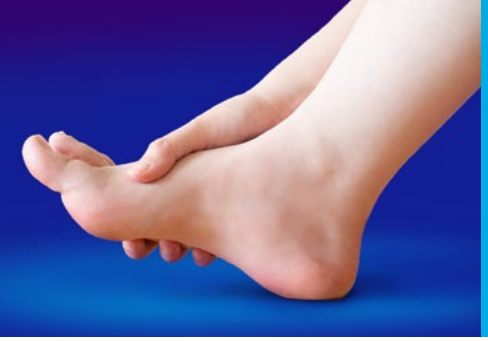

AAN Summary of Practice Guideline Update for **Clinicians**

Oral and Topical Treatment of Painful Diabetic Polyneuropathy Practice Guideline Update

This is a summary of the American Academy of Neurology (AAN) practice advisory update, "Oral and topical treatment of painful diabetic polyneuropathy practice guideline update summary," which was published in *Neurology*® online on December 27, 2021, and appears in the January 4, 2022, print issue.

Please refer to the full guideline at AAN.com/guidelines for more information, including for descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Recommendation 1

Rationale

Painful peripheral neuropathy is a common complication of diabetes and is more common in patients with longer durations of diabetes and poor glycemic control.[1-3] Patients with diabetes should be assessed for the presence of peripheral neuropathy and neuropathic pain periodically, although the optimal frequency of such assessment is not clear. Most studies of treatments for painful diabetic peripheral neuropathy have assessed pain using visual analog scales, numerical rating scales, or similar measures. Such scales are commonly used in practice, but they do not provide insight into the effect of pain on patients' functioning and well-being. Other scales that assess pain interference (BPI-DPN)[4] or effects on quality of life (Norfolk QOL-DN)[5] may provide more relevant information to assess the need for treatment and success of such treatment.

Level	Recommendation
Level B	Clinicians should assess patients with diabetes for peripheral neuropathic pain and its effect on these patients' function and quality of life.

Recommendation 2

Rationale

Several classes of pharmacologic agents have been demonstrated to reduce pain in patients with painful diabetic neuropathy. However, complete resolution of symptoms is often not achieved. Patients expect a high degree of pain relief, and many expect complete pain resolution.[6] In order to promote patient satisfaction, aligning patients' expectations with the expected efficacy of interventions (approximately 30% pain reduction is considered a success in clinical trials) would be beneficial.

Level	Recommendation
Level B	When initiating pharmacologic intervention for painful diabetic neuropathy, clinicians should counsel patients that the goal of therapy is to reduce, and not necessarily to eliminate, pain.

Recommendation 3

Rationale

In treating patients with painful diabetic neuropathy, it is important to assess other factors that may also affect pain perception and quality of life. Patients with diabetes are more likely to have mood disorders (most commonly, major depression) and sleep disorders (especially obstructive sleep apnea) than the general population.[7,8] Mood and sleep can both influence pain perception.[9,10] Therefore, treating concurrent mood and sleep disorders may help reduce pain and improve quality of life, apart from any direct treatment of the painful neuropathy. Some treatments for painful neuropathy may also have beneficial effects on mood and sleep (e.g., TCAs and SNRIs) and, therefore, may produce some of their benefits through these pathways.

Level	Recommendation
Level B	Clinicians should assess patients with painful diabetic neuropathy for the presence of concurrent mood and sleep disorders and treat them as appropriate.

Recommendation 4

Rationale

Painful diabetic neuropathy is a highly prevalent condition that greatly affects quality of life.[11] Four classes of oral medications have demonstrated evidence of pain reduction in meta-analyses: TCAs, SNRIs, gabapentinoids, and sodium channel blockers. The best estimates of the effect sizes and the corresponding CIs are comparable for all of these drug classes, which makes recommendations for one over another difficult.

Level	Recommendation
Level B	In patients with painful diabetic neuropathy, clinicians should offer TCAs, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain.

Recommendation 5

Rationale

Some patients prefer topical, nontraditional, or nonpharmacologic interventions; therefore, it is important to be able to offer interventions that fit with these patient preferences. Furthermore, given the downsides of opioid therapy,[12,13] the ability to offer effective nonopioid interventions to reduce pain in patients failing initial therapies is important. TCAs, SNRIs, gabapentinoids, and sodium channel blockers have all been shown to improve pain in patients with diabetic neuropathy. While other interventions have generally been less well studied, at least 1 randomized controlled trial supports the use of other interventions such as topicals (capsaicin, glyceryl trinitrate spray, *Citrullus colocynthis*), nontraditional interventions (ginkgo biloba), and nonpharmacologic approaches (exercise, cognitive behavioral therapy, mindfulness).[14] Furthermore, there is moderate and consistent evidence for the use of cognitive behavioral therapy (CBT) for many types of chronic pain.[15,16] In addition, while direct evidence on efficacy for CBT for painful neuropathy is not yet robust, there is promising pilot evidence for the use of CBT for some types of neuropathic pain.[17,18]

Level	Recommendation
Level C	Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for painful diabetic neuropathy.
Level C	In patients preferring topical, nontraditional, or nonpharmacologic interventions, providers may offer topicals (capsaicin, glyceryl trinitrate spray, *Citrullus colocynthis*), nontraditional (ginkgo biloba), and/or nonpharmacologic interventions (CBT, exercise, Tai Chi, mindfulness).

Recommendation 6

Rationale

Individual pharmacologic agents from the TCA, SNRI, gabapentinoid, and sodium channel blocker classes have similar efficacy on neuropathic pain outcomes. However, class and agent-specific differences exist in the potential for and nature of adverse effects. For example, the potential anticholinergic side effects of TCAs may be less tolerated in patients with pre-existing constipation, urinary retention, or orthostatic hypotension. Similarly, the potential side effects of SNRIs and sodium channel blockers, such as nausea, fatigue, and dizziness, may be less well tolerated in patients with similar pre-existing symptoms. Given that gabapentinoids can lead to peripheral edema, these medications should be used cautiously in patients with peripheral edema from comorbidities such as cardiac, renal, or liver disease. Valproic acid has potential teratogenic effects such as neural tube defects as well as hepatotoxicity, pancreatitis, hyponatremia, pancytopenia, and many other serious adverse events.[19] Dose adjustment for the level of renal function is required for many of these agents and must be reviewed before prescribing. Discussion of cost and patient preference should be made. Furthermore, patient comorbidities such as depression/anxiety (TCAs and SNRIs) and seizures (gabapentinoids and sodium channel blockers) may make certain therapeutic classes more appropriate given dual indications.

Level	Recommendation
Level B	Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when recommending treatment for painful diabetic neuropathy.
Level B	In patients of child-bearing potential with painful diabetic neuropathy, clinicians should not offer valproic acid.
Level B	In all patients with painful diabetic neuropathy, clinicians should not prescribe valproic acid given the potential for serious adverse events unless multiple other effective medications have failed.

Recommendation 7

Rationale

A series of medications may need to be tried to identify the treatment that most benefits a given patient with painful diabetic neuropathy. A treatment to reduce neuropathic pain in a patient should be considered ineffective when that medication has been titrated to a demonstrated effective dose and duration without significant pain reduction. The typical duration of treatment in which efficacy is demonstrated is approximately 12 weeks, with a range from 4 to 16 weeks. A treatment to reduce neuropathic pain in a patient should be considered intolerable when that medication causes adverse effects that outweigh any benefit in reduced neuropathic pain. While the exact side effect profile is dependent on the individual medication, dizziness, somnolence, and fatigue have been demonstrated with each class of oral medication, and application site reactions have been demonstrated with each topical medication. An intervention to relieve neuropathic pain should be considered a failure for an individual patient when it is either ineffective after 12 weeks or intolerable. Failure with 1 intervention does not preclude a good response, without side effects, to an alternative intervention from the same class or a different class. Choosing a different mechanism of action (class of medication) is expected to increase the likelihood of achieving pain relief or avoiding the side effects encountered with the initial intervention. If only partial efficacy is achieved, adding a second medication of a different class may provide combined efficacy greater than that provided by each medication individually.

Level	Recommendation
Level B	Clinicians should counsel patients that a series of medications may need to be tried to identify the treatment that most benefits patients with painful diabetic neuropathy.
Level B	Clinicians should determine that an individual intervention to reduce neuropathic pain is a failure either when the medication has been titrated to a demonstrated efficacious dose for approximately 12 weeks without clinically significant pain reduction or when side effects from the medication outweigh any benefit in reduced neuropathic pain.
Level B	Clinicians should offer patients a trial of a medication from a different effective class when they do not achieve meaningful improvement or if they experience significant adverse effects with the initial therapeutic class.

Level	Recommendation
Level B	For patients who achieve partial improvement with an initial therapeutic class, clinicians should offer a trial of a medication from a different effective class or combination therapy by adding a medication from a different effective class.

Recommendation 8

Rationale

The use of opioids for chronic, noncancer pain has been strongly discouraged in a position paper published by the American Academy of Neurology in 2014 and a systematic review by the Centers for Disease Control and Prevention primarily because of weak to nonexistent evidence of long-term efficacy and the likelihood of severe long-term adverse consequences.[12,13] The lack of long-term efficacy in association with a very poor risk profile has been subsequently reported in a systematic review from the NIH. This study concluded that "Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms."[20] A 1-year trial of opioids for moderate to severe low back or hip or knee osteoarthritis pain reported that opioids were nonsuperior to nonopioid medications.[21] The most important long-term adverse consequences include nearly universal dependence, high rates of more severe dependence and opioid use disorder, morbidity via overdose events, and excess mortality.[12,13,16,22] Data from the CDC suggests that it is likely that dependence may set in within days to weeks of starting opioids.[23] Severe events are underreported in randomized trials largely because of the relative rarity of these events, enriched recruitment methods, and the brief duration of most of these trials. Although the most severe adverse outcomes are dose related, overdose events can occur with intermittent and nonchronic use as well, especially when opioids are combined with sedative hypnotics, which is common.[24] While short-term pain reduction has been demonstrated in painful diabetic neuropathy patients with opioids, no randomized trial of opioids over a long duration has demonstrated clinically meaningful improvement of pain and function, which would be needed to justify the severity of potential side effects.[20]

Level	Recommendation
Level B	Clinicians should not use opioids for the treatment of painful diabetic neuropathy.
Level C	If patients are currently on opioids for the treatment of painful diabetic neuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies.

Recommendation 9

Rationale

Tramadol was originally approved and marketed as less opioid-like and therefore less risky. It was classified as a Schedule IV drug by the Drug Enforcement Administration (DEA), and until recently, it was not included in most state prescription drug monitoring programs. However, the risk profile of tramadol is also very poor, with respiratory depression, addiction, and overdose reflected in a Food and Drug Administration (FDA) "black box" warning.[25] A recent study reported an increase in all-cause mortality among patients taking tramadol for osteoarthritis.[26] Although true prevalence is unknown, serotonin syndrome has also been associated with tramadol.[27] The abuse liability in terms of reported abuse events per population is substantial and greater than that for morphine.[28]

Tapentadol is also associated with severe adverse events, as specified in an FDA "black box" warning, including life-threatening respiratory depression, addiction, overdose, and death.[29] Tapentadol is a Schedule II opioid (DEA classification), similar to other potent opioids. Its abuse potential, measured as abuse events per dispensed prescription, is higher than that of hydrocodone.[28] The efficacy of tramadol and tapentadol for painful neuropathy is only reported in studies of short duration.[30] Demonstration of long-term efficacy without substantial side effects would be needed to justify the severity of potential side effects.

Level	Recommendation
Level C	Clinicians should not use tramadol and tapentadol (opioids/SNRI dual mechanism agents) for the treatment of painful diabetic neuropathy.
Level C	If patients are currently on tramadol and tapentadol (opioids/SNRI dual mechanism agents) for the treatment of painful diabetic neuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies.

This practice advisory update was endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine.

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