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Treatment of Diabetic Sensory Polyneuropathy

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Opinion statement

No current disease-modifying treatments have been shown definitively in randomized clinical trials to reduce or reverse diabetic sensory polyneuropathy (DSP). It is increasingly recognized that individuals with “prediabetes” or impaired glucose regulation can already have a “small-fiber” neuropathy, or mild DSP, in which sensory axons of both small and larger diameter are damaged. Small-fiber neuropathy is frequently associated with pain, and these patients may present to a neurologist for evaluation before the underlying glucose dysregulation has been diagnosed. It is important to identify these individuals, because aggressive diabetic control and lifestyle interventions can delay the onset of diabetes and may reverse small-fiber neuropathy associated with early diabetes mellitus. Although treatment currently focuses on pain associated with DSP, attention should be paid to potential risk factors for neuropathy. For example, glycemic control and hyperlipidemia should be improved with diet, exercise, and medications. Hypertension that is a risk marker for more severe neuropathy should be treated. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers not only treat hypertension but also may directly reduce the progression of neuropathy. Class I or II clinical studies support the use of sodium valproate, pregabalin, duloxetine, amitriptyline, gabapentin, venlafaxine, opioids, and topical capsaicin in treating diabetic neuropathic pain. Pregabalin and gabapentin are relatively well tolerated and have few medication interactions. Sodium valproate has been shown to be effective but is not recommended for use in women of childbearing potential, and patients must be monitored for hepatotoxicity and thrombocytopenia. Tricyclic antidepressants such as amitriptyline are often used for nocturnal pain but require caution in the elderly or anyone with cardiac disease. Venlafaxine and duloxetine successfully treat neuropathic pain independently of their effect on depression. Opioid medications are associated with a high rate of adverse effects but with careful monitoring, they can be effective in treating resistant neuropathic pain. Capsaicin is an effective topical treatment that lacks systemic side effects. The lidocaine patch is effective in relieving pain associated with postherpetic neuralgia, but only class III evidence supports its use for diabetic neuropathic pain. No current Class I or II studies support other treatment modalities.

Introduction

Type 2 diabetes mellitus is a major public health concern that is projected to affect an estimated 366 million people worldwide by 2030 [1]. The growing prevalence of type 2 diabetes mellitus in the United States and throughout the world will result in a larger number of individuals suffering from diabetic sensory polyneuropathy (DSP). The yearly incidence of distal symmetric polyneuropathy in diabetics is approximately 2%, and the lifetime incidence of neuropathy has been estimated to be 37% to 45% for patients with type 2 diabetes and 54% to 59% for patients with type 1 diabetes [2, 3]. Studies of nerve

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conduction tests performed at the time of diabetes diagnosis demonstrate that neuropathy is already present in 10% to 18% of patients [4, 5], and subclinical neuropathy is also present [6]. These findings suggest that peripheral nerve injury occurs at the earliest stages of diabetes, when there is mild glycemic dysregulation. Consistent with the view that risk of complications can occur early in diabetes, recent guidelines published by the American Diabetes Association identify patients at high risk for future diabetes as those with a glycosylated hemoglobin of 5.7% to 6.4%, as well as patients with impaired fasting glucose (IFG)—fasting plasma glucose of 100 mg/dL to 125 mg/dL—and impaired glucose tolerance (IGT), a 2-hour oral glucose tolerance test value of 140 mg/dL to 199 mg/dL [7, 8].

Painful small-fiber neuropathy can occur in both type 1 and type 2 diabetes, although there are far more cases in patients with type 2 diabetes because of the much higher prevalence of that type. Significant neuropathic pain occurs in 7.5% to 24% of all patients with diabetes [2, 3]. Neuropathic pain is also one of the most common presentations of impaired glucose regulation [9, 10]. Interestingly, although pain-specific medications are required to treat the discomfort, therapies that ameliorate the underlying neuropathy also reduce the severity of the neuropathic pain.

Treatment

Disease-modifying treatment

Currently, no treatments have been shown in randomized trials to restore function to damaged nerve fibers, but there are approaches to reduce the severity of diabetic neuropathy.

Treatment of hypertension—Thiazide diuretics aggravate abnormal glucose metabolism in both diabetic and nondiabetic patients, probably because of decreased sensitivity to glucose of pancreatic beta cells [11]. Thus, in patients with hypertension, the thiazide diuretic should be stopped and an alternative medication considered. Suitable choices include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker, which may reduce the risk of diabetes [12] or the severity of diabetic neuropathy [13]. In preclinical studies, there is also clear evidence that an ACE inhibitor combined with an endopeptidase inhibitor is most effective in reducing the severity of experimental diabetic neuropathy [14].

Improved glycemic control—Tight glycemic control can effectively slow the progression of diabetic neuropathy and delay the onset of neuropathy in type 1 diabetes [15]. The Diabetes Control and Complications Trial (DCCT) demonstrated that patients with type 1 diabetes who underwent intensive diabetes therapy with insulin were 64% less likely than those who received routine care to develop clinically confirmed neuropathy over the 5-year study [15]. Furthermore, intensive glycemic control was found to be significantly more effective in preventing neuropathy progression in patients with early diabetes [15].

Similar improvement has been observed in type 2 diabetes. The most convincing evidence that improvement in glycemic control reduces the severity of type 2 diabetic complications comes from the UK Prospective Diabetes Study (UKPDS), in which 3,867 patients with newly diagnosed type 2 diabetes (median age 54 years) were randomly assigned to intensive therapy with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide), with insulin, or conventional diet therapy [16]. After 10 years, there was an aggregate 25% risk reduction (P=0.001) in microvascular end points [16]. Further analysis showed that for every percentage point decrease in the glycosylated hemoglobin level, there was a 35% reduction in the risk of complications. Thus, intensive blood-glucose control by either sulfonylureas or insulin substantially decreased the risk of microvascular complications in patients with type

2 diabetes, although there was a higher rate of hypoglycemic complications, particularly in the insulin-treatment group [16].

In the Steno type 2 randomized study, improved glycemic control in type 2 diabetes was associated with a lower rate of progression of autonomic neuropathy [17]. In this study, intensive treatment was a stepwise implementation of behavior modification and pharmacologic therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria.

Importantly, improved glycemic control has been shown to have a sustained benefit on diabetes and its complications. For example, the benefits of former intensive glycemic control on peripheral neuropathy were examined in the NeuroEDIC study. This study found a reduced prevalence of neuropathy in a group of type 1 diabetics who received intensive treatment, compared with the standard treatment group in the DCCT study. However, although intensive glycemic control reduced the severity of neuropathy, it was not able to arrest damage to peripheral nerves. Thus, 34% of patients in the former intensive treatment group and 41% of those in the former conventional treatment group developed clinical neuropathy [18]. The NeuroEDIC study provided more conclusive data for cardiac autonomic neuropathy than it did for peripheral neuropathy. After adjusting for the effects of age, it was found that the prevalence and incidence of cardiac autonomic neuropathy remained significantly lower in the former intensive treatment group than in the former conventional treatment group [19]. This beneficial effect of intensive treatment persisted even after adjustment for the presence of cardiac autonomic neuropathy at the end of the DCCT. A possible explanation for the greater effects of early glycemic control on cardiac autonomic neuropathy versus somatic DSP may be that there is a difference in the effect of metabolic memory on the small nerve fibers that are measured by cardiac autonomic tests and the large-fiber function that is measured by traditional nerve conduction studies.

Diet and lifestyle interventions—Glucose-modifying drug therapy is typically not appropriate for patients with impaired glucose regulation because of its cost and the potential for serious adverse effects such as hypoglycemia. A more suitable approach for these patients is a lifestyle intervention that could arrest the underlying process that leads to neuropathy and its associated functional disability. At present, there is no evidence from a randomized study that a lifestyle intervention would reverse somatic neuropathy, but there is evidence that a lifestyle intervention can be more effective than a drug intervention in preventing conversion from IGT to diabetes. The Diabetes Prevention Program (DPP) study was designed to determine whether a more intensive dietary and exercise intervention or metformin treatment was effective in preventing or delaying the onset of type 2 diabetes in people with IGT or IFG. The DPP study demonstrated that lifestyle changes reduced the risk of developing type 2 diabetes mellitus by 58% in adults with IFG or IGT who were at high risk of developing diabetes [20]. Metformin also reduced the risk of developing type 2 diabetes, but it was less effective than weight loss and increased physical activity [20]. To prevent one case of diabetes in 3 years, only 6.9 persons would have to participate in the lifestyle-intervention program, whereas 13.9 would have to receive metformin [20], clearly demonstrating that the lifestyle intervention was nearly twice as effective as drug therapy.

Lifestyle changes in patients with impaired glucose regulation, who are at the earliest definable stages of hyperglycemia, may also be effective in preventing diabetes-associated complications such as peripheral neuropathy. The Impaired Glucose Tolerance Causes Neuropathy (IGTN) study was a natural-history study that enrolled participants with IGT or IFG and mild neuropathy and gave them general dietary and physical activity advice with goals that were similar to those used in the DPP “lifestyle intervention” group. In the IGTN study, participants who lost weight and/or increased their physical activity, with a

concomitant improvement in metabolic control, demonstrated reduced progression of neuropathy, based on the intraepidermal nerve fiber density obtained from a 3-mm skin punch biopsy, and they actually were able to regrow their epidermal nerve fibers [10, 21, 22]. These results underscore the importance of intervention during the earliest stages of impaired glucose regulation, before the development of the typical symptoms of diabetes. Targeted therapies, including lifestyle changes, may be most effective during this time, and it may be possible to either prolong the time to develop diabetes or even to prevent the development of diabetes and its associated complications.

Alpha-lipoic acid—Another therapy that has a disease-modifying effect is alpha-lipoic acid (ALA). Multiple clinical trials have been completed using a variety of study designs, routes of administration, and sample sizes [23, 24].

In the Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN] III trial, which was a multicenter, double-blind, randomized placebo-controlled study, there was a small but significant improvement in the Neuropathy Impairment Score (NIS) of patients treated with ALA, but no significant improvement in the Total Symptom Score (TSS) [24].

In the Deutsche Kardiale Autonome Neuropathie (DEKAN) study, there were small improvements in components of the cardiac autonomic spectral analysis in patients treated with ALA [25, Class II].

The SYDNEY2 trial is the largest randomized, double-blind, placebo-controlled trial of ALA treatment yet published [26, Class I]. In this trial, a total of 181 diabetic patients received once-daily oral doses of 600 mg (ALA600), 1,200 mg (ALA1200), or 1,800 mg (ALA1800) of ALA or placebo for 5 weeks after a 1-week placebo run-in period. The primary outcome measure was the change from baseline of the TSS. Secondary end points included the Neuropathy Symptoms and Change (NSC) score and the NIS. The mean TSS decreased by 51% in ALA600, 48% in ALA1200, and 52% in ALA1800 groups compared with 32% in the placebo group ($P<0.05$ vs placebo). The corresponding response rates (≥50% reduction in TSS) were 62%, 50%, 56%, and 26%, respectively. Significant improvements favoring all three ALA groups were also noted in the NSC score, and the NIS was numerically reduced. Thus, oral treatment with ALA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. Based on this study, 600 mg of ALA once daily appears to provide the optimum risk-to-benefit ratio [26].

Further support for ALA therapy is provided by a meta-analysis of randomized, double-masked, placebo-controlled, parallel-group trials using intravenous infusions of 600 mg of ALA per day for 3 weeks in diabetic patients with positive sensory symptoms of polyneuropathy, with the foot TSS at study end compared with baseline as the primary outcome measure [27]. The NIS for the lower extremity (NIS-LL) was a secondary outcome measure. The analysis included 716 individuals treated with ALA and 542 treated with placebo. After 3 weeks, the relative difference in favor of ALA versus placebo was 24.1% for the TSS and 16.0% for the NIS-LL. The responder rates were 52.7% in patients treated with ALA and 36.9% for those given the placebo ($P<0.05$). The rates of adverse events did not differ between the groups.

Thus, the overall results of these studies indicate that that treatment with 600 mg/day of intravenous ALA over 3 weeks or 600 mg/day (or more) of oral ALA is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in patients with symptomatic diabetic polyneuropathy.

Treatment of neuropathic pain

The neuropathy that occurs in patients with impaired glucose regulation is typically characterized by distal, symmetric sensory symptoms including pain [28]. This pattern suggests prominent involvement of small nerve fibers including unmyelinated (C) fibers and thinly myelinated (Aδ) fibers. Pain is frequently the complaint that motivates patients to seek medical care, and it is often difficult to treat. This is a concern because neuropathic pain can have a negative impact on quality of life; it has been reported to interfere with general activity, mood, mobility, work, social relations, sleep, leisure activities, walking ability, and enjoyment of life. Medications used to treat painful diabetic small-fiber neuropathies include anticonvulsants, antidepressants, topical anesthetics, and both narcotic and non-narcotic analgesics (Table 1) [29••]. In addition, nonpharmacologic approaches such as electrical nerve stimulation also may be helpful; these have been reviewed elsewhere [30•, Class I].

Diet and lifestyle interventions—In addition to their disease-modifying effect, as discussed above, lifestyle interventions also may reduce the severity of neuropathic pain symptoms [10].

Pharmacologic treatment: anticonvulsants

Gabapentin: The exact mechanism of action of gabapentin is unknown, but it is structurally related to the neurotransmitter GABA, which plays a role in pain transmission and modulation. The pain-modulating properties of gabapentin may be linked to its multiple pharmacologic actions, including alteration of the synthesis and release of GABA, binding to voltage-gated calcium channels, inhibition of voltage-gated sodium channels, and alteration of monoamine neurotransmitter release and blood serotonin levels [31].

Gabapentin is generally well tolerated, with a low side effect profile, and it has been found to be effective in animal models of chronic neuropathic pain. It has been used for pain relief in various conditions, including HIV neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy.

There have been two randomized, placebo-controlled studies of gabapentin in the treatment of painful diabetic neuropathy. The first study demonstrated a small but significant decrease in mean daily pain score in patients treated with gabapentin (titrated from 900 to 3,600 mg/d or maximum tolerated dose), compared with placebo. In addition, there was a significant improvement in sleep interference, and quality of life measures also improved [31, Class I]. The second, smaller study did not show a significant difference in pain scores between patients treated with gabapentin (900 mg/d) and placebo [32, Class II].

Standard dosage: Initial dose is 900 mg per day administered in three divided doses. Alternatively, it can be started at 300 mg per day and titrated upward. Maintenance doses can be titrated as tolerated up to 2,400 to 3,600 mg per day.

Contraindications: Hypersensitivity.

Main drug interactions: May enhance the sedating effects of CNS depressants.

Main side effects: The most common side effects are somnolence, dizziness, and ataxia. Peripheral edema, diarrhea, abdominal pain, and weight gain can also be seen.

Special points: Excretion is proportional to renal function, and the dosage must be adjusted in patients with renal impairment.

Cost: 300-mg capsules (90), $59.99.

Pregabalin: Pregabalin is a GABA analogue that selectively binds to voltage-gated calcium channels in the brain and spinal cord and has been shown to inhibit the release of excitatory neurotransmitters in stimulated neurons by reducing the influx of calcium into synaptic endings [33, 34].

It is structurally related to gabapentin, and both medications are widely used because of their limited drug interactions and relatively low side-effect profile. Unlike gabapentin, however, pregabalin has linear pharmacokinetics across different doses. In addition to analgesic effects, it also has anticonvulsant and anxiolytic activity [33, 34].

Pregabalin (300–600 mg/d) has been shown to be effective in improving pain scores in diabetic peripheral neuropathy, with a small improvement in pain relative to placebo. It was also found to have a beneficial effect on sleep and quality of life [33–35, Class I; 36, Class II].

Standard dosage: Initial dose of 150 mg per day in two or three divided doses. Increase based on tolerability and effect, up to 300 mg per day.

Contraindications: Hypersensitivity.

Main drug interactions: May enhance the sedating effects of CNS depressants.

Main side effects: The most common side effects are dizziness and somnolence. There have also been complaints of headache, weight gain, and blurred vision.

Special points: Angioedema has been reported, and concurrent use with other agents that are known to cause angioedema may increase the risk. Dosage must be adjusted in renal impairment.

Cost: 50-mg capsules (30), $83.99.

Sodium valproate: In addition to being used as an anticonvulsant, sodium valproate has been successfully used to treat pain associated with trigeminal neuralgia and migraine headaches.

The mechanism of action of sodium valproate is not fully understood, but it has been shown to increase brain GABA levels, probably by preventing its degradation and neuronal uptake.

Two randomized, controlled studies have demonstrated a moderate reduction in pain with sodium valproate compared with placebo [37, 38, Class I]. Quality of life measures were not included as end points in these studies. The medication was well tolerated in doses up to 1,200 mg per day without the typical side effects of sodium valproate. However, the studies were of relatively short duration (1 month and 3 months).

Standard dosage: Initial dose of 500 mg per day in two divided doses. Titrate based on response, up to 1,000 mg per day.

Contraindications: Hypersensitivity, significant hepatic impairment, or urea cycle disorders.

Main drug interactions: Caution with concomitant use of other medications that have extensive hepatic metabolism.

Main side effects: Headache, somnolence, dizziness, nausea/vomiting, abdominal pain, thrombocytopenia, tremor. There have also been reports of pancreatitis.

Special points: Pregnancy category D because of increased risk of neural tube defects and other major birth defects. This drug requires monitoring of liver enzymes and CBC with platelets because of the risk of hepatotoxicity and thrombocytopenia.

Cost: 250-mg capsules (30), $14.99.

Topiramate: Topiramate is a broad-spectrum anticonvulsant medication that inhibits voltage-gated sodium and calcium channels. It inhibits glutamate-mediated neurotransmission and enhances GABA-mediated neurotransmission.

Topiramate therapy has been shown to produce a small reduction in pain in patients with painful diabetic neuropathy, compared with placebo [39, Class II]. There was also a significant reduction in body weight in the group treated with topiramate, but there was no concurrent change in glycemic control [39].

The dropout rate in the topiramate group in this study was relatively high at 48%, mainly owing to adverse events, thought to be due to the high target dose used in the study. This finding highlights the importance of careful dose titration based on analgesic response [39].

Standard dosage: Initial dose of 25 mg per day. Increase by 25 to 50 mg each week to a target dose of 400 mg per day in two divided doses.

Contraindications: None.

Main drug interactions: Use with valproic acid may increase the risk of encephalopathy due to hyperammonemia. Its use may decrease the concentration of hormonal contraceptives. (This risk is highest for doses of 200 mg/d or higher.)

Main side effects: Diarrhea, loss of appetite with associated weight loss, and somnolence were most common in the trial of painful diabetic neuropathy. Also reported are speech problems, difficulties with memory and concentration, and paresthesias.

Special points: Has been associated with acute myopia discontinue in patients with acute decrease in visual acuity or eye pain. Because of carbonic anhydrase properties, the risk of kidney stones is increased.

Cost: 100-mg capsules (60), $49.99.

Pharmacologic treatment: antidepressants

Venlafaxine: Venlafaxine is approved for treating depression and generalized anxiety disorder. It is a serotonin and norepinephrine reuptake inhibitor and is also a weak inhibitor of dopamine reuptake. Tricyclic antidepressants (TCAs), which are also used to treat painful diabetic neuropathy, also have serotonergic and noradrenergic activity, but the precise mechanism of the analgesic effects of these medications is poorly understood. Unlike TCAs, venlafaxine does not interact with other neurotransmitter systems, so it has fewer side effects.

Monotherapy with extended-release venlafaxine at a dose of 150 to 225 mg per day has been shown to have a moderate effect on pain reduction (compared with placebo) in patients with

painful diabetic neuropathy [40, Class I]. Lower-dose venlafaxine (75 mg) was less effective than the higher dose and reached significance over placebo only on a few measures at a few time points [40, Class I].

In a study of patients with painful diabetic neuropathy whose pain did not improve on gabapentin, the addition of venlafaxine was moderately effective in relieving pain, compared with gabapentin plus placebo [41, Class II]. The combination was well tolerated and the patients treated with gabapentin and venlafaxine had significant improvements in mood disturbance and quality of life [41, Class II].

Standard dosage: Initial dose of 75 mg per day in two or three divided doses. The dose can then be titrated as tolerated to a maximum dose of 225 mg per day.

Contraindications: Hypersensitivity or use of monoamine oxidase (MAO) inhibitors within 14 days.

Main drug interactions: Risk of serotonin syndrome with concurrent use of MAO inhibitors. Venlafaxine may also enhance the serotonergic effect of trazodone.

Main side effects: Nausea, somnolence, headache, insomnia, nervousness.

Special points: There is a risk of clinically important ECG changes during treatment.

Cost: 75-mg tablets (30), $59.99; extended-release 75-mg tablets (90), $366.23.

Duloxetine: Duloxetine is a relatively balanced selective serotonin and norepinephrine reuptake inhibitor. It is thought to exhibit an effect on central sensitization rather than on nociception and is effective in the treatment of persistent pain, such as neuropathic and inflammatory pain, but not acute nociceptive pain [42].

Duloxetine has been shown to reduce pain by 8% on the 11-point Liker scale [42, Class I] and by 13% on the visual analog scale (compared with placebo) in patients with painful diabetic neuropathy [43, 44, Class II]. There was also a high completion rate of approximately 75% [43, 44], and quality of life measures were improved [44, Class II].

Standard dosage: Initial dose of 60 mg per day (20–30 mg available if not tolerated). Dose may be titrated as tolerated to a maximum dose of 120 mg per day. In the clinical trials, doses greater than 60 mg per day showed no additional benefit and were associated with increased side effects.

Contraindications: Use of MAO inhibitors within 2 weeks and uncontrolled narrow-angle glaucoma.

Main drug interactions: May enhance the serotonergic effect of MAO inhibitors and cause serotonin syndrome. Duloxetine also may decrease the metabolism of tamoxifen and TCAs.

Main side effects: Somnolence, headache, dizziness, and nausea.

Special points: Duloxetine is not recommended for use in end-stage renal disease (creatine clearance <30 mL/min) or hepatic impairment.

Cost: 60-mg capsule (30), $154.32.

Amitriptyline: TCAs such as amitriptyline have been proposed as a first-line treatment for neuropathic pain. Their mechanism of action is thought to be inhibition of norepinephrine and/or serotonin reuptake within the central nervous system. However, they also have other possible mechanisms of action, including alpha-adrenergic blockade, sodium channel effects, and NMDA-receptor antagonism [45]. Clinical use of TCAs is often limited by side effects such as sedation, hypotension, dry mouth, and cardiovascular abnormalities.

Amitriptyline has been found to be an effective treatment for painful diabetic neuropathy. Using a primary end point measure of a 20% pain reduction, there were 43% more responders with amitriptyline than with placebo [46, Class I]. Two additional studies demonstrated a large reduction in pain [47, 48, Class II].

Other TCAs, imipramine and nortriptyline, have been studied in diabetic painful neuropathy and the results have been inconclusive [49, 50, Class III]. However, nortriptyline is often used instead of amitriptyline because of reduced side effects.

Standard dosage: Initial dose of 25 mg at night (may start at lower doses if intolerant) titrate as tolerated to 100 mg per day.

Contraindications: Hypersensitivity, use of MAO inhibitors within 14 days, acute recovery phase following a myocardial infarction.

Main drug interactions: Hyperpyrexia has been reported in concurrent use with anticholinergics and/or neuroleptics. Use with MAO inhibitors or St. John's wort may enhance the serotonergic effect of TCAs and cause serotonin syndrome. Concurrent use with duloxetine or selective serotonin reuptake inhibitors (SSRIs) may decrease the metabolism of TCAs. Concurrent use with metoclopramide may enhance the adverse effects of TCAs. Do not use with QTc-prolonging agents because the effects can be additive and cause life-threatening ventricular arrhythmias.

Main side effects: Anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention), sedation, cardiac conduction changes, orthostatic hypotension, and dizziness.

Special points: Use with caution in elderly patients and in patients with a history of cardiovascular disease.

Cost: 25-mg tablets (90), $11.99.

Pharmacologic treatment: opioids

Morphine sulfate: Opioids relieve pain by multiple mechanisms, including a presynaptic effect on small afferent C fiber nerve terminals and a postsynaptic hyperpolarizing effect on spinal neurons [51]. The presynaptic effect of opioids may be lost owing to damage of afferent fibers that occurs in neuropathy; this effect may explain why they are relatively ineffective in some types of neuropathic pain [52].

One study that examined the effects of morphine in diabetic neuropathy and postherpetic neuralgia found that morphine had a small effect on pain and improved mood. In addition, the combination of gabapentin and morphine achieved more pain relief at lower doses of each drug than either alone. However, the combination resulted in a higher incidence of constipation and dry mouth than occurred with either drug individually [53, Class II].

Standard dosage: Initial dose in opiate-naïve patients is 10 mg every 4 h as needed. Conversion to long-acting products should be considered if chronic treatment is required.

Contraindications: Hypersensitivity, respiratory depression, severe asthma or chronic lung disease, and paralytic ileus.

Main drug interactions: May potentiate effects of other sedative drugs.

Main side effects: Bradycardia, hypotension, physical and psychological dependence, respiratory depression, sedation, confusion, pruritus, constipation, nausea and vomiting.

Special points: Patients taking opioids chronically may become tolerant and require higher than usual doses to maintain pain relief. Use with caution in patients with a history of substance abuse because of the potential for drug dependency.

Cost: 30-mg tablets (20), $12.99; morphine sulfate CR 12-hour 30-mg tablet (30), $48.99.

Tramadol: Tramadol is a centrally acting analgesic that probably acts through monoaminergic and opioid mechanisms. The monoaminergic effect is similar to that of TCAs but is much weaker. Long-term treatment with tramadol is unlikely to cause tolerance and dependence, and it has a low potential for abuse [51].

A modest degree of pain relief has been found with tramadol in the treatment of painful diabetic neuropathy [51, 54 Class II]. Tramadol has also been found to improve physical functioning [54, Class II]. The combination of tramadol and acetaminophen has been found to have a small effect on pain; it improved quality of life measures by 10% [55, Class II].

Standard dosage: Initial dose of 50 to 100 mg every 4 to 6 h (immediate release); increase by 50 mg every 3 days to a maximum of 400 mg per day. For the extended-release formulation, start at 100 mg once a day and titrate to a maximum dose of 300 mg per day.

Contraindications: Hypersensitivity. Caution in patients with severe asthma or significant respiratory depression.

Main drug interactions: Avoid use with serotonergic agents because of the risk of serotonin syndrome.

Main side effects: Dizziness, headache, somnolence, pruritus, constipation, and nausea.

Special points: A withdrawal syndrome may occur with abrupt discontinuation. Tramadol also lowers the seizure threshold, and the risk is increased with SSRIs, other opioids, TCAs, neuroleptics, and MAO inhibitors.

Cost: 50-mg tablets (30), $16.99; tramadol ER 100-mg tablets (30), $75.99.

Other pharmacologic agents

Capsaicin: Capsaicin is the active ingredient found in hot peppers. It produces desensitization to noxious stimuli when applied topically by acting on the membranes of C fibers and depleting substance P from nerve terminals. The initial sensation of warmth or burning is due to an accentuated release of substance P, but with continued use the membrane becomes desensitized and the levels of substance P are reduced.

Capsaicin is specific for C fibers and does not affect other sensations such as temperature or vibration [56].

A placebo-controlled study of topical capsaicin in patients with painful diabetic neuropathy who were unresponsive or intolerant to conventional treatment demonstrated a large reduction in pain [57, Class I]. A larger study showed that capsaicin was safe and effective in treating painful diabetic neuropathy, but there was only a small effect on pain [58, Class II].

Standard dosage: 0.075% cream. Apply three to four times per day. The onset of action is 14 to 28 days, and peak effect is seen after 4 to 6 weeks of continuous therapy.

Contraindications: Hypersensitivity.

Main drug interactions: None.

Main side effects: Itching, stinging, erythema, and transient burning on application that diminishes with repeated use.

Special points: Wear gloves to apply and wash hands with soap and water afterwards.

Cost: 0.075% cream (56.6 g), $16.71.

Lidocaine transdermal patch: Lidocaine patches are a peripheral analgesic with minimal systemic absorption. They are often used in combination with systemic analgesic medications. Lidocaine blocks sodium channels and counteracts the hyperexcitability of peripheral nociceptors that contributes to neuropathic pain.

A moderate to large effect on pain was seen in studies on the effectiveness of the lidocaine patch in painful diabetic neuropathy [59, 60, Class III].

Standard dosage: 5% patch. Can apply up to three patches at once, and the patches may remain in place for up to 12 hours in any 24-hour period.

Contraindications: Hypersensitivity to lidocaine or amide anesthetics.

Main drug interactions: None.

Main side effects: Contact dermatitis, itching, and local irritation.

Special points: Do not apply to broken or inflamed skin, as this may lead to increased absorption.

Cost: 5% patch (30), $216.80.

Alpha-lipoic acid: ALA is an antioxidant that has been studied in diabetic neuropathy because of evidence that oxidative stress plays a role in its underlying pathogenesis and may contribute to progressive neuronal damage. Antioxidants diminish increased oxidative stress and have been shown to prevent neurovascular abnormalities associated with experimental models of diabetic neuropathy [61].

This medication was studied for its ability to influence the underlying pathophysiology, not for its ability to relieve pain. The mechanism of improvement of neuropathic pain is thought to be related to improvement in endothelial dysfunction and increased blood flow [26]. Results from clinical trials of ALA in diabetic polyneuropathy have been inconsistent, and

pain was not a primary end point in the studies. Overall, they have shown a moderate benefit in terms of pain reduction [26, Class I; 24, 62, Class II].

Standard dosage: 600 mg once or twice a day.

Contraindications: None.

Main drug interactions: May potentiate the effects of hypoglycemic agents.

Main side effects: Nausea and vomiting, rash.

Special points: Use with caution in patients who may be predisposed to hypoglycemia because ALA may alter glucose regulation. Patients at risk of thiamine deficiency should take a thiamine supplement.

Cost: 600-mg tablets (60), $7.99.

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•• Of major importance

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Table 1

Drugs with Class I or II evidence of efficacy in neuropathic pain associated with diabetic sensory polyneuropathya

Drug	Mechanism of action	Dosage	Adverse effects	Comments
Anticonvulsants				
Gabapentin	Unknown, but affects the synthesis and release of GABA and alters the release of monoamine neurotransmitters and blood serotonin levels	900–3,600 mg/d in 3 divided doses	Somnolence, dizziness, weight gain, occasionally peripheral edema	Dosage must be adjusted in renal impairment
Pregabalin	Binds to calcium channels and inhibits the release of excitatory neurotransmitters	150–300 mg/d in 2–3 divided doses	Somnolence, dizziness, weight gain	Dosage must be adjusted in renal impairment. Linear pharmacokinetics
Sodium valproate	Unknown. The drug is a histone deacetylase inhibitor that inhibits GABA transmission and blocks voltage-gated sodium channels and T-type calcium channels	500–1,000 mg/d in 2 divided doses	Headache, somnolence, dizziness, abdominal pain, tremor	Pregnancy category D. Monitor CBC and BMP
Antidepressants				
Venlafaxine	Inhibits the reuptake of serotonin and norepinephrine	150–225 mg/d in 2–3 divided doses	Nausea, somnolence, headache	Risk of serotonin syndrome with concurrent use of MAO inhibitors
Duloxetine	Balanced reuptake inhibition of serotonin and norepinephrine	60 mg 1–2 times a day	Somnolence, headache, dizziness, nausea	Risk of serotonin syndrome with concurrent use of MAO inhibitors. Not recommended for use with TCAs or in patients with end-stage renal disease or hepatic impairment
Amitriptyline	Inhibits the reuptake of serotonin and norepinephrine	25–100 mg nightly	Anticholinergic effects, sedation, cardiac conduction changes, orthostatic hypotension	Risk of serotonin syndrome with concurrent use of MAO inhibitors. Use with caution in elderly patients
Other Capsaicin	Depletes substance P from nerve endings	0.075% cream, applied 3–4 times daily	Transient sensation of warmth or burning	Patients should wear gloves and wash hands after application
Tramadol	Centrally acting analgesic with monoaminergic and opioid mechanisms	50–100 mg every 4–6 h	Dizziness, headache, somnolence; can lower seizure threshold	A withdrawal syndrome can occur with abrupt discontinuation. Avoid use with serotonergic agents
Alpha-lipoic acid	Antioxidant	600 mg 1–2 times per day	Nausea, vomiting, rash	Use with caution in patients who may be predisposed to hypoglycemia

[a]This list of treatments is not exhaustive. Other options are discussed in the text.

BMP basic metabolic profile; *CBC* complete blood count; *GABA* gamma-aminobutyric acid; *MAO* monamine oxidase; *TCA* tricyclic antidepressant