UnitedHealthcare®

UnitedHealthcare® Commercial and Individual Exchange
Medical Policy

Electrical Stimulation for the Treatment of Pain and Muscle Rehabilitation

Policy Number: 2023T0126MM
Effective Date: October 1, 2023

➲ Instructions for Use

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Community Plan Policy

- Electrical Stimulation for the Treatment of Pain and Muscle Rehabilitation

Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

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).

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 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 any of 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; or
- When used as part of a comprehensive lower limb rehabilitation program following total knee arthroplasty; or
- To improve upper extremity function in persons with partial paralysis following stroke when used as part of a comprehensive rehabilitation program

The following are unproven and not medically necessary due to insufficient evidence of efficacy:
- 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)
- Restorative neurostimulation
- 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 Nerve Injections and Ablation (Including Occipital Neuralgia and Headache).

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

Note: For information regarding cranial electrical stimulation/cranial electrotherapy, refer to the Behavioral Clinical Policy titled Cranial Electrotherapy Stimulation - Behavioral Clinical Policy (providerexpress.com)

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Codes*	Required Clinical Information
Functional Neuromuscular Stimulation (FES)	
63650, 63655, 63663, 63664, 63685, 64555, L8679, L8680,	Medical notes documenting the following, when applicable: • Date of spinal cord injury and/or restorative surgery • Specific device to be implanted • Intact lower motor units (both muscle and peripheral nerve)

CPT/HCPCS Codes*	Required Clinical Information
Functional Neuromuscular Stimulation (FES)	
L8682, L8685, L8686, L8687, L8688	• Muscle and joint stability for weight bearing and the ability to support upright posture independently • Muscle contractions and sensory perception response • Transfer ability and independent standing tolerance • Hand and finger dexterity • Absence of hip and knee degenerative disease • Absence of history of long bone fracture secondary to osteoporosis • High level of motivation, commitment, and cognitive ability for device use
Neuromuscular Electrical Stimulator (NMES)	
L8679 L8680, L8682, L8685, L8686, L8687, L8688	Medical notes documenting the following, when applicable: • Current prescription from physician • Diagnoses for the condition(s) needing treatment • Clinical notes, including: ○ History ○ Physical exam ○ Laboratory testing ○ Physician treatment plan

*For code descriptions, refer to the Applicable Codes section.

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 the member specific benefit plan document 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
0783T	Transcutaneous auricular neurostimulation, set-up, calibration, and patient education on use of equipment
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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***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
A4595	Electrical stimulator supplies, 2 lead, per month, (e.g., TENS, NMES)
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
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
L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
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

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 transcutaneous, 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).

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.

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 sub sensorial, 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 micro electrical therapy (MET) or micro electrical 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™.

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.

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).

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).

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.

Restorative Neurostimulation

Restorative neurostimulation is a minimally invasive method of innervating the multifidus muscle of the lower back to override the underlying cycle of lumbar multifidus muscle degeneration. It is intended to be used as a rehabilitative therapy for patients with impaired neuromuscular control associated with mechanical chronic low back pain (CLBP). After the neurostimulation device is implanted, isolated electrical impulses are stimulated by way of self-anchoring leads placed next to the medial branch of the dorsal ramus (Hayes, 2022).

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 non pain information to the painful area using continuously changing, variable, nonlinear waveforms (Hayes, 2021).

Transcutaneous Electrical Nerve Stimulation (TENS)

A TENS is a device that utilizes electrical current delivered through electrodes placed on the surface of the skin to decrease the perception of pain by inhibiting the transmission of afferent pain nerve impulses and/or stimulating the release of endorphins. A TENS unit must be distinguished from other electrical stimulators (e.g., neuromuscular stimulators) which are used to directly stimulate muscles and/or motor nerves.

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

In a systematic review by Bekhet et al. (2022), the effect of using neuromuscular electrical stimulation (NMES) or FES, or both, on training on body composition parameters in individuals with spinal cord injury (SCI) was evaluated. The review included 46 studies with a total sample size of 414 patients that evaluated NMES loading exercise and FES cycling exercise used in training. The authors reported that there was an average increase in muscle cross-sectional area of 26% (n = 33) and that 15 studies reported changes (both increase and decrease) in lean mass or fat-free mass with a range from -4% to 35%. Limitations noted included broad inclusion criteria for other interventions that made it difficult to determine the benefits that were due specifically to the electrical stimulation, the broad variability of NMES /FES parameters used across the studies, the small sample sizes, the variability of the levels of spinal cord injury included, the wide range of study designs (case reports, crossover, prospective and retrospective) with limited number of RCTs and the variability in durations and interventions. The authors concluded that the systematic review showed that the use of NMES/FES resulted in robust muscle hypertrophy and increase in lean mass and fat-free mass with inconclusive evidence about reduction in intramuscular mass. They recommended multi-center RCTs to consolidate previous research findings on body composition and to reach consensus about the most effective stimulation parameters needed to improve body composition in persons with SCI. The studies reviewed included the Griffin 2009 study previously summarized in this policy.

Hayes published a Health Technology Assessment on FES for rehabilitation following spinal cord injury. Their review of the literature found 15 prospective studies (including the Harvey 2010, Klose 1997 and Needham-Shropshire 1997 studies below) consisting of 9 randomized controlled trials (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 did not identify any studies meeting the inclusion criteria for the use of FES in children and adolescents with incomplete SCI. The report concluded that well-designed studies reporting the effectiveness and safety of long-term use of FES are still needed (2017, updated 2022).

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.

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

In a parallel three-group, randomized, unblinded, single-center, cross-sectional study by Sansare et al. (2021), the effect of two training approaches, cycling with and without FES assistance, to that of a no-intervention control group on the cardiorespiratory fitness of children with Cerebral Palsy (CP) was examined. The study included 39 participants between the ages of 10-18 years. They were randomized to one of the three study groups, FES (received FES-assisted cycle training, n = 15), VOL (underwent volitional cycling only, n = 11) or CON (received no treatment intervention, n = 13) with patient characteristics among the groups showing no significant differences in age, height, weight and BMI among the 3 groups. Both treatment groups underwent a set-up / practice phase prior to baseline testing then were asked to cycle continuously for 30 minutes, three times a week for 8 weeks at the target cycling power corresponding to 50–80% of their Karvonen-predicted target heart rate during the baseline incremental test. All participants were assessed for cardiorespiratory fitness at three time points: prior to training (PRE), at the end of 8 weeks of training (POST), and during a washout period of 8 weeks (WO). An additional assessment was performed midway through training to account for increased cardiorespiratory capacity and motor learning effects, and new HR and power targets were set. The average adherence to the training protocol in both the cycling groups was 91.9%, with no significant difference between the FES and VOL groups. The authors concluded that the study showed that, while FES-assisted cycling can enable children with CP to attain higher cycling cadences than cycling alone, or without any intervention, it did not show any significant improvements in peak VO2 (liters of oxygen per minute per kg body weight), and peak net HR (peak heart rate in beats per minute (bpm). They reported that the FES group made significant gains between PRE to POST and that all 3 study groups showed minimal changes between POST and WO which the authors stated is indicative of the ability to maintain the gains made during training.

Moll et al. (2017) 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 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

In their Health Technology Assessment (HTA) on the effectiveness of rehabilitative FES for foot drop in patients during the acute or subacute phases of stroke recovery, Hayes (2022a) reviewed 10 studies including 9 RCTs and one crossover RCT. The studies varied in their evaluation of FES relative to no placebo or placebo FES, the use of an ankle-foot orthosis (AFO), and adjunct use of electromechanical gait training (EMGT) and neuromuscular electrical stimulation (NMES). The HTA stated that there was an overall low-quality body of evidence due to study limitations (including small sample sizes, attrition, lack of power analysis or blinding, and short-term follow-up), the use of six different FES devices among the 10 studies, the variation in treatment intensity among the studies, the limited number of studies for the different comparators, inconsistencies in the evidence of benefit and insufficient follow up to assess long-term durability of the benefit of FES. The report concluded that, while FES treatment appears relatively safe, there was particular concern across the studies regarding the lack of consistent evidence that FES improved measures of functional recovery and quality of life. They recommended additional RCTs with better standardization of FES devices and treatment protocols with longer follow-up to establish whether FES improves outcomes related to conservative therapies for foot drop due to stroke that occurs less than 1 year prior to starting treatment with FES.

Hayes (2022b) also published an HTA on the effectiveness of FES for foot drop in the chronic phase of stroke recovery that identified 8 RCTs and one crossover RCT which evaluated FES for treatment of foot drop in patients who had experienced a CVA ≥ 1 year before starting FES. The report stated that the body of evidence for assistive FES with skin-surface electrodes and for rehabilitative FES with skin-surface electrodes were both low in quality while the body of evidence for assistive FES with implanted electrodes was very low in quality. The studies in the HTA were downgraded to fair quality due to limitations in the study designs (small size, dropout rate, incomplete statistical analysis, lack of complication reporting, lack of blinding or blind analysis of data, low intensity or short duration of FES treatment and/or short follow up periods. The HTA concluded that FES with skin-surface electrodes did not provide any statistically significant improvements in walking, stroke recovery or quality-of-life measures when compared to ankle-foot-orthoses. However, when assistive use of FES with skin-surface electrodes was compared to conservative therapies that included AFOs or to no FES in patients undergoing physical therapy for gait disorders, the evidence showed limited improvements. The report recommended additional RCTs to demonstrate the benefit of assistive use of FES relative to AFOs and to the benefit of rehabilitative use of FES to ascertain the reliability and durability of benefits that may diminish long-term once FES is discontinued.

A Clinical Evidence Assessment (CEA) published by ECRI (2022) on the safety and effectiveness of FES for physical rehabilitation in patients with hand paralysis found that functional neuromuscular stimulation (FNMS) improved hand function when used to supplement rehabilitation in patients with chronic paresis due to stroke but not in patients with acute or subacute paresis. The CEA included a systematic review with meta-analysis of 26 RCTs (including the Jonsdottir 2017 study below) and review of an additional 7 RCTs that were of high risk of bias from small sample sizes and single-center focus. The authors indicated that the meta-analysis reported pooled outcomes with sufficient precision to support conclusions; however, study heterogeneity was significant, limiting generalizability of the findings to specific patient populations. They noted that most of the studies in the systematic review and the additional studies involved prototype or research devices so the findings may not fully generalize to patients treated with commercial devices in clinical practice.

Loh et al. (2022) completed a meta-analysis of six RCTs published between 2012 and 2020 to evaluate the effectiveness of contralaterally controlled functional electrical stimulation (CCFES) compared to NMES on upper extremity motor recovery in post-stroke patients. The studies included a combined 267 patients (137 in the CCFES treatment group and 130 in the cyclic NMES group) during various phases of post-stroke recovery with 1 that investigated acute phase stroke, 1 studied chronic phase stroke, 3 evaluated subacute phase stroke and 1 that studied both subacute and chronic phase stroke. The participants in both intervention groups in all of the RCTs received treatment and background interventions for the same length of time. The risk of bias assessment indicated that four studies were identified as low risk, one as having some concerns and one was identified as high risk. The authors stated that the results of their meta-analysis showed that the CCFES group demonstrated greater improvement than the NMES group in Upper Extremity Fugl-Meyer Assessment scores (included in all studies), the Box and Block test (included in 3 studies), the active range of motion measurements (included in 4 studies) and the modified Barthel Index (included in 2 studies); however, results for the Arm Motor Abilities Test (included in 3 studies) did not differ significantly between stimulation types. Limitations noted by the authors included the lack of blinding in all of the studies, the small number of RCTs included (of which, half of them originated from the same authors), the variability of the phase of stroke recovery or severity of impairment at baseline, and that all of the comparison groups included only NMES. The authors concluded that CCFES might be an alternative form of intervention for post stroke treatment that may facilitate upper extremity motor function recover. They recommend more RCTs to verify the efficacy and effects of CCFES and to compare CCFES with other modalities or interventions.

Hayes published an HTA that provided a Comparative Effectiveness Review 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 included 10 RCTs (including the Jonsdottir 2017 study below) and 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, updated 2022).

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.

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.

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 sub-scores 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

In a systematic review and meta-analysis of 14 RCTs, Wang et al. (2022a) evaluated the effectiveness of FES of the legs in 518 study participants with heart failure. The authors stated that the pooled estimates demonstrated that FES significantly improved peak oxygen consumption (measure included in 8 of the reviewed RCTs, n = 321), the 6-min walking distance (10 RCTs, n = 380) and in the Minnesota Living with Heart Failure Questionnaire quality of life score (9 RCTs, n = 383) while muscle strength of the lower extremities was not significantly improved in the FES treatment group compared with the control group (5 RCTs, n = 218). They also stated that subgroup analysis showed that FES significantly improved peak oxygen consumption, 6-min walking distance and Minnesota Living with Heart Failure Questionnaire quality of life score in the heart failure with reduced ejection fraction and the heart failure with preserved ejection fraction subgroups. The authors assessed the quality of the RCTs as “fair” for six of the studies and “good” for the other eight studies. The conclusion reached by the authors was that FES can effectively improve cardiopulmonary function and quality of life in patients with heart failure but does not significantly improve muscle strength in legs. Limitations acknowledged by the authors included that most of the included studies had potential bias risks, which limited the strength of the results, the limited availability of studies for inclusion, the heterogeneity of the studies, the FES treatments and muscles stimulated, and that seven of the RCTs used sham FES with sensory input or low-intensity stimulation of the control group which might have influenced outcomes.

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.

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)

In the NICE guideline regarding rehabilitation after traumatic injury, NICE states that, for rehabilitation after spinal cord injury, additional techniques and specialized equipment (such as FES, gait orthoses, bodyweight-supported gait training and robotic devices) should be considered to promote mobility, upper limb function and independent walking (2022).

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 programs will improve health outcomes.

Musculoskeletal System Conditions

Wellauer et al. (2022) conducted a randomized controlled trial (RCT) to compare the effectiveness of a home-based neuromuscular electrical stimulation (NMES) program applied to the quadriceps of the nonoperative side against sham-NMES as a complement to standard rehabilitation on knee extensor neuromuscular function in patients following anterior cruciate ligament (ACL) reconstruction. Twenty-four patients completed the 6-week NMES (n = 12) or sham-NMES (n = 12) post-operative interventions and were tested at different time points for neuromuscular function and self-reported knee function. Isometric, concentric, and eccentric strength deficits (muscle weakness) increased from pre-surgery to 24 weeks post-surgery in the sham-NMES group ($p < 0.05$), while no changes were observed in the NMES group. On the stimulated (nonoperative) side, quadriceps voluntary activation and muscle thickness were respectively maintained ($p > 0.05$) and increased ($p < 0.001$) as a result of the NMES intervention, contrary to sham-NMES. Self-reported knee function improved progressively during the post-operative phase ($p < 0.05$), with no difference between the two groups. Compared to a sham-NMES intervention, a 6-week home-based NMES program applied to the quadriceps of the nonoperative side early after ACL reconstruction prevented the occurrence of knee extensor muscle weakness 6 months after surgery. The authors concluded that nonoperative-side NMES may help counteract muscle weakness after ACL reconstruction. Limitations include small sample size, and NMES use was not fully controlled due to home-based administration of both interventions. Further research is needed to determine the clinical relevance of these findings.

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

Rocha et al. (2022) conducted a systematic review of randomized clinical trials (RCTs) to evaluate the safety and efficacy of non-surgical interventions for the treatment of masticatory muscle spasticity in cerebral palsy (CP) patients. The authors conducted a comprehensive search in the following databases: MEDLINE, Embase, Cochrane Library, LILACS, BBO, PEDro, Clinicaltrials.gov and WHO/ICTRP, without date and language restrictions. RCTs evaluating non-surgical interventions were considered. Primary outcomes such as masticatory function and adverse events were planned to be assessed. The risk of bias assessment was performed using the Cochrane risk of bias tool. The certainty of the evidence was assessed using the GRADE approach. Three RCTs assessing the effects of botulinum toxin, functional masticatory training and neuromuscular electrostimulation (NMES) were included. Evidence with a very low certainty showed: (i) no difference between botulinum toxin and placebo regarding maximum chewing strength, chewing efficiency and global oral health scale; (ii) improvement in masticatory function in favor of functional masticatory training versus conventional exercises, and (iii) in favor of strengthening exercises plus NMES versus placebo. All studies reported the blinding of the outcome as sessors and were of low risk of bias for this domain. No losses were reported from participants in any of the included studies. The authors concluded there was insufficient evidence to support the use of botulinum toxin and masticatory muscle strengthening programs alone and associated with NMES for the treatment of masticatory muscle in patients with CP. The clinical decision must be individualized, and further studies are needed to support or refute the use of different non-surgical interventions for CP. This systematic review is limited by its small sample size (3 RCTs), heterogeneous groups, and a lack of a controlled comparator group. Further research with randomized controlled trials is needed to validate these findings.

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 t0 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

Miller et al. (2022) conducted a systematic review to evaluate the most recent studies regarding a potential effectiveness of neuromuscular electrical stimulation (NMES) as a treatment for oropharyngeal dysphagia. A selective literature research in PubMed has been carried out by the authors on May 5, 2021, using the terms electrical stimulation AND dysphagia and screened for inclusion criteria, resulting in 62 hits. Studies were excluded due to their publication language; because they did not meet inclusion criteria; because the topical focus was a different one; or because they did not qualify as level 2 studies. Eighteen studies were identified with varying patient groups, stimulation protocols, electrode placement and therapy settings. However, 16 studies have reported of beneficial outcomes in relation with NMES. The authors concluded that there is a considerable amount of level 2 studies which suggest that NMES is an effective treatment option, especially when combined with traditional dysphagia therapy (TDT) for patients with dysphagia after stroke and patients with Parkinson's disease, or with different kinds of brain injuries. Further research is still necessary in order to clarify which stimulation protocols, parameters and therapy settings are most beneficial for certain patient groups and degrees of impairment. Data pooling and statistical analysis could not be carried out due to the inhomogeneity of study protocols. Further research with randomized controlled trials is needed to validate these findings.

Ohnishi et al. (2022) conducted a randomized controlled trial (RCT) to investigate the effect of combined therapy with repetitive facilitative exercise (RFE) and neuromuscular electrical stimulation (NMES) on stroke patients with severe upper paresis. This study included a total of 99 stroke patients with very severe paresis and with scores of zero or 1a in the Finger-Function test of the Stroke Impairment Assessment Set (SIAS). Participants were randomly divided into four groups, namely, NMES, RFE, RFE under NMES, and conventional training (CT) groups. A total of 20 minutes of group-specific training in addition to 40 minutes of conventional exercise per day, seven times a week for 4 weeks after admission, was performed. The upper extremity items of the Fugl-Meyer Assessment (FMA) were evaluated before and after the training period. The total score gains of the FMA, FMA wrist item, and FMA finger item were larger in the RFE under NMES group than those in the CT group ($p < 0.05$). The authors concluded that the combination of voluntary movement and electrical stimulation may promote the activation of paralyzed muscles and improve distal function for very severe paralyzed upper limbs. A limitation of this study was that the number of joint movement repetitions was arbitrary, although the training period of each group was defined. The authors suggest that additional studies are warranted to verify the effects of treatments with a fixed number of movements.

Xie et al. (2022) conducted a two-arm randomized controlled trial (RCT) to investigate the effects of simultaneous use of neuromuscular electrical stimulation on median nerve (m-NMES) and language training (m-NMES-LT) on cerebral oscillations and brain connection, as well as the effect on clinical efficacy following cerebrovascular accident (CVA). A total of 21 right-handed adult patients with aphasia after stroke were randomly assigned to language training (LT) group ($n = 10$) and m-NMES-LT group ($n = 11$), and tissue concentration of oxyhemoglobin and deoxyhemoglobin oscillations were measured by functional near-infrared spectroscopy in resting and treatment state during three consecutive weeks. Five characteristic frequency signals (I, 0.6-2 Hz; II, 0.145-0.6 Hz; III, 0.052-0.145 Hz; IV, 0.021-0.052 Hz; and V, 0.0095-0.021 Hz) were identified using the wavelet method. The wavelet amplitude (WA) and wavelet phase coherence (WPCO) were calculated to describe the frequency-specific cortical activities. The m-NMES-LT induced higher WA values in contralesional prefrontal cortex (PFC) in intervals I, II, and V, and ipsilesional motor cortex (MC) in intervals I-V than the resting state. The wavelet phase coherence (WPCO) values between ipsilesional PFC-MC in interval III-IV, and between bilateral MC in interval III-IV were higher than resting state. In addition, there was a positive correlation between WPCO and Western Aphasia Battery in m-NMES-LT group. The authors concluded that the language training combined with neuromuscular electrical stimulation on median nerve could improve and achieve higher clinical efficacy for aphasia. This is attributed to the m-NMES-LT which could enhance cortical activation and brain functional connectivity in patients with aphasia, which was derived from myogenic, neurogenic, and endothelial cell metabolic activities. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Further investigation is needed before clinical usefulness of this procedure is proven.

A randomized controlled trial (RCT) was completed by Huang et al. (2021) to compare the effectiveness of contralaterally controlled functional electrical stimulation (CCFES) versus neuromuscular electrical stimulation (NMES) on motor recovery of the upper limb in subacute stroke patients. A total of 50 patients within six months post-stroke were randomly assigned to the CCFES group (n = 25) and the NMES group (n = 25). Both groups underwent routine rehabilitation plus 20-minute stimulation on wrist extensors per day, five days a week, for 3 weeks. Fugl-Meyer Assessment of upper extremity (FMA-UE), action research arm test (ARAT), Barthel Index (BI), and surface electromyography (sEMG) were assessed at baseline and end of intervention. After a 3-week intervention, FMA-UE and BI increased in both groups ($p < 0.05$). ARAT increased significantly only in the CCFES group ($p < 0.05$). The changes of FMA-UE, ARAT, and BI in the CCFES group were not greater than those in the NMES group. The improvement in sEMG response of extensor carpi radialis by CCFES was greater than that by NMES ($p = 0.026$). The co-contraction ratio (CCR) of flexor carpi radialis did not decrease in both groups. No adverse events were reported during the intervention and follow-up in any of the groups. The authors concluded that CCFES improved upper limb motor function but did not show better treatment effect than NMES. CCFES enhanced the sEMG response of paretic extensor carpi radialis compared with NMES but did not decrease the co-contraction of antagonist. There are multiple limitations to this study. The central plasticity of subject was not evaluated by electrophysiological or functional imaging investigation at baseline, which could be a confounder of the treatment effect of CCFES. The effect of CCFES on central plasticity was not measured in this study, and the duration of intervention was short, which may reduce the effect of CCFES. The findings of this study need to be validated by well-designed studies, and further investigation is needed before clinical usefulness of this procedure is proven.

Kristensen et al. (2021) conducted a systematic review and meta-analysis to (1) elucidate the effectiveness of neuromuscular electrical stimulation (NMES) toward improving activities of daily living (ADL) and functional motor ability post stroke and (2) to investigate the influence of paresis severity and the timing of treatment initiation for the effectiveness of NMES. The inclusion criteria were randomized controlled trials exploring the effect of NMES toward improving ADL or functional motor ability in survivors of stroke. The search identified 6,064 potential articles with 20 being included. Two independent reviewers conducted the data extraction. Methodological quality was assessed using the PEDro scale and the Cochrane Risk of Bias Tool. Data from 428 and 659 participants (mean age, 62.4 years; 54% male) for outcomes of ADL and functional motor ability, respectively, were pooled in a random-effect meta-analysis. The analysis revealed a positive effect of NMES toward ADL (standardized mean difference [SMD], 0.41; 95% CI, 0.14-0.67; $p = .003$), whereas no effect on functional motor ability was evident. Subgroup analyses showed that application of NMES in the subacute stage (SMD, 0.44; 95% CI, 0.09-0.78; $p = .01$) and in the upper extremity (SMD, 0.34; 95% CI, 0.04-0.64; $p = .02$) improved ADL, whereas a beneficial effect was observed for functional motor abilities in patients with severe paresis (SMD, 0.41; 95% CI, 0.12-0.70; $p = .005$). The authors concluded that the results of the meta-analysis are indicative of potential beneficial effects of NMES toward improving ADL post stroke, whereas the potential for improving functional motor ability appears less clear. Furthermore, subgroup analyses indicated that NMES application in the subacute stage and targeted at the upper extremity is efficacious for ADL rehabilitation and that functional motor abilities can be positively affected in patients with severe paresis. Limitations include a high risk of blinding and reporting bias. Further investigation is needed before clinical usefulness of this procedure is proven. This review included the Hsu 2010 study previously summarized in this policy.

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.

Respiratory System Conditions

Donadio et al. (2022) conducted a randomized controlled trial (RCT) to evaluate the effects of a supervised resistance-training program, associated or not with neuromuscular electrical stimulation (NMES), on muscle strength, aerobic fitness, lung function and quality of life in children with cystic fibrosis (CF) presenting with mild-to-moderate pulmonary impairment. A total of 27 patients, aged between 6 and 17 years, were enrolled in this study. Subjects were randomly allocated to control (CON); exercise (EX); or exercise and NMES (EX + NMES) groups and evaluated at baseline and at the end of an 8-week individualized exercise-program (3 days/week, 60min/session). NMES was applied in the quadriceps and the interscapular region, simultaneously to the exercises. CON group followed the CF team recommendations. The main outcome measures were lung function, cardiorespiratory fitness, functional capacity, quality of life and muscle strength. No interactions were found for cardiorespiratory fitness. Functional capacity presented differences, indicating a better performance in both EX and EX + NMES. No changes between groups were seen for quality of life and lung function. As for muscle strength, EX and EX + NMES presented large effect sizes and differences, compared to CON, for quadriceps ($p = 0.004$, $\eta 2p = 0.401$), pectoral ($p = 0.001$, $\eta 2p = 0.487$), dorsal ($p = 0.009$, $\eta 2p = 0.333$) and handgrip ($p = 0.028$, $\eta 2p = 0.278$). The authors concluded a resistance exercise-training program led to improvements in muscle strength and functional capacity in CF patients with mild-to-moderate pulmonary impairment. The addition of NMES to the training program resulted in no extra favorable effects. This study has limitations, including the different in genotyping between groups. Although there is evidence to support that its effect on exercise variables is not substantial, it may have influenced present results. In addition, the mild-to-moderate impairment of the sample could also affect results, as smaller effects are expected in patients with a high aerobic fitness and lower muscular abnormalities. Further investigation is needed before clinical usefulness of this procedure is proven.

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

Nonoyama et al. (2022) conducted a retrospective cohort study to examine the course of critically ill older patients treated with neuromuscular electrical stimulation (NMES) in the intensive care unit (ICU) and to define the impact of its use. This study was conducted using older ICU patients (≥ 65 years) categorized into a control group (n = 20) and an NMES group (n = 22). For subgroup analysis, each group was further classified into pre-old age (65–74 years) and old age (≥ 75 years). The control group showed a decrease in muscle thickness during ICU and hospital stay. The NMES group showed lower reduction in muscle thickness and showed decrease in muscle echo intensity during hospital stay, compared to the control group. NMES inhibited decrease in muscle thickness in the pre-old age group versus the old age group. The decreasing effect of NMES on echo intensity during hospital stay manifested only in the pre-old age group. The authors did not find differences in physical functioning between the NMES and control groups. Lower limb muscle atrophy reduces in critically ill older patients (≥ 65 years) with NMES and is pronounced in patients aged < 75 years. The authors concluded that the impact of NMES on the physical functioning of older patients in ICU needs to be further investigated. The study is limited by its retrospective observations. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

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.

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 published a guideline for the management of knee osteoarthritis (OA) in which they concluded that NMES should not be offered to people with OA because there is insufficient evidence of benefit. The guideline stated that, although there were many studies on electrotherapy, the findings were inconsistent and mostly showed little benefit. The committee found that most studies were small with less than 100 participants and that the evidence from direct comparisons of electrotherapy with other interventions was uncertain (2022).

NICE guidance on transcutaneous NMES for oropharyngeal dysphagia in adults found current evidence on efficacy for adults with dysphagia after a stroke to be limited in quality and quantity although it may have potential benefit. They also noted that, for adults with dysphagia not caused by a stroke, there is insufficient evidence on efficacy to support the use of this procedure. 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

Espejo-Antúnez et al. (2021) conducted a randomized, single-blind, controlled trial to evaluate the effects caused by interferential current therapy (ICT) on perceived pain and heart rate variability (HRV) in patients with non-specific chronic low back pain (NSCLBP). In the study, a total of 49 patients with NSCLBP were randomly divided into an experimental (n = 25) and a sham group (n = 24). All participants received a single intervention, ICT, or simulated intervention during November 1, 2020, through November 30, 2020. Outcome measures including baseline (sit-down position) and postintervention (prone position) pain, heart rate (HR), time domain parameter (rMSSD), diameters of the Poincaré plot (SD1, SD2), stress score (SS), and sympathetic/parasympathetic (S/PS) ratio were investigated. In both groups, significant statistical differences were found in perceived pain and in all HRV parameters except in HRmax. Between-group comparisons showed differences in all variables except for HRmin and HRmean in favor of the experimental group. These changes reported an increase in parasympathetic activity (rMSSD) ($p < 0.05$) and a decrease in sympathetic activity (increase in SD2 and decrease in SS) ($p < 0.001$) and perceived pain ($p < 0.001$), with a greater size effect ($\eta 2 = 0.44$) in favor of the experimental group. The authors concluded that a single session of ICT can shift the autonomic balance towards increased parasympathetic dominance and decreased the sympathetic dominance and intensity of pain perceived by patients with NSCLBP. The primary limitation to this study was that ICT was carried out in a single session and exclusively to males. Also, the lack of measurement of psychosocial factors associated with persistent pain, which could influence HRV. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

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.

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

Chen et al. (2022a) conducted a systematic review and meta-analysis to assess the effectiveness of interferential current therapy (IFC) in patients with knee osteoarthritis. The authors searched PubMed, Cochrane Library, Embase, ClinicalKey, and Scopus for relevant studies from their date of launch to March 22, 2022. They included randomized controlled trials (RCTs) in which IFC was applied to knee osteoarthritis patients and the outcomes of pain scores or functional scales were assessed. Ten RCTs with 493 patients met the inclusion criteria. Nine RCTs were included in the meta-analysis. The IFC groups exhibited significant improvements relative to the control groups for short-term pain scores (SMD = -0.64, 95% CI - 1.04 to -0.25, p = 0.001), long-term pain scores (SMD = -0.36, 95% CI -0.60 to -0.11, p = 0.005), and short-term Western Ontario and McMaster Universities Osteoarthritis Index scores (SMD = -0.39, 95% CI -0.77 to -0.02, p = 0.04). All included studies did not observe any obvious adverse effects of IFC. The authors concluded that IFC can be recommended as a treatment for knee osteoarthritis because it improves short- and long-term pain and short-term function. However, they recommended large-scale and high-quality RCTs with longer follow-up to establish an appropriate standardized treatment. Limitations to this study include a moderate-to-high heterogeneity for some results as the IFC devices, IFC parameter settings, and treatment protocols used by the included studies were inconsistent. In addition, some of the included studies did not implement blinding of therapists and participants, resulting in risks of bias that may have affected the results of this study. Finally, five of the included 10 RCTs reported immediate outcome measurements upon treatment completion, thereby limiting the applicability of long-term results. Well designed, adequately powered, prospective, controlled clinical trials of IFC are needed to further describe safety and clinical efficacy. Authors Alqualo-Costa et al. (2021), which were previously cited in this policy, are included in this systematic and meta-analysis review.

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.

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.

Dissanayake 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 Bower bank (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 published a guideline for the management of knee osteoarthritis (OA) in which they concluded that IFT should not be offered to people with OA because there is insufficient evidence of benefit. The guideline stated that, although there were many studies on electrotherapy, the findings were inconsistent and mostly showed little benefit. The committee found that most studies were small with less than 100 participants and that the evidence from direct comparisons of electrotherapy with other interventions was uncertain (2022).

NICE guidance on the assessment and management of all chronic primary pain included guidance on TENS, ultrasound and IFT for chronic primary pain found no evidence for IFT. In the guidance, the committee stated that they found no evidence for IFT, but they 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

D'Ambrosi et al. (2022) conducted a prospective randomized controlled trial (RCT) to assess pain relief and clinical outcomes in patients undergoing uni-compartmental knee arthroplasty (UKA) stimulated with pulsed electromagnetic fields (PEMFs) compared to a control group. A total of 72 patients undergoing medial UKA were randomized into a control group (n = 36) or an experimental PEMFs group (n = 36). The patients allocated to the experimental group were instructed to use PEMFs for 4 hours per day for 60 days. They were evaluated before surgery and then during the time points corresponding to 1 month, 2 months, 6 months, 12 months, and 36 months after the surgery. No placebo group was included in the RCT. Clinical assessment included the Visual Analogue Scale (VAS) for pain, Oxford Knee Score (OKS), the Short Form 36 (SF-36) health survey questionnaire, and joint swelling. During each follow-up visit, the consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was recorded. The VAS decreased on follow-up visits in both the groups; a statistical difference between the groups was observed during the 6 ($p = 0.0297$), 12 ($p = 0.0003$), and 36 months ($p = 0.0333$) follow-ups in favor of the PEMFs group. One month after UKA, the percentages of patients using NSAIDs in the PEMFs and control group were 71% and 92%, respectively ($p = 0.0320$). At the 2 months point, 15% of the patients in the PEMFs group used NSAIDs compared to 39% in the control group ($p = 0.0317$). The objective knee girth evaluation showed a statistically significant difference at 6 ($p = 0.0204$), 12 ($p = 0.0005$), and 36 ($p = 0.0005$) months with improved values observed in the PEMFs group. The subjective assessment of the swelling demonstrated a statistically significant difference at 2 ($p = 0.0073$), 6 ($p = 0.0006$), 12 ($p = 0.0001$), and 36 ($p = 0.0011$) months with better values noted in the PEMFs group. Last, the OKS result was higher in the experimental group during all the follow-ups (1mth: $p = 0.0295$; 2mths: $p = 0.0012$; 6mths: $p = 0.0001$; 12mths: $p < 0.0001$; 36mths: $p = 0.0061$). The authors concluded that the use of PEMFs leads to pain relief, clinical improvement, and lower NSAIDs consumption after medial UKA when compared to the control group. Limitations to this study include a lack of placebo group, small sample size, and use of a modified Cincinnati Rating System Questionnaire to assess patient satisfaction. Further research with additional randomized controlled trials is needed.

Pareja et al. (2022) conducted a randomized controlled trial (RCT) to investigate the therapeutic effects of pulsed electromagnetic field therapy (PEMF) via transcranial low-intensity magnetic stimulation (LIMS) in women diagnosed with fibromyalgia (FM) at 2, 12 and 24 weeks from the last LIMS administration treatment session. This study consisted of 560 women (age 53.7 ±11.3 years) selected from a pool of 1,200 women treated at the Fibromyalgia Unit of the Viamed Hospital in Seville, Spain, across 3 years. The study participants, diagnosed with FM according to the American College of Rheumatology (ACR) 2016 criteria, were randomly allocated in two groups: 280 received standard pharmacological treatment and 280 received the same treatment plus eight sessions of LIMS, 20 minutes long, once a week. The variables analyzed were the widespread pain index (WPI), symptoms severity score (SS score) and the Spanish-validated version of the FM impact questionnaire (S-FIQ). The evaluations were performed at the beginning of LIMS treatment and at 2, 12 and 24 weeks after the end of the last LIMS treatment session. From the second week after the last LIMS session, there was improvement ($p < 0.001$) in the variables WPI, SS score and S-FIQ. This improvement was maintained throughout the 24 weeks of monitoring after the last intervention. The age of the patients and the severity of the symptoms at the time of diagnosis did not affect the improvement observed in the three variables studied. The authors concluded that treatment with LIMS for eight weeks resulted in improvement in FM diagnostic variables, which was maintained up to 24 weeks after the last treatment session. Based on the data obtained and the evaluation instruments used, the authors stated that LIMS was an effective therapeutic tool for improving FM symptoms and the impact of this disease on the quality of life of patients, independent of age and degree of pain, and could be recommended as a part of a multimodal approach for FM treatment. This study did not address the physiological effects that underlie the improvement observed in patients. Therefore, further studies that explain the neurophysiological foundations that support the use of this therapy are needed. Other limitations of the study were that anthropometric variables such as weight, fat mass, muscle mass and other behavioral changes or alternative therapies that patients performed during the course of this study, such as physical activity, were not controlled.

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 Orthopedic 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 Organization 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.

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).

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.

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: Sprint Peripheral Nerve Stimulation System for Treating Peripheral Nerve Pain (2018, updated 2022), 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.

The Agency for Healthcare Research and Quality (AHRQ) performed a systematic review of 37 RCTs on the comparative effectiveness of 10 interventional therapies for acute and chronic pain for specific conditions. They concluded that the evidence was insufficient to assess peripheral nerve stimulation for upper extremity peripheral neuropathic pain (2021).

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.

Clinical Practice Guidelines

National Institute for Health Care Excellence (NICE)

In its interventional procedures guidance (2022) on neurostimulation of lumbar muscles for refractory non-specific chronic low back pain, NICE concluded that the evidence on the efficacy and safety is limited in quantity and quality. The guideline recommends that neurostimulation of lumbar muscles should only be used with special arrangements for clinical governance, consent and audit or research.

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.

Rigoard et al. (2021) conducted a randomized controlled trial (RCT) with a 12-month follow-up, to assess the potential added value of peripheral nerve field stimulation (PNfS), as a salvage therapy, in persistent spinal pain syndrome-type 2 (PSPS-T2) patients experiencing a "failed spinal cord stimulation (SCS) syndrome" in the back pain component. Fourteen patients between February 2013 and April 2017 were enrolled in this study (clinicaltrials.gov: NCT02110888) and randomized into 2 groups ("SCS + PNfS" group/n = 6 vs. "SCS only" group/n = 8). The primary objective of the study was to compare the percentage of back pain surface decrease after 3 months, using a computerized interface to obtain quantitative pain mappings, combined with multi-dimensional SCS outcomes. The authors concluded that back pain surface decreased over a 12-month period from baseline for the "SCS + PNfS" group (80.2% ±21.3%) compared to the "SCS only" group (13.2% ±94.8%) ($p = 0.012$), highlighting the clinical interest of SCS + PNfS, in cases where SCS fails to address back pain. With paresthesia generated under tonic stimulation, the authors were unable to blind the SCS + PNfS combination. In addition, a small sample size (14 patients) makes it difficult to decide whether these conclusions can be generalized to a larger population. Further investigation is needed before clinical usefulness of this procedure is proven. 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; updated 2022) 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, to determine the long-term efficacy and safety of PNFS versus comparable therapies and definitive alternatives.

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.

Microcurrent Electrical Nerve Stimulation Therapy (MENS)

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.

Bavarian et al. (2021) conducted a systematic review and meta-analysis on the efficacy of MENS in treating masticatory myofascial pain. Four RCTs were included in the qualitative systematic review with a pooled total of 159 participants, while three of the studies (pooled total of 140 participants) had sufficient raw data to be included in the quantitative meta-analysis. The primary outcome measured was relief of pain assessed by any validated scale, such as the visual analog scale (VAS) or numeric verbal pain rating scale. All of the articles included MENS being compared to a control group for the treatment of myofascial pain of the masticatory muscles. The authors determined that three of the four studies were judged to be at low risk of bias with the fourth study deemed as having a high risk of bias. The authors determined that there was a modest reduction in pain score in patients receiving MENS with an increased mean reduction of pain by an additional -0.57 points on the VAS. The authors concluded that the meta-analysis showed that MENS was an effective, non-invasive treatment for reducing pain in patients with myofascial pain of the masticatory muscle. Limitations noted by the authors included the small number of studies available for analysis, the heterogeneity of the study designs, inconsistent reporting of quantitative data and inconsistencies in control groups. This review included the Zuim 2006 study that was previously included in this policy.

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 a specific, 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).

Percutaneous Electrical Nerve Stimulation (PENS)

While some studies have compared the effectiveness of PENS or PENFS 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.

Woodbury et al. (2022) conducted a randomized controlled trial (RCT) to evaluate changes in cortical thickness and right posterior insula (r-pIns) gamma-aminobutyric acid (GABA) concentrations in veterans with fibromyalgia treated with auricular percutaneous electric nerve field stimulation (PENFS). This study was an open label investigation conducted in a government hospital. Twenty-one veterans with fibromyalgia were randomized to receive either standard therapy (ST; i.e., 4 weekly visits with a pain practitioner) or ST with auricular PENFS (ST + PENFS). Neuroimaging data was collected at baseline (i.e. before the first treatment session) and again within 2 weeks post-treatment. Clinical pain and physical function were also assessed at these timepoints. Single-voxel magnetic resonance spectroscopy was carried out in r-pIns to assess changes in r-pIns GABA concentrations and high-resolution T1-weighted images were collected to assess changes in regional gray matter volume using cortical thickness. Both the ST + PENFS and ST groups reported a decrease in pain with treatment. Volumetric: Cortical thickness decreased in the left middle posterior cingulate ($p = 0.018$) and increased in the left cuneus ($p = 0.014$) following ST + PENFS treatment. These findings were significant following false discovery rate (FDR) correction for multiple comparisons. ST group right hemisphere insula cortical thickness increased post-treatment and was ($p = 0.02$) inversely correlated with pain scores. ST + PENFS group right hemisphere posterior dorsal cingulate size ($p = 0.044$) positively correlated with pain scores. GABA: There were no correlations with GABA, though a trend was noted towards increased GABA following treatment in both groups ($p = 0.083$) using a linear mixed effects model. The authors concluded that the results suggested a novel effect of PENFS reflected by differential volumetric changes compared to ST. The changes in GABA that occurred in both groups were more likely related to ST. Insular GABA and cortical thickness in key regions of interest may be developed as potential biomarkers for evaluating chronic pain pathology and treatment outcomes. The GABA analysis was limited by a small number of MRI acquisitions meeting criteria for GABA spectroscopy fit error ($n = 9$ for PENFS with ST, and $n = 4$ for ST alone). While initial results concerning this non-pharmacologic treatment for fibromyalgia are promising, the clinical efficacy of PENFS for fibromyalgia should be explored in larger, randomized, double-blind, placebo-controlled trials.

An Evolving Evidence Review by Hayes (2022) on the use of IB-Stim for the treatment of pain associated with irritable bowel syndrome in adolescents stated that there is no/unclear support of the use of this device for this indication based on a review of full-text clinical studies. The review consisted of one fair-quality (see the Kovacic (2017) study below) that did not compare IB-Stim to any other active treatment. They did not identify any systematic reviews nor any relevant guidelines that addressed the use of IB-Stim for this clinical indication.

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 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 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.

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, updated 2022).

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).

Restorative Neurostimulation

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of restorative neurostimulation for the treatment of chronic low back pain. Additional larger studies comparing restorative neurostimulation to standard of care and current alternative treatments are needed to demonstrate safety and efficacy for this modality.

Hayes (2022) completed a Health Technology Assessment on the use of PNS for the treatment of chronic pain in adults refractory to conservative management. The assessment included a review of the four eligible studies that they found which consisted of 2 RCTs and 2 prospective pretest-posttest studies with follow-up periods of 6 months to 1 year. The report noted an overall very low-quality body of evidence with 2 fair-quality studies, 1 poor-quality study and 1 very poor-quality study which leaves the observed trends of benefit that were observed in the four studies relatively unsubstantiated. Limitations of the four studies included the heterogeneity of the study designs, the small sample sizes, patient attrition, and insufficient follow-up time. Hayes concluded that the small, very low-quality body of evidence suggests that PNS may be associated with pain reduction and improvement in quality of life, activities of daily living and medication utilization

In an Evolving Evidence Review focusing on the ReActiv8 Implantable Neurostimulation System, Hayes (2022) completed a review of full-text clinical studies and found minimal support for using ReActiv8 for chronic low back pain (CLBP). They found one fair-quality RCT (Gilligan, 2021 below) that compared ReActiv8 active treatment to sham that reported only marginal benefits to pain, disability and quality of life (QOL) in patients with CLBP. They also found one prospective pretest-posttest study (Deckers 2018 below) that compared ReActiv8 with baseline and reported statistically and clinically significant improvements in pain, disability, and QOL. Hayes did not find any studies that compared ReActiv8 with an active comparator, nor did they find any systematic reviews addressing this device nor any clinical guidelines that addressed the use of ReActiv8 for CLBP. The Evolving Evidence Review did identify two clinical studies that are in progress that will provide more evidence regarding the clinical effectiveness of ReActiv8 when results are published.

In a prospective, observational follow-up study of 204 implanted trial participants of the ReActiv8-B trial, Gilligan et al. (2022) evaluated the three-year effectiveness and safety of the ReActiv8 Implantable Neurostimulation System in patients with refractory, disabling chronic low back pain (CLBP). Data was collected using the low back pain visual analog scale (VAS), Oswestry Disability Index (ODI), EuroQol quality of life survey, and through assessment of the participant's opioid intake at baseline, six months, and one, two, and three years after activation. There were 45 participants who were withdrawn from the study after device removal (22%) and another 10 participants who were withdrawn due to loss to follow up (5%). The authors collected data from 133 of the participants and noted that 16 of the participants were not able to keep their three-year follow-up due to coronavirus disease restrictions but remain available for future follow-up. They reported that a total of 62% of participants had a ≥ 70% VAS reduction, and 67% reported CLBP resolution (VAS ≤ 2.5cm); 63% had a reduction in ODI of ≥ 20 points; 83% had improvements of ≥ 50% in VAS and/ or ≥ 20 points in ODI, and 56% had these substantial improvements in both VAS and ODI. A total of 71% (36/51) participants on opioids at baseline had voluntarily discontinued (49%) or reduced (22%) opioid intake. The authors concluded that 83% of participants experienced clinically substantial improvements in pain, disability or both at three years and that the results of their study showed durable, statistically significant, and clinically substantial benefits in a cohort of patients with severe, disabling CLBP and multifidus muscle dysfunction who were refractory to conservative care. Limitations of the study include the small sample size, high attrition rate, and a lack of follow-up with those participants who underwent removal of the device.

ECRI (2021) published a Clinical Evidence Assessment focused on the safety and effectiveness of the ReActiv8 Implantable Neurostimulation System for the treatment of chronic low-back pain that does not respond to conservative treatment in patients who are not surgical candidates for spinal procedures. The assessment included studies of any design that reported on clinical outcomes of multifidus stimulation with ReActiv8 in patients with chronic low-back pain. The researchers found two studies to review, including the Gilligan 2021 study below and one prospective, multicenter pre-post study. They found that each of the studies had three or more of the following limitations, which result in a high risk of bias: small sample size, no control group, lack of data on comparisons of interest such as other pain management techniques, short follow-up times and/or active sham was used in the study. The authors concluded that the evidence is inconclusive due to too few data on outcomes as the one RCT showed that the between-group difference in pain relief between ReActiv8 and sham (low level stimulation) was too small to be clinically significant.

Results of an ongoing follow-up of the ReActiv8-A clinical trial were published by Mitchell, et al. (2021) to document the longitudinal benefits of receiving long-term restorative neurostimulation in patients with intractable chronic low back pain (CLBP). This clinical trial was a prospective, single-arm study at nine sites in the United Kingdom, Belgium and Australia that included 53 patients with disabling CLBP with no indications for spine surgery or spinal cord stimulation and failed conventional management including at least physical therapy and medications. The study population had an average age of 44 ±10 years who had experienced back pain for 14 ±11 years. Stimulation parameters were programmed 14 days post implantation and patients were given instructions to activate the device for 30 minutes twice each day. The participants were then followed at 45, 90, 180, and 270 days, then annually for 48 months. Over the four years of follow-up, one patient was lost to follow-up, 11 exited the study following explant without clinical benefit, four exited following explant with clinical benefit and one exited because of a device migration that could not be repositioned. Thirty-four of the initial 53 patients completed the 48-month follow-up. The authors reported that, initially, patient compliance was relatively high with 84.5% ±22.6% of the maximum number of therapy sessions being completed; however, four years after implantation, patient compliance was at 48.8% ±34.0%, or completion of approximately half of maximum number of stimulation sessions. The authors reported that mean improvements from baseline were statistically significant and clinically meaningful for all follow-ups. They concluded that participants with disabling intractable CLBP who received long-term restorative neurostimulation retained treatment satisfaction and improvement in pain, disability and quality-of-life through four years. Limitations include the small number of participants, the high attrition rate, the single-arm design, and lack of follow-up for the participants who exited the study.

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.

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 et al. (2022) conducted a randomized controlled trial (RCT) to evaluate the efficacy of scrambler therapy (ST) for enhancing quality of life (QOL) in cancer patients through minimizing pain and opioid intake. A total of 80 patients with head, neck and thoracic cancer were included in the study. In both arms, patients were given pain management drugs following the World Health Organization (WHO) analgesic ladder for ten consecutive days. ST was given each day in the intervention arm. Pain, morphine intake, and QOL (WHOQOL-BREF) were assessed. All domains of QOL improved in the intervention arm in comparison to the control arm. In comparison to baseline, pain improved in both the intervention and the control arm on day 10 and at follow-up. However, QOL significantly improved in the intervention arm, while morphine intake decreased. In the control arm, QOL deteriorated, while morphine intake increased. The authors concluded ST improved QOL. Since the increase in QOL took place along with a lower morphine intake, the improvement in QOL may not only be explained by lower pain scores but, also, by a reduced intake of morphine, because the lower dosages of morphine will decrease the likelihood of side effects associated with the drug. Further research with randomized controlled trials is needed to validate these findings.

Lee et al. (2022) conducted a prospective, double-blinded, randomized controlled trial (RCT) to evaluate the clinical usefulness of scrambler therapy (ST) and identify the pain network alterations associated with ST for chronic neuropathic pain caused by burns. This study (ClinicalTrials.gov: NCT03865693) included 43 patients who were experiencing chronic neuropathic pain after unilateral burn injuries. The patients had moderate or greater chronic pain (a visual analogue scale (VAS) score of ≥ 5), despite treatment using gabapentin and other physical modalities, and were randomized 1:1 to receive real or sham ST sessions. The ST was performed using the MC5-A Calmare device for ten 45 min sessions (Monday to Friday for 2 weeks). Baseline and post-treatment parameters were evaluated subjectively using the VAS score for pain and the Hamilton Depression Rating Scale; MRI was performed to identify objective central nervous system changes by measuring the cerebral blood volume (CBV). After 10 ST sessions (two weeks), the treatment group exhibited a reduction in pain relative to the sham group. Relative to the pre-ST findings, the post-ST MRI evaluations revealed decreased CBV in the orbito-frontal gyrus, middle frontal gyrus, superior frontal gyrus, and gyrus rectus. In addition, the CBV was increased in the precentral gyrus and postcentral gyrus of the hemisphere associated with the burned limb in the ST group, as compared with the CBV of the sham group. Thus, a clinical effect from ST on burn pain was observed after 2 weeks, and a potential mechanism for the treatment effect was identified. The authors concluded these findings suggest that ST may be an alternative strategy for managing chronic pain in burn patients. Limitations include small sample size (43 patients) and short duration of follow-up (2 weeks).

Wang et al. (2022b) conducted a systematic review to evaluate the best available evidence regarding the use of non-invasive neuromodulation techniques for managing chemotherapy-induced peripheral neuropathy (CIPN). A systematic literature search of the following databases from their inception to October 17, 2021, was performed and was updated on March 2, 2022: AMED via Ovid, CINAHL via the EBSCO Host, Cochrane Library, Embase, PEDro, PubMed, and Web of Science. Randomized controlled trials (RCTs) and quasi-experimental studies examining the safety, feasibility, and efficacy of non-invasive neuromodulation techniques for managing established CIPN were identified. Narrative synthesis was used to analyze data collected from the included studies. Nine RCTs and nine quasi-experimental studies were included. A variety of non-invasive peripheral and central neuromodulation techniques were investigated in those studies, including scrambler therapy, electrical stimulations, photo biomodulation, magnetic field therapy, therapeutic ultrasound, neurofeedback, and repetitive transcranial magnetic stimulation. The authors stated that non-invasive neuromodulation techniques for the management of established CIPN were generally safe and feasible. The efficacy of peripheral neuromodulation techniques such as scrambler therapy and transcutaneous electrical nerve stimulation was mostly unsatisfactory, while central neuromodulation techniques such as neurofeedback and repetitive transcranial magnetic stimulation were promising. The authors concluded the use of non-invasive neuromodulation techniques for managing CIPN, such as scrambler therapy, was still in its early stages. The stated non-invasive central neuromodulation techniques have significant potential for relieving chronic pain and neuropathic symptoms related to CIPN, meriting further exploration. The heterogeneity of the included studies prevented the conducting of a pooled analysis of data from those studies. Therefore, the overall effect of the neuromodulation techniques for managing CIPN could not be estimated. Further research with randomized controlled trials is needed to validate these findings.

A systematic review was conducted by Karri et al. (2022) to summarize the available evidence regarding the use of scrambler therapy (ST) in treating chronic pain syndromes, as well as its analgesic benefits, adverse effects, procedure-specific variables, and other metrics such as sensorimotor tests, medication reduction, and effect on circulation neuropeptides. Two review authors, independently and in a standardized, unblinded fashion, conducted a systematic review to identify relevant studies and extract the necessary outcome measures by surveying multiple data sources from January 1950 through October 2021. A conservative search strategy was implemented to identify all ST studies for the treatment of chronic pain syndromes. Primary outcome parameters collected were analgesic benefit, adverse effects, and other metrics such as sensorimotor testing. A total of 21 studies met the final criteria for study inclusion and comprised randomized controlled trials (n = 8), prospective observational studies (n = 10), and retrospective cohort studies (n = 3). Nearly all the reported studies explored the use of ST for the treatment of neuropathic pain, with chemotherapy-induced peripheral neuropathy being the most studied condition. Most studies were limited by small cohorts but reported ST being safe, well tolerated, and providing clinically meaningful pain reduction. The duration of post-treatment follow-up ranged from ten to 14 days (concordant with completion of typical ST protocols) to three months. Secondary benefits such as medication reduction and improvement of sensory and motor symptoms were noted by some studies. The authors concluded that ST was a safe intervention with potential for analgesic benefit for neuropathic pain conditions. Although the available evidence was most robust for treating chemotherapy-induced peripheral neuropathy, ST was also shown to be effective in treating other neuropathic pain syndromes. Evidence for ST use in nociceptive pain conditions was limited but appears promising. The favorable safety profile and increasing evidence basis for ST warrant more extensive recognition and consideration for use in clinical care. Limitations to this study included performance and detection biases and several included studies reported industry affiliations with the ST manufacturer of the device, and the inventor of the ST device himself was an author of several of the included studies. Further investigation is needed before clinical usefulness of this procedure is proven. The Kashyap and Bhatnagar (2020) study and the Compagnone and Tagliaferri (2015) studies that were previously included in this policy were included in this systematic review.

Hayes (2020, updated 2022) 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.

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)

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)

Hou et al. (2022) conducted a clinical investigative study to evaluate the effectiveness of translingual neural stimulation (TLNS) on patients with mild-to-moderate traumatic brain injury (mmTBI) and related brain connectivity using a resting-state functional connectivity (RSFC) approach. This study is part of the long-term clinical trial (NCT02158494), which was completed to investigate the efficacy of translingual neural stimulation (cranial nerve noninvasive neuromodulation). Nine participants with mmTBI were included in the study (43-62-years-old; mean age was 53.11 ±6.60; three males and six females). Their mmTBI occurred at least 1 year before enrollment. Participants had previously participated in physical therapy, had reached a plateau in their functional recovery. Their mmTBI diagnoses were made according to the guidelines established by the Veterans Affairs/Department of Defense. All participants could independently walk for at least 20 minutes and had no medication changes for at least 3 months before the experiment. They were without other medical problems such as oral health, diabetes, hypertension, chronic infectious disease, or other potentially confounding neurological disorders. Resting-state images with 5-min on GE750 3T scanner were acquired from all participants with mmTBI. Paired t-test was used for calculating changes in

RSFC and behavioral scores before and after the TLNS intervention. The balance and movement performances related to mmTBI were evaluated by Sensory Organization Test (SOT) and Dynamic Gait Index (DGI). Compared to pre-TLNS intervention, behavioral changes in SOT and DGI were observed. The analysis revealed increased RSFC between the left postcentral gyrus and left inferior parietal lobule and left Brodmann Area 40, as well as the increased RSFC between the right culmen and right declive, indicating changes due to TLNS treatment. However, there were no correlations between the sensory/somatomotor (or visual or cerebellar) network and SOT/DGI behavioral performance. The authors concluded this study presents evidence that TLNS effectively improves balance and movement in mmTBI patients accompanied by increased involvement of neural regions associated with gait, balance, and motor control, and is therefore an effective approach to treating the symptoms of mmTBI patients. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Further research is needed to determine the clinical relevance of these findings.

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. Refer to 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 October 6, 2022)

Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation Devices

Products used for NMES for muscle rehabilitation are extensive. Refer to 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 October 6, 2022)

Interferential Therapy (IFT) Devices

Products used for IFT are extensive. Refer to 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 October 6, 2022)

Pulsed Electrical Stimulation (PES) Devices

There are multiple products used for PES. Refer to 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 October 6, 2022)

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. Refer to 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 October 6, 2022)

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. Refer to the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed October 6, 2022)

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). Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170018.pdf. (Accessed October 6, 2022)

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). A newer version, the DrugRelief® v1, with an extended shelf life from 6 to 12 months was approved on June 6, 2022. This newer version is otherwise Identical to the predicate in that both devices are body-worn, have identical indications for use and deliver electrical stimulation therapy as an aid in the reduction of opioid withdrawal symptoms. Both devices deliver biphasic electrical stimulation waveforms hence are charge balanced due to the positive and negative phase between active electrode(s) and the ground electrode. Refer to the following website for more information: **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID = K173861.** (Accessed October 6, 2022)

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. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID = K201873. (Accessed October 6, 2022)

Microcurrent Electrical Nerve Stimulation Therapy (MENS) Devices

MENS devices are categorized as TENS devices intended for pain relief. Refer to 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 October 6, 2022)

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. Refer to 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 October 6, 2022)

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 June 7, 20019 (Product Code QHH). Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID = DEN180057.
(Accessed October 6, 2022)

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. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID = K061166. (Accessed October 6, 2022)

Restorative Neurostimulation

Restorative neurostimulation devices are categorized as implanted neuromuscular stimulators for lower back muscles. The ReActiv8 Implantable Neurostimulation System was granted premarket approval on June 16, 2020. The device is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery. Refer to the following website for more information using Product Code QLK: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed October 12 2022)

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). Refer to the following websites for more information:

- 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 October 6, 2022)

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. Refer to 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 October 6, 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. Refer to the following website for more information https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200050.pdf. (Accessed October 6, 2022)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0126LL

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.