Clinical Policy Bulletin: Diabetic Neuropathy: Selected Treatments
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Policy

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.

- Acupuncture
- Combination electrochemical therapy/treatment (CET)
- Electromagnetic field treatment
- Fulranumab
- Infrared therapy
- Lacosamide
- Low-intensity laser
- Peripheral nerve blocks (continuous or single-injection)
- Reiki therapy
- Surgical decompression*
- Topical ketamine
- 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
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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
(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 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.
CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

64555
64565
64580

CPT codes not covered for indications listed in the CPB:

64400
64402
64405
64408
64410
64412
64413
64415
64416
64417
64418
64445
64446
64447
64448
64449
64450
64455
64505
64520
64702
64704
Other CPT codes related to the CPB:

96365
96366

HCPCS codes not covered for indications listed in the CPB:

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
S8948  Application of modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes

ICD-9 codes not covered for indications listed in the CPB:

249.60  Secondary diabetes with neurological manifestations
249.61
250.60  Diabetes with neurological manifestations
250.63
357.2 Polyneuropathy in diabetes

Other ICD-9 codes related to the CPB (nerve entrapment syndromes):

- 354.0 Carpal tunnel syndrome
- 354.2 Lesion of ulnar nerve
- 355.1 Meralgia paresthetica
- 355.3 Lesion of lateral popliteal nerve
- 355.5 Tarsal nerve syndrome
- 355.79 - Other mononeuritis of upper or lower limb
- 355.9

The above policy is based on the following references:


22. Jeng CL, Rosenblatt MA. Overview of peripheral nerve blocks. Last reviewed November 2012. UpToDate Inc. Waltham, MA.


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