



**Indian Health Service  
National Pharmacy and Therapeutics Committee  
Formulary Brief: Diabetic Neuropathy  
-February 2018-**



**Background:**

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed pharmacotherapeutic treatment of diabetic neuropathy at the February 2018 Winter meeting. The NPTC last reviewed diabetic neuropathy in September 2010. This current review included clinical, utilization/procurement, and pharmacoepidemiologic data for applicable medications. Following comprehensive clinical and pharmaco-economic analyses, the NPTC voted to **add duloxetine** to the IHS National Core Formulary.

**Discussion:**

The most prevalent chronic complications of diabetes are diabetic neuropathies and, as such, are the leading cause of morbidity in patients with diabetes. Neuropathies are a group of heterogeneous conditions that affect different segments of the nervous system and typically present in various clinical manifestations. Distal symmetrical polyneuropathy (DSPN) is the most common of the diabetic neuropathies, occurring in about 75% of patients<sup>1</sup>. DSPN is diagnosed by exclusion, as non-diabetic neuropathy can be present in patients with diabetes. The exact pathophysiology of DSPN is unknown but is multifactorial. Additionally, approximately 50% of diabetic peripheral neuropathies (DPN) are asymptomatic. Incidence and prevalence of DSPN vary greatly, with the incidence of DSPN in newly diagnosed patients with type 2 diabetes mellitus (T2DM) ranging from 10-15%. Rates increase to ~50% after 10 years from T2DM onset<sup>1</sup>. It is critical to diagnose and treat DSPN in order to improve symptoms, reduce sequelae, and improve quality of life<sup>1</sup>. It is estimated that 12% of patients with painful DSPN do not report symptoms and 39% do not receive any treatment<sup>2</sup>. As for pain, a 30% reduction in the pain intensity, regardless of the baseline pain score, is considered a meaningful reduction<sup>3</sup>.

Currently, treatment revolves around the control of symptoms no available medications target the pathophysiology of DSPN or reverse it. Additionally, therapies focusing on glycemic control and lifestyle management have shown little to no improvement in neuropathic pain. As a result, the goal of therapy focuses on pain relief through pharmacotherapy. There are three medication in the U.S. currently approved for treatment of DSPN; namely pregabalin, duloxetine, and the opioid tapentadol. Numerous other medication classes have been used for DSPN pain with limited utility including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and opioids<sup>1</sup>.

A suggested treatment algorithm was published in 2016 by the [American Academy of Family Physicians](#) for painful DSPN. Recommended first-line therapies were amitriptyline, duloxetine, gabapentin and pregabalin (in no particular order) while second-line options included the SNRIs, desvenlafaxine and venlafaxine, and the opioids agents, tapentadol and tramadol. More recently, the American Diabetes Association (ADA) [2018 Standards for Medical Care in Diabetes guidelines](#) and the [2017 ADA Position Statement on Diabetic Neuropathy](#) both recommend duloxetine or pregabalin as initial treatments (Level A recommendation) for DPN. The 2017 ADA document adds that gabapentin may be considered as an initial approach (Level B) in certain circumstances and, although not FDA-approved, that TCAs offer some benefit in DPN. Use of TCAs is cautioned however due to the potential risk of adverse effects. Lastly the opioids, tapentadol and tramadol, are not recommended as first- or second-line therapies for DPN treatment.

Several important studies helped lay the foundation for current guidelines in treating DSPN. In 2014, a noteworthy meta-analysis of medications used in DSPN was published in the *Annals of Internal Medicine*. In their review of 65 RCTs, authors reported that (in studies less than 3 months in duration) anticonvulsants, SNRIs, topical capsaicin 0.075%, and TCAs all resulted in statistically significant reductions in pain compared with placebo<sup>4</sup>. In 2017, the American Academy of Neurology published an update to their initial 2011 review with a focus on both pain reduction and quality of life (QoL). Their 2017

review found that duloxetine and venlafaxine were superior to placebo in reducing pain associated with DSPN (moderate Strength of Evidence {SoE}) and that pregabalin and oxcarbazepine were also effective, albeit with a lower SoE. Other agents with a low SoE shown to be more effective than placebo included the TCAs, opioids and botulinum. Authors concluded that there were too few head-to-head comparisons available and that QoL outcomes could not be determined due to incomplete reporting in studies<sup>5</sup>.

A 2014 Cochrane review of duloxetine included patients treated for painful neuropathy, chronic pain or fibromyalgia. Eight studies involving 2728 patients were used in the analysis. Data showed statistically significant improvement with 60 mg duloxetine (vs. placebo) in pain scales of at least 30% and 50% or more. For all doses, duloxetine was superior to placebo (RR 1.53, 95% CI: 1.21 to 1.92; NNTB = 7). The withdrawal rate from adverse events for all duloxetine doses was 12.6% while the placebo rate was 5.8% (RR 1.99, 95% CI: 1.67 to 2.37). Overall, reviewers rated the studies as low risk for bias, although significant dropouts, imputation methods, and manufacture sponsorship added to the potential bias risk. In conclusion, reviewers recommended  $\geq 60$  mg/day duloxetine for DSPN; doses less than 60mg were not endorsed. The quality of evidence was rated as moderate<sup>6</sup>.

A 2017 Cochrane review evaluated gabapentin in neuropathy, predominantly in post-herpetic and DPN patients. Thirty-seven RTCs were reviewed which included 5,914 participants. Reviewers noted a high risk of bias because of small sample sizes, especially with the handling of data after patient withdrawal. Thirty-eight (38) percent of participants experienced significant benefit with gabapentin doses of  $\geq 1200$  mg/day compared to placebo (21%), (RR 1.9, 95% CI: 1.5 to 2.3; NNT = 5.9). Approximately 52% of participants had moderate benefit compared to placebo, which was also statistically significant. Adverse events were greater with gabapentin (11%) than placebo (8.2%) although adverse events deemed “serious” were similar between groups. Authors concluded that there is moderate-quality evidence to suggest that gabapentin at  $\geq 1200$  mg daily has an important effect on pain in patients with moderate to severe neuropathic pain after shingles or due to diabetes<sup>7</sup>.

A Cochrane review on tramadol in 2017 for neuropathic pain updated findings from a 2006 Cochrane review. Because various neuropathies were combined, specific outcomes regarding DSPN were not available. The reviewers concluded that there was only modest evidence for tramadol use in neuropathic pain, primarily from small, inadequately-sized studies with a high potential for bias<sup>8</sup>.

Lastly, the COMBO-DN study addressed whether increasing first-line monotherapy (up to maximal doses) or combining two different first-line drugs in non-responding patients was superior. The study measured the effects of duloxetine 60 mg/day or pregabalin 300 mg/day for 8 weeks. After the 8-week period, non-responders were then blinded to either combination therapy (duloxetine 60 mg/day and pregabalin 300mg/day) or the control group, which employed maximal doses of each agent (duloxetine 120 mg/day or pregabalin 600 mg/day). The primary outcome was change in pain scale, measured by the Brief Pain Inventory-Modified Short Form. Ultimately, combination therapy was non-inferior to either high-dose monotherapy in pain reduction ( $p=0.37$ ). Both safety and tolerability were similar between high-dose and combination groups<sup>9</sup>.

#### **Findings:**

Duloxetine, the opioids (tapentadol and tramadol), pregabalin, TCAs, and venlafaxine all have supporting data for use in DPN, however head-to-head comparisons are lacking. Current guidelines recommend duloxetine and pregabalin as first-line monotherapy and both have FDA indications for DPN. Clinical reviews indicate both medications offer similar benefit in DPN patients while agency-specific pharmaco-economic indices favor duloxetine from a value perspective. When first-line monotherapy (at moderate doses) is ineffective, the combination of duloxetine and pregabalin may offer additional pain relief without increased rates of adverse effects. In patients with a history of medication misuse and abuse, opioids and gabapentin/pregabalin should be reserved as second or third-line therapies.

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*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

## References:

1. Pop-Busui R, Boulton AJ, Feldman EL, et al. [Diabetic Neuropathy: A Position Statement by the American Diabetes Association](#). *Diabetes Care* 2017; 40(1): 136-154.
2. Snyder MJ, Gibbs LM, Lindsay TJ. [Treating Painful Diabetic Peripheral Neuropathy: An Update](#). *Am Fam Physician*. 2016; 94(3):227-234.
3. Cohen K, Shinkazh N, Frank J, et al. [Pharmacological treatment of diabetic peripheral neuropathy](#). *P&T*. 2015; 40(6):372-88.
4. Griebeler ML, Morey-Vargas OL, Brito JP, et al. [Pharmacologic Interventions for Painful Diabetic Neuropathy: An Umbrella Systematic Review and Comparative Effectiveness Network Meta-analysis](#). *Ann Intern Med*. 2014; 61:639–649.
5. Waldfogel JM, Nesbit SA, Dy SM. [Pharmacotherapy for diabetic peripheral](#). *Neurology*, 2017; 88: 1958-1967.
6. Lunn MP, Hughes RA, Wiffen PJ. [Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia \(Review\)](#). Cochrane Database of Systematic Reviews, 2015; Issue 1. Art. No.: CD007115.DOI: 10.1002/14651858.CD007115.pub3.
7. Wiffen PJ, Derry S, Bell R., et al. [Gabapentin for chronic neuropathic pain in adults](#). *Cochrane Database of Systematic Reviews*, 2017; Issue 6. Art. No.: CD007938. DOI: 10.1002/14651858.CD007938.pub4.
8. Duehmke RM, Derry S, Wiffen PJ, et al. [Tramadol for neuropathic pain in adults \(Review\)](#). *Cochrane Database of Systematic Reviews*. 2017 Issue 6. Art. No.: CD003726. DOI:10.1002/14651858.CD003726.pub4.
9. Tesfaye S, Wilhelm S, Lledo A, et al. [Duloxetine and pregabalin: High-dose monotherapy or their combination? The “COMBO-DN study” – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain](#). *Pain* 2013; 154:2616-2625.