Treatment :: Peripheral and Autonomic Neuropathies

Related article - Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. https://www.dovepress.com/critical-appraisal-of-the-use-of-alpha-lipoic-acid-thioctic-acid-in-th-peer-reviewed-article-TCRM

Peripheral and autonomic neuropathies are a major cause of morbidity in patients with diabetes mellitus. There are three main elements in the treatment regimen:

GLYCEMIC CONTROL FOR ESTABLISHED NEUROPATHY — Optimal glucose control is important for the prevention of diabetic neuropathy, at least in patients with type 1 diabetes mellitus. In the longitudinal follow-up in the large Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial of type 1 patients, glucose control ameliorated the onset of neuropathy as well as progression of surrogate electrophysiologic markers of neuropathy [1,2]. A practice statement issued by the American Diabetes Association in 2005 recommended that the first step in the management of patients with symptomatic diabetic polyneuropathy should be to aim for stable and optimal glycemic control [3]. In a 2012 systematic review, enhanced glucose control led to statistically significant improvements in surrogate measures of neuropathy, including nerve conduction velocity and vibration perception thresholds [4]. These data support the possibility of symptomatic improvement. In addition, clinical experience suggests that vigorous glycemic control is associated with improvement in symptoms for patients who develop acute painful diabetic neuropathy after a period of extreme hyperglycemia such as diabetic ketoacidosis. Nevertheless, established symptomatic diabetic neuropathy is generally not reversible even with intensive glucose control, emphasizing the importance of prevention. Findings from a small observational study suggest but do not establish that surgical treatment (ie, gastric bypass) of obese patients with type 2 diabetes can lead to short-term improvement in both glycemic control and diabetic neuropathy symptoms [5]. Data from larger and more rigorous studies are necessary to determine whether this approach provides long-term benefit for patients with obesity-related type 2 diabetes and neuropathy.

FOOT CARE — We combine good glucose control with foot care. On a daily basis, patients need to inspect their feet for the presence of dry or cracking skin, fissures, plantar callus formation, and signs of early infection between the toes and around the toe nails. Regular foot examinations by the physician to detect early neuropathy are also an essential component of the treatment of diabetic patients. Once a patient has diabetic neuropathy, foot care is even more important to prevent ulceration, infection, and amputation.

PAINFUL DIABETIC NEUROPATHY — Only a small fraction of patients with diabetic polyneuropathy have painful symptoms. Patients with painful diabetic neuropathy should be treated with a systematic, stepwise approach [3]. Before initiating therapy, it is important to confirm that the pain is due to neuropathy. The diagnosis of diabetic polyneuropathy is reviewed here briefly and discussed in detail separately. The onset of severe pain in the feet and lower limbs can be very distressing and disabling. A disc lesion should be considered if the pain has developed in relation to recent trauma or its onset is abrupt. In addition, pain due to disc disease is more often unilateral than pain related to peripheral neuropathy. In the absence of these features, the differential diagnosis is neuropathy or peripheral vascular disease. The physical examination may be helpful (decreased sensation or loss of deep tendon reflexes), but these signs of neuropathy do not necessarily mean that the pain is due to the neuropathy. Several clues that the patient has neuropathic pain are the location of pain (feet more than calves), the quality of the pain, and the timing of pain (present at rest, improves with walking). Each of these features is different from those of the pain due to ischemic vascular disease. Although uncommon compared with symmetric diabetic polyneuropathy, there are several other types of acute painful diabetic neuropathy syndromes. These are:

- In general, these conditions are characterized by severe neuropathic pain, autonomic dysfunction, and a potentially reversible course that may last for many months.

- Finally, diabetic amyotrophy typically occurs in patients with type 2 diabetes mellitus. The traditional features include the acute, asymmetric, focal onset of pain followed by weakness involving the proximal leg, with associated autonomic failure and weight loss. Progression occurs over months and is followed by partial recovery in most patients.
- Spontaneous resolution — Once the diagnosis of painful diabetic polyneuropathy is established, the patient should be informed that the condition is sometimes self-limited. In a prospective study of 29 patients, for example, pain remitted within 12 months in 16 patients (55 percent) [6]. Remission was more likely if the onset of symptoms had followed a sudden metabolic change (either an episode of diabetic ketoacidosis or occasionally an improvement in glycemic control), when the duration of diabetes was relatively short, or when marked weight loss preceded the onset of pain [1]. The mechanisms responsible for the resolution of pain are not understood. Proposed mechanisms include altered perception of pain, further deterioration of the nerve so that it no longer responds to stimulation (so that the patient is at even greater risk from trauma), or improvement in nerve function. As an example, a neuron may spontaneously fire and cause pain while it is being damaged or while it is recovering. Thus, in a patient who has poor glycemic control, the nerves may be starved of nutrients, leading to acute but reversible nerve injury. On the other hand, a previously injured (electrically silent) nerve may recover during improved glycemic control, leading to spontaneous firing and the perception of pain.

PAIN CONTROL — Treatments that are probably beneficial for painful diabetic neuropathy include a number of antidepressants (eg, amitriptyline, duloxetine, venlafaxine), anticonvulsants (eg, pregabalin, sodium valproate), and capsaicin cream [7,8].
Other treatments that may be beneficial include lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation. The supporting evidence for these interventions is reviewed in the sections that follow, as are guideline recommendations and approaches to treatment.

Antidepressants — There is evidence from randomized controlled trials that tricyclic drugs (mainly amitriptyline) and other antidepressants (mainly duloxetine) are beneficial for reducing pain associated with diabetic neuropathy.

Tricyclic drugs — Several tricyclic antidepressant drugs (but not selective serotonin reuptake inhibitors) have been found in double-blind, randomized controlled trials to improve symptoms in patients with painful diabetic neuropathy [9-12]. Tricyclics may act by altering the central perception of pain.

The therapeutic effect usually occurs sooner (within six weeks) and at lower doses than is typical when these drugs are given for the treatment of depression. These points are illustrated by the following trials:

We use either amitriptyline or desipramine in patients with severe pain. This class of drugs can be added to pregabalin or anticonvulsants but not to duloxetine. The starting dose of desipramine is 25 mg, taken at bedtime.

The dose can be increased to a maximum of 200 mg/day over a few weeks. The choice of a specific drug may vary:
In a placebo-controlled, double-blind, randomized cross-over trial, amitriptyline and desipramine were equally effective and superior to fluoxetine or placebo [10]. The benefit of the tricyclic drugs was noted within two weeks and continued to increase at six weeks. Desipramine had somewhat fewer side effects than amitriptyline, particularly dry mouth. The average effective dose, titrated over six weeks to achieve control of symptoms, was 111 mg/day for desipramine and 105 mg/day for amitriptyline. There was no correlation between relief of pain, dosage, or plasma drug concentrations, suggesting that the clinical response and tolerability of side effects are the best guides to dose titration.

A randomized, blinded cross-over trial of 58 adults with painful diabetic neuropathy that compared amitriptyline (10 to 50 mg daily) and duloxetine (20 to 60 mg daily) given at bedtime found a significant improvement in pain with both medications compared with pretreatment baseline [13]. A good outcome, defined as a median pain score reduction of >50 percent, was reported at a similar rate for amitriptyline and duloxetine (55 versus 59 percent), and the difference was not significant. Dry mouth was significantly more frequent with amitriptyline compared with duloxetine (55 versus 24 percent), while constipation was non-significantly more frequent with duloxetine (37 versus 17 percent).

Duloxetine — A systematic review published in 2014 concluded that duloxetine, a dual serotonin and norepinephrine reuptake inhibitor, is effective for treating pain in diabetic polyneuropathy [14]. The benefit of duloxetine was established in three 12-week randomized, blinded, controlled trials involving 1102 subjects [15-17]. In these trials, pain improvement occurred significantly more frequently with duloxetine 60 or 120 mg daily than with placebo (47 and 48 percent, versus 29 percent with placebo). Pain improvement was noted as early as the first week of treatment and continued for the duration of the studies. Duloxetine showed rapid onset of action and sustained benefit, and it was also effective in relieving pain at night. The 120 mg daily dose was not as well tolerated as 60 mg daily, although both were beneficial. While duloxetine was more effective than placebo, all three trials were of relatively short duration, and the long-term effectiveness and safety of duloxetine is uncertain [18]. Furthermore, in clinical trials evaluating painful diabetic polyneuropathy, duloxetine treatment resulted in modest increases in fasting plasma glucose [19]. Although comparative trials are few, amitriptyline appears to be as effective as duloxetine for the treatment of painful diabetic neuropathy, and is less expensive. (See 'Tricyclic drugs' above.) The most common reported side effects of duloxetine were nausea, somnolence, dizziness, decreased appetite, and constipation. Hot flashes and erectile dysfunction were also reported infrequently. Because nausea is common, patients are encouraged to take the drug on a full stomach. Duloxetine should not be taken with other serotonin or norepinephrine uptake inhibitors but can be combined with anticonvulsant therapy.

Venlafaxine — A 2015 systematic review of six randomized controlled trials with 460 participants, most having painful diabetic neuropathy, found little compelling evidence that venlafaxine is effective for neuropathic pain [20]. All the included trials showed some benefit for venlafaxine, but all had limitations that could cause an overestimation of effect size. In the largest trial included the systematic review, extended-release (ER) venlafaxine was evaluated in 244 patients with painful diabetic neuropathy [21]. At six weeks, treatment with ER venlafaxine at higher (150 to 225 mg daily) but not lower (75 mg daily) doses was associated with significant benefit in the primary outcome measures of pain intensity and pain relief compared with placebo. The strength of this finding is limited by the short duration of this trial and by a risk of selection bias due to unclear procedures for randomization and allocation concealment [20]. Nausea and somnolence were the most common side effects of venlafaxine, and blood pressure and cardiac rhythm changes occurred more often with venlafaxine treatment than with placebo.

Anticonvulsants — Both newer (pregabalin) and older (valproate) anticonvulsants may be useful for treating painful diabetic polyneuropathy. The utility of gabapentin is uncertain.

Pregabalin — Pregabalin is an alpha2-delta ligand that is structurally related to gabapentin but without known activity at GABA or benzodiazepine receptors [22]. It appears to act as a presynaptic inhibitor of the release of excitatory neurotransmitters including glutamate, substance P, and calcitonin gene-related peptide (CGRP) [23,24]. The effectiveness of pregabalin for the treatment of painful diabetic neuropathy was evaluated in a pooled analysis of seven randomized clinical trials, of 5 to 13 weeks duration, with a total of 1510 patients in the intention-to-treat population [25].

The following observations were reported:

- Amitriptyline and nortriptyline are both contraindicated in patients with cardiac disease. In these patients, we consult with the patient's cardiologist and give either doxepin, the least cardiotoxic tricyclic antidepressant, or antidepressant drugs unrelated to the tricyclic family such duloxetine or venlafaxine.
- Pregabalin is started at 25 to 75 mg once daily or in two to three divided doses and can be titrated upwards based on response and tolerability in increments of up to 75 mg every week to 150 mg two times a day or 100 mg three times a day. A total daily dose of 300 mg is the maximum dose approved by the US Food and Drug Administration (FDA) for diabetes-associated neuropathic pain, although some patients may require 450 mg per day. The FDA has approved doses of pregabalin of up to 600 mg per day for other indications. Higher doses are generally less well tolerated and may have limited additional efficacy. Pregabalin can cause a number of side effects, including dizziness, vertigo, incoordination, ataxia, diplopia, blurred vision, sedation, and confusion [26]. It may be habit forming and is classified as a Schedule V drug in the United States. It is generally held that more clinical experience with the drug will delineate if its efficacy outweighs its potential habit-forming classification.
- Gabapentin — There is controversy regarding the effectiveness of gabapentin for the treatment of painful diabetic neuropathy:

- Given that the available evidence is incomplete, the role of gabapentin for the treatment of painful diabetic neuropathy is controversial. Some experts no longer use gabapentin for painful diabetic neuropathy, believing it to be no better than placebo. However, the clinical experience of other experts and the published data from randomized trials suggest that gabapentin has a role. Typical starting doses for gabapentin are 100 to 300 mg three times daily; the drug can be titrated slowly up to 900 mg four times daily. The major side effects of gabapentin are somnolence, dizziness, and ataxia.
- Other anticonvulsants — Valproic acid (500 to 1200 mg daily) was effective for reducing pain in diabetic neuropathy in two small placebo-controlled trials from a single center [30,31]. However, it should not be used to treat diabetic neuropathy in women of childbearing potential because of teratogenic effects. Carbamazepine may also have some benefit, but it has not been evaluated in modern randomized trials for the treatment of painful diabetic neuropathy [32,33]. A systematic review that analyzed data from three randomized trials concluded that topiramate is not effective for painful diabetic polyneuropathy [34].

Compared with placebo, pregabalin treatment at total daily doses of 150, 300, and 600 mg resulted in a statistically significant reduction in the mean pain score, the primary end point of all included studies. The median time to a sustained 1-point improvement on an 11-point pain score for pregabalin (at 150 mg, 300 mg, and 600 mg) and placebo was 13, 5, 4, and 60 days, respectively.

With higher doses, there was a clear dose-related increase in effectiveness, and an increase in the incidence of most adverse events.

The most common adverse events were dizziness, somnolence, and peripheral edema. The incidence of clinically meaningful weight gain (defined as a ≥7 percent weight increase from baseline to end point) was significantly higher for patients assigned to pregabalin than for those assigned to placebo (2.0 to 3.9 percent versus 0.7 percent), but weight gain did not affect diabetes control.

In a systematic review, with data from six trials and 1277 participants, the proportion of patients achieving at least a 50 percent pain intensity reduction was significantly higher with gabapentin (dosed at ≥1200 mg daily) compared with placebo (38 versus 21 percent, relative risk 1.9, 95% CI 1.5-2.3) [27]. All of the evidence was considered "second tier" with potentially important residual biases.

The existence of unpublished randomized controlled trials evaluating gabapentin for the treatment of painful diabetic neuropathy has raised significant concerns that gabapentin is not more effective than placebo [2729], and a review of published and unpublished trials called into question the efficacy of gabapentin [29].

Capsaicin — Capsaicin is a naturally occurring component of many hot peppers and causes analgesia through local depletion of substance P. It is available as a cream and other formulations (gel, liquid, lotion, and patch) for topical application. In randomized trials in patients with painful diabetic neuropathy, capsaicin has been associated with modest but statistically significant improvement in pain compared with placebo [35-39]. We add capsaicin cream (0.075 percent applied topically four times daily) for patients with symptomatic painful diabetic polyneuropathy who are refractory to or intolerant of antidepressants (eg, amitriptyline, duloxetine, venlafaxine) or anticonvulsants (eg, pregabalin) discussed above. Local burning and skin irritation can occur, but this becomes less of a problem with continued use. Nevertheless, many patients are unable to tolerate the local burning pain, which is exacerbated by contact with warm water and hot weather [38].

Anesthetic drugs — A systematic review published in 2011 concluded that the evidence for the effectiveness of mexiletine is conflicting [38]. The highest-quality trial evaluated found no significant benefit of mexiletine compared with placebo [40]. However, other trials suggested benefit [41,42]. Limited evidence suggests that application of lidocaine patches (5 percent) can improve pain in patients with painful diabetic neuropathy [43]. Patches may remain in place for no more than 12 hours in any 24 hour period.

Alpha-lipoic acid — One of the mechanisms implicated in the pathogenesis of diabetic neuropathy is increased oxidative stress. As a result, antioxidants have been studied for their potential to diminish oxidative stress, improve the underlying pathophysiology of neuropathy, and reduce pain.

Alpha-lipoic acid (ALA), a potent antioxidant, has been associated with benefit for symptomatic diabetic neuropathy in several prospective, placebo-controlled studies [44-47]. In the SYDNEY 1 trial, daily intravenous ALA for three weeks was associated with reduced pain, paresthesia, and numbness [45]. In the SYDNEY 2 trial, 181 patients with diabetes and symptomatic distal symmetric polyneuropathy were randomly assigned to one of three doses of orally administered ALA (600, 1200, or 1800 mg daily) or to placebo for five weeks [47].

The following observations were reported:
The strength of these findings is limited by the short duration of this trial [47]. There are no long-term studies that assess the effect of alpha-lipoic acid on progression of neuropathy. However, based upon these data, we suggest treatment with oral ALA 600 mg once daily for patients with symptomatic painful diabetic polyneuropathy who are refractory to or intolerant of antidepressants (eg, amitriptyline, duloxetine, venlafaxine) or anticonvulsants (eg, pregabalin) that have been established as beneficial for this condition.

Opioids — A number of opioids have been studied for the treatment of painful diabetic neuropathy.
All three doses of oral ALA treatment were associated with a statistically significant reduction in the primary outcome measure, the neuropathy total symptom score (a summation of stabbing pain, burning pain, paresthesia, and asleep numbness), compared with placebo [47].

The optimal dose of ALA was 600 mg once daily, as higher doses were limited by increasing adverse events (nausea, vomiting, and vertigo) without increasing efficacy.

In both reports, the benefit of combination treatment was small but statistically significant.

- Electrical nerve stimulation — Although data are limited, a 2010 statement from the American Academy of Neurology (AAN) assessing the use of TENS for pain in neurologic disorders concluded that TENS is probably effective for reducing pain from diabetic polyneuropathy [58], based upon the following evidence:
- Dextromethorphan, a weak sigma opioid receptor agonist and an N-methyl-D-aspartate (NMDA) receptor antagonist, was moderately beneficial compared with placebo in two small trials for reducing pain in patients with diabetic neuropathy [48,49].
- In two small randomized, double-blind trials tramadol, at an average dose of 210 mg/day, was more effective than placebo for relieving pain [50,51]. The most frequent adverse effects were nausea, constipation, headache, and somnolence.
- Controlled release (CR) oxycodone at a daily dose of 10 to 60 mg may be more effective than placebo for the treatment of painful diabetic polyneuropathy, as suggested by several low-quality randomized controlled trials [52].
- In a single-center randomized trial of 44 patients with neuropathic pain (a majority with diabetic polyneuropathy), gabapentin combined with morphine was more effective than either agent alone for reducing the mean intensity of pain during week four of treatment at the maximum tolerated daily dose (mean, gabapentin 1705 mg and morphine 34 mg in combination) [56]. Constipation, sedation, and dry mouth were the most frequent side effects of the combination therapy.
- A similar single center randomized trial of 47 patients (most with diabetic polyneuropathy) found that the combination of nortriptyline with gabapentin was more effective than either agent alone for reducing the mean intensity of daily pain during week four of treatment at the maximum tolerated daily dose (mean, nortriptyline 50 mg and gabapentin 2180 mg in combination) [57].
- One trial assigned 31 patients with chronic painful diabetic neuropathy to either TENS or sham treatment to the legs for 30 minutes daily for four weeks [59]. Symptomatic improvement (of at least one grade on a unique zero to five scale) occurred in 15 of 18 patients (83 percent) with TENS treatment, compared with five of 13 patients (38 percent) who received sham treatment (odds ratio 6, 95% CI 1.1-33.4) [59].

- Another trial evaluated 19 patients with mild to moderate symptomatic diabetic polyneuropathy [60]. Compared with sham treatment, active treatment with TENS led to a statistically significant reduction in total
- A subsequent 2011 guideline from the AAN evaluating the treatment of painful diabetic neuropathy concluded that percutaneous electrical nerve stimulation is probably effective [38], based upon three small trials [61-63]. However, the percutaneous techniques evaluated in the 2011 AAN guideline are not widely available in clinical practice. Other interventions — Several other approaches have been tried in patients with painful diabetic neuropathy.

Acetyl-L-carnitine — Acetyl-L-carnitine (ALC), the acetylated ester of the amino acid L-carnitine, has been evaluated in patients with diabetic peripheral neuropathy [64]. In data from two randomized controlled trials of identical design, an intention to treat analysis of 1257 patients with diabetic polyneuropathy found that ALC 1000 mg (but not 500 mg) three times daily compared with placebo was associated with significant improvement in pain scores in one of the studies and in the combined cohort [65]. The benefit of ALC requires confirmation, particularly since significant improvement was not seen in both trials or at the lower dose of ALC. Isosorbide — A placebo-controlled pilot study of isosorbide dinitrate topical spray in 22 diabetic patients reported a significant reduction in overall neuropathic pain and burning sensation in the treatment group [66].

NSAIDs — Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in patients with musculoskeletal or joint abnormalities secondary to long-standing neuropathy; the joint deformities may actually be the primary source of pain. Both ibuprofen (600 mg four times daily) and sulindac (200 mg twice daily) can lead to substantial pain relief in patients with diabetic neuropathy [67]. There is a theoretical concern that NSAIDs may impair nerve circulation and worsen nerve injury due to inhibition of prostacyclin synthesis. Cautious use of this class of drugs is warranted until this possibility is fully evaluated.

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 [68]. Further trials are needed to confirm the efficacy of this approach. Guidelines — The American Academy of Neurology (AAN) performed a systematic review and published guidelines in 2011 for the treatment of painful diabetic neuropathy [38]. The following observations were made:
symptom score at six and twelve weeks.

In addition, TENS therapy was associated with a statistically significant but modest improvement in pain on the visual analog scale at six weeks.

Pregabalin (300 to 600 mg daily) was regarded as effective [38].

A number of treatments were regarded as probably effective [38]:
- Gabapentin, 900 to 3600 mg daily
- Sodium valproate, 500 to 1200 mg daily
- Amitriptyline, 25 to 100 mg daily
- Duloxetine, 60 to 120 mg daily
- Venlafaxine, 75 to 225 mg daily
- Dextromethorphan, 400 mg daily
- Morphine sulphate, titrated to 120 mg daily

A management algorithm outlined by a statement published in 2005 from the American Diabetes Association (ADA) recommended treatment in sequential steps ordered as follows [3]: The ADA statement noted that nonpharmacologic, topical, or physical therapies might be useful at any stage. These measures include acupuncture, capsaicin, glyceryl trinitrate spray or patches, and other therapies [3,69].

Choice of therapy — We suggest using one of the antidepressants (eg, amitriptyline, duloxetine, venlafaxine) or anticonvulsants (eg, pregabalin) discussed above as initial therapy for patients with painful diabetic neuropathy. The available evidence suggests that these agents have similar modest benefit, though few high-quality comparative trials have been done [13,70,71]. Among these options, we prefer to start with amitriptyline, particularly in younger healthier patients, because of its effectiveness and low cost. Patients who fail to improve with a reasonable trial of one of these agents can be switched to monotherapy with another agent. For patients who do not improve on one drug, we suggest combination therapy employing two drugs from different medication classes as the next step in the treatment paradigm. For patients who are unable to tolerate any of these drugs, alternative treatments include capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation. The use of opioids for chronic nonmalignant pain is controversial. We suggest not using opioids for the treatment of painful diabetic neuropathy because of the lack of evidence regarding long-term effectiveness, and because of the potential for opioid tolerance, addiction, and overdose. However, other experts believe that opioids have a role in the management of painful diabetic neuropathy despite these concerns [38].

The treatment options and suggested doses are:

- Oxycodone, mean 37 mg daily, maximum 120 mg daily
- Tramadol, 210 mg daily
- Capsaicin, 0.075 percent four times daily
- Isosorbide dinitrate spray

Percutaneous electrical nerve stimulation for three to four weeks
Lidocaine patch was regarded as possibly effective [38].

NONGLYCEMIC MEASURES — Multifactorial risk factor reduction and aldose reductase inhibitors are potential strategies for treating diabetic neuropathy. Multifactorial risk factor reduction — The potential efficacy of intensive combined therapy in patients with type 2 diabetes and microalbuminuria was examined in the Steno type 2 trial [72]. In this prospective study, 160 patients were randomly assigned to standard or multifactorial intensive therapy. The intensive regimen consisted of behavioral therapy (including advice concerning diet, exercise, and smoking cessation) and pharmacologic intervention (consisting of the administration of multiple agents to attain several aggressive therapeutic goals). Diabetic autonomic and peripheral neuropathy were present at baseline in 28 and 34 percent, respectively. At a mean follow-up of 7.8 years, there was a significantly lower rate of progression of autonomic neuropathy in the intensive therapy group (30 versus 54 percent, relative risk 0.37), but no slowing of progression of peripheral neuropathy [72]. The details of the protocol and overall results of this study are discussed elsewhere.

Surgical decompression — Surgical decompression of multiple peripheral nerves (called the Dellon procedure) is an alternative, controversial method for treating diabetic polyneuropathy [73]. The purported rationale for surgical decompression is based on the notion that the metabolic stress of diabetes renders peripheral nerves susceptible to compressive injury at sites of potential nerve entrapment [74-76], and that compressive injury of multiple peripheral nerves is what leads to symptoms in most patients [77]. However, there are no adequately designed trials to support the use of surgical decompression of multiple peripheral nerves as a treatment for symptomatic diabetic polyneuropathy [74]. Therefore, this treatment is not recommended.

REFERENCES

1. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol 1995; 38:869.

2. Martin CL, Albers JW, Pop-Busui R, DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37:31.

- Optimal glucose control is considered the cornerstone for the treatment of diabetes and its complications. Intensive glucose control has been shown to prevent the development of peripheral neuropathy. However, whether near-normal glycemic control can ameliorate established symptomatic diabetic neuropathy, and painful neuropathy in particular, is not as clear. (See 'Glycemic control for established neuropathy' above.)
- For patients with diabetic neuropathy, foot care is important to prevent ulceration, infection, and amputation. (See 'Foot care' above and "Management of diabetic foot ulcers".)
- Only a small fraction of patients with diabetic polyneuropathy have painful symptoms. In addition, the pain associated with diabetic polyneuropathy is often self-limited; evidence from a small prospective study suggests that resolution occurs over 12 months in approximately one-half of patients. (See 'Painful diabetic neuropathy' above and 'Spontaneous resolution' above.)
- For patients with painful diabetic neuropathy, we suggest initial therapy using either amitriptyline (Grade 2B), venlafaxine (Grade 2C), or duloxetine or pregabalin (Grade 2A). Among these options, we prefer to start with amitriptyline, particularly in younger healthier patients, because of its effectiveness and low cost. For patients who do not improve on one drug, we suggest combination therapy employing two drugs from different medication classes (Grade 2C). For patients who are unable to tolerate any of these drugs, alternative treatments include capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation.
- The use of opioids for chronic nonmalignant pain is controversial. We suggest not using opioids for the treatment of painful diabetic neuropathy (Grade 2C).
- Nonglycemic interventions (eg, multifactorial risk factor reduction and aldose reductase inhibitors) are under investigation for treating or preventing diabetic neuropathy.

3. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28:956.

4. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012; :CD007543.

5. Müller-Stich BP, Fischer L, Kenngott HG, et al. Gastric bypass leads to improvement of diabetic neuropathy independent of glucose normalization--results of a prospective cohort study (DiaSurg 1 study). Ann Surg 2013; 258:760.

6. Young RJ, Ewing DJ, Clarke BF. Chronic and remitting painful diabetic polyneuropathy. Correlations with clinical features and subsequent changes in neurophysiology. Diabetes Care 1988; 11:34.

7. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014; 161:639.

8. Dy SM, Bennett WL, Sharma R, et al. Preventing complications and treating symptoms of diabetic peripher al neuropathy. Comparative Effectiveness Review No. 187. AHRQ Publication No. 17-EHC005-EF. Rockvill e, MD: Agency for Healthcare Research and Quality; March 2017. https://effectivehealthcare.ahrq.gov/ehc/ products/612/2436/diabetic-neuropathy-report-170324.pdf (Accessed on April 06, 2017).

9. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987; 37:589.

10. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992; 326:1250.

11. Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. JAMA 1984; 251:1727.

12. Vrethem M, Boivie J, Arnqvist H, et al. A comparison a amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain 1997; 13:313.

13. Kaur H, Hota D, Bhansali A, et al. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care 2011; 34:818.

14. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014; :CD007115.

15. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005; 116:109.

16. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005; 6:346.
17. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006; 67:1411.
18. Duloxetine (Cymbalta) for diabetic neuropathic pain. Med Lett Drugs Ther 2005; 47:67.
19. Hardy T, Sachson R, Shen S, et al. Does treatment with duloxetine for neuropathic pain impact glycemic control? Diabetes Care 2007; 30:21.
20. Gallagher HC, Gallagher RM, Butler M, et al. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev 2015; :CD011091.
21. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004; 110:697.
22. Bryans JS, Wustrow DJ. 3-substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999; 19:149.
23. Dooley DJ, Mieske CA, Borosky SA. Inhibition of K(+)-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. Neurosci Lett 2000; 280:107.
24. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003; 105:133.
25. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008; 31:1448.
26. Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011; 52:826.
27. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014; :CD007938.
28. Doshi P, Dickersin K, Healy D, et al. Restoring invisible and abandoned trials: a call for people to publish the findings. BMJ 2013; 346:f2865.
29. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 2009; 361:1963.
30. Kochar DK, Jain N, Agarwal RP, et al. Sodium valproate in the management of painful neuropathy in type 2 diabetes - a randomized placebo controlled study. Acta Neurol Scand 2002; 106:248.
31. Kochar DK, Rawat N, Agrawal RP, et al. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. QJM 2004; 97:33.
32. Rull JA, Quibrera R, González-Millán H, Lozano Castañeda O. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia 1969; 5:215.
33. Chakrabarti AK, Samantaray SK. Diabetic peripheral neuropathy: nerve conduction studies before, during and after carbamazepine therapy. Aust N Z J Med 1976; 6:565.
34. Wiffen PJ, Derry S, Lunn MP, Moore RA. Topiramate for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2013; :CD008314.
35. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. Diabetes Care 1992; 15:159.
36. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehiclecontrolled study. The Capsaicin Study Group. Arch Intern Med 1991; 151:2225.
37. Tandan R, Lewis GA, Krusinski PB, et al. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care 1992; 15:8.
38. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011; 76:1758.
39. Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. J Pain 2017; 18:42.
40. Wright JM, Oki JC, Graves L 3rd. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. Ann Pharmacother 1997; 31:29.
41. Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet 1988; 1:9.

42. Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. Diabetes Care 1997; 20:1594.
43. Barbano RL, Herrmann DN, Hart-Gouleau S, et al. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol 2004; 61:914.
44. Ruhnau KJ, Meissner HP, Finn JR, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. Diabet Med 1999; 16:1040.
45. Ametov AS, Barinov A, Dyck PJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. Diabetes Care 2003; 26:770.
46. Ziegler D, Nowak H, Kempler P, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabet Med 2004; 21:114.
47. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006; 29:2365.
48. Sang CN, Booher S, Gilron I, et al. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. Anesthesiology 2002; 96:1053.
49. Nelson KA, Park KM, Robinovitz E, et al. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology 1997; 48:1212.
50. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998; 50:1842.
51. Sindrup SH, Andersen G, Madsen C, et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 1999; 83:85.
52. Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database Syst Rev 2016; 7:CD010692.
53. Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009; 10:147.
54. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev 2013; :CD006146.
55. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010; 152:85.
56. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005; 352:1324.
57. Gilron I, Bailey JM, Tu D, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 2009; 374:1252.
58. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2010; 74:173.
59. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. Diabetes Care 1997; 20:1702.
60. Forst T, Nguyen M, Forst S, et al. Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device. Diabetes Nutr Metab 2004; 17:163.
61. Hamza MA, White PF, Craig WF, et al. Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. Diabetes Care 2000; 23:365.
62. Oyibo SO, Breislin K, Boulton AJ. Electrical stimulation therapy through stocking electrodes for painful diabetic neuropathy: a double blind, controlled crossover study. Diabet Med 2004; 21:940.
63. Bosi E, Conti M, Vermigli C, et al. Effectiveness of frequency-modulated electromagnetic neural stimulation in the treatment of painful diabetic neuropathy. Diabetologia 2005; 48:817.
64. Quatraro A, Roca P, Donzella C, et al. Acetyl-L-carnitine for symptomatic diabetic neuropathy. Diabetologia 1995; 38:123.
65. Sima AA, Calvani M, Mehra M, et al. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. Diabetes Care 2005; 28:89.
66. Yuen KC, Baker NR, Rayman G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. Diabetes Care 2002; 25:1699.

67. Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. Arch Intern Med 1987; 147:1442.
68. de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014; 155:2426.
69. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004; 27:1458.
70. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012; 35:2451.
71. Boulton AJ. Is duloxetine more effective than amitriptyline for painful diabetic neuropathy? Curr Diab Rep 2011; 11:230.
72. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348:383.
73. Dellon AL. Treatment of symptomatic diabetic neuropathy by surgical decompression of multiple peripheral nerves. Plast Reconstr Surg 1992; 89:689.
74. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, Chaudhry V, Stevens JC, et al. Practice Advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2006; 66:1805.
75. Upton AR, McComas AJ. The double crush in nerve entrapment syndromes. Lancet 1973; 2:359.
76. Dellon AL, Mackinnon SE, Seiler WA 4th. Susceptibility of the diabetic nerve to chronic compression. Ann Plast Surg 1988; 20:117.
77. Dellon AL, Mackinnon SE. Chronic nerve compression model for the double crush hypothesis. Ann Plast Surg 1991; 26:259.