Diabetic Neuropathy: Selected Treatments

Number: 0729

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers percutaneous electrical stimulation medically necessary for the treatment of members with diabetic neuropathy who failed to adequately respond to conventional treatments including anti-convulsants (especially pregabalin), anti-depressants (e.g., amitriptyline, and duloxetine), opioids (e.g., morphine sulphate and tramadol), and other pharmacological agents (e.g., capsaicin and isosorbide dinitrate spray).

Note: Use of percutaneous electrical stimulation for more than 4 weeks for diabetic neuropathy is considered not medically necessary.

Aetna considers the following interventions experimental and investigational for the treatment of diabetic neuropathy because their clinical value for this indication has not been established.

Policy History

Last Review: 08/10/2017
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Next Review: 08/09/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Acupuncture
- Aldose reductase inhibitors
- Angiotensin II type 2 receptor antagonists (e.g., candesartan, irbesartan, losartan, and valsartan)
- Botulinum toxin
- Combination electrochemical therapy/treatment (CET)
- Electroanalgesia (e.g., Sanexas SLV2 and Synaptic 4000)
- Electromagnetic field treatment
- Erythropoietin analogs
- Fulranumab
- Ghrelin
- Infrared therapy
- Interleukin-6
- Lacosamide
- Low-intensity laser
- Monochromatic infrared phototherapy
- Ozone therapy
- Peripheral nerve blocks (continuous or single-injection)
- Plantar electrical-stimulation
- Reiki therapy
- Sodium channel blockers
- Spinal cord stimulation (see CPB 0194 - Spinal Cord Stimulation)
- Surgical decompression*
- Topical ketamine
- Tumor necrosis factor-alpha inhibitors (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab)
- Vibrating insoles.

* Surgical decompression may be considered medically necessary for entrapment syndromes even though the person has the concomitant diagnosis of diabetic neuropathy.

See also CPB 0011 - Electrical Stimulation for Pain, CPB 0135 - Acupuncture, CPB 0536 - Vitamin B-12 Therapy, and CPB 0604 - Infrared Therapy.

**Background**

Diabetic neuropathy (DN) refers to signs and symptoms of neuropathy in patients with diabetes in whom other causes of neuropathy have been excluded. Distal symmetrical neuropathy is the most common form accounting for 75% of DN.
Asymmetrical neuropathies may involve cranial nerves, thoracic or limb nerves; and are of acute onset resulting from ischemic infarction of vasa nervosa. For clinical diagnosis of DN, 2 of the following 5 are recommended: (i) signs, (ii) symptoms, (iii) quantitative sensory testing, (iv) nerve conduction study, and (v) autonomic testing. Management of patients with DN entails control of hyperglycemia, other cardiovascular risk factors, alpha lipoic acid and L-carnitine. For neuropathic pain, analgesics, non-steroidal anti-inflammatory drugs, anti-depressants, and anti-convulsants are recommended. The treatment of autonomic neuropathy is symptomatic.

The natural history of DN is progressive and irreversible loss of sensibility in the feet, and may lead to ulceration and/or amputation. Studies have reported that surgical decompression of lower extremity peripheral nerves in patients with DN can relieve pain, restore sensation, and prevent ulceration and amputation.

The American Academy of Neurology (AAN)’s practice advisory on surgical decompression for the treatment of DN (Chaudhry et al, 2006) stated that systemic review of the scientific literature revealed only Class IV studies (uncontrolled studies, case series, case reports, or expert opinion) concerning this approach. The AAN concluded that surgical decompression for DN is unproven, and stated that prospective, randomized, controlled trials with standard definitions of peripheral neuropathy, functional outcome measures with independent, blinded evaluations are needed to ascertain the clinical value of this intervention.

Halle-Caffee (2000) reported the findings of a series of 58 operations on 36 patients who received decompression of the posterior tibial nerve for the treatment of DN. Pre-operative symptoms included lack of sensation, pain, or both. Eleven of the 36 patients had neurotrophic ulcers, which were treated simultaneously. The operation was found to be effective for relief of pain in 24 of the 28 patients with that complaint (86 %). Restoration of sensation was less consistent with improvement noted in 18 of the 36 patients (50 %). The mean follow-up period was 32 months with a range of 12 to 84 months, and 5 patients
had some degree of recurrent symptoms. No patient has developed a new ulcer after nerve decompression. Wound complications were minimal (12%), even though ulcers were treated simultaneously. No patient required surgical treatment for the decompression incision, although 1 subject was hospitalized for treatment of a wound infection. The author stated that the procedure appeared to be a worthwhile treatment, which should be considered for selected diabetics with symptomatic neuropathy.

Wood and Wood (2003) presented the short-term results of 33 lower extremities treated with external neurolysis of the common peroneal, deep peroneal, and tarsal tunnel nerves. Mean follow-up was 3 months with a range of 1 to 6 months. The surgery was performed in an attempt to relieve pain, and to restore normal sensation in the foot. All procedures were performed under spinal or general anesthesia. Subjects for the procedure were type 1 or type 2 diabetics with symptomatic somatosensory neuropathy (e.g., pain, burning, tingling, and/or numbness) and pre-operative computer-assisted neurosensory testing that confirmed the presence of elevated nerve threshold levels and axonal degeneration in the foot and leg. External neurolysis of the involved nerves provided good to excellent results in 90.0% of those patients with pre-operative neuropathic pain, and restored sensation at good to excellent levels in 66.7% of those patients with pre-operative neuropathic numbness. The mean visual analog score (VAS) for pain assessment was 9.0 pre-operatively and 3.2 post-operatively for those patients with pain as a symptomatic complaint (n = 30). There were 4 complications (12%) and all were early cases consisting of a non-infected wound dehiscence of the tarsal tunnel incision, which went on to heal without consequence. These initial short-term results suggested that external neurolysis of the common peroneal, deep peroneal, and tarsal tunnel nerves in selected patients with symptomatic DN and an overlying compression neuropathy as determined by using computer-assisted neurosensory testing appears to be an effective treatment for providing pain relief and restoration of sensation in the foot.

The impact of surgical decompression on the development of
ulcers and amputations in both the operated and the contralateral, non-operated limb was evaluated in a retrospective analysis of 50 patients with diabetes a mean of 4.5 years (range of 2 to 7 years) from the date of surgery (Aszmann et al, 2004). No ulcers or amputations occurred in the index limb of these patients. In contrast, there were 12 ulcers and 3 amputations in 15 different patients in contralateral limbs (p < 0.001). The authors concluded that decompression of lower extremity nerves in DN changes the natural history of this disease, representing a paradigm shift in health care costs (Aszmann et al, 2004).

In a prospective study, Valdivia and associates (2005) reported the findings of 100 consecutive patients (60 with diabetes and 40 with idiopathic neuropathy) operated on by 2 surgeons; with the post-operative results reviewed by someone other than these two surgeons. Each patient had neurolysis of the peroneal nerve at the knee and the dorsum of the foot, and the tibial nerve released in the four medial ankle tunnels. After at least 1 year of follow-up, 87 % of patients with pre-operative numbness reported improved sensation, 92 % with pre-operative balance problems reported improved balance, and 86 % whose pain level was 5 or greater on VAS from 0 (no pain) to 10 (the most severe pain) before surgery reported an improvement in pain. These researchers concluded that decompression of compressed lower extremity nerves improves sensation and decreases pain, and should be recommended for patients with DN who have failed to improve with traditional medical treatment.

In a review on the role of surgical decompression for DN, Biddinger and Amend (2004) stated that while some studies reported decreased pain, others showed improved sensory function. These investigators noted that the role of surgical decompression for treating DN remains controversial.

Karagoz and associates (2008) studied the effect of peripheral nerve decompression on DN on the 1st day and 6 months post-operatively (n = 24). The common peroneal, the posterior tibial, and the deep peroneal nerves were decompressed. Pain relief was assessed by the VAS. Patients were screened with neurosensory testing by means of a Pressure-Specified Sensory
Device. Pre-operative values and values on the 1st day and 6 months post-operatively were compared. Pain relief was reported to be 80% and 85% at 1st day and 6 months after the surgery, respectively. Mean 2-point discrimination length improvements were found to be 72.6% and 89% at 1st day and 6 months, respectively. The authors concluded that peripheral nerve decompression can be used effectively in the treatment of patients with DN.

On the other hand, Chaudhry and colleagues (2008) concluded in a Cochrane review that the role of decompressive surgery for diabetic symmetric distal neuropathy is unproven. These researchers examined the evidence from randomized controlled trials concerning the role of decompressive surgery of lower limbs for symmetrical diabetic peripheral neuropathy. They included all randomized or quasi-randomized controlled human trials in which any form of decompressive surgery of the lower limbs nerves had been used to treat diabetic symmetrical distal polyneuropathy (DSDP) compared with no treatment or medical therapy. Patients with DSDP were included if they had decompression (with or without neurolysis) of at least 2 of the following nerves in both lower limbs, for the treatment of DSDP: the posterior tibial nerve (including calcaneal, medial and lateral plantar nerves), deep peroneal nerve at the ankle, common peroneal nerve at the knee, lateral femoral cutaneous nerve and sural nerves in the posterior calf region. The primary outcome measure was the change in pain measured by the VAS between the baseline and a follow-up period of greater than 3 months. A total of 142 publications from the above search strategies were identified. The 3 authors of this manuscript reviewed abstracts of all papers independently. Only 8 of these were considered relevant to the question at hand. The data from these 8 studies were entered onto standardized data extraction forms. The authors used Review Manager to pool the results from appropriate studies comparing the same treatments; dichotomous outcomes to obtain pooled relative risks (RR); measured outcomes to obtain pooled weighted mean differences; and a fixed-effect analysis unless there was evidence of serious heterogeneity between studies sufficient to justify the use of random-effects analysis. This review failed to identify a single randomized controlled trial or any other well designed
prospective study controlling for the non-operated limb that showed improvements in pre-defined end points after decompressive surgery.

In a randomized, double-blind, placebo-controlled parallel study, Weintraub et al (2009) examined if repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields (PEMF) targeting painful feet can reduce neuropathic pain (NP), influence sleep in symptomatic diabetic peripheral neuropathy (DPN), and influence nerve regeneration. Subjects (n = 225) with DPN stage II or III were randomly assigned to use identical devices generating PEMF or sham (placebo) 2 hrs/day to feet for 3 months. Nerve conduction testing was performed serially. Main outcome measures included pain reduction scores using a VAS, the Neuropathy Pain Scale (NPS), and the Patient's Global Impression of Change (PGIC). A subset of subjects underwent serial 3-mm punch skin biopsies from 3 standard lower limb sites for epidermal nerve fiber density (ENFD) quantification. Subjects (n = 225) were randomized with a drop-out rate of 13.8 %. There was a trend toward reductions in DPN symptoms on the PGIC, favoring the PEMF group (44 % versus 31 %; p = 0.04). There were no significant differences between PEMF and sham groups in the NP intensity on NPS or VAS. A total of 27 subjects completed serial biopsies; 29 % of PEMF subjects had an increase in distal leg ENFD of at least 0.5 SDs, while none did in the sham group (p= 0.04). Increases in distal thigh ENFD were significantly correlated with decreases in pain scores. The authors concluded that PEMF at this dosimetry was non-effective in reducing NP. However neurobiological effects on ENFD, PGIC and reduced itching scores suggested that future studies are indicated with higher dosimetry (3000 to 5000 G), longer duration of exposure, and larger biopsy cohort.

The American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Physical Medicine & Rehabilitation, and the AAN's evidence-based guideline on the treatment of painful DN (Bril et al, 2011) stated that pregabalin is established as effective and should be offered for relief of painful DN (Level A). Amitriptyline, capsaicin, duloxetine, gabapentin, isosorbide dinitrate spray, opioids (e.g.,
morphine sulfate, and tramadol), valproate, and venlafaxine are probably effective and should be considered for the treatment of painful DN (Level B). Percutaneous electrical nerve stimulation should be considered for the treatment of painful DN (Level B). The recommended duration for electrical stimulation is 3 to 4 weeks.

Ites et al (2011) evaluated the effectiveness of interventions used by physical therapists to minimize balance dysfunction in people with DPN. Currently, no systematic review exists that explores the effectiveness of these interventions. When conducting this systematic review, these investigators searched the electronic databases CINAHL, EMBASE, Cochrane Review, and Medline using specific search terms for the period from inception of each database to June 2009. Two independent reviewers analyzed the abstracts obtained to determine whether the article focused on balance interventions that are within the scope of physical therapy practice. All study designs were eligible for review with the exception of case reports and systematic reviews. The Delphi criteria was used to assess methodological quality. This literature search and methods assessment resulted in 2,213 titles, 82 abstracts, and 6 articles, including 1 randomized controlled trial eligible for inclusion. The 6 articles contained 4 physical therapy interventions including monochromatic infrared energy therapy, vibrating insoles, lower extremity strengthening exercises, and use of a cane. Upon thorough analysis of outcome measures, statistical significance, and clinical relevance, the intervention of lower extremity strengthening exercises was given a fair recommendation for clinical use in treating balance dysfunction in patients with DPN. All others had insufficient evidence to either support or refute their effect on balance in this population.

In a randomized, placebo-controlled, double-blind study, Mahoney et al (2012) examined if topical 5% ketamine cream is effective in reducing the pain of DN. A total of 17 diabetic patients completed the study. The Michigan Neuropathy Screening Instrument was used to determine whether the neuropathy was likely caused by the diabetic condition. Hemoglobin A(1c) levels were measured before treatment. Patients applied 1 ml of either ketamine cream or placebo cream
for 1 month. The intensity of 7 different pain characteristics was evaluated before and after treatment. A 2-way repeated analysis of variance design was used to test for differences between treatments and within patients (time). These investigators found no significant treatment main effect, but pain improved significantly over time in both groups. There was no statistical interaction effect (treatment × time) in any of the pain characteristics, indicating that pain improved in the 2 treatment groups similarly with time. The authors concluded that the 5% topical ketamine cream was no more effective than placebo in relieving pain caused by DN.

In a Cochrane review, Hearn et al (2012) evaluated the analgesic efficacy and adverse effects of lacosamide in the management of chronic neuropathic pain or fibromyalgia. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register (2011, Issue 4), CENTRAL (2011, Issue 3), MEDLINE (January 2000 to August 2011) and EMBASE (2000 to August 2011) without language restriction, together with reference lists of retrieved papers and reviews. They included randomized, double-blind studies of 8-week duration or longer, comparing lacosamide with placebo or another active treatment in chronic neuropathic pain or fibromyalgia. Two review authors independently extracted data for efficacy and adverse events and examined issues of study quality, including risk of bias assessments. Where possible, they calculated numbers needed-to-treat to benefit from dichotomous data for effectiveness, adverse events and study withdrawals. They included 6 studies -- 5 (1,863 participants) in painful DN (PDN) and 1 (159 participants) in fibromyalgia. All were placebo-controlled and titrated to a target dose of 200 mg, 400 mg or 600 mg lacosamide daily, given as a divided dose. Study reporting quality was generally good, although the imputation method of last observation carried forward used in analyses of the primary outcomes is known to impart major bias where, as here, adverse event withdrawal rates were high. This, together with small numbers of patients and events for most outcomes at most doses meant that most results were of low-quality, with moderate-quality evidence available for some efficacy outcomes for 400 mg lacosamide. There were too few data for analysis of the 200-mg
dose for painful diabetic neuropathy or any dose for fibromyalgia. In painful DN, lacosamide 400 mg provided statistically increased rates of achievement of "moderate" and "substantial" benefit (at least 30% and at least 50% reduction from baseline in patient-reported pain, respectively) and the patient global impression of change outcome of "much or very much improved". In each case the extra proportion benefiting above placebo was about 10%, yielding numbers needed-to-treat to benefit compared with placebo of 10 to 12. For lacosamide 600 mg, there was no consistent benefit over placebo. There was no significant difference between any dose of lacosamide and placebo for participants experiencing any adverse event or a serious adverse event, but adverse event withdrawals showed a significant dose response. The number needed-to-treat to harm for adverse event withdrawal was 11 for lacosamide 400 mg and 4 for the 600-mg dose. The authors concluded that lacosamide has limited efficacy in the treatment of peripheral DN. Higher doses did not give consistently better efficacy, but were associated with significantly more adverse event withdrawals. Where adverse event withdrawals are high with active treatment compared with placebo and when last observation carried forward imputation is used, as in some of these studies, significant over-estimation of treatment efficacy can result. It is likely, therefore, that lacosamide is without any useful benefit in treating neuropathic pain; any positive interpretation of the evidence should be made with caution if at all.

Peripheral nerve blocks (PNBs) entail the injection of corticosteroids, local anesthetics, neurolytic agents and/or sclerosing agents into or near peripheral nerves resulting in the temporary interruption of conduction of impulses in peripheral nerves or nerve trunks (somatic and sympathetic nerves).

Peripheral nerve blocks can either be “single-injection” -- refers to one-time injection of local anesthetic to the target nerve for peri-operative analgesia and/or surgical anesthesia, or “continuous” -- refers to the percutaneous insertion of a catheter directly adjacent to the target peripheral nerve(s). The latter approach is to provide prolonged nerve block by continuous infusion of local anesthetic for longer procedures, as well as post-operative analgesia. Continuous PNB (cPNB) is primarily used for
inpatient procedures, but can also be used in outpatients (Jeng and Rosenblatt, 2012).

Hartemann et al (2011) stated that the prevalence of painful diabetic neuropathy (PDN) is approximately 20 % in patients with type-2 diabetes and 5 % in those with type-1 diabetes. Patients should be systematically questioned concerning suggestive symptoms, as they are not usually volunteers. As PDN is due to small-fiber injury, the 10 g monofilament pressure test as well as the standard electrophysiological procedures may be normal. Diagnosis is based on clinical findings: type of pain (burning discomfort, electric shock-like sensation, aching coldness in the lower limbs); time of occurrence (mostly at rest and at night); and abnormal sensations (such as tingling or numbness). The DN4 questionnaire is an easy-to-use validated diagnostic tool. Three classes of drugs are of equal value in treating PDN: (i) TCAs; (ii) anticonvulsants; and (iii) selective serotonin-reuptake inhibitors (SSRIs). These compounds may be prescribed as first-line therapy following pain assessment using a visual analog scale (VAS). If the initial drug at its maximum tolerated dose does not lead to a decrease in pain of at least 30 %, another drug class should be prescribed; if the pain is decreased by 30 % but remains greater than 3/10, a drug from a different class may be given in combination.

The American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation (Bril et al, 2011) developed a scientifically sound and clinically relevant evidence-based guideline for the treatment of PDN. The basic question that was asked was: "What is the efficacy of a given treatment (pharmacological: anticonvulsants, antidepressants, opioids, others; non-pharmacological: electrical stimulation, magnetic field treatment, low-intensity laser treatment, Reiki massage, others) to reduce pain and improve physical function and QOL in patients with PDN"? A systematic review of literature from 1960 to August 2008 was performed, and studies were classified according to the AAN classification of evidence scheme for a therapeutic article. Recommendations were linked to the strength of the evidence. The results indicated that pregabalin is
established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence, or the evidence is negative. Effective treatments for PDN are available, but many have side effects that limit their usefulness. Few studies have sufficient information on their effects on function and quality of life (QOL).

The South African Expert Panel’s clinical practice guidelines for management of neuropathic pain (Chetty et al, 2012) stated that neuropathic pain (NeuP) is challenging to diagnose and manage, despite ongoing improved understanding of the underlying mechanisms. Many patients do not respond satisfactorily to existing treatments. There are no published guidelines for diagnosis or management of NeuP in South Africa. A multi-disciplinary expert panel critically reviewed available evidence to provide consensus recommendations for diagnosis and management of NeuP in South Africa. Following accurate diagnosis of NeuP, pregabalin, gabapentin, low-dose TCAs (e.g., amitriptyline) and SSRIs (e.g., duloxetine and venlafaxine) are all recommended as first-line options for the treatment of peripheral NeuP. If the response is insufficient after 2 to 4 weeks, the recommended next step is to switch to a different class, or combine different classes of agent. Opioids should be reserved for use later in the treatment pathway, if switching drugs and combination therapy fails. For central NeuP, pregabalin or amitriptyline are recommended as first-line agents. Companion treatments (e.g., cognitive behavioral therapy and physical therapy) should be administered as part of a multi-disciplinary approach. Dorsal root entry zone rhizotomy (DREZ) is not recommended to treat NeuP.

In an evidence-based guideline on “Neuropathic pain interventional treatments”, Mailis and Taenzer (2012) states that “Based on limited evidence that selective transforaminal nerve root blocks (extraforaminal root injections, periradicular steroid injections, intraforaminal oxygen-ozone injections and epidural
perineural autologous conditioned serum injections can provide up to 8 to 12 weeks of relief from lumbar radicular pain, the task force cannot justify a general recommendation, but suggests that these interventions be used with caution depending on the circumstances, with full disclosure to the patient of the limited evidence and potential risks. Evidence quality: Fair; Certainty: Moderate; Strength of recommendation: Grade C (May recommend depending on circumstances. At least moderate certainty with small net benefit).

Furthermore, UpToDate reviews on “Treatment of diabetic neuropathy” (Feldman and McCulloch, 2012), “Overview of lower extremity peripheral nerve syndromes” (Rutkove, 2012), and “Epidemiology, clinical manifestations, diagnosis, and treatment of HIV-associated peripheral neuropathy” (Nardin and Freeman, 2012) do not mention the use of PNBs.

Stein and colleagues (2013) evaluated the effect of treatment with electrical stimulation and electromagnetic fields on pain and sensitivity in patients with painful diabetic neuropathy compared with placebo or another intervention. These investigators searched the following electronic databases (from inception to April 2012): MEDLINE (accessed by PubMed), LILACS, Physiotherapy Evidence Database (PEDro), EMBASE and Cochrane CENTRAL. They included randomized trials that compared electrical stimulation or electromagnetic fields with control groups in which the objective was to assess pain and sensitivity in patients with PDN. Two reviewers independently extracted the data. A random-effects model was used for the main analysis. The search retrieved 1,336 articles, of which 12 studies were included. Reductions in the mean pain score were significantly greater in the TENS (transcutaneous electrical nerve stimulation) group than in the placebo group [-0.44 (95 % confidence interval [CI]: -0.79 to -0.09; I2: 0 %)]. There was no improvement in pain relief when electromagnetic fields were compared with the control group [-0.69 (95 % CI: -1.86 to 0.48; I2: 63 %)]. The authors concluded that TENS improved pain relief in patients with diabetic neuropathy, while no such improvement was observed with the use of electromagnetic field treatment. Due to the methodological differences between the studies, a meta-analysis
for the outcome of sensitivity could not be performed.

Chen and colleagues (2013) performed a systematic review to evaluate the potential benefits and harms of manual acupuncture for DPN to justify its clinical use. These investigators searched for published and unpublished randomized controlled trials of manual acupuncture for DPN till March 31, 2013. Revman 5.2 software was used for data analysis with effect estimate presented as RR and mean difference (MD) with a 95 % CI. A total of 25 trials involving 1,649 participants were included. The methodological quality of included trials was generally poor. Meta-analysis showed that manual acupuncture had better effect on global symptom improvement compared with mecobalamin (RR 1.31, 95 % CI: 1.21 to 1.42), vitamin B1 and B12 (RR 1.55, 95 % CI: 1.33 to 1.80), and no treatment (RR 1.56, 95 % CI: 1.31 to 1.85), and that the combination of manual acupuncture and mecobalamin had better effect compared with mecobalamin alone on global symptom improvement (RR 1.56, 95 % CI: 1.28 to 1.90). Adverse events were not reported in any trials. The asymmetric funnel plot suggested publication bias. The authors concluded that despite the number of trials of manual acupuncture for DPN and their uniformly positive results, no clinically relevant conclusions can be drawn from this review due to the trials' high risks of bias and the possibility of publication bias. They stated that clearly defined and internationally acknowledged outcome measures are needed for future study. They noted that there remains an urgent need for training Chinese researchers in conducting unbiased trials as well as prospectively registering all initiated Chinese trials to avoid publication bias.

An UpToDate review on “Treatment of diabetic neuropathy” (Feldman and McCulloch, 2014) does not mention combinational electrochemical therapy/treatment (CET) as a therapeutic option.

In a phase II, double-blind, placebo-controlled trial, Wang et al (2014) evaluated the safety and effectiveness of fulranumab, a fully human monoclonal antibody against nerve growth factor (NGF), in patients with diabetic peripheral neuropathic pain (DPNP). Patients with moderate-to-severe DPNP were
randomized to treatments with fulranumab (1, 3, or 10 mg) or placebo administered subcutaneously every 4 weeks. Because of early study termination (clinical hold) by the U.S. Food and Drug Administration (FDA), 77 (intent-to-treat) of the planned 200 patients were enrolled. The primary end-point, the mean reduction of average daily pain at week 12 compared with baseline, showed a positive dose-response relationship ($p = 0.014$, 1-sided); the pair-wise comparison between the 10-mg group and placebo was significant (unadjusted $p = 0.040$, 2-sided). An exploratory responder analysis revealed that a greater proportion of patients in the 10-mg group reported greater than or equal to 30% reduction in the average DPNP intensity compared with placebo at week 12 ($p = 0.006$).

Although not statistically significant, several secondary end-points showed directionally similar results to the primary efficacy dose-response relationship. During the combined efficacy and safety extension phases, the top 3 treatment-emergent adverse events in the combined fulranumab group were arthralgia (11%), peripheral edema (11%), and diarrhea (9%). No cases of joint replacement or death were reported. The authors concluded that despite early study termination, fulranumab treatment resulted in dose-dependent efficacy and was generally well-tolerated. The major drawback of this phase II study was its small sample size because of the FDA clinical hold. Also, patients who discontinued the study were often lost to follow-up for safety. Because of the small sample size, these researchers stated that they cannot conclude that there is no risk of joint destruction and/or osteonecrosis, which is a specific safety concern for the anti-NGF class. Moreover, they stated that long-term trials involving more patients are needed to fully characterize the efficacy, safety, and tolerability of this potentially new class of analgesic drug for the treatment of DPNP.

Bannwarth and Kostine (2014) stated that it is unanimously accepted that there is an unmet need for pain medications that are both safe and effective. Unfortunately, no really novel analgesics have been approved over the past 3 decades. In view of both experimental and clinical evidence of a major role for NGF in the generation and maintenance of a wide range of pain states, drug discovery efforts focusing on the development of anti-NGF
agents have aroused particular interest. Several humanized anti-NGF monoclonal antibodies (mAbs) have entered clinical trials as potential analgesics. In this respect, tanezumab is at an advanced stage of clinical development while fulranumab, fasinumab and ABT-110, previously known as PG110, are in early phases of clinical development. This Current Opinion article aimed at describing the rationale for targeting NGF for pain, reviewing the analgesic safety and effectiveness of anti-NGF agents based on data from fully published studies, conference abstracts, and the FDA website, and discussing the possible future of these agents in managing chronic pain. Anti-NGF mAbs produced significant pain relief and functional improvement in patients with osteoarthritis of the knee and/or hip. Conversely, studies in non-specific lower back pain generated mixed results; overall, this condition appeared to be less responsive to anti-NGF agents than osteoarthritis. Finally, there was no conclusive evidence of the effectiveness of anti-NGF mAbs in some types of chronic visceral or neuropathic pain. Furthermore, these studies raised safety concerns about anti-NGF mAbs. As a class, these drugs may cause or worsen peripheral neuropathies. But the most problematic issue -- which prompted the FDA to place studies of these compounds on clinical hold in 2010 -- was rapid joint destruction leading to joint replacement surgery. The etiologies of these side effects have been much debated and their pathophysiology is poorly understood. After an Arthritis Advisory Committee meeting held in March 2012, pharmaceutical companies negotiated with the FDA on the conditions for restarting clinical studies. Although the FDA lifted its clinical hold, there remain many unresolved issues about the long-term safety and effectiveness of anti-NGF mAbs. The authors concluded that while acknowledging that the future of these drugs is unforeseeable, it appears that they may not be the safe and effective painkillers that have been awaited for decades.

Electro-analgesia treatment (EAT) refers to the combination of nerve block therapy and electrical stimulation. However, there is a lack of evidence regarding its clinical effectiveness for the treatment of DN.

Slangen et al (2014) stated that painful diabetic peripheral
neuropathy (PDPN) is a common complication of diabetes mellitus. Unfortunately, pharmacological treatment is often partially effective or accompanied by unacceptable side effects, and new treatments are urgently needed. Small observational studies suggested that spinal cord stimulation (SCS) may have positive effects. These researchers performed a multi-center randomized clinical trial (RCT) in 36 PDPN patients with severe lower limb pain not responding to conventional therapy: 22 patients were randomly assigned to SCS in combination with the best medical treatment (BMT) (SCS group) and 14 to BMT only (BMT group). The SCS system was implanted only if trial stimulation was successful. Treatment success was defined as greater than or equal to 50 % pain relief during daytime or nighttime or "(very) much improved" for pain and sleep on the patient global impression of change (PGIC) scale at 6 months. Trial stimulation was successful in 77 % of the SCS patients. Treatment success was observed in 59 % of the SCS and in 7 % of the BMT patients (p < 0.01). Pain relief during daytime and during nighttime was reported by 41 % and 36 % in the SCS group and 0 % and 7 % in the BMT group, respectively (p < 0.05). Pain and sleep were "(very) much improved" in 55 % and 36 % in the SCS group, whereas no changes were seen in the BMT group, respectively (p < 0.001 and p < 0.05). One SCS patient died because of a subdural hematoma. The authors concluded that treatment success was shown in 59 % of patients with PDPN who were treated with SCS over a 6-month period, although this treatment is not without risks.

An UpToDate review on “Treatment of diabetic neuropathy” (Feldman and McCulloch, 2015) states that “Spinal cord stimulation -- Spinal cord stimulation is an invasive method involving implantable electrodes that deliver electrical stimulation to the dorsal columns of the spinal cord. Preliminary data from a small open-label trial suggest that spinal cord stimulation reduces pain for patients with refractory painful diabetic neuropathy affecting the legs. Further trials are needed to confirm the efficacy of this approach .... Non-glycemic interventions (e.g., multi-factorial risk factor reduction and aldose reductase inhibitors) are under investigation for treating or preventing diabetic neuropathy”. In addition, this review does
not mention electroanalgesia/nerve block as a therapeutic option.

Intiso and associates (2015) stated that the management of neuropathic pain (NP) is a clinical challenge and several non-pharmacological and pharmacological interventions have been proposed with variable benefits. Botulinum toxin (BTX) as an adjunct to other interventions can be a useful therapeutic tool for the treatment of disabled people. Although type A BTX (BTX-A) is predominantly used to reduce spasticity in a neuro-rehabilitation setting, it has been used in several painful conditions including disorders characterized by NP. The underlying pharmacological mechanisms that operate in reducing pain are still unclear and include blocking nociceptor transduction, the reduction of neurogenic inflammation by inhibiting neural substances and neurotransmitters, and the prevention of peripheral and central sensitization. Some neurological disorders requiring rehabilitative intervention can show neuropathic pain resistant to common analgesic treatment. These investigators addressed the effect of BTX-A in treating NP that complicates frequent disorders of the central and peripheral nervous system such as spinal cord injury, post-stroke shoulder pain, and PDPN, which are commonly managed in a rehabilitation setting. Furthermore, BTX-A has an effect in relief pain that may characterize less common neurological disorders including post-traumatic neuralgia, phantom limb, and complex regional pain syndrome with focal dystonia. The authors concluded that the use of BTX-A could represent a novel therapeutic strategy in caring for neuropathic pain whenever common pharmacological tools have been ineffective. However, they stated that large and well-designed RCTs are needed to recommend BTX-A use in the relief of neuropathic pain.

Lakhan and co-workers (2015) noted that recent studies showed a promising analgesic effect using BTX-A for NP. These investigators performed a meta-analysis of 2 studies using BTX-A in the treatment of NP. Electronic searches of MEDLINE/PubMed, EMBASE, and Cochrane Libraries using the terms "botulinum neurotoxin" and "neuropathic pain" were conducted. Only class I and class II therapeutic trials, as classified by the AAN were
The primary outcome measured was the difference in VAS from pre-intervention and post-intervention after 1 month. Data were analyzed for biases and heterogeneity following Cochrane and PRISMA guidelines. Two studies on PDN were analyzed in the meta-analysis showing improvement of 1.96 VAS points (95% CI: -3.09 to -0.84; Z score = 3.43, p < 0.001) following treatment with BTX-A. This corresponded to clinically significant improvement of "minimum change in pain". The adverse effects of infection at injection site was not statistically significant (p = 0.49); BTX-A may be effective for PDN. The authors concluded that tests for significance, low overall risk of bias, and almost no statistical heterogeneity suggested that there is a correlation between BTX-A and improvement of pain scores in PDN. Moreover, they stated that further large-scale RCTs are needed.

Javed and colleagues (2015a) noted that DPN is a common and devastating complication of diabetes, with multiple clinical manifestations. The most common is a symmetrical length-dependent dysfunction and damage of peripheral nerves. The management of DPN rests on 3 tenets: (i) intensive glycemic control, even though the evidence of benefit is questionable in people with type 2 diabetes; (ii) pathogenetic therapies, and (iii) symptomatic treatment. A number of pathogenetic treatments have evaluated in phase III clinical trials, including α-lipoic acid (stems reactive oxygen species formation), benfotiamine (prevents vascular damage in diabetes) and aldose-reductase inhibitors (reduces flux through the polyol pathway), protein kinase C inhibitors (prevent hyperglycemia-induced activation of protein kinase C), nerve growth factors (stimulate nerve regeneration) and Actovegin (improved tissue glucose and oxygen uptake). However, none has gained FDA approval, questioning the validity of current trial designs and the end-points deployed to define efficacy. For PDPN, clinical guidelines recommend atypical analgesics for pain relief, including duloxetine and amitriptyline, the γ-aminobutyric acid analogs gabapentin and pregabalin, opioids including tapentadol and topical agents such as lidocaine and capsaicin. However, no single effective treatment exists for PDPN, highlighting a growing need for studies to evaluate more potent and targeted drugs, as well as combinations. The authors stated that a number of novel
potential candidates, including erythropoietin analogs, angiotensin II type 2 receptor antagonists, intrathecal drug delivery systems, and sodium channel blockers (Javed et al, 2015b) are currently being evaluated in phase II clinical trials.

Ozone Therapy:

In a Cochrane review, Liu and colleagues (2015) evaluated the effects of ozone therapy on the healing of foot ulcers in people with diabetes mellitus (DM). In March 2015, these investigators searched the Cochrane Wounds Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library), Ovid Medline, Ovid Medline (In-Process & Other Non-Indexed Citations), Ovid Embase, EBSCO CINAHL, Science Citation Index, Chinese Biomedical Literature Database and The Chinese Clinical Registry. There were no restrictions based on language, date or study setting. They included RCTs that compared ozone therapy with sham ozone therapy or any other interventions for foot ulcers in people with DM, irrespective of publication date or language. Two reviewers independently screened all retrieved citations, selected relevant citations and extracted data. Disagreements were resolved by discussion with a 3rd reviewer. The methodological quality of included studies and the evidence level of outcomes were assessed using the Cochrane risk of bias tool and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, respectively. Data were expressed using RR for dichotomous outcomes and MD for continuous outcomes with their 95 % CI. Review Manager (RevMan) software was used to analyze the data. A total of 3 studies (212 participants) were included in this review. The overall risk of bias was high for 2 trials and unclear for 1. One trial (101 participants) compared ozone treatment with antibiotics for foot ulcers in people with DM. The study had a follow-up period of 20 days. This study showed that ozone treatment was associated with a greater reduction in ulcer area from baseline to the end of the study than treatment with antibiotics (MD -20.54 cm(2), 95 % CI: -20.61 to -20.47), and a shorter duration of hospitalization (MD -8.00 days, 95 % CI: -14.17 to -1.83), but did not appear to affect the number of ulcers healed over 20 days (RR 1.10, 95 % CI: 0.87 to 1.40). No
side effects were observed in either group. The other 2 trials (111 participants) compared ozone treatment plus usual care with usual care for foot ulcers in people with DM. The meta-analysis results did not show evidence of a difference between groups for the outcomes of reduction of ulcer area (MD -2.11 cm², 95 % CI: -5.29 to 1.07), the number of ulcers healed (RR 1.69, 95 % CI: 0.90 to 3.17), adverse events (RR 2.27, 95 % CI: 0.48 to 10.79), or amputation rate (RR 2.73, 95 % CI: 0.12 to 64.42). The authors concluded that the available evidence was 3 small RCTs with unclear methodology, so they were unable to draw any firm conclusions regarding the effectiveness of ozone therapy for foot ulcers in people with DM.

**Spinal Cord Stimulation:**

Tajti and associates (2016) noted that PDN is a disabling pain condition. Its etiology remains unknown, but a sensitization and neuronal hyperexcitability have been suggested. Only symptomatic pharmacological pain management treatment is currently available. The origin of PDN is enigmatic, and the evidence-based therapeutic guidelines therefore consist only of anti-depressants and anti-epileptics as 1st-line recommended drugs. The results of the meta-analysis from the aspect of the effectiveness of amitriptyline, duloxetine, venlafaxine, gabapentin and pregabalin are favorable, but the placebo response rate was relatively high in patients with neuropathic pain. For personalization of the medication of PDN patients, the optimum dosing, the genotyping of the metabolizing enzymes and optimum biomarkers are needed. Regarding the future perspectives, specific sodium channel subtype inhibitors acting on peripheral nociceptive neurons or modified T-type voltage-gated calcium channel blockers may be promising targets for pharmaceutical innovations. Another attractive strategy for the treatment is based on the effects of monoclonal antibodies against nerve growth factor, sodium channels, specific receptor and cytokines. The authors also stated that botulinum toxin A, capsaicin patch and spinal cord stimulation therapies are the nearest future therapeutic options for the treatment of PDN patients.
**Ghrelin:**

Ueno and colleagues (2017) stated that DPN is the most common complication of diabetes, and its progression significantly worsens the patient's QOL. Although several drugs are available for DPN, all of these provide only symptomatic relief. These investigators examined the therapeutic effects of ghrelin for DPN, based on its various physiological functions. A total of 7 patients with type-2 DM (T2DM) with typical clinical signs and symptoms of DPN were hospitalized. Synthetic human ghrelin (1.0 μg/kg) was administered intravenously for 14 days. Motor nerve conduction velocity (MCV) of the posterior tibial nerve improved significantly after the treatment, compared to that at baseline (35.1 ± 1.8 to 38.6 ± 1.8 m/s, p < 0.0001), while the MCV in 6 untreated patients did not change throughout hospitalization. The subjective symptoms assessed based on the total symptom score also significantly improved (15.6 ± 3.1 to 11.1 ± 2.2, p = 0.047). Although sensory nerve conduction velocity (SCV) of the sural nerve could not be detected in 3 patients at baseline, it was detected in 2 of the 3 patients after 14 days of ghrelin administration; overall, SCV did not change significantly. Plasma glucose, but not serum C peptide, levels during a liquid meal tolerance test significantly improved after treatment. The authors concluded that these findings suggested that ghrelin may be a novel therapeutic option for DPN; however, a double-blind, placebo-controlled trial is needed to examine the effect of ghrelin on DPN as well as its underlying mechanisms.

**Interleukin-6:**

Cox and colleagues (2017) noted that DPN remains one of the most common and serious complications of diabetes. Currently, pharmacological agents are limited to treating the pain associated with DPN, and do not address the underlying pathological mechanisms driving nerve damage, thus leaving a significant unmet medical need. Interestingly, research conducted using exercise as a treatment for DPN has revealed interleukin-6 (IL-6) signaling to be associated with many positive benefits such as enhanced blood flow and lipid metabolism, decreased chronic inflammation, and peripheral nerve fiber regeneration. IL-6, once
known solely as a pro-inflammatory cytokine, is now understood to signal as a multi-functional cytokine, capable of eliciting both pro- and anti-inflammatory responses in a context-dependent fashion. IL-6 released from muscle in response to exercise signals as a myokine and as such has a unique kinetic profile, whereby levels are transiently elevated up to 100-fold and return to baseline levels within 4 hours. Importantly, this kinetic profile is in stark contrast to long-term IL-6 elevation that is associated with pro-inflammatory states. Given exercise induces IL-6 myokine signaling, and exercise has been shown to elicit numerous beneficial effects for the treatment of DPN, a causal link has been suggested. These researchers discussed both the clinical and pre-clinical evidence related to the application of IL-6 as a therapeutic strategy for DPN. In addition, they discussed how IL-6 may directly modulate Schwann and nerve cells to explore a mechanistic understanding of how this treatment elicits a neuro-protective and/or regenerative response. The authors concluded that available evidence suggested that IL-6, when administered in a low-dose pulsatile strategy to mimic the body's natural response to exercise, may prove to be an effective treatment for the protection and/or restoration of peripheral nerve function in DPN. They stated that this review provided rationale for continued investigation of IL-6 as a therapeutic option for DPN.

**Monochromatic Infrared Phototherapy:**

Robinson and colleagues (2017) stated that monochromatic infrared energy (MIRE) or phototherapy has been employed to improve plantar sensitivity and pain in lower limbs of patients with diabetic sensorimotor peripheral neuropathy (DSPN), but the available primary results are inconsistent. These investigators reviewed the effects of MIRE on plantar sensitivity and neuropathic pain in patients with DSPN. Medline, Embase, Cochrane CENTRAL, and Google Scholar were searched up to September 2016; RCTs addressing the effects of MIRE on plantar sensitivity and neuropathic pain in patients with DSPN were selected. Study inclusion, risk of bias and quality assessment, and data extraction were completed by 2 independent reviewers. Of 2,549 records identified, 6 studies met the selection criteria, with
304 patients (594 feet) randomized; MIRE was not associated with improvement in plantar tactile sensitivity (standard mean difference [SMD] = 0.22, 95% CI: -0.07 to 0.51, low quality of evidence). Subgroups of studies with short-term (up to 2 weeks) follow-up showed significant improvement in plantar sensitivity (SMD = 0.41, 95% CI: 0.18 to 0.64). Neuropathic pain increased significantly in patients who received MIRE (MD = 0.49, 95% CI: 0.30 to 0.68, low quality of evidence). The authors concluded that there was limited evidence that MIRE results in short-term improvement of tactile sensitivity probably not sustained over time. Limited evidence also suggested that MIRE does not provide relief for neuropathic pain. They stated that as quality of evidence is low, further studies are likely to change the estimated effect.

**Plantar Electrical Stimulation:**

Najafi and colleagues (2017) examined the effectiveness of plantar electrical-stimulation therapy to enhance motor-performance among patients with DPN. Using a double-blinded model, 28 volunteers with DPN (age of 57.8 ± 10.2 years) were recruited and randomized to either intervention (IG: n = 17) or control (CG: n = 11) group. Both groups received identical plantar-stimulation devices for 6 weeks of daily use at home; however, only the IG devices were set to deliver stimulation. Balance (ankle, hip, and center of mass [COM] sway) and gait (stride velocity [SV], stride time [ST], stride length [SL], and cadence) were measured using validated wearable sensors. Outcomes were assessed at baseline and at 6-week. Clinical assessment including vascular as measured by ankle-brachial-index (ABI) and plantar-sensation as quantified by vibratory plantar threshold (VPT) were also measured at baseline and 6 weeks. No difference were observed between groups for baseline characteristics (p > 0.050). Post-therapy, ankle and COM sway with eyes open were significantly improved (p < 0.05, Cohen's effect size d = 0.67 to 0.76) in the IG with no noticeable changes in CG. All gait parameters were significantly improved in the IG with highest effect size observed for cadence (d = 1.35, p = 0.000). Results revealed improvement in VPT (p = 0.004, d = 1.15) with significant correlation with stride velocity improvement (r =
1.56, \( p = 0.037 \)); ABI was improved in the IG in particulate among those with ABI greater than 1.20 (\( p = 0.041, d = 0.99 \)). The authors concluded that the findings of this study suggested that daily home use of plantar electrical-stimulation may be a practical means to enhance motor-performance and plantar-sensation in patients with DPN.

*Tumor Necrosis Factor-Alpha Inhibitors:*

Mu and colleagues (2017) stated that tumor necrosis factor-alpha (TNF-\( \alpha \)) is a cell signaling protein involved in systemic inflammation, and is also an important cytokine in the acute phase reaction. Several studies suggested a possible association between TNF-\( \alpha \) and DPN in T2DM patients, but no accurate conclusion was available. These researchers performed a systematic review and meta-analysis of observational studies to evaluate the association between serum TNF-\( \alpha \) levels and DPN in T2DM patients. They searched PubMed, Web of Science, Embase, and China Biology Medicine (CMB) databases for eligible studies. Study-specific data were combined using meta-analysis. A total of 14 studies were finally included into the meta-analysis, which involved 2,650 participants. Meta-analysis showed that there were obviously increased serum TNF-\( \alpha \) levels in DPN patients compared with T2DM patients without DPN (SMD = 1.203, 95 % CI: 0.795 to 1.611, \( p < 0.001 \)). There were also obviously increased levels of serum TNF-\( \alpha \) in diabetic patients with DPN when compared with healthy controls (SMD = 2.364, 95 % CI: 1.333 to 3.394, \( p < 0.001 \)). In addition, there were increased serum TNF-\( \alpha \) levels in painful DPN patients compared with painless DPN patients (SMD = 0.964, 95 % CI: 0.237 to 1.690, \( p = 0.009 \)). High level of serum TNF-\( \alpha \) was significantly associated with increased risk of DPN in patients with T2DM (odds ratio [OR] = 2.594, 95 % CI: 1.182 to 5.500, \( p = 0.017 \)). Increased serum levels of TNF-\( \alpha \) was not associated with increased risk of painful DPN in patients with T2DM (OR = 2.486, 95 % CI: 0.672 to 9.193, \( p = 0.172 \)). Sensitivity analysis showed that there was no obvious change in the pooled estimates when omitting single study by turns. The authors concluded that T2DM patients with peripheral neuropathy have obviously increased serum TNF-\( \alpha \) levels than T2DM patients without peripheral neuropathy and healthy
controls, and high level of serum TNF-α may be associated with increased risk of peripheral neuropathy independently. Moreover, they stated that further prospective cohort studies are needed to examine the association between TNF-α and DPN.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64555</td>
<td>Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)</td>
</tr>
<tr>
<td>64565</td>
<td>Incision for implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve) neuromuscular</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

*Combination electrochemical therapy/treatment (CET) - No specific code:*

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>63650</td>
<td>Percutaneous implantation of neurostimulator electrode array, epidural</td>
</tr>
<tr>
<td>63655</td>
<td>Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural</td>
</tr>
<tr>
<td>63661</td>
<td>Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed</td>
</tr>
<tr>
<td>63662</td>
<td>Removal of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed</td>
</tr>
<tr>
<td>63663</td>
<td>Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed</td>
</tr>
<tr>
<td>63664</td>
<td>Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>63685</td>
<td>Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling</td>
</tr>
<tr>
<td>63688</td>
<td>Revision or removal of implanted spinal neurostimulator pulse generator or receiver</td>
</tr>
<tr>
<td>64400</td>
<td>Injection, anesthetic agent; trigeminal nerve, any division or branch</td>
</tr>
<tr>
<td>64402</td>
<td>Injection, anesthetic agent; facial nerve</td>
</tr>
<tr>
<td>64405</td>
<td>Injection, anesthetic agent; greater occipital nerve</td>
</tr>
<tr>
<td>64408</td>
<td>Injection, anesthetic agent; vagus nerve</td>
</tr>
<tr>
<td>64410</td>
<td>Injection, anesthetic agent; phrenic nerve</td>
</tr>
<tr>
<td>64413</td>
<td>Injection, anesthetic agent; cervical plexus</td>
</tr>
<tr>
<td>64415</td>
<td>Injection, anesthetic agent; brachial plexus, single</td>
</tr>
<tr>
<td>64416</td>
<td>Injection, anesthetic agent; brachial plexus, continuous infusion by catheter (including catheter placement)</td>
</tr>
<tr>
<td>64417</td>
<td>Injection, anesthetic agent; axillary nerve</td>
</tr>
<tr>
<td>64418</td>
<td>Injection, anesthetic agent; suprascapular nerve</td>
</tr>
<tr>
<td>64445</td>
<td>Injection, anesthetic agent; sciatic nerve, single</td>
</tr>
<tr>
<td>64446</td>
<td>Injection, anesthetic agent; sciatic nerve, continuous infusion by catheter (including catheter placement)</td>
</tr>
<tr>
<td>64447</td>
<td>Injection, anesthetic agent; femoral nerve, single</td>
</tr>
<tr>
<td>64448</td>
<td>Injection, anesthetic agent; femoral nerve, continuous infusion by catheter (including catheter placement)</td>
</tr>
<tr>
<td>64449</td>
<td>Injection, anesthetic agent; lumbar plexus, posterior approach, continuous infusion by catheter (including catheter placement)</td>
</tr>
<tr>
<td>64450</td>
<td>Injection, anesthetic agent; other peripheral nerve or branch</td>
</tr>
<tr>
<td>64455</td>
<td>Injection(s), anesthetic agent and/or steroid, plantar common digital nerve(s) (eg, Morton's neuroma)</td>
</tr>
<tr>
<td>64505</td>
<td>Injection, anesthetic agent; sphenopalatine ganglion</td>
</tr>
<tr>
<td>64520</td>
<td>Injection, anesthetic agent; lumbar or thoracic (paravertebral sympathetic)</td>
</tr>
<tr>
<td>64702</td>
<td>Neuroplasty; digital, one or both, same digit</td>
</tr>
</tbody>
</table>
64704 nerve of hand or foot
64708 Neuroplasty, major peripheral nerve, arm or leg, open; other than specified
64712 sciatic nerve
64713 brachial plexus
64714 lumbar plexus
64716 Neuroplasty and/or transposition; cranial nerve (specify)
64718 ulnar nerve at elbow
64719 ulnar nerve at wrist
64721 median nerve at carpal tunnel
64722 Decompression; unspecified nerve(s) (specify)
64726 plantar digital nerve
97026 Application of a modality to 1 or more areas; infrared
97810 - Acupuncture
97814

Other CPT codes related to the CPB:

96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

HCPCS codes covered if selection criteria are met:

C1767 Generator, neurostimulator (implantable), nonrechargeable
C1778 Lead, neurostimulator (implantable)
C1787 Patient programmer, neurostimulator
C1816 Receiver and/or transmitter, neurostimulator (implantable)
C1820 Generator, neurostimulator (implantable), non high-frequency with rechargeable battery and charging system
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1822</td>
<td>Generator, neurostimulator (implantable), high frequency, with rechargeable</td>
</tr>
<tr>
<td></td>
<td>battery and charging system</td>
</tr>
<tr>
<td>C1883</td>
<td>Adaptor/extension, pacing lead or neurostimulator lead (implantable)</td>
</tr>
<tr>
<td>E0745</td>
<td>Neuromuscular stimulator, electronic shock unit</td>
</tr>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each (not covered for spinal cord</td>
</tr>
<tr>
<td></td>
<td>stimulation)</td>
</tr>
<tr>
<td>L8681</td>
<td>Patient programmer (external) for use with implantable programmable</td>
</tr>
<tr>
<td></td>
<td>neurostimulator pulse generator, replacement only</td>
</tr>
<tr>
<td>L8682</td>
<td>Implantable neurostimulator radiofrequency receiver</td>
</tr>
<tr>
<td>L8683</td>
<td>Radiofrequency transmitter (external) for use with implantable neurostimulator</td>
</tr>
<tr>
<td></td>
<td>radiofrequency receiver</td>
</tr>
<tr>
<td>L8684</td>
<td>Radiofrequency transmitter (external) for use with implantable sacral root</td>
</tr>
<tr>
<td></td>
<td>neurostimulator receiver for bowel and bladder management, replacement</td>
</tr>
<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable,</td>
</tr>
<tr>
<td></td>
<td>includes extension</td>
</tr>
<tr>
<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, non-rechargeable,</td>
</tr>
<tr>
<td></td>
<td>includes extension</td>
</tr>
<tr>
<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable,</td>
</tr>
<tr>
<td></td>
<td>includes extension</td>
</tr>
<tr>
<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable,</td>
</tr>
<tr>
<td></td>
<td>includes extension</td>
</tr>
<tr>
<td>L8689</td>
<td>External recharging system for battery (internal) for use with implantable</td>
</tr>
<tr>
<td></td>
<td>neurostimulator, replacement only</td>
</tr>
<tr>
<td>L8695</td>
<td>External recharging system for battery (external) for use with implantable</td>
</tr>
<tr>
<td></td>
<td>neurostimulator, replacement only</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

*Fulranumab, Ozone Therapy* - No specific code:

A4639 Replacement pad for infrared heating pad system, each
C9254 Injection, lacosamide, 1 mg
E0221 Infrared heating pad system
G0295 Electromagnetic therapy, to one or more areas, for wound care other than described in G0329 or for other uses
G0329 Electromagnetic therapy, to one or more areas for chronic stage III and stage IV pressure ulcers and venous stasis ulcers not demonstrating measurable signs of healing after 30 days of conventional care as part of a therapy plan of care
J0585 Injection, onabotulinumtoxinA, 1 unit,
J0586 Injection, abobotulinumtoxina, 5 units
J0587 Injection, rimabotulinumtoxinB, 100 units
J0588 Injection, incobotulinumtoxinA, 1 unit
J0885 Injection, incobotulinumtoxinA, 1 unit
J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non-ESRD use)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)
S8948 Application of modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes

**ICD-10 codes covered for indications listed in the CPB:**

E08.40 Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E08.41 Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E08.42 Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E09.40 Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy unspecified
E09.41 Drug or chemical induced diabetes mellitus with neurological complications with diabetic mononeuropathy

E09.42 Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy

E10.40 Type 1 diabetes mellitus with diabetic neuropathy, unspecified

E10.41 Type 1 diabetes mellitus with diabetic mononeuropathy

E10.42 Type 1 diabetes mellitus with diabetic polyneuropathy

E11.40 Type 2 diabetes mellitus with diabetic neuropathy, unspecified

E11.41 Type 2 diabetes mellitus with diabetic mononeuropathy

E11.42 Type 2 diabetes mellitus with diabetic polyneuropathy

E13.40 Other specified diabetes mellitus with diabetic neuropathy, unspecified

E13.41 Other specified diabetes mellitus with diabetic mononeuropathy

E13.42 Other specified diabetes mellitus with diabetic polyneuropathy

The above policy is based on the following references:


3. Aszmann OC, Kress K, Dellon AL. Results of decompression of peripheral nerves in diabetics: A prospective, blinded study utilizing computer-assisted sensorimotor testing.


26. Rutkove SB. Overview of lower extremity peripheral nerve syndromes. Last reviewed November 2012. UpToDate Inc. Waltham, MA.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0729 Diabetic Neuropathy:
Selected Treatments

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania  revised 10/27/2017