Pharmacological Treatment Of Diabetic Peripheral Neuropathy

Kenneth Cohen, PharmD, PhD, CGP; Nataliya Shinkazh, PharmD, BCPS, CDE; Jerry Frank, MD, FAAFP; Igor Israel, MD; and Chris Fellner

DISEASE OVERVIEW

Pathogenesis

Diabetic peripheral neuropathy (DPN) has been recognized as a major complication of diabetes since the mid-1800s.[1] Dyck et al. described the disorder as a symmetrical sensorimotor polyneuropathy attributable to chronic hyperglycemia, associated metabolic derangements, cardiovascular risk covariates, and microvessel alterations. Abnormal nerve conduction appears to be the first objective indication of DPN.[2]

Both vascular and metabolic factors are involved in the development of DPN.[3,4] Patients with the disorder typically experience the loss of nerve fibers due to impaired blood flow, resulting in impaired nerve sensitivity or pain.[5–7] Patients with DPN also develop vascular deformities and hypertrophy as well as reduced oxygen tension compared with normal individuals.[5] These effects underscore the relationship between vascular and neurostructural changes in patients with DPN.[8]

Further, elevated intracellular glucose levels in both vascular and neural tissues can lead to oxidative stress, which limits antioxidant and detoxification pathways.[9] The excess glucose may also bind with essential proteins, altering their structures. These glucose complexes, called advanced glycation end products (AGEs), in turn create abnormal vascular tissue and clotting factors.[10] Ultimately, the accumulation of AGEs can lead to atherosclerosis as well as renal and ocular disease.[11]

Among individuals with prediabetes (i.e., impaired glucose tolerance), up to 25% have peripheral neuropathy and up to 21% have neuropathic pain.[12] Those with prediabetes have a shorter duration of symptoms, with the neuropathy restricted to smaller nerve fibers.[13] In general, prediabetic neuropathy is less severe than the diabetic form.[14] One study suggests that many patients diagnosed with idiopathic neuropathy may actually have prediabetic neuropathy.[15]

Metabolic syndrome, which is related to obesity and insulin resistance, has been implicated in the development of peripheral neuropathy independent of frank diabetes.[16]

Epidemiology

Neuropathy is one of the leading causes of morbidity in patients with diabetes. According to the 2014 National Diabetes Statistics Report from the Centers for Disease Control and Prevention, 29 million Americans, or 9.3% of the U.S. population, have diabetes.[17] Epidemiologic data have indicated that the prevalence of neuropathy is 30% in hospitalized diabetic patients and 20% in ambulatory patients.[18] Further, while an estimated 7% to 10% of newly diagnosed diabetic patients have neuropathy, this number increases to 50% in patients with chronic disease (i.e., more than 25 years' duration).[19]

Risk Factors

The major risk factor for diabetic neuropathy is hyperglycemia.[20] In addition to poor glycemic control, more-severe symptoms of diabetic neuropathy are associated with advanced age, hypertension, the duration of diabetes, dyslipidemia, smoking, and heavy alcohol intake.[20] Data have shown that the progression of neuropathy is inversely dependent on the level of glycemic control in patients with both type-1 and type-2 diabetes.[21] As the duration of diabetes increases, so does the risk of associated neuropathy.[22]

In a study of the risk factors for DPN, half of the subjects (388 of 775) had neuropathy at baseline. Of the remaining subjects, 20% developed DPN.[21] In the Rochester Diabetic Neuropathy Study, the severity of diabetic retinopathy, the duration of diabetes, and the presence of elevated glycosylated hemoglobin (HbA_{1c}) were the main risk factors for diabetic polyneuropathy.[23] The Seattle Diabetic Foot Study found that both sensory and autonomic neuropathy independently influenced the risk of foot ulcers in diabetic veterans.[24]

Classification

DPNs range from mild sensory disturbances to painful, debilitating syndromes.[23] One classification system divides DPNs into symmetrical and asymmetrical neuropathies.[25] The former disorders include diabetic peripheral neuropathy and diabetic autonomic neuropathy, whereas the latter group includes mononeuropathies at the wrist or elbow as well as diabetic radiculoplexus neuropathies in the thoracic, cervical, and lumbosacral areas.

Another system for the classification of DPNs includes the following disorders:[26]

- Hyperglycemic neuropathy
- Generalized symmetrical polyneuropathies
- Sensory neuropathy
- Distal sensorimotor neuropathy
- Autonomic neuropathy
- Focal and multifocal neuropathies
- Superimposed chronic inflammatory demyelinating polyneuropathy

The staging of DPN may also be helpful in classifying the disorder. Ayad suggests the following relevant clinical stages:[27]

- N1a—signs but no symptoms of diabetic neuropathy
- N2a—mild, symptomatic diabetic polyneuropathy
- N2b—severe, symptomatic diabetic polyneuropathy
- N3—disabling diabetic polyneuropathy

Clinical Presentation

Patients with diabetes may develop symmetrical lower-limb polyneuropathies after only a few years. These disorders differ from asymmetrical neuropathies, such as carpal tunnel syndrome and thoracic, lumbosacral, and cervical neuropathies.[1]

DPN has a variety of clinical symptoms. Its sensory symptoms may be either negative or positive. Negative symptoms include numbness or "deadness," which patients may describe as similar to the feeling of wearing gloves or socks. Positive sensory symptoms include tingling, burning, an "electric shock" sensation, aching, or hypersensitivity to touch.[28]

Motor symptoms of DPN may be proximal or distal, and focal or diffuse. In the hands, motor symptoms can involve impaired coordination, as demonstrated by difficulty using a key or opening a jar. Because

Dr. Cohen is an Associate Professor of Pharmacy Practice at Touro College of Pharmacy in New York, New York. Dr. Shinkazh is an Assistant Professor of Pharmacy Practice at Touro College. Dr. Frank is a Clinical Assistant Professor in the Department of Family Medicine at SUNY Stony Brook School of Medicine in Stony Brook, New York. Dr. Israel is Associate Medical Director at the Parker Jewish Institute in New Hyde Park, New York. Chris Fellner is Editor of PTCommunity.com at MediMedia Managed Markets in Yardley, Pennsylvania.

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of this loss of dexterity, patients may be unable to check their blood pressure, draw up the proper insulin dose, and maintain their prescribed exercise regimen. Patients with motor symptoms may also show limb weakness, with frequent tripping or toe scraping; difficulty getting up from a prone position; or weakness in the knees when walking up stairs.[28]

The involvement of small autonomic nerve fibers can cause changes in sweating, incontinence, constipation, or gastroparesis.[29] When large nerve fibers are involved, patients may lose the sensation of touch and may experience pain, the loss of muscle coordination, and muscle weakness.[30]

Autonomic neuropathy typically involves the major organ systems, such as the gastrointestinal (GI), cardiovascular, and genitourinary systems. GI symptoms can include dysphagia, abdominal pain, nausea, vomiting, diarrhea, and incontinence;[31] cardiovascular symptoms can include orthostatic hypotension, arrhythmias, tachycardia, and near-syncope; and genitourinary symptoms can include poor urinary stream, impotence, and straining to void.[26]

The potentially severe pain associated with DPN may lead to insomnia, depression, anxiety, work and activity impairments, and a reduced quality of life (QOL).[32] DPN can also negatively affect patients' gait and posture, which increases their risk of accidental injury compared with healthy individuals.[33] If undiagnosed, DPN can lead to foot ulcers and amputation, especially when the disorder is concurrent with peripheral artery disease.[34,35]

MANAGEMENT OVERVIEW

Goals of Therapy

Treatment goals in DPN patients include pain modulation, enhanced glucose control, restoration of function, and patient education.[36]

With regard to pain modulation, a 30% reduction in pain, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with DPN.[37,38] Clinicians should use a pain scale that allows both nocturnal and diurnal mapping so that they may target the patient's treatment to problematic time periods.[36]

The value of tight glucose control in DPN patients was demonstrated in both the United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial (DCCT).[39,40] In an extension of the DCCT, the reduced risk of neuropathy achieved with enhanced glucose control persisted during eight years of follow-up.[41]

Improving or restoring function in a patient with DPN may require referral to a physical/occupational therapist.[36]

Finally, it is the responsibility of all physicians involved in managing DPN to provide their patients with information on the symptoms of the disease and the risks associated with it.[36]

Prevention and Treatment Strategies

A healthy diet and structured exercise that includes balance and resistance training have been shown to increase cutaneous re-innervation, reduce pain, and reduce the risk of falls in patients with DPN.[42,43]

Lowering HbA_{1c} levels can improve peripheral small nerve-fiber function, nerve conduction, and vibration threshold abnormalities.[44,45] The HbA_{1c} goal is generally less than 7% for most DPN patients, and clinicians should take into account the risks of hypoglycemia and a reduced life expectancy with more stringent targets.[46,47] In patients with type-1 diabetes, intensive therapy may prevent the development of DPN.[41] There is even evidence suggesting that patients with a history of intensive glycemic control have a "metabolic memory," which can play an important role in preventing the development of DPN.[48,49] In patients with type-2 diabetes, intensive treatment can achieve significant improvements in the sensation of touch in the upper extremities.[50] In the BARI 2D trial, the use of sensitizing oral medications, such as metformin and thiazolidinediones, significantly reduced the incidence of DPN.[51]

The American Diabetes Association recommends that screening for DPN be performed at the initial diagnosis in patients with type-2 diabetes and five years after the diagnosis in patients with type-1 disease, and then annually thereafter.[46] Moderate exercise, such as walking 150 minutes per week, does not increase the risk of ulceration and may improve outcomes in patients with mild forms of DPN.[46] Unfortunately, once patients with DPN experience painful symptoms, tight glucose control and moderate exercise may not be sufficient to reverse disease progression, and pharmacological therapy becomes necessary.[46,52]

Several guidelines have recommended the use of pharmacological treatments—both approved and off-label—to reduce pain and to improve QOL in DPN patients.[53–55] These treatments include antidepressant, anticonvulsant, analgesic, and topical medications (Table 1).

ANTIDEPRESSANTS

Studies have suggested that DPN is associated with an unbalanced release of norepinephrine and serotonin from neurons.[56,57] For that reason, serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are a promising category of antidepressants for DPN treatment.[58] Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, have also shown promise in patients with DPN[59] and are considered first-line treatment for DPN at many centers.[60] The use of TCAs, however, is restricted by the frequency and severity of their adverse effects, which can include sedation, cardiac arrhythmias, and postural hypotension.[60] In general, SNRIs are better tolerated than TCAs.[58]

Duloxetine

In September 2004, the SNRI duloxetine (Cymbalta, Eli Lilly) became the first drug to be approved for the treatment of the neuropathic pain associated with DPN.[61] It is also indicated for use in patients with major depressive disorder, generalized anxiety disorder, fibromyalgia, or chronic musculoskeletal pain.[62]

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake. Although the exact mechanism of action of the drug's central pain-inhibitory activity is unknown, it is believed to be related to the potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).[62] The blockade of norepinephrine reuptake, in particular, is known to have a beneficial effect on neuropathic pain.[63]

Key Clinical Trials

Goldstein and colleagues compared duloxetine (administered at dosages of 20 mg daily, 60 mg daily, or 60 mg twice daily [120 mg per day]) and placebo in a 12-week, double-blind study involving 457 patients with pain due to DPN. Duloxetine 60 mg per day and 120 mg per day demonstrated significantly greater improvements versus placebo on the 24-hour average pain score, beginning one week after randomization and continuing through the 12-week trial period.[64]

Raskin et al. also compared duloxetine and placebo in a double-blind study. A total of 348 patients with DPN were randomly assigned to receive treatment with duloxetine (60 mg once or twice daily) or placebo for 12 weeks. Compared with placebo-treated patients, both duloxetine groups showed significant improvements ($P < 0.001$) on the 24-hour average pain score. Moreover, duloxetine demonstrated superiority to placebo in all secondary analyses.[65]

Wernicke and colleagues conducted a similar trial, treating DPN patients with duloxetine (60 mg once or twice daily) or placebo for 12 weeks. Once again, both dosages of duloxetine demonstrated improvement on the 24-hour pain severity scale compared with placebo. Further, all secondary measures of pain (except allodynia) showed an advantage for duloxetine over placebo, with no significant difference between 60 mg daily and 60 mg twice daily.[57]

Tanenberg and colleagues conducted an open-label trial to determine whether duloxetine was inferior to the anticonvulsant agent pregabalin in DPN patients who had shown an inadequate response to gabapentin (900 mg per day or more). A total of 407 patients were randomly assigned to receive duloxetine monotherapy (60 mg once daily), pregabalin monotherapy (300 mg per day [100 mg three times daily]), or a combination of duloxetine (60 mg per day) and gabapentin (900 mg or more daily) for

Table 1 Pharmacotherapy of Diabetic Peripheral Neuropathy

Medication	FDA-Approved for DPN Treatment?	Recommended Dosage	Estimated AWP for 30 days[72]*	Comments
Antidepressants				
Amitriptyline	No	25–100 mg at bedtime[71]	$10–$33	• Not recommended over duloxetine or venlafaxine.[71] • AEs include dry mouth, urinary retention, sedation, vertigo, constipation.[184] • Monitor BP, heart rate, ECG before and during initiation; weight; mental status.[74] • Avoid use in patients older than 60 years of age.[54]
Desipramine	No	10–25 mg titrated to 100–150 mg at bedtime[91]	$14–$25 to $115–$160	• Safer alternative to amitriptyline (less-severe anticholinergic effects, less sedation).[60,79,82] • Preferred TCA for elderly patients.[92] • AEs include dry mouth, sedation, dizziness, confusion, orthostatic constipation, urinary retention, blurred vision, weight gain, arrythmias.[74] • Monitor BP, heart rate, ECG before and during initiation; weight; mental status.[74]
Duloxetine (Cymbalta)	Yes	60 mg/day [62]	$58	• First drug approved for treatment of DPN (2004).[61] • AEs include nausea, somnolence, hyperhidrosis, anorexia, vomiting, constipation, fatigue, dry mouth.[184] • Monitor BP, mental status, liver enzymes.[74] • Avoid use in hepatic impairment; avoid use with CrCl < 30 mL/min.[144]
Venlafaxine	No	75–225 mg/day[71]	$14–$26	• AEs include nausea, somnolence, ECG changes.[184] • Monitor BP, cholesterol, heart rate.[74] • May be added to gabapentin for better response.[71]
Anticonvulsants				
Carbamazepine	No	600 mg/day (200 mg TID) to 800 mg day (200 mg QID)[60,91]	$40–$53	• AEs include agitation, dry mouth, sedation, ataxia, nausea, vomiting, blurred vision, confusion, fatigue, nystagmus, aplastic anemia (rare).[74] • Monitor CBC with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium, ophthalmic exams (papillary reflexes); observe patient for excessive sedation.[74]
Gabapentin	No	900–3,600 mg/day in three divided doses[71,184]	$3–$13	• AEs include dizziness, somnolence, diarrhea, fatigue, GI upset, peripheral edema.[144,184] • Monitor serum levels of concomitant antiepileptic therapy.[74] • Reduce dosage if GFR < 60 mL/min.[112]
Pregabalin (Lyrica)	Yes	150 mg/day (50 mg TID) to 300 mg/day (100 mg TID) [94]	$519 (brand)	• Second agent approved for treatment of DPN (2004).[97] • AEs include somnolence, dizziness, peripheral edema, weight gain.[184] • Monitor degree of sedation, symptoms of myopathy or ocular disturbance, weight gain/edema, creatine phosphokinase, skin integrity (in diabetic patients).[74] • Treatment may lead to physical or psychological dependence.[94,103,104]
Valproate sodium	No	500–1,200 mg/day in two or three divided doses[71]	$4–$10	• AEs include elevated liver enzymes, nausea.[184] • Monitor liver enzymes, CBC with platelet count.[74]

Table 1 Pharmacotherapy of Diabetic Peripheral Neuropathy (continued)

Medication	FDA-Approved for DPN Treatment?	Recommended Dosage	Estimated AWP for 30 days[72]*	Comments
Opioids				
Morphine sulfate (MS Contin)	No	15–30 mg every 12 to 24 hours [144]	Every 12 hours: $188–$356 Every 24 hours: $94–$178 (brand)	• Typical opioid effects should be expected (e.g., constipation, somnolence, dizziness, nausea, vomiting, itchiness).[144,184] • Chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia.[71,132,133] • Data are insufficient to recommend this drug over oxycodone, dextromethorphan, or tramadol.[71]
Oxycodone CR (OxyContin)	No	Maximum dosage: 120 mg/day in two divided doses of CR formulation[71]	$876 (brand)	• Typical opioid effects should be expected (e.g., constipation, somnolence, dizziness, nausea, vomiting, itchiness).[144,184] • Chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia.[71,132,133] • Data are insufficient to recommend this drug over dextromethorphan, morphine sulfate, or tramadol.[71]
Opioid-Like Analgesics				
Dextromethorphan	No	400 mg/day in four divided doses[71,184]	$126	• Dissociative anesthetic with powerful psychedelic effects at high doses.[158] • Primary AE is sedation (at recommended doses).[184] • Data are insufficient to recommend this drug over oxycodone, morphine sulfate, or tramadol.[71]
Tapentadol (Nucynta ER)	Yes	50–250 mg BID	$309–$935 (brand)	• Third agent approved for DPN treatment (2012).[145] • AEs include nausea, dizziness, somnolence, constipation, vomiting, headache.[146] • Potential for addiction, abuse, misuse; life-threatening respiratory depression; neonatal opioid withdrawal syndrome; interaction with alcohol.[146]
Tramadol	No	210 mg/day in two or four divided doses[71,184]	$96 (for 200-mg dose)	• AEs include nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures.[74] • Monitor respiratory rate, BP, heart rate, signs of tolerance or abuse.[74] • Data are insufficient to recommend this drug over oxycodone, morphine sulfate, or dextromethorphan.[71]
Topical Medications				
Capsaicin (cream) (Trixaicin HP)	No	0.075% TID or QID[71,144]	$27 for one 60-g tube (brand)	• May be used as adjunct to oral medications.[144] • AEs include localized stinging, burning, and itching; coughing; sneezing; rash.[74,144,184] • Monitor skin breakdown.[74]
Lidocaine patch (Lidoderm)	No	Maximum of three 5% medicated patches applied once for up to 12 hours within a 24-hour period[144,169]	$842	• May be used as adjunct to oral medications.[144] • Key AEs include application-site reactions (e.g., blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation).[144,169]

* Generic pricing unless otherwise noted; prices have been rounded to the nearest dollar.

AE = adverse event; AWP = average wholesale price; BID = twice daily; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CR = controlled release; CrCl = creatinine clearance; DPN = diabetic peripheral neuropathy; ECG = electrocardiogram; ER = extended release; GI = gastrointestinal; GFR = glomerular filtration rate; QID = four times daily; TCA = tricyclic antidepressant; TID = three times daily

12 weeks. Noninferiority would be declared if the mean improvement for duloxetine was no worse than the mean improvement for pregabalin by a margin of –0.8 in the weekly mean of a diary-based daily pain score (on a scale of 0 to 10 points) at the study's end. The mean change in the pain rating was –2.6 for duloxetine and –2.1 for pregabalin, establishing noninferiority between the two drugs. Noninferiority between duloxetine monotherapy and the duloxetine/gabapentin combination (the study's secondary objective) was also demonstrated.[66]

In a meta-analysis of randomized, double-blind, placebo-controlled studies evaluating duloxetine or pregabalin in DPN patients, an indirect comparison of the two drugs found no significant differences on the 24-hour pain severity scale. For patient global-impression outcomes,

however, pregabalin showed an improvement over duloxetine that just reached statistical significance. The authors concluded that duloxetine and pregabalin had comparable efficacy.[67]

Kaur and colleagues compared duloxetine with amitriptyline in DPN patients in a randomized, double-blind, crossover trial. A total of 58 patients received duloxetine (20, 40, or 60 mg daily at bedtime) or amitriptyline (10, 25, or 50 mg daily at bedtime) for 14 weeks. Both treatments achieved a significant improvement in pain compared with their baseline values ($P < 0.001$ for both). Good, moderate, and mild pain relief was achieved in 59%, 21%, and 9% of patients, respectively, on duloxetine and in 55%, 24%, and 15% of patients, respectively, on amitriptyline. There were no significant differences in other outcome measures between the two groups.[68]

A four-week, randomized, double-blind, placebo-controlled, parallel-group study compared the analgesic efficacy of duloxetine, pregabalin, and amitriptyline in 65 patients with DPN. For the first two weeks, the patients received low-dose regimens (i.e., duloxetine 60 mg once daily, pregabalin 150 mg twice daily, and amitriptyline 25 mg twice daily). During the next two weeks, the dosages were increased to duloxetine 60 mg twice daily, pregabalin 300 mg twice daily, and amitriptyline 25 mg in the morning and 50 mg at bedtime. All three treatments reduced pain compared with placebo, but no one drug was superior to any other.[69]

Tesfaye and colleagues investigated whether combining duloxetine and pregabalin in DPN patients not responding to either drug would be superior to increasing each drug to its maximum recommended dosage. For the first eight weeks, patients received either duloxetine 60 mg per day or pregabalin 300 mg per day. Thereafter, nonresponders received duloxetine 120 mg per day, pregabalin 600 mg per day, or a combination of duloxetine 60 mg per day and pregabalin 300 mg per day for an additional eight weeks. A total of 804 patients received initial therapy, and 339 received high-dose or combination therapy. No significant differences were noted between the combination treatment and the high-dose monotherapies in terms of the Brief Pain Inventory Modified Short Form 24-hour average change in pain severity ($P = 0.370$) and on most secondary endpoints.[70]

Treatment Considerations

The Mayo Clinic recommends duloxetine as the first choice for DPN treatment, followed by pregabalin, TCAs, and oxycodone controlled release (CR).[54] According to guidelines from the American Academy of Neurology (AAN), however, duloxetine may be considered for the treatment of DPN, but the data are insufficient to recommend it over amitriptyline or venlafaxine.[71]

The approved target (and maximum) dosage of duloxetine in DPN patients is 60 mg per day, administered once daily. Since diabetes is often complicated by renal disease, a lower starting dose and a gradual increase in dose should be considered for DPN patients with renal impairment.[62]

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial months of a course of drug therapy or at times of dose increases or decreases.[62]

Treatment with extended-release (ER) duloxetine (Cymbalta) has been associated with hepatotoxicity; orthostatic hypotension, falls, and syncope; serotonin syndrome; abnormal bleeding; severe skin reactions; activation of mania or hypomania; angle-closure glaucoma; seizures; hyponatremia; and urinary hesitation and retention.[62]

In DPN patients, small increases have been observed in fasting blood glucose in HbA_{1c}. Blood pressure should be monitored before initiating treatment and periodically throughout treatment. Duloxetine should be used with caution in patients with conditions that slow gastric emptying. The drug should not be administered with inhibitors of cytochrome P450 1A2 or thioridazine.[62]

The estimated average wholesale price (AWP) for treatment with duloxetine (as well as the other treatments discussed in this paper) is given in Table 1.[72]

Venlafaxine

Venlafaxine (Effexor XR, Wyeth/Pfizer) is a potent SNRI approved for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. It is not indicated for use in DPN patients.[73] The exact mechanism of venlafaxine's antidepressant action is unknown, but it is thought to be related to the potentiation of serotonin and norepinephrine in the CNS through inhibition of their reuptake.[73] Venlafaxine is also thought to work centrally to decrease the perception of pain.[74] Importantly, venlafaxine does not block muscarinic, histaminergic, or adrenergic receptors, thereby avoiding some adverse effects associated with TCAs.[75]

Key Clinical Trials

In an early report, Davis and Smith treated 11 DPN patients with an ER formulation of venlafaxine (37.5 to 75 mg per day). All of the patients had 75% to 100% reductions in pain within three to 14 days with no adverse effects.[76]

Rowbotham et al. conducted a double-blind, randomized, placebo-controlled study to evaluate the efficacy of venlafaxine ER (75 mg and 150–225 mg) in 244 adults with painful DPN. The baseline pain intensity was 68.7 mm (moderately severe) on a 100-mm Visual Analog Scale for pain intensity (VAS-PI). At week 6, the percentage reduction from baseline in the VAS-PI was 27% for placebo, 32% for venlafaxine 75 mg, and 50% for venlafaxine 150–225 mg ($P < 0.001$ versus placebo). Seven venlafaxine-treated patients experienced clinically important electrocardiographic (ECG) changes during treatment.[77]

Sindrup and colleagues compared venlafaxine (225 mg per day) with the TCA imipramine (150 mg per day) in DPN patients. They found no significant difference in efficacy between the two agents. Twenty-nine patients completed the randomized, double-blind, placebo-controlled study with a three-way crossover. During the three treatment periods, each lasting four weeks, patients rated pain paroxysms, constant pain, and touch- and pressure-evoked pain. The sum of the individual pain scores during treatment week 4 did not show a significant difference between venlafaxine and imipramine ($P = 0.44$). The number needed to treat (NNT) to obtain one patient with moderate-or-better pain relief was 5.2 for venlafaxine and 2.7 for imipramine.[78]

Treatment Considerations

According to AAN guidelines, venlafaxine may be considered for the treatment of DPN, but the available data are insufficient to recommend it over duloxetine or amitriptyline. The recommended off-label dosage for DPN patients is 75 to 225 mg per day. The AAN guidelines also suggest that venlafaxine may be added to gabapentin for a better response.[71]

Venlafaxine may increase the risk of clinically significant ECG changes, which should be considered before initiating treatment in patients at risk of cardiac arrhythmias.[77] The mean heart rates of patients taking venlafaxine may increase by 4 to 9 beats per minute. In addition, patients treated with venlafaxine (especially those with a history of hypertension) must be monitored carefully for increases in blood pressure.[74]

Amitriptyline

The mechanism of action of TCAs such as amitriptyline is unclear, but they are believed to inhibit the reuptake of serotonin and norepinephrine.[60] In addition, they are known to antagonize *N*-methyl-d-aspartate (NMDA) receptors, which mediate hyperalgesia and allodynia.[79,80]

Amitriptyline was first studied for DPN treatment in 1977,[81] and it has been used as a first-line therapy for years.[79] The most commonly used TCAs in this setting (listed in order from greatest to smallest anticholinergic effects) are amitriptyline, imipramine, nortriptyline, and desipramine.[27] Thus, for patients who cannot tolerate amitriptyline, desipramine may represent the safest TCA alternative.[82] As with other agents of this class, the use of amitriptyline is limited by the potential for serious adverse events (AEs), including cardiac arrhythmias and orthostatic hypotension, which are related to the drug's anticholinergic effects.[60]

Key Clinical Trials

In an early study, Max and colleagues evaluated the efficacy of amitriptyline in DPN patients with normal or depressed mood. A total of 29 patients received amitriptyline (25 mg per day titrated up to 150 mg per day; mean dosage, 90 mg per day) or placebo for six weeks in a randomized, double-blind, placebo-controlled, crossover design. Amitriptyline was judged superior to placebo in relieving pain from weeks 3 through 6. In addition, patients who were able to tolerate higher amitriptyline doses experienced greater relief, up to the maximum dosage of 150 mg per day. Anticholinergic AEs were noted.[83]

In a subsequent trial, Max and colleagues compared amitriptyline (12.5 to 150 mg per day; mean dosage, 105 mg per day) and desipramine (12.5 to 150 mg per day; mean dosage, 11 mg per day) in a randomized, double-blind, crossover study involving 38 DPN patients. The assessment of treatment efficacy was based on pain ratings during week 6 of treatment. Moderate-or-greater pain relief was achieved in 28 of 38 patients (74%) treated with amitriptyline compared with 23 of 38 (61%) of those treated with desipramine. The authors concluded that the two drugs were similarly effective in DPN and that desipramine offered an alternative for patients unable to tolerate amitriptyline.[79]

Amitriptyline also failed to demonstrate superiority over pregabalin in relieving DPN pain. A total of 51 patients received either amitriptyline (10, 25, or 50 mg at night-time) or pregabalin (75, 150, or 300 mg twice daily) for five weeks in a randomized, double-blind, head-to-head study. The McGill pain questionnaire and the Likert pain scale showed no significant differences between the two treatments. The overall response rates were 73% for amitriptyline and 77% for pregabalin.[84]

Morello and colleagues compared the efficacy of amitriptyline with that of gabapentin in a prospective, randomized, double-blind study. A total of 28 patients with neuropathic pain were treated with amitriptyline (25 to 75 mg per day; mean dosage, 59 mg per day) or gabapentin (900 to 1,800 mg per day; mean dosage, 1,565 mg per day) for six weeks. The authors reported that pain relief was not significantly different between the two treatments ($P = 0.26$).[85]

As noted previously, amitriptyline was also compared with the SNRI duloxetine in 58 patients with DPN. After 14 weeks of treatment, both drugs achieved a significant improvement in pain compared with their baseline values ($P < 0.001$ for both), and no significant differences were noted in other outcome measures.[68]

Treatment Considerations

According to AAN guidelines, amitriptyline may be considered for use in DPN patients, but the available data are insufficient to recommend it over the SNRIs duloxetine and venlafaxine.[71] A systematic review found no significant differences in analgesic efficacy among the available TCAs.[86] The AAN guidelines recommend a single 25-mg to 100-mg dose of amitriptyline at bedtime for DPN patients,[71] while Boulton suggests a dosage range of 25 to 150 mg per day.[60]

As a TCA, amitriptyline should be used with caution. One in five patients is unable to tolerate TCA therapy.[59] Clinicians must be aware of and monitor for potential AEs, especially in patients with narrow-angle glaucoma, benign prostatic hypertrophy, orthostasis, urinary retention, impaired liver function, or thyroid disease. In addition, the QTc interval should be assessed in patients with additional cardiovascular risk factors, including syncope or presyncope, cardiovascular disease, electrolyte disturbance, and advanced age. If QTc prolongation is present, other treatments should be used to avoid the risk of torsades de pointes.[59] Desipramine may be a safer alternative.[79,82]

Amitriptyline should not be used in patients older than 60 years of age because of the likelihood of comorbidities.[54] Moreover, TCAs are contraindicated in patients who have received monoamine oxidase inhibitors within the previous 14 days and during the acute recovery phase from a myocardial infarction.[87]

Desipramine

Desipramine (Norpramin, Sanofi-Aventis) is indicated for the treatment of depression.[88] As a TCA, it has basically the same analgesic mechanism of action as amitriptyline in DPN patients, i.e., serotonin/norepinephrine reuptake inhibition (particularly norepinephrine blockade) and NMDA receptor antagonism.[60,79,80,88] However, unlike amitriptyline, desipramine has a low affinity for cholinergic (muscarinic) receptors[89] and is therefore associated with less-severe anticholinergic AEs.[60,79]

Key Clinical Trials

In an early double-blind crossover trial, Max et al. compared six weeks of treatment with desipramine (mean dose, 201 mg per day) or placebo in 20 patients with DPN. Pain relief with desipramine was significantly higher than that with placebo in weeks 5 and 6; 11 patients reported at least moderate relief with desipramine compared with two patients given placebo.[63]

As noted previously, Max and colleagues also compared desipramine with amitriptyline in a randomized, double-blind, crossover study involving 38 DPN patients. After six weeks of treatment, the authors concluded that the two treatments were similarly effective.[79]

More recently, Hearn and colleagues reviewed five small, randomized, double-blind studies comparing desipramine with placebo or another active treatment in patients with DPN (n = 104) or postherpetic neuralgia (n = 73). The study durations ranged from two to six weeks, and the comparators included amitriptyline, fluoxetine, and clomipramine. According to the authors, the data demonstrated "some benefit" from desipramine (usually at dosages between 100 and 150 mg per day) compared with placebo at the expense of increased AEs. There was too little information, however, to substantiate that desipramine works as a pain medication in either DPN or postherpetic neuralgia.[90]

Treatment Considerations

The usual dosage schedule of desipramine in DPN patients is 10 to 25 mg at bedtime initially, increasing as tolerated to 100 or 150 mg as a single bedtime dose. [91] Since desipramine has less-severe anticholinergic AEs and is less sedative than amitriptyline,[60] it offers a safer alternative for patients who cannot tolerate amitriptyline[79,82] and is the preferred TCA for elderly patients.[92] Nevertheless, clinicians should use extreme caution when administering desipramine in patients with cardiovascular disease; a family history of sudden death, cardiac dysrhythmias, or cardiac-conduction disturbances; a history of urinary retention or glaucoma; thyroid disease or current use of thyroid medications; or a history of seizure disorders.[88]

ANTICONVULSANTS

Anticonvulsants comprise two general categories: traditional agents (e.g., carbamazepine and valproate sodium) and newer agents (e.g., pregabalin and gabapentin).[58] Traditional anticonvulsants have been used to treat neuropathy since the 1960s.[93]

Pregabalin

Pregabalin (Lyrica, Parke-Davis/Pfizer, and generics) is a structural derivative of gamma-aminobutyric acid (GABA),[94] the primary inhibitory neurotransmitter in the CNS.[95] It is structurally related to the antiepileptic drug gabapentin, and both agents have the same site of action: the alpha$_2$-delta protein, an auxiliary subunit of voltage-gated calcium channels.[96] Although pregabalin's precise mechanism of action is unknown, binding of the alpha$_2$-delta subunit may be related to the drug's antinociceptive activity.[94] Preclinical findings were consistent with a mechanism of action that might involve the reduction of abnormal neuronal excitability through reduced release of the GABA neurotransmitter.[96]

In December 2004, pregabalin was the second agent to be approved by the FDA specifically to treat the neuropathic pain of DPN,[97] three months after duloxetine was approved for the same indication.[61] AAN guidelines recommend pregabalin as first-line therapy

for DPN because of its effectiveness in reducing pain and pain-related sleep interference.[53,54] In addition to treating the pain associated with DPN, pregabalin is indicated for patients with postherpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal-cord injury in adults, and for adjunctive therapy in adults with partial-onset seizures.[94]

Key Clinical Trials

Rosenstock and colleagues conducted an eight-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effectiveness of pregabalin in alleviating DPN pain. A total of 146 patients were randomly assigned to receive pregabalin 300 mg per day (n = 76) or placebo (n = 70). Compared with placebo, pregabalin provided significant improvements in mean pain scores ($P < 0.0001$), mean sleep interference scores ($P < 0.0001$), the total Short-Form McGill Pain Questionnaire (SF-MPQ) score ($P < 0.01$), and the Short Form-36 (SF-36) bodily pain subscale ($P < 0.03$). Pain relief and improved sleep began during week 1 and remained significant throughout the study ($P < 0.01$).[98]

In another randomized controlled trial, 338 patients with DPN were treated with pregabalin (75, 300, or 600 mg per day) or placebo for five weeks. Patients receiving the 300-mg and 600-mg daily dosages showed significant improvements in the endpoint mean pain score (the trial's primary efficacy measure) compared with placebo ($P = 0.0001$). Pregabalin also improved the weekly pain score, the sleep interference score, the SF-MPQ, and multiple domains of the SF-36 Health Survey. Improvements in pain intensity were observed as early as the first week and were sustained throughout the five weeks of treatment. The response rates were 46% for pregabalin 300 mg per day, 48% for pregabalin 600 mg per day, and 18% for placebo.[99]

Freeman et al. pooled data from seven double-blind, randomized, placebo-controlled studies in which DPN patients received pregabalin dosages of 150, 300, and 600 mg per day, administered two or three times daily, for treatment durations ranging from five to 13 weeks. One trial included all three dosages, and three-times-daily dosing was used in four trials. Pregabalin significantly reduced the pain and pain-related sleep interference associated with DPN at all three thrice-daily dosages (150, 300, and 600 mg per day) compared with placebo ($P \leq 0.007$). Only the 600-mg per day dosage of pregabalin showed efficacy when administered twice daily ($P \leq 0.001$).[100]

Huffman et al. recently assessed the efficacy of pregabalin in patients with painful DPN and pain on walking. This randomized, double-blind, placebo-controlled study consisted of two six-week treatment periods separated by a two-week washout period. A total of 203 patients were treated with pregabalin (150 to 300 mg per day; n = 198) or placebo (n = 186). The authors found no significant difference between the two treatment groups on the study's coprimary efficacy endpoints of mean DPN pain ($P = 0.0659$) and mean DPN pain on walking ($P = 0.4120$). However, an analysis of the coprimary endpoints for the first six-week treatment period showed significant differences between pregabalin and placebo for DPN pain ($P = 0.0338$) and DPN pain on walking ($P = 0.0011$).[101]

As noted previously, pregabalin was compared with amitriptyline in a randomized, double-blind, head-to-head study involving 51 DPN patients. In this five-week trial, patients received either pregabalin 75, 150, or 300 mg twice daily or amitriptyline 10, 25, or 50 mg at nighttime. The McGill pain questionnaire and the Likert pain scale showed no significant differences between the two treatments.[84]

Studies that compared or combined pregabalin with duloxetine are described above in the section on anticonvulsants.

Treatment Considerations

Pregabalin is the only anticonvulsant approved by the FDA for use in DPN patients.[94] AAN guidelines recommend pregabalin for DPN treatment if clinically appropriate.[71] In the United Kingdom, guidelines issued by the National Institute for Health and Care Excellence (NICE) state that pregabalin reduces peripheral neuropathic pain compared with placebo, but the clinical trial evidence was judged to be of "very low quality."[102]

The maximum recommended dosage of pregabalin is 100 mg three times daily (300 mg per day) in DPN patients with a creatinine clearance of at least 60 mL/min. The starting dosage of 50 mg three times daily (150 mg per day) may be increased to 300 mg per day within one week based on efficacy and tolerability. Dosage adjustments may be necessary in patients with reduced renal function (i.e., a glomerular filtration rate [GFR] of less than 60 mL/min).[94]

Treatment with pregabalin may lead to physical or psychological dependence, so the drug is classified as a Schedule V controlled substance.[94,103,104]

In clinical trials involving 979 DPN patients, the most common AEs associated with pregabalin (75 to 900 mg per day) included xerostomia (5%), asthenia (5%), constipation (4%), and accidental injury (4%).[94] The product labeling includes warnings and precautions related to the occurrence of angioedema, hypersensitivity reactions, increased seizure frequency, increased risk of suicidal thoughts, peripheral edema, dizziness, and somnolence.[94]

Treatment with pregabalin at dosages greater than 300 mg per day (100 mg three times daily) is not recommended because of the potential for dose-dependent AEs.[94]

Gabapentin

Like pregabalin, gabapentin (Neurontin, Parke-Davis/Pfizer, and generics) is structurally related to GABA and shares the same therapeutic target: the alpha$_2$-delta subunit of voltage-gated calcium channels.[105] The precise mechanism of action by which gabapentin produces its analgesic effects is unknown,[105] but animal studies suggest that its pain-modulating properties may be linked to the release of GABA in spinal-cord pathways that modify pain perception.[106]

Gabapentin is FDA-approved for the treatment of postherpetic neuralgia in adults, and for adjunctive therapy of partial-onset seizures in adult and pediatric patients 3 years of age and older with epilepsy. It is not indicated for the treatment of DPN patients.[105] Nevertheless, published treatment guidelines have supported the use of gabapentin for this indication as a less-expensive alternative to pregabalin.[54,55]

Key Clinical Trials

In an early study, Backonja et al. evaluated gabapentin for the symptomatic treatment of patients with DPN. A total of 165 patients received gabapentin (titrated from 900 to 3,600 mg per day or the maximum tolerated dosage) or placebo for eight weeks. At the study endpoint, the mean daily pain score was significantly lower ($P < 0.001$) among the gabapentin-treated patients (baseline, 6.4; endpoint, 3.9; n = 82) compared with the placebo-treated group (baseline, 6.5; endpoint, 5.1; n = 80).[107]

Moore and colleagues investigated the effects of gabapentin (more than 1,200 mg per day) in patients with chronic neuropathic pain or fibromyalgia. Evidence for the outcome of at least a 50% reduction in pain intensity showed that gabapentin was effective in treating a subgroup of patients with DPN, with an NNT of 5.9 for a substantial benefit. This degree of pain relief was achieved by 38% of gabapentin-treated patients compared with 21% of those given placebo.[108]

As noted previously, Morello and colleagues compared the efficacy of gabapentin (900 to 1,800 mg per day; mean dosage, 1,565 mg per day) with that of amitriptyline (25 to 75 mg per day; mean dosage, 59 mg per day), a widely accepted DPN treatment, in a six-week, prospective, randomized, double-blind, double-dummy, crossover study. Pain relief was not significantly different between the two groups ($P = 0.26$).[85]

In a subsequent open-label study, however, gabapentin (1,200 to 2,400 mg per day) produced significantly better outcomes compared with amitriptyline (30 to 90 mg per day) in 25 patients with painful DPN. Both drugs were titrated over a four-week period and were maintained at the maximum tolerated dose for an additional eight weeks. The mean final pain scores were 1.9 and 1.3 points below baseline for gabapentin and amitriptyline, respectively ($P = 0.026$).[109]

Simpson reported on two eight-week studies in which gabapentin

was combined with venlafaxine in DPN patients. The first study—a randomized, double-blind, placebo-controlled trial—compared gabapentin plus venlafaxine with gabapentin plus placebo. The patients who received the combination therapy showed significant improvements in pain reduction. In the second study, patients who did not improve on gabapentin alone were given venlafaxine in addition to gabapentin. Again, the patients receiving combination therapy showed significant improvements in pain.[110]

Treatment Considerations

The AAN guidelines state that gabapentin may be considered for the treatment of DPN after pregabalin has been offered.[55] Chong et al., on the other hand, cite gabapentin as the preferred anticonvulsant drug for DPN treatment because of the availability of less-expensive generic formulations compared with pregabalin, as well as the extensive clinical experience with its use.[111] In the United Kingdom, NICE treatment guidelines state that gabapentin reduces peripheral neuropathic pain compared with placebo, but the clinical trial evidence was judged to be of "very low quality."[102]

When used to treat adults with postherpetic neuralgia, gabapentin is initially administered as a single 300-mg dose, which can be titrated as needed up to 1,800 mg per day (600 mg three times daily).[105] For DPN patients, the recommended off-label dosage is 900 to 3,600 mg per day.[71] The dosage should be reduced if the patient's GFR is less than 60 mL/min.[112]

Patients who cannot control their pain with gabapentin may respond to equivalent doses of pregabalin.[113] The conversion factor between these drugs is 6:1, so that a patient receiving 1,800 mg of gabapentin would require 300 mg of pregabalin to achieve a comparable effect.[112]

When used for its approved indication of postherpetic neuralgia in adults, gabapentin has been associated with multiorgan hypersensitivity (i.e., drug reactions with eosinophilia and systemic symptoms), driving impairment, somnolence, sedation, dizziness, and suicidal behavior and ideation.[105]

Valproate Sodium

Valproate sodium (Depacon, Abbott Laboratories, and generics), the sodium salt of valproic acid, is one of several valproate products. Others include valproic acid (Depakene, Abbott Laboratories; Stavzor, Noven) and divalproex sodium (Depakote, Depakote CP, and Depakote ER, AbbVie), along with their generics. Valproate sodium and the other valproate products are FDA-approved to treat seizures and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. They are also used off-label for other conditions, particularly psychiatric disorders.[114]

As Depacon, valproate sodium is indicated as an intravenous (IV) alternative for patients in whom oral administration of valproate products is temporarily not feasible in the following clinical situations: monotherapy and adjunctive therapy of complex partial seizures and of simple and complex absence seizures; and adjunctive therapy in patients with multiple seizure types, including absence seizures.[115]

Valproate sodium's mechanism of action is unknown. It is believed, however, that its activity in epilepsy is related to increased brain concentrations of GABA.[111,115]

Key Clinical Trials

Two randomized, double-blind, placebo-controlled trials have evaluated valproate sodium in DPN patients. In the first study,[116] 52 patients received valproate sodium or placebo for four weeks. The authors reported significant improvements in the pain scores (SF-MPQ) of patients treated with valproate sodium compared with those given placebo ($P < 0.05$).

In the other study,[117] 39 DPN patients were treated with valproate sodium or placebo for 12 weeks. Again, active treatment significantly improved pain scores. With valproate sodium, the mean SF-MPQ decreased from 19.47 at baseline to 9.66 ($P < 0.001$), the mean VAS pain score fell from 6 to 3 ($P < 0.001$), and the mean Present Pain Intensity score fell from 2.71 to 1.33 ($P < 0.001$). Placebo-treated patients showed no significant changes in these parameters.

Treatment Considerations

According to AAN guidelines, valproate sodium is "probably effective" in treating DPN. Recommended off-label dosages range from 500 to 1,200 mg per day.[71] However, valproate sodium is potentially teratogenic and should be avoided in diabetic women of childbearing age.[53,71] Moreover, because of its potential AEs, such as weight gain and possible worsening of glycemic control, it is unlikely to be the initial treatment choice for DPN.[53,71]

Carbamazepine

As Tegretol (Novartis), carbamazepine is approved for the treatment of seizures and trigeminal neuralgia. Its mechanism of action in trigeminal neuralgia is unknown.[118]

Key Clinical Trials

Although carbamazepine was the first medication studied in a randomized controlled trial for DPN treatment (in 1969),[119] only limited evidence exists for its efficacy in this setting.[60] Wiffen et al. reviewed 10 studies involving 480 participants with DPN, trigeminal neuralgia, or post-stroke pain treated with carbamazepine. The drug generally provided better short-term pain relief than placebo in DPN patients, but the authors noted that the relevant studies had poorly defined outcomes, incomplete reporting, and small numbers of participants.[120]

Treatment Considerations

Close laboratory monitoring is necessary when administering carbamazepine.[58] Testing should include blood urea nitrogen, creatinine, transaminase, iron levels, complete blood count (including platelets), reticulocyte count, liver function tests, and urinalysis.[118,121] Moreover, Tegretol's labeling includes a boxed warning regarding the risk of serious and sometimes fatal dermatological reactions, as well as aplastic anemia and agranulocytosis.[118] Because of the need for extensive monitoring and the risk of serious AEs, newer anticonvulsants (e.g., pregabalin and gabapentin) are preferred over carbamazepine for use in DPN patients.[122]

The initial dosage of carbamazepine in patients with trigeminal neuralgia is 200 mg per day, which may be increased in increments of 200 mg per day as needed, not to exceed 1,200 mg per day.[118] Suggested effective dosages of carbamazepine in DPN patients have ranged from 600 mg per day (200 mg three times daily)[74] to 800 mg per day (200 mg four times daily).[60,91]

Other Anticonvulsants

Lacosamide

As Vimpat (UCB, Inc.), lacosamide is indicated for use in patients with partial-onset seizures.[123] In July 2008, the FDA rejected lacosamide for the treatment of adults with DPN.[124] According to AAN guidelines, the drug "should probably not be considered" as a therapy for DPN patients.[71]

Hearn and colleagues reviewed five studies of lacosamide (200, 400, or 600 mg per day in divided doses) in 1,863 DPN patients. They concluded that lacosamide had limited efficacy in this setting. Moreover, higher doses did not consistently result in better efficacy but were associated with significantly more AE-related withdrawals.[125]

Lamotrigine

As Lamictal (GlaxoSmithKline), lamotrigine is indicated for patients with epilepsy or bipolar I disorder.[126] The AAN guidelines state that lamotrigine "should probably not be considered" for the treatment of DPN patients.[71] A review of four randomized controlled trials of

lamotrigine (approximately 200 to 400 mg per day) in DPN patients found no evidence that the drug was effective.[127]

Oxcarbazepine

As Trileptal (Novartis), oxcarbazepine is approved as monotherapy or adjunctive therapy in patients with partial seizures.[128] The AAN guidelines state that it should probably not be considered for the treatment of DPN.[71] Zhou et al. reviewed four randomized controlled trials of oxcarbazepine in 634 patients with painful DPN. They reported that oxcarbazepine provided pain relief in this setting. Their conclusion, however, was based on results from the sole positive trial and did not take into account negative results from the other three studies because of incomplete outcomes data.[129]

Topiramate

As Topamax (Janssen Pharmaceuticals), topiramate is approved for use in patients with epilepsy or migraine headaches.[130] According to AAN guidelines, there is insufficient clinical evidence to support or refute topiramate's use for DPN treatment.[71] Wiffen and colleagues reviewed four pivotal trials of topiramate (200 to 400 mg per day) in 1,684 DPN patients and found no evidence for its superiority over placebo.[131]

OPIOIDS

The use of opioids for the treatment of chronic, nonmalignant pain has increased during the last decade. Opioid drugs, however, can cause novel pain syndromes, such as rebound headaches, and their chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia.[71,132,133] For this reason, the use of opioids in the setting of DPN is controversial.[91] Monotherapy with these medications should be reserved for patients who do not achieve pain relief with other therapies.[58] Despite concerns about dependency, consensus guidelines have suggested that chronic opioid therapy may benefit DPN patients.[134]

Oxycodone

Oxycodone is an opioid analgesic drug that was introduced in the U.S. in the late 1930s and is now used in more than 50 drug formulations. It is a Schedule II controlled substance with an abuse liability similar to that of other opioid agonists.[135]

The precise mechanism of action behind the analgesic effect of oxycodone is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the drug's analgesic activity.[136]

Oxycodone is often combined with aspirin or acetaminophen in immediate-release pain medications, such as Percodan (oxycodone/aspirin, Endo Pharmaceuticals), Percocet (oxycodone/acetaminophen, Endo Pharmaceuticals), and Tylox (oxycodone/acetaminophen, PriCara/Ortho–McNeil–Janssen). Oxycodone is also available alone in other formulations, such as Roxicodone (Mallinckrodt). OxyContin (Purdue Pharma) is a long-acting oxycodone formulation (oxycodone CR).[135]

Key Clinical Trials

Although extensive clinical evidence supports the use of oxycodone in patients with moderate-to-severe pain, few studies have examined this powerful opioid as a DPN treatment.[92]

Gimbel and colleagues evaluated oxycodone CR as a DPN therapy in a six-week, randomized, double-blind, placebo-controlled, parallel-group study. Treatment began with one 10-mg tablet of either oxycodone CR (n = 82) or placebo (n = 77) every 12 hours. The doses could be increased every three days to a maximum of six tablets (60 mg) administered every 12 hours. Oxycodone CR provided significantly more analgesia compared with placebo at a mean dosage of 37 mg per day (range, 10 to 99 mg per day) ($P = 0.002$). AEs occurred in 96% of the oxycodone CR group and 68% of the placebo group. The oxycodone AEs were opioid-related.[137]

In a randomized crossover trial, oxycodone CR (10 mg) was compared with active placebo (benztropine 0.25 mg) in 36 DPN patients. Both treatments were administered every 12 hours. The doses were increased approximately weekly to a maximum of 40 mg every 12 hours for oxycodone CR and 1 mg every 12 hours for benztropine, with crossover to the alternate treatment after a maximum period of four weeks. At the end of the study, treatment with oxycodone CR resulted in a significantly lower mean daily pain score ($P = 0.0001$) and in significantly lower total pain and disability scores ($P = 0.004$).[138]

Gaskell et al. reviewed three short-term (four to six weeks), randomized, placebo-controlled trials in which oxycodone CR was used to treat pain in a total of 254 participants with DPN (n = 204) or postherpetic neuralgia (n = 50). Oxycodone CR was titrated to a maximum dosage of 60 to 120 mg per day; mean dosages ranged from 37 to 45 mg per day. The authors found no "convincing, unbiased" evidence that oxycodone CR was of value in treating DPN patients. At least one AE was experienced by 86% of the participants treated with oxycodone CR compared with 63% of those given placebo.[139]

Hanna and colleagues investigated the addition of oxycodone CR to gabapentin in 308 patients with moderately to severely painful DPN despite maximal gabapentin therapy. After 12 weeks of treatment, the oxycodone/gabapentin combination reduced pain scores by 33% compared with baseline. The overall treatment effect was greater with oxycodone/gabapentin than with placebo/gabapentin ($P = 0.007$). Oxycodone/gabapentin also significantly improved pain relief compared with gabapentin alone ($P = 0.003$).[140]

Treatment Considerations

According to AAN guidelines, oxycodone may be considered for the treatment of DPN, but the available data are insufficient to recommend it over dextromethorphan, tramadol, or morphine sulfate. The recommended mean dosage for DPN patients is 37 mg per day, with a maximum dosage of 120 mg per day.[71]

The labeling for oxycodone CR (OxyContin) includes a boxed warning regarding the potential for addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; and interaction with CYP3A4.[136] As an opioid, oxycodone may cause somnolence, nausea, and constipation.[60]

Morphine Sulfate

Morphine sulfate is a potent, relatively selective mu-opioid receptor agonist. Its principal therapeutic effect is analgesia, which it produces by interacting with one or more classes of opioid receptors throughout the body.[141] Long-acting formulations of morphine sulfate include Avinza (Pfizer) and Kadian (Actavis) ER capsules and MS Contin (Purdue Pharma) CR tablets. Numerous generic formulations of morphine sulfate are also available in the form of long-acting tablets (Endo, Mallinckrodt, Milan, Nesher, Ranbaxy, Rhodes) and capsules (Watson).[142]

Key Clinical Trials

Gilron and colleagues compared the efficacy of a combination of sustained-release morphine and gabapentin with that of each drug administered separately in 57 patients with DPN (n = 35) or postherpetic neuralgia (n = 22). Forty-one patients completed the trial. In this randomized, double-blind, active placebo-controlled, four-period crossover trial, patients received daily active placebo (lorazepam), sustained-release morphine, gabapentin, or a combination of morphine and gabapentin for five weeks. Mean daily pain scores on a scale of 0 to 10 at maximal tolerated doses (starting from 5.72 at baseline) were 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin/morphine combination ($P < 0.05$ for the combination versus placebo, morphine alone, or gabapentin alone). The mean daily doses of morphine and gabapentin were 45.3 mg and 2,207 mg, respectively, when used individually, and 34.4 mg and 1,705 mg, respectively, when used in combination.[143]

Treatment Considerations

According to AAN guidelines, morphine sulfate may be considered for the treatment of DPN patients, but the available data are insufficient to recommend it over oxycodone, dextromethorphan, or tramadol.[71] The recommended dosage of ER morphine sulfate in this setting is 15 to 30 mg every 12 to 24 hours.[144] Because of the risks of addiction, abuse, and misuse with opioids—even at recommended doses—and because of the greater risks of overdose and death with ER opioid formulations, long-acting morphine sulfate should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient pain management.[141]

OPIOID-LIKE ANALGESICS

Tapentadol

Tapentadol ER (Nucynta ER, Janssen), a synthetic mu-opioid receptor agonist and norepinephrine reuptake inhibitor, received FDA approval for DPN treatment in July 2012[145]—the third agent, besides duloxetine and pregabalin, to have this indication. Specifically, tapentadol ER is indicated for adults with DPN who have pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[146]

Key Clinical Trials

Schwartz and colleagues conducted a phase 3, randomized-withdrawal, placebo-controlled study of tapentadol ER in 588 patients with DPN. All of the patients had received opioid and/or nonopioid analgesics for at least three months and were dissatisfied with their current treatment. The subjects initially received an optimal dose of tapentadol ER (100 to 250 mg twice daily) during a three-week open-label phase. Subsequently, 395 patients with at least a 1-point reduction on an 11-point pain-intensity scale were randomly assigned to receive placebo or the optimal fixed dose of tapentadol ER (determined during the open-label phase) in a 12-week double-blind phase. Of the patients who received tapentadol ER, 53.6% (105 of 196) reported at least a 30% improvement from pretitration to week 12 of the double-blind phase. The most common treatment-emergent AEs included nausea, anxiety, diarrhea, and dizziness.[147]

In a similar study, 358 adults with moderate-to-severe DPN pain received tapentadol ER (100 to 250 mg twice daily) during a three-week open-label titration phase; of these patients, 318 demonstrated at least a 1-point reduction in pain intensity on an 11-point scale and were randomly assigned to receive placebo or tapentadol ER (at the optimal dose determined during titration) for 12 weeks (the double-blind, fixed-dose maintenance phase). The mean changes in the pain-intensity score from the start of double-blind treatment to week 12 were 0.28 for tapentadol ER compared with 1.30 for placebo ($P < 0.001$). The most common AEs for tapentadol ER during the double-blind phase were nausea and vomiting.[148]

Treatment Considerations

When used as the first opioid analgesic in DPN patients, ER tapentadol is initiated at a dosage of 50 mg twice daily (approximately every 12 hours). This starting dosage is also used in patients who are not opioid-tolerant; the use of a higher starting dose in these individuals may cause fatal respiratory depression. Patients are titrated to adequate analgesia with dose increases of 50 mg twice daily every three days to an effective dosing range of 100 to 250 mg twice daily.[146]

The labeling for Nucynta ER includes a boxed warning regarding the potential for addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; and interaction with alcohol.[146]

In clinical studies of DPN patients, the most common AEs associated with ER tapentadol included nausea, dizziness, somnolence, constipation, vomiting, and headache.[146] In general, the gastrointestinal AEs associated with ER tapentadol are less severe than those of standard opioids, possibly because of the drug's dual opioid/norepinephrine mechanism of action.[149]

Tramadol

Tramadol (Ultram ER, Janssen Pharmaceuticals) is a centrally acting synthetic analgesic agent in an ER formulation. Its analgesic activity appears to involve at least two complementary mechanisms: binding of the parent drug and its metabolite to mu-opioid receptors, and weak inhibition of both norepinephrine and serotonin reuptake.[150,151]

Tramadol is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period. It is not approved specifically for patients with DPN.[150]

Key Clinical Trials

In a randomized, placebo-controlled, parallel-group trial, Harati et al. treated 131 DPN patients with tramadol (n = 65) or placebo (n = 66) four times a day for six weeks. The average tramadol dosage was 210 mg per day. Tramadol reduced pain-intensity scores by 28% compared with placebo ($P < 0.001$).[152]

Harati and colleagues then enrolled 117 patients from this study (56 former tramadol and 61 former placebo recipients) in a six-month extension trial in which all patients received tramadol at dosages of 50 to 400 mg per day. On the first day of the study (baseline), patients formerly treated with placebo had a significantly higher mean pain-intensity score (2. 2 versus 1.4; $P < 0.001$) and a lower pain-relief score (0.9 versus 2.2; $P < 0.001$) than former tramadol patients. By day 90, however, both groups attained a mean pain-intensity score of 1.4, which was maintained throughout the rest of the study.[153]

Tramadol was combined with acetaminophen in a randomized, placebo-controlled trial involving 160 patients with DPN. The patients received tramadol/acetaminophen 37.5 mg/325 mg or placebo, up to one or two tablets four times daily, for 66 days. The tramadol/acetaminophen combination reduced average daily pain significantly compared with placebo from baseline to the final week (–2.71 versus –1.83, respectively; $P = 0.001$). In addition, the combination treatment was associated with significantly greater improvements ($P \leq 0.05$) in all measures of pain intensity and sleep interference.[154]

Treatment Considerations

According to AAN guidelines, tramadol may be considered for DPN treatment, but the available data are insufficient to recommend it over oxycodone, morphine sulfate, or dextromethorphan. The recommended dosage for DPN patients is 210 mg per day.[71]

Because tramadol lowers the seizure threshold,[151] its use should be avoided in patients with epilepsy or at risk of seizures.[155] Although tramadol has a lower potential for abuse compared with opiates, it should not be used in patients who are opiate-dependent or who have a tendency to abuse drugs.[152] Warnings related to tramadol ER (Ultram ER) include suicide risk, serotonin syndrome risk, anaphylactoid reactions, and respiratory depression.[150] In studies of patients with lower-back pain or osteoarthritis pain, the most common AEs associated with tramadol ER included dizziness, nausea, constipation, headache, and somnolence.[150]

Dextromethorphan

Dextromethorphan (DXM) is a synthetic NMDA receptor antagonist currently found in approximately 70 over-the-counter medications as an antitussive and expectorant.[156] Clinically, DXM has proven useful in controlling pain because of its ability to bind to NMDA receptors in the spinal cord and CNS, thereby blocking the generation of central acute and chronic pain sensations.[157]

DXM has few adverse effects when used at recommended doses. However, it is a dissociative anesthetic, similar to ketamine and phencyclidine, and can produce powerful psychedelic effects at high doses.[158] The popularity of DXM as an illicit recreational drug has been recognized for decades.[159]

Key Clinical Trials

Nelson et al. conducted two randomized, double-blind, crossover studies of DXM in a total of 31 DPN patients, who received DXM at a mean dosage of 381 mg per day for six weeks. Thirteen patients completed the study. Compared with placebo, DXM reduced pain by a mean of 24% ($P = 0.01$). Five of the original 31 patients withdrew from the study because of sedation or ataxia during dose escalations.[160]

In another study, DXM was compared with memantine (another NMDA receptor antagonist) in 19 patients with DPN. The median DXM dosage was 400 mg per day. DXM reduced pain intensity by a mean of 33% from baseline, compared with a mean reduction of 17% with memantine. Similarly, 68% of the DXM group and 47% of the memantine group achieved more than moderate pain relief.[161]

Treatment Considerations

According to AAN guidelines, DXM is "probably effective" in lessening DPN pain and may be considered as a treatment for that disorder, but the available data are insufficient to recommend it over oxycodone, morphine sulfate, or tramadol. The suggested dosage for DPN patients is 400 mg per day.[71]

TOPICAL MEDICATIONS

Capsaicin

Capsaicin is an alkaloid derived from chili peppers that desensitizes afferent sensory nerves, resulting in pain relief.[111,162] Topical treatment, however, may cause burning, stinging, and erythema in some patients.[162]

Key Clinical Trials

In an early study, Tandan et al. demonstrated that topical capsaicin (0.075%) had no detrimental effects on sensory function in subjects with DPN.[163]

The Capsaicin Study Group investigated 0.075% capsaicin cream in a double-blind comparison trial involving 252 patients with DPN. Capsaicin cream or vehicle cream was applied four times daily for eight weeks. At the final visit, capsaicin showed significant superiority over vehicle in the proportion of patients with pain relief (58% versus 45%, respectively) and decreased pain intensity (38% versus 27%). Capsaicin cream was well tolerated, with the exception of transient burning, sneezing, and coughing.[164]

In another double-blind, vehicle-controlled investigation, the Capsaicin Study Group compared 0.075% capsaicin cream with vehicle cream in 277 patients with painful DPN. Again, both treatments were applied four times daily for eight weeks. Capsaicin was significantly more effective than vehicle in achieving a clinical improvement in pain status (70% versus 53%, respectively; $P = 0.012$).[165]

Low and colleagues reported, however, that 0.075% capsaicin cream was no more effective than placebo cream in treating patients with chronic distal painful polyneuropathy. Thirty-nine patients received treatment four times daily for 12 weeks. The investigators found no statistical evidence for the efficacy of capsaicin over placebo on any of the study's pain indices.[166]

Biesbroeck et al. compared topical capsaicin with oral amitriptyline in an eight-week, double-blind, parallel-group study. A total of 235 patients with DPN were randomly assigned to receive either capsaicin cream or amitriptyline capsules. The capsaicin-treated patients received inactive capsules, and the amitriptyline-treated patients applied vehicle cream. The two active treatments produced equal and statistically significant improvements in pain over the course of the study. By the end of week 8, 76% of patients in each group experienced less pain, with a mean reduction in pain intensity of more than 40%.[167]

Treatment Considerations

According to AAN guidelines, topical capsaicin may be considered for the treatment of DPN patients.[71] A notable disadvantage of the topical cream, however, is that it must be applied three to four times daily for up to two months to achieve optimal pain relief.[162] Moreover, many patients are intolerant of the adverse effects of topical capsaicin, mainly burning pain on contact with warm or hot water or in hot weather.[71] The AAN guidelines recommend a dosage of 0.075% four times daily in DPN patients.[71]

In 2009, the FDA approved a high-concentration transdermal capsaicin 8% patch (Qutenza, Acorda Therapeutics) for long-term pain relief after shingles attacks. The patch must be applied to the skin by a health care professional because its placement can be painful, requiring the use of a local topical anesthetic as well as additional pain relief, such as ice or opioid pain relievers. The patient must also be monitored for at least one hour because of the risk of a significant increase in blood pressure after the patch has been placed.[168]

Lidocaine

Lidocaine is an amide-type local anesthetic agent that blocks neuronal sodium channels, thereby blunting the sensitization of peripheral nociceptors and, ultimately, CNS hyperexcitability.[60,169]

Early studies suggested that IV lidocaine might be beneficial in relieving neuropathic pain, but the inconvenience and potential complications of IV administration, along with possible AEs, proved to be problematic.[60] Today, lidocaine 5% patches (Lidoderm, Endo Pharmaceuticals) are a common topical treatment for patients with painful DPN,[58] although this approach is approved only for patients with postherpetic neuralgia.[169]

Key Clinical Trials

Derry and colleagues reviewed 12 studies of topical lidocaine (5% medicated patch, 5% cream, 5% gel, and 8% spray) in patients with neuropathic pain and found no evidence to support the use of these products in this setting. "Very low quality" evidence indicated that topical lidocaine was better than placebo for "some measure" of pain relief.[170]

The oral analog of lidocaine, mexiletine, is an antiarrhythmic agent that acts peripherally as an ion channel blocker to prevent the perception of pain.[74] Mexiletine appeared to offer some benefit for patients with DPN in early studies,[171–175] but it is not widely used today because of the potential for arrhythmias and the need for regular ECG monitoring.[60,91]

In a three-week, open-label study of lidocaine 5% topical patches, 70% of treated patients with DPN reported at least a 30% reduction in mean daily pain compared with baseline values. The patients received a maximum of four patches over 18 hours.[176]

In another open-label trial, Baron and colleagues compared lidocaine 5% medicated plaster with twice-daily pregabalin capsules in 204 patients with painful DPN. After four weeks of treatment, the proportions of patients responding to treatment were similar in the two groups (66.7% for topical lidocaine versus 69.1% for oral pregabalin). Improvements in painful DPN were also comparable.[177]

Wolff et al. reviewed 33 studies of various DPN treatments and found that lidocaine 5% medicated plaster was comparable with all of the other interventions (amitriptyline, capsaicin, gabapentin, and pregabalin) in terms of pain reduction.[178]

Treatment Considerations

According to the labeling for the lidocaine 5% medicated patch (Lidoderm), the prescribed number of patches (up to a maximum of three) should remain in place on intact skin for 12 hours, and then be removed for 12 hours, in patients with postherpetic neuralgia. Application to broken or inflamed skin may result in higher blood concentrations of lidocaine from increased absorption. Moreover, excessive dosing by applying lidocaine 5% patches to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious AEs.[169]

The AAN guidelines indicate that there is only "weak evidence" for considering lidocaine 5% medicated patches for the treatment

of patients with DPN.[71] Montfort and colleagues suggest that if the patches are used in DPN patients, they should be applied only once for up to 12 hours within a 24-hour period.[144]

Application-site reactions are the primary AEs associated with the lidocaine 5% medicated patch. These reactions can include blisters, bruising, a burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechiae, pruritus, and vesicles.[169]

Mexiletine, the oral analog of lidocaine, has been associated with agranulocytosis, hepatotoxicity, and toxic epidermal necrolysis, and may have proarrythmic effects.[74] Patients treated with mexiletine should be monitored with complete blood counts, including platelet measurements, along with regular ECGs and liver enzyme tests.[74]

The AAN guidelines state that mexiletine "should probably not be considered" for the treatment of DPN.[71] Boulton suggests, however, that topical mexiletine may be administered at a maximal dosage of 450 mg per day in DPN patients.[60]

Topical Amitriptyline

TCAs, such as amitriptyline, are believed to exert peripheral analgesic effects by activating adenosine receptors and by inhibiting voltage-dependent sodium channels.[179] Clinical investigations, however, have shown little benefit with topical amitriptyline in patients with painful DPN.

In a double-blind, randomized, placebo-controlled, crossover study, Ho et al. evaluated the efficacy of three topical creams—5% amitriptyline, 5% lidocaine, and placebo—in 35 patients with various types of neuropathic pain, including DPN. Topical lidocaine significantly reduced pain-intensity scores, but topical amitriptyline and placebo did not. The authors concluded that 5% amitriptyline cream was ineffective in this setting.[180]

Similar results were reported by Lynch and colleagues, who compared topical amitriptyline cream with topical ketamine in 98 patients with various forms of neuropathy, including DPN. The three-week, double-blind, randomized, placebo-controlled study evaluated four creams: placebo, 2% amitriptyline, 1% ketamine, and a combination of 2% amitriptyline and 1% ketamine. The authors found no difference between the active treatments and placebo in reducing pain.[181]

In a case report, a 39-year-old man with painful DPN affecting his hands and feet was treated with topical amitriptyline. The patient experienced pain relief only in his hands after the application of a 5% formulation, but a 10% formulation provided a "total reduction in pain" that occurred within 20 minutes and lasted the entire day.[182]

Importantly, Estebe and Myers point out that systemic treatment with amitriptyline can have significant dose-related toxic effects in the CNS and the cardiovascular system. For that reason, they strongly recommend that amitriptyline not be used as a local anesthetic agent until its peripheral neurotoxic effects have been thoroughly investigated.[183]

SELECTION OF OPTIMAL PHARMACOTHERAPY

Only three pain-relieving treatments have secured FDA approval for use in DPN patients: the antidepressant duloxetine (2004),[62] the anticonvulsant pregabalin (2005),[94] and the opioid-like analgesic tapentadol (2012).[146] Nevertheless, as this article has shown, numerous other agents—including gabapentin, venlafaxine, duloxetine, amitriptyline, and oxycodone—are commonly used off-label for that indication.

In AAN guidelines, pregabalin is the preferred treatment for patients with DPN (Level A recommendation). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (i.e., morphine sulfate, tramadol, and oxycodone CR), and topical capsaicin are "probably effective" and should be considered for these patients (Level B recommendation). Other treatments have negative or less-robust evidence for their use as DPN therapies.[53]

According to the Mayo Clinic, the first tier of drugs for patients with DPN includes duloxetine, oxycodone CR, pregabalin, and TCAs. The second tier consists of carbamazepine, gabapentin, lamotrigine, tramadol and venlafaxine ER. The Mayo Clinic also suggests the use of topical capsaicin and topical lidocaine.[54]

In the United Kingdom, NICE clinical guidelines recommend duloxetine as the first-line treatment for patients with DPN. If contraindicated, this drug may be replaced with amitriptyline. Second-line treatment consists of amitriptyline or pregabalin. The latter agent may be used alone or in combination with either amitriptyline or duloxetine. If second-line therapy is ineffective, the patient should be referred to a specialist pain service. While awaiting this referral, tramadol may be started as a third-line treatment.[55]

According to the AAN guidelines, certain agents should be avoided in DPN patients because of a lack of benefit or inadequate trial designs. These treatments include oxcarbazepine, lamotrigine, lacosamide, clonidine, pentoxifylline, and mexiletine.[53] The Mayo Clinic adds the following drugs to this list: acetaminophen (because of hepatotoxicity with large doses); amitriptyline (in patients older than 60 years of age); nonsteroidal anti-inflammatory drugs (because of an increased risk of bleeding, GI upset, and cardiovascular and cerebrovascular events); meperidine and propoxyphene (because of CNS toxicity); and pentazocine (because of CNS toxicity and reversal of the drug's analgesic effect).[54]

CONCLUSION

Neuropathy is a leading cause of morbidity in patients with diabetes.[17,18] Numerous pharmacological treatments—both approved and off-label—have been used to reduce the pain associated with DPN and to improve patients' quality of life.[53–55] These treatments include antidepressant, anticonvulsant, analgesic, and topical medications. AAN guidelines recommend the anticonvulsant drug pregabalin as first-line therapy. Other suggested treatments include venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (i.e., morphine sulfate, tramadol, and oxycodone CR), and topical capsaicin.[54] A 30% reduction in pain intensity, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with DPN.[37,38]

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