis to determine the effects of NMES on exercise capacity, functional performance, symptoms and health-related quality of life (HRQoL) in patients with COPD. They reviewed 13 RCTs, of which, 7 studies explored the effect of NMES versus usual care and 6 studies compared NMES plus conventional exercise versus exercise training alone with or without sham training for NMES. Study participants totaled 447 adults with confirmed diagnosis of severe or very severe stable COPD. The authors noted no statistical increase in HRQoL among participants allocated with NMES and that NMES had no benefit for the peak rate of oxygen uptake and peak power. The authors stated that the results of the study showed there was insufficient evidence to support the positive effects exerted by NMES in COPD patients. The authors concluded that, based on current available data, NMES should not be regarded as a replacement for pulmonary rehabilitation completely, for the combination does not result in further improvement. The fundamental limitation noted by the authors was that the quality of the evidence in their meta-analysis was very low and limited by poor methodology leading to the risk of bias. Other limitations noted include the lack of blinding of the assessors and that estimates of random variability was present in only 7 of the 13 studies. The authors recommend that future studies add the data describing the intrinsic muscle function or peripheral muscle force, and following up the adverse signs or events, in which NMES is applied alone or in isolation from rehabilitation strategies.

A 2018 Cochrane review by Hill et al. evaluated the effects of NMES, either alone or concurrently with conventional exercise therapy, to determine if this treatment might improve the overall physical condition and health-related QOL in people with chronic obstructive pulmonary disease (COPD). Nineteen studies met the inclusion criteria, of which 16 contributed data on 267 individuals with COPD. Of these 16 studies, 7 explored the effect of NMES versus usual care. Nine explored the effect of NMES plus conventional exercise training vs conventional exercise alone. The reviewers concluded that NMES, when applied alone, increased quadriceps force and endurance, 6-minute walking distance, time to symptom limitation exercising at a submaximal intensity, and reduced the severity of leg fatigue on completion of exercise testing. Evidence quality was considered low or very low due to risk of bias within the studies, imprecision of the estimates, small number of studies and inconsistency between the studies.

Miscellaneous Conditions

A systematic review and meta-analysis by Sun et al (2020) evaluating the efficacy of transcutaneous NMES on suprahyoid muscle groups and on infrahyoid muscle groups for treatment of swallowing disorders determined that there was no firm evidence to conclude on the efficacy of NMES on swallowing disorders. The authors reviewed 11 studies consisting of 8 RCTs and 3 quasi-RCTs involving 585 adults between the ages of 46 and 68.5 years from 5 countries with variable etiologies including stroke, traumatic brain injury (TBI), head and neck cancer and Parkinson disease. While most of the included studies were deemed by the authors to have low risk of bias for their design, eight of the 11 studies had small sample sizes (<57 participants) and one study had the participants complete the treatment at home which contributed to high risk of bias. The reviewers deemed the quality of evidence overall was low to very low. Treatment duration, NMES frequency and intensity and traditional therapies as well as the swallowing function outcome measures differed across trials. Limitations that were noted by the authors included the considerable difference in patient characteristics, stimulation parameters and outcome measurements that contributed to the evident heterogeneity. They also noted that only three of the 11 studies provided limited evidence on long-term effectiveness and that their systematic review only included studies published in English which may cause bias. The authors recommended larger-scale and well-designed RCTs with attention paid to the most optimal NMES protocol (eligible participants, stimulation muscle groups, duration) and long-term effects of NMES be studied to reach robust conclusions about the efficacy of NMES on swallowing disorders.

Liu et al (2020) conducted a systematic review and meta-analysis evaluating the efficacy of the early use of NMES to prevent intensive care unit acquired weakness (ICU-AW). The study reviewed 11 RCTs (including the Patsaki et al study below) where patients received NMES with routine treatments and nursing care and the control group was either minimum intensity sham NMES and/or routine treatment and nursing care. The studies included 576 adults between the ages of 18 and 85 who received mechanical ventilation for at least 24 hours. The authors determined that the meta-analysis showed that NMES can improve muscle strength, shorten mechanical ventilation time, ICU length of stay and total length of stay, improve the ability of patients to perform activities of daily living (ADLs) and increase walking distance. They also noted that NMES does not appear to improve the functional status of ICU patients during hospitalization, promote early awakening of patients or reduce mortality. Limitations identified by the authors include the heterogeneity of the outcome indicators in the included studies, the risk of publication bias due to the small number of studies included, the inclusion of only studies published in English and Chinese, and that the adverse effects and cost-effectiveness of NMES were not assessed.

~~NICE guidance on transcutaneous NMES for oropharyngeal dysphagia found current evidence on efficacy to be limited in quality. They did not cite any major safety concerns, although they considered the safety evidence to be limited in both quality and quantity. NICE states that this technology should only be used with special arrangements for clinical governance, consent and audit or research; and encourages further research into transcutaneous NMES for this condition, which clearly documents indications for treatment and details of patient selection (2018).~~

Patsaki et al. (2017) studied the effects of NMES along with individualized rehabilitation on muscle strength of ICU survivors. Following ICU discharge, 128 patients were randomized to either daily NMES sessions and individualized rehabilitation (NMES group) or to the control group. Muscle strength was assessed by the Medical Research

Council (MRC) score and hand grip at hospital discharge. Secondary outcomes were functional ability and hospital length of stay. The authors found that NMES and personalized physiotherapy in ICU survivors did not result in greater improvement of muscle strength and functional status at hospital discharge. However, they concluded that NMES may be effective in this subset of patients, and that the potential benefits of rehabilitation strategies should be explored in larger numbers in future studies.

Clinical Practice Guidelines

National Institute for Health and Clinical Excellence (NICE)

NICE guidance on transcutaneous NMES for oropharyngeal dysphagia found current evidence on efficacy to be limited in quality. They did not cite any major safety concerns, although they considered the safety evidence to be limited in both quality and quantity. NICE states that this technology should only be used with special arrangements for clinical governance, consent and audit or research; and encourages further research into transcutaneous NMES for this condition, which clearly documents indications for treatment and details of patient selection (2018).

American Heart Association/American Stroke Association (AHA/ASA)

In its Guidelines for Adult Stroke Rehabilitation and Recovery, the AHA/ASA state that NMES combined with therapy may improve spasticity, but there is insufficient evidence that the addition of NMES improves functional gait or hand use. The AHA/ASA guidelines are endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Society of Neurorehabilitation (Winstein et al., 2016).

Interferential Therapy (IFT)

Low Back Pain

Rajfur et al. (2017) conducted a pilot study to compare the effects of treating low back pain (LBP) using selected electrotherapy methods, assessing the influence of individual electrotherapeutic treatments on reduction of pain, improvement of the range of movement in lower section of the spine, and improvement of motor functions and mobility. Participants were assigned to 6 comparison groups: A - conventional TENS, B - acupuncture-like TENS, C - high-voltage ES, D - IFT stimulation, E - diadynamic current, and F - control group. Of the 127 qualified participants, 123 completed the 3-week study. Authors determined that selected electrical therapies (IFT, TENS< and high voltage ES) appear to be effective in treating chronic LBP.

Franco et al. (2016) conducted a double-blind single institution RCT on 148 patients with chronic nonspecific low back pain (LBP) to determine whether IFT before Pilates exercises is more effective than placebo. The primary outcome measures were pain intensity, pressure pain threshold, and disability after 6 weeks of therapy. The study groups consisted of active IFT + Pilates group, and placebo IFT + Pilates group. Eighteen treatment sessions were offered 3 times a week for 6 weeks. Both groups showed significant improvement in outcomes after 6 weeks, with improvements in pain and disability being considered clinically significant as well. However, the authors concluded that active IFT combined with Pilates exercises is no better than placebo IFC plus Pilates. Further studies are suggested.

To assess the influence of TENS and IFT on pain relief and to compare the analgesic efficacy of the 2 modalities, Grabiańska et al. (2015) studied 60 patients with LBP. The participants were equally and randomly divided into 2 groups. Depending on the groups,

patients were given a series of ten 20-minute sessions over a 2-week period using either IFT or TENS currents. In all patients, VAS and Laitinen modified scale were taken before and after treatment. At the end of the 2 weeks, there was improvement in nearly all components of the VAS and Laitinen scale for both groups. There was no statistically significant difference between the groups in reducing the intensity and other aspects of pain (e.g., frequency, pain medication and activity limitation). The authors concluded that both IFT and TENS therapy are effective for pain relief in patients with LBP, as their study results demonstrated equal analgesic efficacy of both therapy modalities.

Hurley et al. (2004) investigated the outcomes of manipulative therapy and IFT used as sole modalities or in combination for treatment of acute LBP. Eighty patients received manipulative therapy, 80 received IFT, and 80 received a combination of both. The primary outcome was a change in functional disability on the Roland Morris Disability Questionnaire. Follow-up questionnaires were posted at discharge and at 6 and 12 months. At discharge, all interventions significantly reduced functional disability. At 12 months, there were no significant differences found between the groups for recurrence of back pain, work absenteeism, medication consumption, exercise participation or the use of healthcare. The authors concluded that there was no difference between the effects of a combined manipulative therapy and IFT package and either of the therapy modalities alone.

Hurley et al. (2001) conducted a single-blind, RCT on 60 subjects with LBP, evaluating whether the IFT applied to the associated spinal nerve is more efficacious than placing the current over the painful area. These investigators found a statistically significant reduction in functional disability scores for the spinal nerve therapy group compared with the control group or the painful area therapy group. However, no advantage was observed for the spinal nerve therapy group in pain or QOL scores. The authors' findings showed that IFT electrode placement technique affects LBP-specific functional disability, providing preliminary implications for future clinical studies.

~~Professional Societies~~

~~*American College of Physicians (ACP)*~~

~~In their clinical practice guideline addressing noninvasive treatments for acute, subacute, and chronic LBP, the ACP states clinicians and patients should initially select non-pharmacologic treatments including but not limited to exercise (e.g., tai chi, yoga, motor control exercise) and multidisciplinary rehabilitation (e.g., ES therapies) when managing chronic LBP (Qaseem et al., 2017).~~

Osteoarthritis of the Knee/Anterior Cruciate Ligament/Menisccectomy/Knee Chondroplasty/Knee Arthroplasty

In a placebo-controlled, single-center, double-blind RCT, Alqualo-Costa et al (2021) evaluated the effects of IFT and photobiomodulation (PBMT) in patients with knee osteoarthritis. The study included 168 participants divided into four groups of 42 participants each that received one of the following modalities: IFT, PBMT, IFT plus PBMT, or placebo. Participants were evaluated at baseline, after 12 sessions, and at three- and six-months post-treatment. The study was designed such that both the participants and the outcome assessors were blinded to the treatment regimen and all participants were assessed by the same evaluator blinded to group allocation pre-treatment and after the 12th treatment, and at three and six months after the end of the treatment. The authors concluded that the combination of IFT plus PBMT significantly reduced pain intensity at rest and during movement compared to IFT alone and to placebo

in patients with knee osteoarthritis. They also determined that the benefits seem to be maintained for six months after the end of treatment. Similar improvements were not noted by the authors in the group that received IFT alone. The authors noted that the study was limited by the small numbers in each group, lack of evaluation of the use of concomitant pain medication, and the multiple statistical comparisons. The authors recommended further studies with larger populations of participants, studies that evaluate the efficacy of different parameters, treatment frequency and electrodes size for IFT.

Kadı et al (2019) conducted a single-center, double-blind RCT to investigate the effectiveness of IFT following total knee arthroplasty (TKA). Of the 98 people who completed the study, 49 were in the treatment group where they received IFT for 30 minutes, twice a day for five days post-operatively and 49 were in the sham control group where the same pads were applied but no IFT stimulation was given. At the baseline, there were no statistically significant differences between the groups in respect of demographic and clinical data. The authors concluded that no significant difference was seen between the two groups in respect of pain, range of motion and edema at days 0, 5, and 30 and that IFT did not show to be an effective modality for pain management in patients who had undergone TKA. They observed that the amount of paracetamol used was significantly lower in the IFT group; however, the authors noted that the difference did not continue after the end of the first month and they stated that this cannot be argued as showing the effectiveness of IFT. The main limitations documented by the authors included the relatively short duration of the treatment and the lack of preoperative data for the participants. They recommended high-quality, multi-center RCTs and studies with long-term follow-up be conducted to show the exact effects of ICT on functional recovery when it is added as a supplement to a postoperative rehabilitation program.

Zeng et al. (2015) performed a systematic review and Bayesian network meta-analysis of 27 RCTs over a 30-year period, which compared different ES therapies (high-frequency TENS (h-TENS), low-frequency TENS (l-TENS), NMES, IFC, PES and noninvasive interactive neurostimulation (NIN)) with the control group (sham or no intervention) for relief of knee pain in 1253 patients with OA. The primary goal was to identify whether or not the different ES modalities offered pain management by measuring the degree of pain intensity and the change pain score at last follow-up time point. Of the 6 therapy modalities, IFT was the only significantly effective treatment in both pain intensity and changed pain score at last follow-up time point when compared with the control group. In addition, IFT was deemed the best probable option for pain relief among the 6 therapy modalities. The authors' conclusions were that IFT was the most promising for management of knee pain related to OA. The other ES therapies were considered safe for patients with knee OA, although some were considered inappropriate. Study limitations included a small number of included trials, heterogeneity of the evidence, and the indirectness of comparisons inherent to network meta-analyses.

A multi-center, single-blind, RCT by Burch et al. (2008) investigated the benefits of combined interferential (IF) and patterned muscle stimulation in the treatment of OA of the knee. The study randomized 116 patients to a test or control group. The test group received 15 minutes of IF stimulation followed by 20 minutes of patterned muscle stimulation. The control group received 35 minutes of low-current TENS. Both groups were treated for 8 weeks. Subjects completed questionnaires at baseline and after 2, 4 and 8 weeks. Primary outcomes included the pain and physical function subscales of the WOMAC OA Index and VAS for pain and QOL. Compared to the control group, the test group showed reduced pain and increased function. The test group showed a greater decrease in the WOMAC pain subscale (P=0.002), function subscale (P=0.003) and stiffness subscale (P=0.004). More than 70% of the test group, compared to less than 50% of the control

group, had at least a 20% reduction in the WOMAC pain subscale. When analyzing only patients who completed the study (n=49 in test group, n=50 in control group), the test group had a nominally significant greater decrease in overall pain VAS. No significant differences were observed between groups related to incidence of adverse events (AEs). The authors concluded that in patients with OA of the knee, home-based patterned stimulation appears to be a promising therapy for relieving pain, decreasing stiffness, and increasing function. Study limitations included manufacturer sponsoring, 10% drop out rate and the treatment effect did not reflect a sufficient significant difference.

Jarit et al. (2003) conducted a randomized, double-blind, placebo-controlled trial of home-based IFT in 87 patients who had undergone ACL reconstruction, meniscectomy, or knee chondroplasty. Patients were divided into 3 groups based on type of knee surgery and within each group randomized into treatment and placebo group. All patients were given home IFT devices. The treatment groups received working IFT units while the placebo groups received units set to deliver no current. At baseline, there were no statistically significant differences between IFT and control groups in edema or ROM. All IFT subjects reported significantly less pain and had significantly greater ROM at all postoperative time points. ACL and meniscectomy IFT subjects experienced significantly less edema at all time points, while chondroplasty subjects experienced significantly less edema until 4 weeks postoperatively. The authors concluded that IFT may help to reduce pain, need for pain medication and edema as well as enhance recovery of function after knee surgery. The study is limited by subjective reporting of edema by patients, small treatment and control groups and lack of comparison to other treatment modalities. In addition, the control group may have been aware they were not receiving IFT, thereby confounding the results.

~~Professional Societies~~

~~*American Academy of Orthopaedic Surgeons (AAOS)*~~

~~In its clinical practice guideline on the treatment of OA of the knee, the AAOS cannot recommend for or against the use of physical agents (including electrotherapeutic modalities) due to inconsistent findings (2013).~~

Other Musculoskeletal Pain

In a systematic review and meta-analysis evaluating the efficacy of IFC in alleviating musculoskeletal pain in adults, Hussein et al (2021) reviewed 35 RCTs of variable methodological quality from which 19 trials were included in the meta-analysis. The RCTs included 14 studies involving low back pain (LBP), seven with shoulder issues, six with knee pain, five with neck pain, two with lumbar discogenic pain and one each for carpal tunnel syndrome and plantar fasciitis. In reviewing the methodologies, the studies included six that were placebo-controlled, four that included IFC as part of the control or standard therapy and the remaining 25 included IFC as part of the experimental arm or compared IFC to another experimental treatment. The results of the critical appraisal for the studies revealed that 16 of the 35 RCTs were of high methodological quality, 16 were of medium quality, and three studies demonstrated low quality. The 19 trials that they included in the meta-analysis included a total sample size of 1,167 participants. The other trials were not included in the meta-analysis due to a lack of required data, the inclusion of IFC as part of the standard treatment arm or because they consisted of more than one experimental IFC or control group. The authors determined that, in general, IFC could have a significant pain-relieving effect compared to placebo; however, the low number of studies raised suspicions about this conclusion. The authors also concluded that IFC showed no significant difference when it was added to a standard treatment

protocol compared to placebo plus standard treatment or compared to standard treatment alone. They also found that IFC showed no significant difference when compared to other single interventions such as laser, TENS or cryotherapy. Limitations identified by the authors included the heterogeneity of the population of the trials, the exclusion of non-English language publications, the subjective nature of the pain measures and the lack of a validation study in the quality assessment method used in the review.

Albornoz-Cabello et al. (2019) conducted a single-blinded, single-center RCT to investigate the effects of adding IFT to usual care after surgery in adults with subacromial pain syndrome (SAPS). The study included 56 adults with SAPS who underwent acromioplasty in the past 12 weeks. All participants underwent a two-week intervention, three times a week of either a 15-minute IFT electro-massage plus usual care (treatment group; n=28) or usual care only (control group; n=28). There were no adverse reactions or dropouts during the study protocol . A blinded evaluator collected outcomes at baseline and after the last treatment session. The authors concluded that IFT plus usual care resulted in significant improvement in shoulder pain intensity, upper limb function, and shoulder flexion, abduction, internal and external rotation; however, there was no difference between groups for shoulder extension and adduction. The authors stated that the study was limited by the lack of a sham IFT group, that there was a lack of data beyond the immediate results after the last treatment and that the therapist that provided the interventions was not blinded to the participant allocation group. They recommend further research to investigate if different results would be expected using different IFT current parameters and to identify the medium and long-term effects of IFT on post-operative pain in adults with SAPS.

Dissanayak~~a~~e et al. (2016) compared the effectiveness of TENS and IFT in a single-blind RCT on individuals with myofascial pain syndrome (MPS). The aim of this study was to compare the effectiveness of these treatment modalities both in combination with hot pack, myofascial release, AROM exercise, and a home exercise program on MPS patients with upper trapezius myofascial trigger point. A total of 105 patients with an upper trapezius myofascial trigger point were randomly allocated to 3 groups, 3 therapeutic regimens-control-standard care (hot pack, AROM exercises, myofascial release, and a home exercise program with postural advice), TENS-standard care and IFT-standard care-were administered 8 times during 4 weeks at regular intervals. Pain intensity and cervical range of motions (cervical extension, lateral flexion to the contralateral side, and rotation to the ipsilateral side) were measured at baseline, immediately after the first treatment, before the eighth treatment, and 1 week after the eighth treatment. Immediate and short-term improvements were marked in the TENS group (n=35) compared with the IFT group (n=35) and the control group (n=35) with respect to pain intensity and cervical range of motions. The IFT group showed more significant improvement on these outcome measurements than the control group did. The authors concluded that TENS with standard care facilitates recovery better than IFT does in the same combination.

To evaluate the effectiveness of passive physical modalities (which included IFT) on soft tissue injuries of the shoulder, Yu et al. (2015) conducted a systematic review of literature published between January 1, 1990, and April 18, 2013. RCTs and cohort and case-control studies were eligible. Of the 22 eligible articles, 11 studies were found to have a low risk of bias and so were analyzed, although the collective number of patients within the 11 studies was not cited. IFT was one of multiple modalities that were ineffective in reducing shoulder pain. The authors concluded that most passive physical modalities, including IFT, do not benefit patients with subacromial impingement syndrome.

In 2010, Fuentes and colleagues published a systematic review and meta-analysis of studies evaluating the effectiveness of IFS for treating pain. A total of 20 studies met the following inclusion criteria: RCT; included adults diagnosed with a painful musculoskeletal condition; compared IFS (alone or as a co-intervention) to placebo, no treatment, or an alternative intervention; and assessed pain on a numeric scale. Fourteen of the trials reported data that could be included in a pooled analysis. IFS as a stand-alone intervention was not found to be more effective than placebo or an alternative intervention.

Tibial Fractures

Fourie and Bowerbank (1997) studied IFT as a treatment to accelerate healing of tibial fractures in a double blind, RCT. Forty-one men received IFT, 35 received sham, and 151 received no intervention. Outcomes were measured by the time to union or incidence of nonunion. IFTs were applied to the experimental group via suction electrodes for 30 minutes per day for 10 days. The placebo group had only suction electrodes applied producing a rhythmical massage effect. The control group received no intervention. The data analysis reflected no difference in the time for union in the 3 groups. The authors concluded that IFT did not reduce healing time for new tibial fractures or prevent nonunion, and that further investigation was recommended.

Clinical Practice Guidelines

National Institute for Health and Clinical Excellence (NICE)

NICE guidance on transcutaneous electrical nerve simulation (TENS), ultrasound and IFT for chronic primary pain found no evidence for IFT. The committee noted that IFT has been around for some time so that it is unlikely that new research will be done. The committee agreed that IFT should not be offered for chronic primary pain and made a recommendation against its use (2021).

NICE updated their guidance on the use of TENS, percutaneous electrical nerve simulation (PENS) and IFT for managing low back pain with or without sciatica and stated that these modalities should not be offered for treatment of low back pain with or without sciatica due to the paucity of evidence available that included mostly small individual studies of low or very low quality. No difference between interventions was seen when comparing IFT with sham or traction in people with low back pain without sciatica or when IFT was combined with education, exercise and self-management. The committee found that the studies had inconsistencies across domains and in terms of their efficacy in long or short term. The Guideline Development Group concluded that there was a lack of evidence of clinical benefit to support a recommendation for the use of IFT as a treatment for low back pain or sciatica (2016, updated 2020).

American College of Physicians (ACP)

In their clinical practice guideline addressing noninvasive treatments for acute, subacute, and chronic LBP, the ACP states clinicians and patients should initially select non-pharmacologic treatments including but not limited to exercise (e.g., tai chi, yoga, motor control exercise) and multidisciplinary rehabilitation (e.g., ES therapies) when managing chronic LBP (Qaseem et al., 2017).

Pulsed Electrical Stimulation (PES)/ Pulsed Electromagnetic Field (PEMF) Stimulation

In a double-blind, prospective RCT, Karakaş and Gök (2020) studied the efficacy of pulsed electromagnetic field (PEMF) therapy when added to a conventional physical therapy

program in reducing pain and functional limitation in patients with chronic non-specific neck pain. The study included 63 patients (15 males, 48 females, age range 25 to 59 years) that were divided into either a PEMF therapy group (n=33) that received 20 minutes of PEMF in addition to a physical therapy program or a control group (n=30) that received only the physical therapy program. The groups were similar in terms of demographic and clinical characteristics and both showed improvement in pain and functionality. The authors noted that the study limitations included the use of the conventional physical therapy program in both study groups, the lack of monitoring of the use of paracetamol for pain control in the study participants, lack of long-term measurements, the subjective measurement tools used and the heterogeneity of the etiology of neck pain among the participants. They concluded that PEMF is safe in patients with non-specific neck pain, but it is not superior in improving pain and functional limitation and that further large-scale, prospective RCTs using a standard dose of PEMF with a more specific patient sample are needed to demonstrate evidence for the effectiveness of PEMF.

Yang et al. (2020) completed a systematic review of 16 RCTs and a meta-analysis of 15 RCTs to evaluate the effects of PEMF therapy and PEMF parameters on symptoms and quality of life (QOL) in people with osteoarthritis (OA). The total population in the 16 studies was 1078 with 554 in treatment groups and 524 in placebo-controlled groups. Treatment time varied between 10 days and 6 weeks so two different treatment durations (<4 weeks and 4-6 weeks) were used in the subgroup analysis. The longest follow-up time was 12 weeks. Fourteen of the studies involved OA of the knee while one study included the ankle, two studies addressed OA of the hand and two studies addressed OA of the cervical spine. The authors determined that, compared with placebo, there was a beneficial effect of PEMF therapy on pain and stiffness regardless of the treatment duration while benefit in physical function in people with OA was only seen if the therapy regimen lasted for 4 to 6 weeks. They did not observe any association between PEMF therapy and QOL in people with OA regardless of the length of the treatment program. Limitations noted by the authors included the high levels of heterogeneity across outcome measures, the small number of studies included, the short length of time for the treatment phases (<6 weeks) and follow-up (maximum of 12 weeks) They recommended further studies to explore efficacy with long-term follow-up and to assess the effects of this modality on QOL.

ECRI published a Custom Product Brief (2019) on the SofPulse targeted pulsed electromagnetic field (them) device that is intended to reduce pain and swelling post-operatively. Based on the limited evidence from three very small RCTs on the use of SofPulse following breast surgeries, they concluded that the device may relieve short-term pain, and may reduce (but not eliminate) narcotic use when compared to a sham (placebo) device. The report stated that the evidence is inconclusive as the studies assessed too few patients and that results need to be confirmed in larger, longer-term RCTs examining different surgery types and comparing the device to other pain control methods.

Chen et al (2019) completed a systematic review and meta-analysis evaluating the efficacy of PEMF therapy on pain, stiffness and physical function in patients with knee osteoarthritis. The review included eight RCTs that that compared PEMF of various parameters and treatment regimens with placebo. The studies involved 421 patients of similar age, sex ratio, and body mass index. All the included studies were determined by the reviewers to have a low or moderate risk of bias. The limitations noted by the authors included the small number of RCTs and sample size available for review, the inclusion of only articles published in English and that there was significant heterogeneity in the meta-analysis of the visual analogue scale (VAS) for pain. The authors concluded that PEMF is beneficial for improving physical function of the knee

joint despite not having any advantage in treating pain or stiffness. They recommend further RCTs to confirm their findings and to determine the optimal frequency, intensity, treatment regimen and duration of PEMF therapy.

Newberry et al. (2017) conducted a systematic review to assess the efficacy of a variety of noninvasive interventions (including but not limited to ES techniques [including TENS], NMES, and pulsed electromagnetic field therapy [PEMF]) for OA treatment of the knee. A search was conducted using PubMed, Embase, the Cochrane Collection, Web of Science, the Physiotherapy Evidence Database, ClinicalTrials.gov, and abstracts from professional practice society annual meetings (e.g., American College of Rheumatology, American Academy of Orthopaedic Surgery). Eligible studies were those that were RCTs that enrolled adults 18 years or over who were diagnosed with OA of the knee and compared any of the interventions of interest with placebo (sham) or any other intervention of interest that reported a clinical outcome (including pain, function, and quality of life). The investigators also included single-arm and prospective observational studies that analyzed the effects of weight loss in individuals with OA of the knee on a clinical outcome. Findings were stratified according to duration of interventions and outcomes: short term (4–12 weeks), medium term (12–26 weeks), and long term (>26 weeks). A total of 107 studies were included in the review and of those, 3 studies evaluated treatment with pulsed electromagnetic field therapy. Based on a pooled analysis, PEMF had a statistically nonsignificant beneficial effect on short-term pain. In addition, the investigators reported that the evidence is insufficient to assess the effects of PEMF on short-term or other outcomes, and that larger randomized controlled trials are needed.

Negm et al. (2013) conducted a systematic review and meta-analysis to determine if low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through pulsed electromagnetic field (PEMF) or pulsed electrical stimulation (PES) vs. sham PEMF/PES intervention is effective in improving pain and physical function at treatment completion in adults with knee OA blinded to treatment. A search was conducted using MEDLINE, CINAHL, EMBASE, CENTRAL and AMED as well as in three clinical trial registries including Clinical Trials Registry, Current Controlled Trials and the World Health Organisation International Clinical Trials Registry Platform. Eligible studies included those with: 1) participants with clinically and/or radiological confirmed knee OA; 2) PEMF/PES frequency was ≤100 Hz; 3) the comparator was sham PEMF/PES; 4) the primary outcome was pain and/or physical function; 5) the study design was RCT with blinded participants; 6) data for knee OA participants were reported independently pre- and post-treatment; and 7) participants were over 30 years of age. A total of seven RCTs (459 participants/knees) were included. PEMF/PES appeared to improve physical function (standardized mean difference [SMD]=0.22, 95% CI, 0.04 to 0.41, *p*=0.02), and did not reduce pain (SMD=0.08, 95% CI, −0.17 to 0.32, p=0.55). The strength of the body of evidence was low for physical function and very low for pain. The authors concluded that current evidence is of low and very low quality suggesting that low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES vs. sham PEMF/PES is effective in improving physical function but not pain intensity at treatment completion in adults with knee OA blinded to treatment. The authors also stated that methodologically rigorous and adequately powered RCTs are still needed to confirm and extend the findings of this review.

Farr et al. (2006) reported on a prospective, cohort study examining the use of PES for the treatment of OA of the knee in 288 patients. The device was used for 16-600 days with a mean of 889 hours. Improvement in all efficacy variables was reported. A dose-response relationship between the effect and hours of usage was observed as cumulative time increased to more than 750 hours. Improvements in the patient's or physician's global

evaluation of the patient's condition occurred in 59% of patients who used PES less than 750 hours and in 73% of patients who used it more than 750 hours. The lack of a control group weakens the evidence in this study.

~~Professional Societies~~Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

In its clinical practice guideline on non-arthroplasty management of OA of the knee, the AAOS reviewed one high quality study on the use of a wearable PEMF device for pain management in patients with knee osteoarthritis. The Society downgraded their recommendation one level to Limited due to feasibility issues in that PEMF is not widely used in practice settings where patients are treated for knee OA which may limit access for some patients. They recommend continued research with larger RCTs that examine the long-term effectiveness of PEMF and studies that identify factors that distinguish between patients who respond and those who don't respond to PEMF (2021).

~~In its clinical practice guideline on the treatment of OA of the knee, the AAOS cannot recommend for or against the use of physical agents (including electrotherapeutic modalities) due to inconsistent findings (2013).~~

Percutaneous Peripheral Nerve Stimulation (PNS)

There is insufficient evidence to support the use of PNS for the treatment of pain. While some studies have compared the effectiveness of PNS to placebo, the overall quality of the evidence is weak and limited. Most of the published studies consist of retrospective reviews, case reports, small case series and small randomized controlled trials. Further large, multi-centered, blinded, long-term RCTs are needed to evaluate the efficacy of PNS. Ongoing studies may provide more definitive evidence of safety and efficacy of PNS. These studies include, among others: NCT04713098, NCT03481725, NCT04246281, NCT03752619, NCT02928055, NCT02893267, and NCT04454671.

Hayes published an Evolving Evidence Review on the SPRINT PNS System and its application for the treatment of chronic pain (2021). The report concluded that, based on a review of published clinical studies, there is minimal support for using this device for treatment of chronic pain. They also noted that there were no published systematic reviews and no published guidelines or position statements specifically addressing Sprint PNS for chronic pain.

Another Hayes publication was an Evidence Analysis Research Brief on the use of peripheral nerve stimulation systems as a methodology for treatment of chronic pain (2021). Hayes determined that there is adequate published, peer-reviewed, literature to evaluate the evidence on PNS for chronic pain but the full evaluation has not yet been published.

Two additional Evidence Analysis Research Briefs have been published by Hayes on PNS with the SPRINT PNS System for chronic knee pain (2021), and PNS for treatment of back pain (2021). Both of these reports conclude that there is an insufficient quantity of published, peer-reviewed, human clinical data to evaluate the use of these technologies.

ECRI published a Clinical Evidence Assessment on implantable PNS devices for treating chronic pain (2021) and determined that the evidence is inconclusive due to too few data. The report stated that the studies are at high risk of bias due to various reasons including small sample size, single-center focus, retrospective design, and lack of

controls, randomization and/or blinding. The report also stated that the findings may not generalize across patients with different pain etiologies, and they noted that there were no published studies that compared PNS with other chronic pain management methods, such as spinal cord stimulation, transcutaneous electric stimulation, peripheral nerve field stimulation or nerve blocks. The report suggested additional larger RCTs are needed to permit conclusion.

ECRI also published the following reports for PNS for pain: ReActiv8 Implantable Neurostimulation System for Treating Chronic Pain (2021), Sprint Peripheral Nerve Stimulation System for Treating Peripheral Nerve Pain (2020), StimRouter Neuromodulation System for Treating Peripheral Nerve Pain (2020), and StimQ Peripheral Nerve Stimulator System for Treating Peripheral Nerve Pain (2018). All of these reports indicate that the evidence is inconclusive since there are too few data.

Gilligan et al (2021) conducted a randomized double-blinded, sham-controlled clinical trial at 26 specialist pain centers to determine the safety and efficacy of an implantable, restorative neurostimulator, the ReActiv8 Implantable Neurostimulation System. This study included 240 participants with refractory mechanical chronic low back pain (LBP) with an impaired multifidus control who continued with LBP despite >90 days of medical management and at least one attempt of physical therapy. The participants were implanted and randomized using a permuted block scheme for each investigational site to the therapeutic group (N=102) or the sham control group (N=102). All participants received stimulation, either therapeutic or low-level sham, twice a day for 120 days. After the primary endpoint, all reported outcomes were unblinded and all participants received therapeutic stimulation. All study participants were evaluated through 1 year for long-term outcomes and adverse events. The authors reported that 64% of participants had a 50% or greater improvement in their LBP, mean disability improved by 51% from borderline "severe" to "minimal" and that 18 of the 65 participants who were on opioids at baseline discontinued their use. They also reported a 4% serious adverse events rate, including 6 pocket infections requiring system removal. The authors concluded that this study provided important insights and design considerations for future neuromodulation trials.

In a prospective, multicenter single-arm case series on the effect of PNS on treating chronic axial back pain, Gilmore et al (2021), determined that percutaneous PNS may provide a promising first-line neurostimulation treatment option. The study included 81 participants and was conducted across a variety of clinical care settings. All participants were implanted with percutaneous open-coil PNS leads which were then connected to the SPRINT PNS System. The participants were instructed to use PNS for 6–12 h/day for up to 60 days, after which the leads were withdrawn. No additional interventions apart from percutaneous PNS was provided to any participants for their back pain prior to the primary end point of the study. The authors reported that 57% of the 51 participants who completed a 14-month visit sustained clinically meaningful reductions in average back pain intensity through the 14 months. The authors acknowledged that this was not a randomized trial and that it did not include a control group. They concluded that patients with chronic axial back pain who have failed multiple prior treatments may receive significant benefit from percutaneous PNS.

Helm et al (2021) conducted a systematic review of the effectiveness and safety of PNS for chronic pain that included one RCT of high quality which evaluated the efficacy of PNS on 28 traumatic lower extremity amputees (Gilmore 2019b study below), four RCTs of moderate quality (including Wilson, 2014 reviewed below) and four case series of moderate quality. The studies included in the systemic review evaluated the use of PNS to treat

refractory peripheral nerve neuropathic pain (including complex regional pain syndrome, nerve entrapment, and post-stroke pain), cluster headache and pelvic pain. The authors reported that three of the RCTs evaluated relief of peripheral nerve neuropathic pain at a minimum of 3 months, with two showing greater than 50% relief at the end point and the third showing a mean reduction of 27% versus essentially no relief in the control group. They also found that the case series supported the RCTs, with greater than 50% relief in roughly two-thirds of the patients, although they noted that the studies included in the systematic review lacked sufficient homogeneity to support a meta-analysis. The authors noted that the majority of reviewed studies had small sample sizes and that the systematic review was limited by the paucity of high-quality literature supporting its use. They concluded that PNS requires further research on the efficacy of therapy and on the mode of action to become more widely accepted.

Ilfeld et al. (2021) conducted a multicenter randomized, sham-controlled pilot study to determine the feasibility and optimize the protocol for a subsequent clinical trial and estimate the treatment effect of percutaneous peripheral nerve stimulation on postoperative pain and opioid consumption. Preoperatively, an electrical lead was percutaneously implanted to target the sciatic nerve for major foot/ankle surgery (e.g., hallux valgus correction), the femoral nerve for anterior cruciate ligament reconstruction, or the brachial plexus for rotator cuff repair, followed by a single injection of long-acting local anesthetic along the same nerve/plexus. Postoperatively, participants were randomized to 14 days of either electrical stimulation (n = 32) or sham stimulation (n = 34) using an external pulse generator in a double-masked fashion. The dual primary treatment effect outcome measures were (1) cumulative opioid consumption (in oral morphine equivalents) and (2) mean values of the "average" daily pain scores measured on the 0 to 10 Numeric Rating Scale within the first 7 postoperative days. During the first 7 postoperative days, opioid consumption in participants given active stimulation was a median (interquartile range) of 5 mg (0 to 30) versus 48 mg (25 to 90) in patients given sham treatment (ratio of geometric means, 0.20 [97.5% CI, 0.07 to 0.57]; P < 0.001). During this same period, the average pain intensity in patients given active stimulation was a mean ± SD of 1.1 ± 1.1 versus 3.1 ± 1.7 in those given sham (difference, -1.8 [97.5% CI, -2.6 to -0.9]; P < 0.001). The investigators concluded that percutaneous peripheral nerve stimulation reduced pain scores and opioid requirements free of systemic side effects during at least the initial week after ambulatory orthopedic surgery. The limitations of this study include a small sample size and a short follow-up period.

Xu et al. (2021) conducted a systematic review to assess the clinical evidence for PNS in the treatment of acute or chronic pain. Study selection criteria included randomized trials, observational studies, and case reports of PNS used for in acute or chronic pain. Data extraction and methodological quality assessment were performed using Cochrane review methodologic quality assessment and Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) and Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR). The evidence was summarized utilizing principles of best evidence synthesis on a scale of 1 to 5. A total of 227 studies met inclusion criteria and were included in qualitative synthesis. Evidence synthesis based on randomized controlled trials (RCTs) and observational studies showed Level II evidence (evidence obtained from at least one relevant high-quality RCT or multiple relevant moderate- or low-quality RCTs) of PNS for postamputation pain, chronic pelvic pain, chronic low back pain, shoulder pain, and lower extremity pain; and Level IV evidence (evidence obtained from multiple moderate- or low-quality relevant observational studies) in peripheral neuropathic pain and postsurgical pain. A meta-analysis was not possible

due to wide variations in experimental design, research protocol, and heterogeneity of study population. According to the authors, there is a lack of high-quality RCTs for the use of PNS. The authors indicated that rigorously designed RCTs are needed to further validate the use of percutaneous PNS for most indications in pain management.

Deer et al. (2020) performed a systematic review of PNS for pain. An international interdisciplinary work group conducted a literature search for PNS. Inclusion criteria included prospective RCTs with meaningful clinical outcomes that were not part of a larger or previously reported group. Excluded studies were retrospective, had less than two months of follow-up, or existed only as abstracts. Full studies were graded by two independent reviewers using the modified Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment, the Cochrane Collaborations Risk of Bias assessment, and the US Preventative Services Task Force level-of-evidence criteria. Peripheral nerve stimulation was studied in 14 RCTs for a variety of painful conditions (headache, shoulder, pelvic, back, extremity, and trunk pain). Moderate to strong evidence supported the use of PNS to treat pain. According to the authors, there was moderate evidence (Level II) that implanted PNS can be expected to provide at least modest improvements in mono-neuropathic pain (Deer et al., 2016) and hemiplegic shoulder pain (Wilson et al., 2014; Wilson et al., 2017). The authors indicated that additional prospective trials could further refine appropriate populations and pain diagnoses.

Gilmore et al. (2019a) conducted a multicenter, double-blinded, randomized, placebo-controlled study to assess the safety and effectiveness of percutaneous PNS for chronic neuropathic pain following amputation. Twenty-eight lower extremity amputees with postamputation pain were enrolled in the study. Subjects underwent ultrasound-guided implantation of PNS leads and were randomized to receive PNS or placebo for 4 weeks. The placebo group then crossed over and all subjects received PNS for four additional weeks. The primary efficacy endpoint evaluated the proportion of subjects reporting ≥50% pain reduction during weeks 1-4. A significantly greater proportion of subjects receiving PNS (n=7/12, 58%, p=0.037) demonstrated ≥50% reductions in average postamputation pain during weeks 1-4 compared with subjects receiving placebo (n=2/14, 14%). Two subjects were excluded from efficacy analysis due to eligibility changes. Significantly greater proportions of PNS subjects also reported ≥50% reductions in pain (n=8/12, 67%, p=0.014) and pain interference (n=8/10, 80%, p=0.003) after 8 weeks of therapy compared with subjects receiving placebo (pain: n=2/14, 14%; pain interference: n=2/13, 15%). The investigators concluded that this study demonstrates that percutaneous PNS therapy may provide enduring clinically significant pain relief and improve disability in patients with chronic neuropathic postamputation pain. Study limitations included small sample size, short follow-up period (4 weeks.), no significant difference in opioid usage reductions between groups, even though the PNS therapy group had greater absolute and percent reductions in average opioid usage.

Gilmore et al. (2019b) evaluated changes in chronic pain and functional outcomes after amputation up to 12 months as a follow-up to a 60-day PNS treatment (Gilmore et al., 2019a). Significantly more participants in group 1 reported ≥50% reductions in average weekly pain at 12 months (67%, 6/9) compared with group 2 at the end of the placebo period (0%, 0/14, p=0.001). Similarly, 56% (5/9) of participants in group 1 reported ≥50% reductions in pain interference at 12 months, compared with 2/13 (15%, p=0.074) in group 2 at crossover. Reductions in depression were also statistically significantly greater at 12 months in group 1 compared with group 2 at crossover. The investigators concluded that this study suggests that percutaneous PNS therapy delivered over a 60-day period may provide significant carry-over effects including pain relief, potentially avoiding the need for a permanently implanted system while enabling improved function in patients with

chronic pain. The investigators indicated that although the pain relief and pain interference outcomes were clinically meaningful and statistically significant, the sample sizes made some outcomes difficult to interpret, such as the trend in both group 1 and group 2 towards greater pain relief during follow-up compared with the end of treatment. The investigators indicated that it is possible that the loss of 4 participants to follow-up influenced the average pain relief at later time points.

Peripheral Subcutaneous Field Stimulation (PSFS) or Peripheral Nerve Field Stimulation (PNFS)

Evidence on PNFS is limited, consisting of small trials and case studies. More robust prospective controlled trials comparing PSFS or PNFS with placebo or alternative treatment modalities are needed to evaluate the efficacy of this treatment for chronic pain.

In an Evolving Evidence Review on the use of the Bridge device (formerly NSS-2) on alleviating symptoms of opioid withdrawal, Hayes (2021) identified one study for review. While the study indicated the device was effective in alleviating symptoms of opioid withdrawal, it lacked a control group to demonstrate how the efficacy of the device compares with sham devices, pharmacologic treatments or behavioral interventions. The review noted that there is a comparative study underway with results expected in 2023.

Hayes (2021) published a Health Technology Assessment on the efficacy of using PNFS on adults with nonresponsive refractory chronic low back pain (CLBP) and gave the technology an overall low rating. The assessment included six identified studies (including the Verrills and van Gorp studies below): two RCTs, two prospective comparative cohort studies, one prospective pretest-posttest study and one retrospective pretest-posttest study. The comparisons included sham, optimal medical management and the use of PNSF with spinal cord stimulation(SCS) vs. SCS alone. Overall, the evidence suggested that PNFS is safe for use in the selected adult population; however, the overall body of evidence was considered by the authors to be of very low quality due to small sample sizes, heterogeneity of comparators, inconsistency in treatment procedures across the studies, limited follow-up data and individual study limitations. The Hayes assessment noted that this treatment approach is not curative as it only temporarily relieves pain and dysfunction for only while the device is implanted and functioning. The duration of pain relief needs further investigation as does identifying specific patient selection criteria to determine who might benefit from this procedure.

In a follow up to their 2016 multicenter RCT below, van Gorp et al. (2019) continued with an open phase part of the study where all participants received optimal spinal cord stimulation (SCS) and PNFS simultaneously for treatment of low back pain due to failed back surgery syndrome (FBSS). Outcome data were collected from the 50 participants by analyzing their questionnaires using multilevel regression models at 12 months and compared with the data collected at baseline. The authors found improvement in all secondary measurements including functional capacity and in overall quality of life to be statistically significant. They noted that more than 40% of the participants reported a reduction of back pain >50%. The authors concluded that PNFS in addition to SCS provides a statistically significant and relevant relief of low back pain in FBSS patients in whom SCS alone is only effective for relief of leg pain. They noted that the study is limited due to the controlled part of the study only lasting for three months, that the study could not be blinded and that the study combined participants from both arms into the analysis. They recommend future studies to target optimization of the technique and pattern analysis.

Eldabe et al (2019) conducted the SubQStim study, a prospective multicenter RCT to compare the effectiveness of PNFS (referred to as subcutaneous nerve stimulation (SQS) in this study) plus optimized medical management (OMM) to OMM alone in people with back pain due to failed back surgery syndrome (FBSS). There were 116 participants recruited from 21 centers, which was short of the goal of 314 evaluable subjects due to the sponsor ending the study because of prolonged recruitment challenges. In the first phase of the trial, 56 participants were randomized to receive PNFS plus OMM and 60 received OMM only for nine months. Due to early study termination, participants were not able to complete the study and attend all visits as they were discontinued at various time points; in all, 74 participants were able to complete the nine-month primary endpoint visit. The authors recognized that the study had a few potential limitations. First, there was a lack of blinding as insertion of the PNFS was a surgical intervention. Second, that participants in the study could be considered as having already failed OMM by definition of FBSS which may predispose those in the OMM alone arm to not experience significant improvement. Third, the decision to end the study early resulted in a smaller number of participants contributing to the data analysis and affected the study's ability to inform on the long-term effectiveness of PNFS. The authors concluded that, despite early termination of the study, the addition of PNFS to OMM was clinically and statistically more effective than OMM alone in relieving low back pain at up to nine months.

van Gorp et al. (2016) conducted a multicenter, RCT investigating the efficacy of subcutaneous stimulation (SubQ) as ADD-ON therapy to traditional spinal cord stimulation (SCS) in treating back pain in failed back surgery syndrome patients. Individuals with a minimal pain score of 50 on a 100 mm VAS for both leg and back pain were eligible. If pain reduction after trial SCS was ≥ 50% for the leg but < 50% for the back, patients received additional SubQ leads and were randomized in a 1:1 ratio in a study arm with subcutaneous leads switched on (SubQ ADD-ON), and an arm with subcutaneous leads switched off (Control). The primary outcome was the percentage of the patients, at 3 months post-implantation, with ≥ 50% reduction of back pain. A total of 97 patients were treated with SCS for leg and back pain. Of these, 52 patients were randomized and allocated to the Control group (n=24) or to the SubQ ADD-ON group (n=28). The percentage of patients with ≥ 50% reduction of back pain was significantly higher in the SubQ ADD-ON group (42.9%) compared to the Control group (4.2%). Mean VAS score for back pain at 3 months was a statistically significant 28.1 mm lower in the SubQ ADD-ON group compared to the Control group. The authors concluded that subcutaneous stimulation as an ADD-ON therapy to SCS is effective in treating back pain in failed back surgery syndrome patients where SCS is only effective for pain in the leg.

McRoberts et al. (2013) conducted a multi-site, 2-phase, crossover RCT evaluating the safety and efficacy of PNFS in 44 patients with localized chronic intractable pain of the back. During phase I, patients rotated through 4 stimulation groups (minimal, subthreshold, low frequency, and standard stimulation). If a 50% reduction in pain was achieved during any of the 3 active stimulation groups (responder), the patient proceeded to phase II, which began with implant of the permanent system and remained in place for 52 weeks. The primary endpoint was a reduction in pain, assessed by the VAS. Of the 44 patients enrolled, 30 completed phase I. Twenty-four patients were classified as responders in phase I, and 23 received permanent system placement. Significant differences in VAS scores were observed between baseline and all follow-up visits during phase II. The authors concluded that PNFS is safe and effective as an aid in the management of chronic, localized back pain. Limitations to this trial are small study group size.

Yakovlev et al. (2011) conducted a case series study to evaluate PNFS as an alternative treatment option for patients with post-laminectomy syndrome when conventional treatments did not provide adequate relief of intractable LBP. Eighteen patients underwent an uneventful PNFS trial with percutaneous placement of 4 temporary quadripolar leads. The leads were placed subcutaneously over the lumbar or thoraco-lumbar area. The temporary leads were removed when patients experienced excellent pain relief over the next 2 days. The patients were then implanted with permanent leads. All patients reported sustained pain relief 12 months after implantation. The authors concluded that PNFS may be more effective in treating intractable LBP than SCS in patients with post-laminectomy syndrome after multilevel spinal surgeries. The lack of a control group limits the validity of the conclusions of this study.

Verrills et al. (2011) evaluated the clinical outcomes of 100 consecutive patients receiving PNFS for chronic pain in a prospective, observational study. The patients received PNFS for the treatment of chronic craniofacial, thorax, lumbosacral, abdominal, pelvic, and groin pain conditions. Overall, 72% of patients reduced their analgesic use following PNFS. Patients receiving a lumbosacral PNFS for chronic LBP reported a significant reduction in disability following treatment, as determined by the Oswestry Disability Index. No long-term complications were reported. The authors concluded that PNFS can be a safe and effective treatment option for intractable chronic pain conditions. This study was not randomized or controlled.

To aid in alleviating symptoms associated with opioid withdrawal, a PNFS delivery system known as the Bridge device (formerly known as the NSS-2 Bridge is marketed for use as a non-pharmacologic component of an inpatient or outpatient detoxification treatment program. One single-arm retrospective pilot study has been published (Miranda and Taca, 2017), citing 64 of 73 patients successfully transitioning to medically-assisted treatment after using the device with no reports of AEs. While several guidelines on the management of opioid withdrawal are available, none addressed the use of this type of device for this indication. Prospects for the Bridge System are unclear at this time (Hayes, 2021).Other FDA approved PNFS systems similar to the Bridge are the DrugRelief® stimulator and the Sparrow Therapy System™. These auricular neurostimulation devices are also used to reduce the symptoms of opioid withdrawal during detoxification. At present, there are no studies or published literature relating to these devices. More information on these devices can be found using Product Code PZR on the following FDA website: 510(k) Premarket Notification (fda.gov). Accessed December 1, 2021.

~~Evidence on PNFS is limited, consisting of small uncontrolled and case studies. Prospective controlled trials are needed to evaluate the efficacy of this treatment.~~

Microcurrent Electrical Nerve Stimulation Therapy (MENS)

~~A 2018 Hayes report evaluated the use of microcurrent electrical therapy (MET) for the treatment of musculoskeletal pain in comparison with usual care. The literature search identified 6 eligible studies that compared MET with an alternative treatment in patients with musculoskeletal pain (lateral epicondylitis, LBP, Achilles tendinopathy, temporomandibular joint pain, and masticatory pain associated with bruxism (teeth grinding)). Evidence was considered to be very low quality. The authors concluded that there is insufficient evidence to assess the efficacy of MET for the treatment of pain associated with any of these conditions due to the paucity of evidence evaluating MET in any one indication. Additionally, the report concluded that there is substantial~~

~~uncertainty regarding whether MET provides reduction in pain compared with usual care in patients with lateral epicondylitis.~~

~~MET was also evaluated by Hayes for the treatment of postoperative pain in adults. The literature search identified only 3 studies that evaluated MET for post-TKA (2 studies) and total hip arthroplasty (1 study). The authors concluded that there is insufficient evidence to evaluate use of MET for this indication, and there is substantial uncertainty regarding whether this technology provides pain relief in adults undergoing total joint arthroplasty (2018).~~

MENS therapy has been studied in several small RCTs and case series for conditions such as delayed onset muscle soreness (Curtis et al. 2010) and diabetes, hypertension, and chronic wounds (Lee, et al. 2009). None of these studies are large, controlled trials designed to test the effectiveness of MENS therapy against a placebo device. Therefore, due to the limited evidence in the peer reviewed literature, conclusions cannot be reached regarding the safety, efficacy, or utility of MENS therapy to decrease pain and/or facilitate healing for any condition.

A systematic review and meta-analysis completed by Iijima and Takahashi (2021) determined that microcurrent therapy (MCT) significantly improved shoulder pain and knee pain compared with sham MCT without any severe adverse events. Their review included four RCTs and five non-RCTs that studied the effectiveness of MCT for treating neck pain (1 non-RCT), shoulder pain (1 RCT), elbow pain (1 non-RCT), low back pain (1 RCT and 2 non-RCTs) and knee pain (including the Lawson and Ranker RCTs below and 1 non-RCT). No serious adverse events requiring medical treatment were reported among the 281 pooled participants. The authors also stated that placebo response may be joint- or disease-dependent and that sham MCT may elicit a clinically beneficial response in subacute to chronic knee pain as was supported by the high quality of evidence established by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) with high reproducibility using the Template for Intervention Description and Replication (TIDieR) checklist. The authors noted that their review was limited by only having a single reviewer rather than the preferred independent review by 2 reviewers, that their review did not include studies where MCT was compared with other treatment approaches and that the small number of included studies limited their analysis so generalizability could not be addressed. They suggested future research include high-quality clinical trials for shoulder pain and low back pain as well as the treatment effects of MCT on pain from multiple sites, and studies on the mechanism of MCT itself.

Lawson et al (2021) conducted a randomized, double-blinded, placebo-controlled clinical trial to determine if microcurrent therapy increased function and decreased pain in people with acute knee pain. The study was conducted in their university laboratory and in the homes of the 52 self-referred study participants. The participants were randomized into the treatment group (n=26) or the placebo-control group (n=26). Participants wore the electrodes with the active or placebo microcurrent treatment for three consecutive hours per day and abstained from pain or anti-inflammatory medications throughout the four-week study. Daily text reminders were sent to use the device. This method demonstrated high compliance as it required participants to respond with an affirmative response or repetitive reminder texts would be sent until confirmation of compliance was achieved. The authors reported the study showed a trend in increased function that correlated well with a decrease in pain, especially in the 3rd week, and decreased effusion on musculoskeletal ultrasound imaging over the first two weeks in the active MENS group versus the placebo group. Limitations noted by the authors include the small number of participants, the use of the Lower Extremity Function Scale (LEFS) as it

appeared to not be sensitive enough in this population to capture changes in function, and the lack of long-term follow-up. They concluded that MENS decreased knee pain and increased function and that it may be an alternative or be used with a pharmacological approach for people with acute knee pain. The authors recommend future studies evaluate the effect MENS has on edema via musculoskeletal ultrasound elastography, the effect different dosages of MENS have in the perception of specific acute knee pain and function, longer term follow-up to observe post-treatment effect of MENS on pain, function, muscle or edema and the effect of MENS on chronic knee pain especially around knee osteoarthritis.

A retrospective, case-control study by Shetty et al (2020) showed that a higher percentage of adult patients treated in their facility with adjuvant frequency-specific microcurrent (FSM) in addition to physical rehabilitation for low back pain (LBP) had significantly improved pain and disability when compared to patients in a control group who chose not receive FSM. In their study, they retrospectively reviewed data from the records of 213 patients (167 with LBP and 46 with neck pain) who received FSM in addition to their personalized therapy program along with the records of 78 patients (61 with LBP and 17 with neck pain) who only received their personalized therapy program. Each patient's rehabilitation protocol was varied and personalized based on their severity of pain and response to movement testing. All patients underwent a minimum rehabilitation treatment of 30 days and a maximum of 90 days with a minimum of 6 supervised physiotherapy sessions at the clinic. The authors concluded that the use of adjuvant FSM therapy along with active rehabilitation significantly reduced pain and disability when compared to patients treated with active rehabilitation alone for low back pain; however, the addition of FSM to therapy did not appear to significantly affect clinical outcomes of pain and disability in patients with neck pain. The authors noted that their study was limited by its retrospective design, the reporting period for results of 90 days did not reflect medium- and long-term implications of adjuvant FSM therapy, and the study measurements did not consider the effect of neurophysiological and psychosocial factors. They recommend future well-designed, placebo controlled randomized trials to confirm the benefits of adjuvant FSM therapy for treating LBP or neck pain.

In a single-center, four-arms, double-controlled pilot RCT, Ranker et al (2020) evaluated the potential effects of MET on pain in patients with knee osteoarthritis (OA), to explore effects of different treatment parameters and to distinguish these effects from placebo-effects. The study included 52 participants who were randomized into four groups: MET with 100 µA (n=14), MET with 25 µA (n=13), a sham treatment group (n=12), and a control group with no intervention (n=13). In the intervention groups, all participants received 10 treatment sessions total given over a three-week period. The participants and therapists were blinded to the treatment allocation. The authors observed that evening pain was reduced significantly in the groups that received MET compared to the sham and control groups. They also found that the difference between the sham group and the control group was not significant and that all but the sham group improved in activities of daily living. They concluded that MET has beneficial effects on pain in people with OA that are not explained by a placebo effect; however, they also recognized that further confirmation is needed before recommendations can be given. Limitations of the study that were noted by the authors included the lack of systematic tracking of additional therapies during the study and of self-medication of analgesics that could bias the results.

Kwon et al. (2017) conducted a prospective, double-blinded, sham-controlled RCT to evaluate the effects of short-term MENS on muscle function in the elderly. A total of 38 healthy elderly participants aged 65 years and above were enrolled and randomly divided

into a real MENS or a sham MENS stimulation group. Both groups received stimulation to the 8 anatomical points of the dominant arm and leg during the course of 40 minutes. The authors report that their hypothesis was accurate that real MENS was superior to sham in enhancing muscle function in healthy elderly subjects following short term application. Limitations to this study included the lack of definition of the "healthy elderly", short application time of the MENS, and lack of follow-up evaluation. Long-term RCTs with follow-up assessments are needed to confirm these results.

Gossrau et al. (2011) conducted a single-blinded, placebo-controlled randomized trial to assess the efficacy of MENS for reduction of painful diabetic neuropathy (PDN) in 41 patients. Participants were divided into 2 groups: 22 treated with MENS therapy and 19 with placebo. Treatment plan was 3 therapy sessions per week for 4 weeks. Primary outcomes measured included pain intensity, pain disability, and QOL at baseline, and the end of treatment, and 4 weeks post-treatment using standardized questionnaires. Patients with a minimum of 30% reduction in neuropathic pain score (NPS) were defined as therapy responders. After 4 weeks, only 6 of 21 patients in the study group (30%) responded to MENS therapy versus 10 of 19 (53%) of the placebo group. The differences in Pain Disability Index (PDI) for both groups were not statistically significant. The authors concluded that MENS therapy for PDN is not superior to placebo.

Koopman et al. evaluated the efficacy of MENS in treating aspecific, chronic LBP in a double-blind, randomized, crossover pilot trial. Ten succeeding patients presenting with nonspecific, chronic LBP in the university setting were included. Patients started with two, 9-day baseline periods followed by a 5-day treatment period. During the treatment periods, either a placebo or MCT (verum) patch was randomly assigned. Mean and worst pain scores were evaluated daily by VAS score. Analgesic use, side effects, and QOL 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 also compared. A 20-mm VAS score reduction was considered clinically relevant. All outcome measures demonstrated efficacy with the verum treatment, except for an increase in NSAID use. However, none of the findings were statistically significant. The authors concluded that a positive trend in MENS use for a specific, chronic LBP could be reported, but that further research is required to evaluate the significance and relevance of these findings (2009).

~~MENS therapy has been studied in other small RCTs and case series for conditions such as delayed onset muscle soreness (Curtis et al. 2010) and diabetes, hypertension, and chronic wounds (Lee, et al. 2009). None of these studies are large controlled trials designed to test the effectiveness of MENS therapy against a placebo device. Therefore, due to the limited evidence in the peer reviewed literature, conclusions cannot be reached regarding the safety, efficacy, or utility of MENS therapy to decrease pain and/or facilitate healing for any condition.~~

Zuim et al. (2006) evaluated the effect of MENS therapy compared with occlusal splint therapy in temporomandibular disorders (TMD) patients with muscle pain. Twenty patients with TMD were divided into 4 groups: occlusal splint therapy and MENS (group I); occlusal splints and placebo MENS (group II); only MENS (group III), and placebo MENS (group IV). Sensitivity derived from muscle palpation was evaluated using a VAS. There was reduction of pain level in all groups: group I reported a 47.7% reduction rate; group II, 66.7%; group III, 49.7% and group IV, 16.5%. However, the differences between groups relating to TMD muscle pain reduction were not statistically significant after 4 weeks. The authors concluded that MENS was not statistically superior to occlusal splints in the treatment

of masticatory muscle pain in TMD patients. Study limitations include small study group and short follow-up period.

Percutaneous Electrical Nerve Stimulation (PENS)

~~A Hayes report evaluated the peer-reviewed literature related to PENS for the treatment of chronic LBP and PNT for the treatment of LBP. Evidence from the available studies (which included 3 RCTs with a range of 34-200 participants and 1 pretest/posttest study) was considered to be fair, poor, or very poor quality. The 3 RCTs evaluated the efficacy and safety of PENS for chronic LBP in adults and remaining study evaluated PNT for subacute radiating LBP. The authors concluded that there was insufficient published evidence to assess the clinical validity of PENS alone or in combination with physical therapy or general conditioning exercise in patients with chronic LBP. Additionally, the report concluded that there is insufficient published evidence to assess the impact of PNT on health outcomes or patient management for the treatment of LBP (2019).~~

~~A Hayes evidence brief concluded that there is insufficient published evidence to evaluate the IB-Stim PENFS device (Innovative Health Solutions, Inc., Versailles, IN) for treatment of pain associated with irritable bowel syndrome (2019).~~

While some studies have compared the effectiveness of PENS or PENTS to placebo, the overall quality of the evidence is weak and quite limited as published studies have included small patient populations and short-term follow-ups. Further robust studies are needed to evaluate the efficacy of this therapy for chronic pain.

An updated Hayes evidence analysis research brief concluded that there is still insufficient published evidence to evaluate the IB-Stim PENFS device (Innovative Health Solutions, Inc., Versailles, IN) for treatment of pain associated with irritable bowel syndrome in patients aged 11 to 18 years (2019, updated 2021).

ECRI (2021) published a Clinical Evidence Assessment on the IB-Stim device (Innovative Health Solutions) that is intended to treat adolescents (aged 11 to 18 years) with abdominal pain related to irritable bowel syndrome (IBS). The authors identified a single, published post hoc subgroup analysis of adolescents with IBS who were included in the IB-Stim pivotal trial that compared the efficacy of the device in a sham controlled trial with 27 adolescents who received IB-Stim treatment with 23 adolescents who received sham stimulation. This study suggested that IB-Stim reduces abdominal pain more than sham stimulation by 3-week follow-up, but that benefits were not sustained through 12-week follow-up. The authors excluded the pivotal trial itself from the Assessment because it included pooled outcomes from patients with other gastrointestinal disorders as well as IBS. The authors stated that the major limitations of the post hoc analysis were that it does not permit conclusions because of the design of the pivotal study itself, that the subgroup analysis compromised the pivotal study's randomization because the randomization was not stratified by patient condition, the analysis had a small sample size, a single center design and a lack of published independent studies to validate the findings. They also noted the post hoc analysis had a high risk of bias which rendered the evidence inconclusive. The authors recommended RCTs comparing IB-Stim with pharmacotherapy and other noninvasive pain management techniques in adolescents and reporting on patient-oriented outcomes to address evidence gaps.

In a multicenter RCT, Gao et al (2021) assessed the preventive effectiveness of transcutaneous electrical acupoint stimulation (TEAS) on postoperative paralytic ileus (POI) after colorectal surgery. The study included 610 participants from 10 hospitals who

were randomly allocated into the TEAS group or a sham group with 307 patients allocated to the sham group and 303 patients to the TEAS group. All participants, the researchers, surgeons, and anesthesiologists were blinded to the study group allocation. TEAS treatment or sham was administered in the PACU and once a day for the first three postoperative days. The authors found that TEAS lowered the incidence of postoperative paralytic ileus following colorectal surgery by 8.7% and decreased the risk of postoperative paralytic ileus by 32%. They also noted that TEAS enhanced gastrointestinal functional recovery with shortened recovery time to flatus, defecation, normal diet and bowel sounds. No statistically significant difference was found in the 30-day postoperative complication rate or with the total length of stay between the TEAS and sham groups. The authors noted that the study was limited by the fact that the participants could not be blinded to the treatment due to the nature of the intervention itself, that the efficacy of reducing POI after other kinds of surgery is unknown, that the study excluded participants with prophylactic ileostomy due to the difficulties in evaluating for flatus, that the block randomization methodology may not have completely avoided the violation of allocation concealment and that the study was not undertaken in combination with a comprehensive Enhanced Recovery After Surgery (ERAS) program. They recommend future studies to assess the long-term surgical outcomes when TEAS is included in the treatment protocol.

Chen et al. (2020) conducted a meta-analysis of 14 RCTs with 1653 participants (835 received TEAS in experimental group, 818 received sham TEAS in control group) to evaluate the effectiveness of transcutaneous electrical acupoint stimulation (TEAS) for preventing postoperative nausea and vomiting (PONV) after general anesthesia. The authors reported no publication bias was detected and that the meta-analysis showed that the addition of TEAS to postoperative care resulted in lower incidence of PONV, fewer patients needing antiemetic rescue, lower incidence of dizziness and pruritis compared with controlled intervention. They concluded that TEAS is a reasonable modality to incorporate into a multimodal management approach for the prevention of PONV, postoperative nausea, postoperative vomiting. They stated that their findings should be interpreted with caution because of the limitations in the meta-analysis which include that the specific mechanism of TEAS is not clear and limits the promotion of its use, that 12 of the studies were conducted in China where the technique may be more popular, the small sample sizes (<100 participants) in all of the studies, short-term follow-up with symptoms only being recorded within 24 hours after surgery. The authors recommend more studies to focus on the long-term effect of TEAS on PONV and relevant outcomes, and whether TEAS could prevent PONS secondary to other types of anesthesia beyond general anesthesia.

To evaluate the effects of PENS alone or as an adjunct with other interventions on pain and related disability in musculoskeletal pain conditions, Plaza-Manzano et al (2020) conducted a systematic review and meta-analysis of 19 parallel or cross-over RCTs with various musculoskeletal conditions with short- or midterm follow-ups. They found most studies to be of high methodological quality except for three that were considered poor quality and that most the trials were biased due to the inability to blind the therapists and participants; however, in general, the risk of bias of the trials in the meta-analysis was low. The authors concluded that there was a low level of evidence indicating the effects of PENS alone had a large effect compared with sham and a moderate effect when compared with other interventions for decreasing pain intensity at short term. The authors acknowledged that the systematic review and meta-analysis were limited by the number of RCTS looking at the effect of PENS on specific musculoskeletal pain conditions was small, that the method of evaluation of PENS varied and that the results of some of the RCTs were inconsistent and unprecise. They recommended well-designed RCTS to examine the effect of PENS alone or in combination with other therapeutic interventions with

long-term follow-up periods and that the trials be designed to compare the effect of real vs. sham PENS as well as the most appropriate treatment parameters and anatomical locations to create reproducible results.

In a single-center, double-blind RCT, Kong et al (2020) evaluated the effect of electroacupuncture (EA) on pain severity in adults with chronic low back pain (CLBP). The study included 121 adults who were randomized into either a treatment group (n=59) or a sham (n=62) group and then treated by one of 10 acupuncturists for 12 sessions of real or placebo (sham) electroacupuncture administered twice a week over 6 weeks. Outcome measures were collected, and participants were followed for two weeks beyond completion of the six-week treatment protocol. The authors found no significant difference in CLBP scores between real and sham electroacupuncture treatment; however, post hoc analyses did find a significant treatment effect of EA in reducing disability associated with CLBP. They stated that the finding of an association between positive coping strategies and functional improvement that was seen on both the univariate and multivariate analyses is unique to the study. The authors also found that the White race was associated with worse outcomes in pain and felt that the racial influence may be caused by differences in cultural backgrounds in that participants with backgrounds that include traditional Chinese medicine may be more likely to respond to acupuncture. Limitations they noted included that the study does not quantify the specific effect of EA vs manual acupuncture, that there was missing blinding data due to implementation imperfections and that the outcome collection spanned a total of only 10 weeks. The authors recommend larger studies with multicultural samples and testing the interaction between cultural background and treatment allocation, as well as collecting longer-term outcomes.

Meng et al. (2018) conducted a multicenter RCT to investigate the effects of electroacupuncture (EA) on reducing inflammatory reaction and improving intestinal dysfunction in patients with sepsis-induced intestinal dysfunction with syndrome of obstruction of the bowels. A total of 71 patients were randomly assigned to control group (n=36) and treatment group (n=35). Patients in the control group were given conventional therapies including fluid resuscitation, anti-infection, vasoactive agents, mechanical ventilation, supply of enteral nutrition, and glutamine as soon as possible. In addition to conventional therapies, patients in treatment group underwent 20 minutes of EA twice a day for 5 days. At baseline, day 1, day 3, and day 7 after treatment, biomarkers assessing intestinal inflammation and dysfunction were measured and recorded, respectively. Additionally, days on mechanical ventilation (MV), length of stay in intensive care unit (ICU), and 28-day mortality were also recorded. The authors concluded that EA, as a supplement to conventional therapy, can reduce inflammatory reaction and has protective effects on intestinal function than conventional therapy alone in patients with sepsis-induced intestinal dysfunction with syndrome of obstruction of the bowels. However, there were no significant differences identified between the 2 groups relative to number of days on MV, length of stay in ICU, and 28-day mortality. Limitations to this study include small sample size and single-center investigation. Further studies are required.

Mi et al. (2018) conducted a randomized observational trial to evaluate the effect of transcutaneous electrical acupoint stimulation (TEAS) on dosages of anesthetic and analgesics as well as the quality of recovery during the early period after laparoscopic cholecystectomy. One hundred patients who underwent laparoscopic cholecystectomy with grade I and II of the American Society of Anesthesiologists criteria were evenly and randomly assigned into an observation group and a control group. The patients in the observation group were treated with TEAS from 30 minutes prior to anesthesia induction to the end of operation. The patients in the control group received stimulation electrode(s)

in the corresponding points without ES for the same time period. Researchers concluded that TEAS **could**~~can~~ reduce the dosage of anesthetic and analgesic delivered intraoperatively, as well as improve the quality of recovery during the early period after laparoscopic cholecystectomy.

Kovacic et al. (2017) conducted a single center, blinded, sham RCT evaluating the efficacy of a PENFS device known as Neuro-Stim (Innovative Health Solutions, Versailles, IN) in adolescents with abdominal pain-related functional gastrointestinal disorders. Adolescents (aged 11-18 years) who met Rome III criteria with abdominal pain-related functional gastrointestinal 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 (1 in the study group, 7 in the sham group) and those who were excluded after randomization because they had organic disease (2 and 1 in the study and sham groups, respectively), 57 patients in the PENFS group and 47 patients in the sham group were included in the primary analysis. The primary efficacy endpoint was change in abdominal pain scores measured via the Pain Frequency-Severity-Duration (PFSD) scale. Patients in the PENFS group had greater reduction in worst pain compared with sham after 3 weeks of treatment. Participants from each group (n=10) discontinued the study due to side-effects, none of which were serious. Symptoms included ear discomfort, adhesive allergy, and syncope due to needle phobia. The researchers concluded that PENFS with Neuro-Stim is has sustained efficacy for abdominal pain-related functional gastrointestinal disorders in adolescents. Study limitations include small sample size and short follow up period and exclusions after randomization.

Rossi et al. (2016) conducted a multicenter, prospective, observational study to evaluate the short- and long-term efficacy of a single probe and single shot PENS approach to treat chronic neuropathic pain. Seventy-six patients affected by neuralgia were enrolled in the study and divided into 3 groups depending on the etiology of the neuralgia (21 herpes zoster infection, 31 causalgia, 24 postoperative pain). In the study, Numerical Rating Scale (NRS) and Neuropathic Pain Scale (NPS) were assessed at baseline, 60 minutes after PENS, 1 week, and 1, 3, and 6 months post-therapy. Perceived health outcome was measured with Euroqol-5 dimension (EQ-5D) questionnaire at baseline and at 6 months. Pain assessment ratings decreased significantly after 60 minutes of PENS therapy and the reduction remained constant throughout the follow up period. Perceived health outcome measured with EQ-5D increased significantly from baseline. The authors concluded that PENS therapy produced significant and long-lasting pain relief in chronic peripheral neuropathic pain of different etiologies. The study limitations included small sample size, non-randomized observational study, short follow up period, and high prevalence of post-herpetic and occipital neuralgias.

~~In 2013, NICE published guidance related to the use of PENS to control neuropathic pain. The guidance states, "The current evidence on the safety of 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. The guideline also indicates that NICE encourages further research into PENS for refractory neuropathic pain, particularly to provide more information about selection criteria and long-term outcomes, with clear documentation of the indications for treatment.~~

In 2011, Wanich and colleagues conducted a RCT to study the use of the Deepwave PNT system in patients who underwent primary TKA. Trial participants (n=23) were categorized into 2 groups (experimental or control). Following surgery, patients underwent either Deepwave or sham treatments. A Brief Pain Inventory questionnaire and the amount of all

pain medications taken were recorded. The study results demonstrated a significant reduction in patient's subjective rating of pain and VAS score in the experimental group ($p < 0.05$), with a trend toward decreased opioid use but this was not statistically significant ($p = 0.09$). The authors concluded that the Deepwave device was effective in reducing the subjective measures of pain with a trend toward decreased opioid use in patients following TKA. Details regarding the duration of treatments or the length of follow up were not documented.

Raphael et al. (2011) conducted a randomized double-blind sham-controlled crossover trial on 31 patients suffering from chronic pain with surface hyperalgesia to investigate the efficacy of PENS. The study results demonstrated statistically significant improvements from pre-therapy ratings and assessment of pain in the PENS group versus the sham group using the numerical rating scale (NRS) and the pain pressure threshold (PPT). The authors concluded that PENS therapy appeared to be effective in providing short-term pain relief in chronic pain conditions; however, studies, involving larger sample sizes and longer follow-up were recommended.

~~While some studies have compared the effectiveness of PENS to placebo, the overall quality of the evidence is weak and quite limited. Further robust studies are needed to evaluate the efficacy of this therapy for chronic pain.~~

~~*Professional Societies*~~*Clinical Practice Guidelines*

American Academy of Orthopaedic Surgeons (AAOS)

In the updated evidence-based clinical practice guideline on non-arthroplasty management of osteoarthritis of the knee, the AAOS reviewed one high quality study and downgraded their recommendation one level to Limited due to feasibility issues. The authors noted that PENS is feasible but requires a practitioner trained in PENS which may limit access for some patients. The guideline stated that continued research with larger RCTs that examine the long-term effectiveness of PENS is needed and that the studies that identify responders and non-responders to PENS would also be important (2021).

National Institute for Health and Clinical Excellence (NICE)

NICE updated their guidance on the use of TENS, percutaneous electrical nerve simulation (PENS) and IFT for managing low back pain with or without sciatica and stated that these modalities should not be offered for treatment of low back pain with or without sciatica due to the paucity of evidence available that included mostly small individual studies of low or very low quality. No clinical benefit was found for PENS on improving pain and function when compared to usual care in a mixed population of people with or without sciatica. Clinical benefit for pain and function was observed at less than four months but no clinical benefit was found after 4 months. The Guideline Development Group GDG) noted that, although there was evidence in places positive for people with low back pain, it was of low quality with low patient numbers. It was also noted that PENS is not widely used so a recommendation for its use would be a significant change in practice. The GDG concluded that there was insufficient evidence of clinical benefit to support a recommendation for the use of PENS for low back pain or sciatica (2016, updated 2020).

In 2013, NICE published guidance related to the use of PENS to control neuropathic pain. The guidance states, "The current evidence on the safety of 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. The guideline also indicates that NICE encourages further research into PENS for refractory neuropathic pain, particularly to provide more

information about selection criteria and long-term outcomes, with clear documentation of the indications for treatment.

American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), American Academy of Physical Medicine and Rehabilitation (AAPMR)

In a joint guideline report on the treatment of painful diabetic neuropathy (PDN), the AAN, AANEM, and AAPMR concluded that PENS should be considered for the treatment of PDN (Bril et al., 2011).

~~Dorsal Root Ganglion (DRG) Stimulation~~

~~Kretzschmar et al. (2020) conducted a single-center, retrospective case series study to evaluate safety and effectiveness outcomes of dorsal root ganglion (DRG) stimulation for peripheral nerve injuries (PNI). A total of 27 individuals with PNI received a five- to six-day trial of a DRG neurostimulation system. Trial success (defined as ≥ 50% pain relief) was 85% and 23 patients received a permanent stimulator. Outcomes included pain, quality of life, mental and physical function, and opioid usage and were assessed at baseline and at 3-, 6-, 12-, 18-, 24-, and 36 months post-permanent implant. Implant-related complications were also documented. Thirty-six months of follow-up data were available for 21 patients (67% female), mean (SD) age was 52.5 ± 14.2 years, and PNI was diagnosed in the upper extremity in 4 patients and in the lower extremity in 17 patients. Compared to baseline, there was significant pain relief (p<0.001) at 3 (58%), 12 (66%), 18 (69%), 24 (71%), and 36 months (73%), respectively. Mental and physical function showed immediate and sustained improvements. Participants reported improvements in quality of life. Opioid dosage reduced significantly (p<0.001) at 3 (30%), 12 (93%), 18 (98%), 24 (99%), and 36 months (99%), and 20 of 21 patients were completely opioid-free after 36 months. There were five electrode dislocations and two electrode fractures during the follow up (between 2 and 15 months after primary surgery); four leads were replaced during an additional surgery intervention without any complications, three leads could not be replaced and therefore, their position had to be changed to a neighboring foramen. One patient developed a superficial wound infection which was conservatively treated and controlled. Two patients asked for the device to be removed within the first year after complete implantation despite good pain relief under therapy due to subjective discomfort caused by the implant (pocket pain). The authors concluded that DRG neuromodulation appears to be a safe, effective, and a durable option for treating neuropathic pain caused by PNI. They also stated that the treatment allows cessation of often ineffective pharmacotherapy (including opioid misuse) and significantly improves quality of life. Caution should be used when interpreting the study results as there are several limitations. Those include the study design, a case series lacking randomization and contemporaneous comparison group, the study data, that was retrospectively collected survey data from a single provider, and its small sample size. Additional multi-center, prospective, randomized trials with longer follow-up are still needed to elucidate DRG's role in the treatment of PNI.~~

~~Hayes performed an evidence review from 3 studies that evaluated DRG stimulation for treatment of complex regional pain syndrome (CRPS) in adults. Overall, a very-low-quality body of evidence suggests that DRG stimulation may result in treatment success, reductions in pain, and improvements in QOL compared with baseline assessments or SCS treatment. However, this body of evidence is limited by individual study limitations, limited quantity of evidence, and the availability of a single study comparing groups of patients that received DRG stimulation or spinal cord stimulation (SCS). In addition,~~

~~current evidence suggests a potential safety concern for procedure-related AEs with DRG stimulation. Currently, there is insufficient evidence to draw conclusions regarding the safety and effectiveness of DRG stimulation for the treatment of CRPS in adults (2020).~~

~~Deer et al (2017) conducted a prospective, multicenter, randomized comparative effectiveness trial (known as the ACCURATE trial) in 152 subjects diagnosed with CRPS or causalgia in the lower extremities. Subjects received neurostimulation of the DRG or dorsal column (SCS via the Axium™ DRG system. The primary end point was a composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and AEs. The predefined primary composite end point of treatment success was met for subjects with a permanent implant who reported 50% or greater decrease in VAS score from pre-implant baseline and who did not report any stimulation-related neurological deficits. No subjects reported stimulation-related neurological deficits. The percentage of subjects receiving ≥ 50% pain relief and treatment success was greater in the DRG arm (81.2%) than in the SCS arm (55.7%) at 3 months. Device-related and serious AEs were not different between the 2 groups. DRG stimulation also demonstrated greater improvements in QOL and psychological disposition. Finally, subjects using DRG stimulation reported less postural variation in paresthesia and reduced extraneous stimulation in non-painful areas, indicating DRG stimulation provided more targeted therapy to painful parts of the lower extremities. The researchers concluded that DRG stimulation provided a higher rate of treatment success with less postural variation in paresthesia intensity compared to SCS. Additional prospective randomized trials with longer follow-up are still needed to clarify the safety and efficacy of DRG in patients with CRPS or causalgia.~~

~~Liem et al. conducted a multi center prospective case series study to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the DRG neurophysiologically associated with painful regions of the limbs and/or trunk. The first publication (Liem 2013) reported outcomes from 32 subjects who were implanted with a novel neuromodulation device. Pain ratings during stimulation were followed up to 6 months and compared with baseline ratings. Subjects also completed 2 separate reversal periods in which stimulation was briefly stopped in order to establish the effects of the intervention. At all assessments, more than half of subjects reported pain relief of 50% or better. At 6 months post implant, average overall pain ratings were 58% lower than baseline, and the proportions of subjects experiencing 50% or more reduction in pain specific to back, leg, and foot regions were 57%, 70%, and 89%, respectively. When stimulation was discontinued for a short time, pain returned to baseline levels. Discrete coverage of hard-to-treat areas was obtained across a variety of anatomical pain distributions. Paresthesia intensity remained stable over time and there was no significant difference in the paresthesia intensity perceived during different body postures/positions (standing up vs. lying down). The authors concluded that this trial demonstrated that neurostimulation of the DRG is a viable neuromodulatory technique for the treatment of chronic pain. Additionally, the capture of discrete painful areas such as the feet combined with stable paresthesia intensities across body positions suggest that this stimulation modality may allow more selective targeting of painful areas and reduce unwanted side-effects observed in traditional SCS.~~

~~Acknowledging their earlier research, Liem et al. (2015) reported on the maintenance of pain relief, improvement in mood, and QOL over 12 months. Subjects with intractable pain in the back and/or lower limbs were implanted with an active neurostimulator device. Up to 4 percutaneous leads were placed epidurally near DRGs. Overall pain was reduced by 56% at 12 months post-implantation, and 60% of subjects reported greater than 50% improvement~~

~~in their pain. Pain localized to the back, legs, and feet was reduced by 42%, 62%, and 80%, respectively. Measures of QOL and mood were also improved over the course of the study, and subjects reported high levels of satisfaction. Importantly, excellent pain-paresthesia overlap was reported, remaining stable through 12 months. There were 86 safety events reported across 29 subjects; approximately half were judged by the investigators to be related to the device. The most common adverse events were temporary motor stimulation (12 events; 14.6%), cerebrospinal fluid leak with associated headache (7 events; 8.5%), and infection (7 events; 8.5%). The authors concluded that improvements in ratings of pain, mood, and quality of life with DRG-SCS have been demonstrated through 12 months of therapy. They also noted that there was good agreement in pain-paresthesia overlap and high levels of user satisfaction. Caution should be use when interpreting these study results as there are several limitations. Those include the study design as a case series lacking randomization and contemporaneous comparison group, the number of safety events that investigators deemed to be related to the device, and lack of long-term outcomes. Additional prospective randomized trials are needed to evaluate the utility of DRG stimulation in patients with back and/or lower limb pain.~~

~~Schu et al. (2015) conducted a retrospective review of data from patients with groin pain of various etiologies treated using neuromodulation of the DRG. Twenty-nine patients with neuropathic groin pain were reviewed. Patients underwent trial therapy where specifically designed leads were implanted at the target DRGs between T12 and L4. Patients who had a successful trial (> 50% improvement) received the fully implantable neuromodulation system. Pain scores were captured on a VAS at baseline and at regular follow-up visits. Twenty-five patients (86.2%) received fully implantable neurostimulators, and the average follow-up period was 27.8 ± 4.3 weeks. The average pain reduction was 71.4 ± 5.6%, and 82.6% (19/23) of patients experienced a > 50% reduction in their pain at the latest follow-up. Individual cases showed improvement with a variety of etiologies and pain distributions; a subanalysis of post-herniorrhaphy cohort also showed significant improvement. The authors concluded that early findings suggest that neuromodulation of the DRG may be an effective treatment for chronic neuropathic pain conditions in the groin region. This technique offers a useful alternative for pain conditions that do not always respond optimally to traditional SCS therapy. Neuromodulation of the DRG provided excellent cross-dermatomal paresthesia coverage, even in cases with patients with discrete pain areas. The therapy can be specific, sustained, and independent of body position. Study limitations include non-randomization and small sample size.~~

~~Several clinical trials studying DRG stimulation in patients with various conditions are active or recruiting. For more information, go to www.clinicaltrials.gov. (Accessed November 18, 2020)~~

Scrambler Therapy (ST)

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of Scrambler Therapy / transcutaneous electrical modulation pain reprocessing (TEMPR) therapy. Studies comparing TEMPR to conventional treatment options and to sham therapy are lacking.

Kashyap and Bhatnagar (2020) conducted a systematic review to detect possible gaps in the literature regarding the efficacy of ST for cancer pain and formulate recommendations for research. Using predetermined terms, a search was conducted in PubMed and Embase. A total of 27 studies were retrieved. Ten were articles that were categorized as literature reviews, including 7 narrative reviews, 1 editorial, and 2 systematic reviews. Seventeen were original studies, including 2 single-arm trials, 1 randomized controlled trial, 4

pilot trials, 4 case reports, 2 retrospective studies, and 4 prospective studies. The authors state that in general, the available literature supports the use of ST as an effective therapy for the management of refractory cancer pain. However, the level of evidence for its application to cancer pain is not particularly strong, and improvement in pain with ST may even be due to a placebo effect. The authors concluded that methodologically sound, large randomized control trials are needed in this area however, ST may be considered a good option for patients with cancer who are suffering from pain that does not respond to pharmacologic treatment.

~~A~~ Hayes (2020**, updated 2021**) conducted a systematic review to evaluate evidence on the use of Scrambler Therapy (ST), also referred to as Calmare Pain Therapy and transcutaneous electrical modulation pain reprocessing, for the management chronic pain not related to cancer or cancer treatment. The literature search identified 9 relevant clinical studies that met inclusion criteria: 2 RCTs, 1 quasi-RCT, and 6 single-arm studies, including 1 repeated measures time series, 3 pretest/posttest studies, and 2 retrospective database reviews. **Hayes noted that a majority of these studies had limited follow-up of ≤ 6 months, making it hard to evaluate long-term effects of ST and that the generalizability of the results was unclear because of the varied treatment regimens across studies and heterogeneity of pain etiologies in the evaluated populations.** The findings included that the body of evidence, which was considered low or very low quality, is insufficient to draw conclusions regarding the effectiveness, efficacy, and safety ST for the management of chronic pain not related to cancer or cancer treatment in adults and as a result, there is a need for additional large, well-designed clinical studies to evaluate the comparative and long-term effectiveness and safety of ST, and to delineate patient selection criteria.

Compagnone and Tagliaferri (2015) conducted a multicenter, retrospective analysis on the safety and efficacy of ST after 10 sessions. All the patients (n=201) were suffering from chronic neuropathic pain of multiple etiologies. The mean number of sessions per patient was 10, but 39 subjects had complete absence of pain sooner and used fewer sessions. Seven patients stopped treatment due to lack of results, and 2 withdrew for personal reasons not ascribable to the treatment. Stimulation pain score of 0 during treatment, and not just pain reduction, is believed to be a predictor of long-term effectiveness. The authors concluded that ST is an efficient and safe alternative for several different types of refractory chronic neuropathic pain, with a very rare possibility of adverse events. Further studies are needed to optimize electrode positioning and correct fine-tuning of stimulation intensity.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In the updated evidence-based clinical practice guideline by Loprinzi et al (2020) on the prevention and management of chemotherapy-induced peripheral neuropathy (CIPN) in survivors of adult cancers, the ASOC reviewed two randomized trials evaluating scrambler therapy. The Guideline stated that, outside the context of a clinical trial, no recommendation for its use in the treatment of CIPN could be made due to low strength of evidence and low benefits. The authors noted that, while the evidence suggested a potential for benefit from scrambler therapy, larger sample-sized definitive studies are needed to confirm efficacy and clarify risks.

Translingual Stimulation (TLS)

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of translingual stimulation. Robust studies evaluating the long-term safety and efficacy of TLS to treat gait disorders secondary to multiple sclerosis, cardiovascular accident and traumatic brain injury are lacking.

ECRI published a Clinical Evidence Assessment on the Portable Neuromodulation Stimulator™ (PoNS) device and its safety and efficacy for treating chronic balance deficits due to neurologic disorders. The PoNS device is a portable, non-implantable neuromuscular electrical stimulation device with a mouthpiece that sends NMES to the dorsal surface of a patient's tongue.
The Assessment included three RCTs and 1 non-randomized controlled study and concluded that the evidence was inconclusive due to too few data on the safety and efficacy of PoNS. The authors noted that the same research center that developed the PoNS device directed the three RCTs. They determined that the RCTs had a low risk of bias though because of the way that the trials blinded the participants, trainers and investigators; however, the non-randomized controlled study had a high risk of bias due to the lack of randomization and blinding. The authors noted that PoNS with physical therapy appeared to improve gait and balance in people with mild-to-moderate traumatic brain injury and that it may also benefit those with MS and cerebral palsy; however, the authors recommended additional studies to confirm the results and to determine how long improvements last (2021).

Multiple Sclerosis (MS)

Hayes published an Emerging Technology Report (2021) on use of the Portable Neuromodulation Stimulator™ (PoNS) device in addition to targeted physical therapy to treat gait deficits associated with MS. In the two clinical studies that the FDA reviewed in their authorization for the MS indication, the PoNS device was used during supervised sessions with a trained physical therapist, followed by use at home with prescribed home exercises. The Report concluded that additional research is needed to determine the extent of improvement in gait deficit and impact on daily functioning and quality of life associated with the PoNS device in patients with MS.

Leonard et al. (2017) completed a pilot study of the effects of noninvasive tongue stimulation using the PoNS device combined with intensive cognitive and physical rehabilitation on working memory, gait, balance, and concomitant changes in the brain. Their study included 14 patients with MS who were randomly assigned to a PoNS stimulation group (n=7) or to a sham PoNS™ stimulation group (n=7). At the end of the study, participants in the sham group were offered the opportunity to use the PoNS device, and five individuals returned and completed the active training. The authors concluded that there were significant effects of interventions across the wide range of cognitive domains both in the active and in the sham groups, although there was a trend of greater improvement in the active group. The data demonstrated an improvement over time following PoNS training for both the active and for the rollover group suggesting that the training can have a positive effect on balance in patients with MS. The authors noted that a major shortcoming of the study was the low number of participants in each group and recognized the need for a larger study that balances disease duration across groups.

In a randomized, double-blind, controlled pilot trial of PoNS, Tyler et al. (2014) evaluated the effect of targeted physical therapy with and without non-invasive neuromodulation to improve gait in chronic MS. The study included twenty chronic MS patients with an identified gait disturbance who were randomly assigned by the primary

investigator to either an active group (n=10) that received electrical stimulation on the tongue or to a control group (n=10) that used a device that did not provide a physiologically significant stimulation on the tongue. The participants and the therapists were blinded as to which group the participant was assigned. Both groups completed a 14-week therapy program with a standardized combination of exercise and the PoNS device that provided electrical stimulation to the tongue. The authors noted that all participants appeared to demonstrate improvements initially, but only the active group continued to improve over the length of the study. Data showed that participants who trained using exercise only without stimulation (control group) continued to improve for the first month at home and then exhibited a plateau or even a decrease in performance. The authors concluded that the active group showed statistically greater improvement in gait than the control group and that non-invasive electro tactile stimulation, when combined with targeted physical therapy exercises, can significantly reduce clinical symptoms of gait dysfunction in multiple sclerosis.

Traumatic Brain Injury (TBI)

Ptito et al (2021) conducted a multicenter RCT with 122 adults, aged 18-65, to assess the safety and efficacy of translingual neurostimulation (TLNS) in patients with a chronic balance deficit who had received physical therapy following a mild to moderate TBI (mmTBI) and had plateaued in recovery. TLNS was delivered through the portable neuromodulation stimulator (PoNS). Randomized participants received PT plus either high-frequency pulse (active therapy; *n* = 59) or low-frequency pulse (control group; *n* = 63) TLNS during a 5-week treatment program. All participants followed the same TLNS use and PT regimen with a customized training intensity that was based on the individual's presentation and abilities. Adherence was monitored and verified through the TLNS device automatically by logging usage and showed overall compliance was a mean of 94% across weeks 2 through 5 of the study. The authors noted that participants in both the active and the control group had significant and clinically meaningful improvements in sensory organization test composite score and the dynamic gait index. They noted that the results of this study are limited by the small sample size, the fact that there were two times more female to male participants which is not consistent with the incidence of TBI in the general population, and that there was great variability in previous therapy programs which may have influenced the efficacy of the physical therapy program in the study. The authors concluded that the combination of TLNS plus targeted PT resulted in significant improvements in balance, gait and sleep quality, in addition to reductions in the frequency of headaches and falls.

Tyler et al (2019) conducted a single-site, double-blind RCT to compare the efficacy of the dosage of high- and low-frequency noninvasive portable neuromodulation stimulator (PoNS) plus targeted physical therapy for treating chronic balance and gait deficits in participants with mmTBI. In their study, 44 participants (18-65y) were randomized 1:1 into either a high-frequency pulse (HFP) group or a low-frequency pulse (LFP) group. All participants received TLNS (HFP or LFP) with PT for a total of 14 weeks (2 in clinic, 12 at home), twice daily followed by another 12 weeks without treatment. The authors found that both groups had a significant improvement in balance, gait, and sleep quality along with reduction in headache severity and frequency. They also found that the improvements were sustained through the 12 weeks after discontinuing TLNS and that results between the groups did not differ significantly from each other. Limitations identified by the authors include the inherent variable presentation of TBI, differences in the nature of mmTBI, participant age, symptom number and severity, time since injury, age at time of injury and degree of success with prior therapy programs might have influenced the variability seen with each assessment. They also noted that there was variability in each

participant's physical, cognitive, and emotional capacity for the training program as well as the impact of the placebo effect, Hawthorne effect, and nonspecific attention and care on study outcomes. The authors recommended future research to assess the dosing parameters of TLNS, a well as additional and longer-term benefits of this treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Functional Electrical Stimulation (FES) Devices

Products used for FES are extensive. See the following website for more information and search by either product code GZI or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 9, 2021)

Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation Devices

Products used for NMES for muscle rehabilitation are extensive. See the following website for more information and search by either product code IPF or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 9, 2021)

Interferential Therapy (IFT) Devices

Products used for IFT are extensive. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2021)

Pulsed Electrical Stimulation (PES) Devices

There are multiple products used for PES. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2021)

Percutaneous Peripheral Nerve Stimulation (PNS)

There are several devices used for PNS such as the StimRouter Neuromodulation System, SPRINT PNS System, and StimQ Peripheral Nerve Stimulator System. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 9, 2021)

Peripheral Subcutaneous Field Stimulation (PSFS) or Peripheral Nerve Field Stimulation (PNFS) Devices

PSFS or PNFS using a fully implantable system is not currently approved by the FDA. See the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2021)

The Bridge System (previously, the NSS-2 System), a PNFS system marketed as an aid to reduce the symptoms of opioid withdrawal, was FDA approved on November 15, 2017 (Product Code PZR). For more information, go to:

https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170018.pdf. (Accessed November 30, 2021)

The DrugRelief® auricular stimulator, a PNFS system marketed as an aid to reduce symptoms of opioid withdrawal, was FDA approved on May 2, 2018 (Product Code PZR). For more information, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K173861. (Accessed November 30, 2021)

The Sparrow Therapy System™ is a transcutaneous auricular neurostimulation device that was FDA approved on January 2, 2021 (Product Code PZR) to be used in patients experiencing opioid withdrawal in conjunction with standard of care for opioid withdrawal symptoms under the supervision of trained clinical personnel. For more information, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K201873. (Accessed November 30, 2021)

Microcurrent Electrical Nerve Stimulation Therapy (MENS) Devices

MENS devices are categorized as TENS devices intended for pain relief. They are regulated by the FDA's premarket approval (PMA) process. See the following website for more information and search by Product Code GZJ with specific product name in device name section: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed December 2, 2021)

Percutaneous Electrical Nerve Stimulation (PENS) or Percutaneous Electrical Nerve Field Stimulation (PENFS)

The FDA regulates PENS stimulators as class II devices (Product Code NHI). Several PENS devices have been approved by the FDA. See the following website for more information and search by product name in device name section: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed December 2, 2021)

The IB-Stim, a PENFS system intended for use with functional abdominal pain associated with irritable bowel syndrome (IBS) in patients 11-18 years of age, was FDA approved on 6/7/19 (Product Code QHH). For more information, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN180057. (Accessed December 2, 2021)

The Deepwave Percutaneous Neuromodulation Pain Therapy System received FDA 510K approval on April 27, 2006 (Product Code NHI) as a PENS device used for the treatment of pain. For more information , go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K061166. (Accessed December 7, 2021)

Scrambler Therapy (ST)

The Calmare®/ST MC-5A TENS Device was initially approved by the FDA on February 20, 2009. A second 510(k) clearance was issued on May 22, 2015, for the ST MC-5A Device which has also been replaced by the Scrambler Therapy Technology (Model ST-5A) on December 23, 2020 (Product Code GZJ). For more information, go to the following websites:

- https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142666.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201458.pdf

(Accessed December 2, 2021)

Transcutaneous Electrical Nerve Stimulators

Transcutaneous electrical nerve stimulators (TENS) are regulated by the FDA as Class II devices. Products for TENS are too numerous to list. See the following website for more information (use product codes GZJ, NUH, or NGX). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 11, 2022)

Translingual Stimulation Devices

TLS devices are categorized as neuromuscular tongue stimulators to treat motor deficits. The Portable Neuromodulation Stimulator (PoNS) device was granted De Novo approval on March 25, 2021. The device is indicated for use as a short-term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program in patients 22 years of age and over by prescription only. See the following website for more information https://www.accessdata.fda.gov/cdrh docs/pdf20/DEN200050.pdf. (Accessed December 8, 2021)
~~This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.~~

~~Functional Electrical Stimulation (FES) Devices~~

~~Products used for FES are extensive. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation Devices~~

~~Products used for NMES for muscle rehabilitation are extensive. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~Interferential Therapy (IFT) Devices~~

~~Products used for IFT are extensive. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~Pulsed Electrical Stimulation (PES) Devices~~

~~There are multiple products used for PES. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~Peripheral Subcutaneous Field Stimulation (PSFS) or Peripheral Nerve Field Stimulation (PNFS) Devices~~

~~PSFS or PNFS using a fully implantable system is not currently approved by the FDA.~~

~~The NSS-2 System, a PNFS system marketed as an aid to reduce the symptoms of opioid withdrawal, was FDA approved on November 15, 2017 (Product Code PZR). For more~~

~~information, go to: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170018.pdf. (Accessed November 30, 2020)~~

~~The DrugRelief® auricular stimulator, a PNFS system marketed as an aid to reduce symptoms of opioid withdrawal, was FDA approved on May 2, 2018 (Product Code PZR). For more information, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K173861. (Accessed November 30, 2020)~~

~~Microcurrent Electrical Nerve Stimulation Therapy (MENS) Devices~~

~~MENS devices are categorized as TENS devices intended for pain relief. They are regulated by the FDA's premarket approval (PMA) process.~~

~~Percutaneous Electrical Nerve Stimulation (PENS) or Percutaneous Electrical Nerve Field Stimulation (PENFS)~~

~~The FDA regulates PENS stimulators as class II devices (Product Code NHI). Several PENS devices have been approved by the FDA. See the following website for more information and search by product name in device name section: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~The IB-Stim, a PENFS system intended for use with functional abdominal pain associated with irritable bowel syndrome (IBS) in patients 11-18 years of age, was FDA approved on 6/7/19 (Product Code QHH). For more information, go to: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN180057. (Accessed November 30, 2020)~~

~~Dorsal Root Ganglion (DRG) Stimulation Devices~~

~~There are several devices used for DRG stimulation. See the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 30, 2020)~~

~~Scrambler Therapy (ST)~~

~~The Calamare/ST MC-5A TENS Device was initially approved by the FDA on February 20, 2009. A second 510(k) clearance was issued on May 22, 2015, for the ST MC-5A Device (Product Code GZJ). For more information, go to the following websites:~~

- ~~https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf~~
- ~~https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142666.pdf~~

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Policy History/Revision Information

Date	Summary of Changes

TBD	**Coverage Rationale** • Added language to indicate: ○ Transcutaneous electrical nerve stimulator (TENS) is proven and medically necessary in certain circumstances; for medical necessity clinical coverage criteria, refer to the InterQual® CP: Durable Medical Equipment, Transcutaneous Electrical Nerve Stimulation (TENS) ○ Neuromuscular electrical stimulation (NMES) is proven and medically necessary when used as part of a comprehensive lower limb rehabilitation program following total knee arthroplasty ○ Percutaneous peripheral nerve stimulation (PNS) and translingual stimulation (TS) for gait rehabilitation is unproven and not medically necessary • Replaced language indicating: ○ "Functional electrical stimulation (FES) is proven and medically necessary as a component of a comprehensive rehabilitation program in members with lower limb paralysis due to spinal cord injury (SCI) when all the [listed] criteria are met" with "FES is proven and medically necessary as a component of a comprehensive *ambulation* rehabilitation program in members with lower limb paralysis due to spinal cord injury (SCI) when all the [listed] criteria are met" ○ "NMES is proven and medically necessary to improve *wrist and finger* function *and prevent or correct shoulder subluxation* in persons with partial paralysis following stroke" with "NMES is proven and medically necessary to improve *upper extremity* function in persons with partial paralysis following stroke *when used as part of a comprehensive rehabilitation program*" • Removed language indicating dorsal root ganglion (DRG) stimulation is unproven and not medically necessary • Added reference link to the Medical Policy titled: ○ *Occipital Neuralgia and Headache Treatment (for Louisiana Only)* for information regarding percutaneous peripheral nerve stimulation for occipital neuralgia and headache ○ *Implanted Electrical Stimulator for Spinal Cord (for Louisiana Only)* for information regarding dorsal root ganglion (DRG) stimulation **Applicable Codes** • Added CPT/HCPCS codes 63650, 63655, 63663, 63664, 63685, 63663, 63664, 64555, 64999, A4556, A4557, A4558, A4595, A4630, E0720, E0730, E0731, and K1023 • Added notation to indicate CPT/HCPCS codes 0278T, 0720T, 64555, A4558, A4595, A4630, E0720, E0730, E0731, E0744, E0745, E0762, E0764, K1023, L8679, L8680, L8682, L8685, L8686, L8687, L8688, S8130, and S8131 are not on the State of Louisiana Medicaid Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program • Updated list of functional electrical stimulation (FES) devices verified by the Centers for Medicare & Medicaid Services (CMS) Pricing, Data Analysis, and Coding (PDAC) to be reported with HCPCS code E0770; added "Deluxe Digital Electronic Muscle Stimulator (Drive medical)"

Date	Summary of Changes
	Supporting Information • **Updated *Description of Services, Clinical Evidence, FDA, and References* sections to reflect the most current information** • **Archived previous policy version CS036LA.N**

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.