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Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update

Report of the Guidelines Subcommittee of the American Academy of Neurology

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Guideline Endorsement

This guideline was endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine.

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Presentation Objectives

- To present evidence for and against different oral and topical neuropathic pain medications, including the effects of different medication classes on painful diabetic neuropathy.
- To present practice recommendations regarding the use of oral and topical neuropathic pain medications in the treatment of painful diabetic neuropathy.

Overview

- Introduction
- Clinical questions
- AAN guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

This practice guideline updates the 2011 American Academy of Neurology (AAN) practice guideline on the treatment of painful diabetic neuropathy. An update was needed to review a large number of new randomized controlled trials of the treatment of pain in people with painful diabetic neuropathy and to highlight the alternatives to opioid use in this population.

This guideline also evaluates the effects of different medication classes on painful diabetic neuropathy, whereas most previous guidelines and systematic reviews have focused solely on individual medications. Understanding whether medications of the same class have similar or different effects on pain reduction has implications for optimal treatment of this common condition, such as considering other factors such as cost when choosing between pain medications of the same class and which medications to switch to after a treatment failure.

Clinical Questions

This guideline addresses the following questions:

- In people with painful diabetic polyneuropathy, what is the efficacy of using oral pharmacologic interventions to reduce pain compared with placebo or an active comparator?
- In people with painful diabetic polyneuropathy, what is the efficacy of using topical pharmacologic interventions to reduce pain compared with placebo or an active comparator?

AAN Guideline Process*

Clinical Questions

Evidence

Conclusions

Recommendations

*Guideline developed using the *AAN 2017 Edition Clinical Practice Guideline Process Manual*.

Literature Search/Review

Rigorous, Comprehensive, Transparent

1098 abstracts

133 included articles

Cochrane Library and Medline databases were searched for randomized studies published between January 1991 and April 2013. The search was updated in December 2016 and again in March 2020.

Inclusion criteria:

- Randomized controlled trials

Exclusion criteria:

- Cohort studies, case series, and control studies
- Studies with 20 or fewer participants
- Studies not relevant to the clinical questions, studies including participants who had unrelated diseases or were outside of the study population
- Studies that were not peer reviewed.

AAN Classification of Evidence (2017)

Criteria for Rating Therapeutic Studies

Class I

- Randomized controlled clinical trial (RCT) in a representative population
- Triple-masked studies (i.e., the patient, treating provider, and outcome assessors are unaware of treatment assignment)
  - Relevant baseline characteristics of treatment groups (or treatment order groups for crossover trials) are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences

Class I *(continued)*

- Additional Class I criteria:
  a. Concealed allocation
  b. Nomore than two primary outcomes specified
  c. Exclusion and inclusion criteria clearly defined
  d. Adequate accounting of dropouts (with at least 80 percent of participants completing the study) and crossovers

AAN Classification of Evidence (2017)

Prognostic Accuracy Scheme

Class I *(continued)*

e. For noninferiority or equivalence trials claiming to prove efficicacy for one or both drugs, the following are also required*:

i.The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority

ii. The standard treatment used in the study is substantially similar to that used in previous studies extablishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)

iii. The inclusion and exclusion criteria for participant selection and the outcomes of participants on the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment

iv. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

v. For crossover trials, both period and carryover effects are examined and statistical adjustments performed, if appropriate

Class II

- RCT that lacks one or two Class I criteria a-e
- Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics (e.g., propensity score matching) meeting Class I criteria b-e
- Randomized crossover trial missing one of the following two criteria:
  - a. Period and carryover effects described
  - b. Baseline characteristics of treatment order groups presented
- All relevant baseline characteristics are presented and substantially equivalent across treatment groups (or treatment order groups for crossover trials), or there is appropriate statistical adjustment for differences
- Masked or objective** outcome assessment

*Numbers i-iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

AAN Classification of Evidence (2017)

Prognostic Accuracy Scheme

Class III

- Controlled studies (including studies with external controls such as well-defined natural history controls)
- Crossover trial missing both of the following two criteria:
  a. Period and carryover effects
  b. Presentation of baseline characteristics
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment performed by someone who is not a member of the treatment team

Class IV

- Studies not meeting Class I, II, or III criteria

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Clinical Question: Oral Medications

In people with painful diabetic polyneuropathy, what is the efficacy of using oral pharmacologic interventions to reduce pain compared with placebo or an active comparator?

Conclusion—Gabapentinoids/Gabapentinoid Class Effect

- Gabapentin is probably more likely than placebo to improve pain (SMD 0.53; 95% confidence interval [CI], 0.22–0.84; medium effect, moderate confidence; 1 Class I study).
- Pregabalin is possibly more likely than placebo to improve pain (SMD 0.29; 95% CI, 0.13–0.45; small effect, low confidence; 8 Class I and 7 Class II studies).
- Mirogabalin is possibly more likely than placebo to improve pain (SMD 0.21; 95% CI, 0.02–0.40; small effect, low confidence; 2 Class II studies).

- Gabapentinoids are probably more likely than placebo to improve pain (SMD 0.44; 95% CI, 0.25–0.63; small effect, moderate confidence; 8 Class I studies and 8 Class II studies). The I^2 value for heterogeneity across studies was 86%.

Conclusion—Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)/SNRI Class Effect

- Duloxetine is probably more likely than placebo to improve pain (SMD 0.50; 95% CI, 0.26–0.74; moderate effect, moderate confidence; 2 Class I and 5 Class II studies).
- Desvenlafaxine is possibly more likely than placebo to improve pain (SMD 0.25; 95% CI, 0.07–0.43; small effect, low confidence; 1 Class II study).

- Three Class I[16-18] and 6 Class II[19-24] studies were included for medications of this class, including 1 for venlafaxine, 1 for desvenlafaxine, and 7 for duloxetine. SNRIs are probably more likely than placebo to improve pain (SMD 0.47; 95% CI, 0.34–0.60; small effect, moderate confidence; 3 Class I and 6 Class II studies). I^2 value for heterogeneity was 43%.

Conclusion—Tricyclic Antidepressants (TCAs)/TCA Class Effect

- In addition to 1 new study, 2 Class I or Class II studies were identified for amitriptyline from the systematic review of the 2011 guideline.11 Amitriptyline is possibly more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies).

- No Class I or Class II studies were found for other TCAs; therefore, the best estimate for the class effect is based solely on amitriptyline studies. TCAs are possibly more likely than placebo to improve pain (SMD 0.95; 95% CI, 0.15–1.8; large effect, low confidence; 1 Class I study and 2 Class II studies). The I^2 value for heterogeneity was 80%.

Conclusion—Sodium Channel Blockers/Sodium Channel Blocker Class Effect

- Valproic acid is possibly more likely than placebo to improve pain (SMD 0.86; 95% CI, 0.38–1.33; large effect, low confidence; 3 Class II studies).

- Five Class II studies were included formedications of this class: 1 lamotrigine,[25] 2 lacosamide,[26,27] 1 oxcarbazepine,[28] and 1 valproic acid.[29] Sodium channel blockers are probably more likely than placebo to improve pain (SMD 0.56; 95% CI, 0.25–0.87; medium effect, moderate confidence; 5 Class II studies). The I^2 value for heterogeneity was 80%.

Conclusion—Other Oral Medications

- Nabilone, a synthetic cannabinoid, is probably more likely than placebo to improve pain (SMD 1.32; 95% CI, 0.52–2.13; large effect, moderate confidence; 1 Class I study). Ginkgo biloba is possibly more likely than placebo to improve pain (SMD 0.83; 95% CI, 0.48–1.18; large effect, low confidence; 1 Class II study).
- Ginkgo biloba is possibly more likely than placebo to improve pain (SMD 0.83; 95% CI, 0.48–1.18; large effect, low confidence; 1 Class II study).
- ABT 639, a selective voltage-dependent T-type calcium channel blocker that is not available, is probably no more likely than placebo to improve pain (SMD –0.04; 95% CI, –0.41 to 0.32; moderate confidence; 1 Class I study).
- ABT 894, a nicotinic acetylcholine receptor agonist that is not available, is probably no more likely than placebo to improve pain (SMD –0.06; 95% CI, –0.24 to 0.13; moderate confidence; 1 Class I study).
- Filorexant, an orexin antagonist that is not available, is possibly no more likely than placebo to improve pain (SMD 0.21; 95% CI, –0.36 to 0.79; low confidence; 1 Class II study).
- Tocotrienols, which belong to the vitamin E family, are possibly no more likely than placebo to improve pain (SMD 0.09; 95% CI, –0.14 to 0.32; low confidence; 1 Class II study).

Conclusion—Other Oral Medications *(Continued)*

- Nutmeg extract is possibly no more likely than placebo to improve pain (SMD –0.01; 95% CI, –0.46 to 0.44; low confidence; 1 Class II study).
- Metanx, consisting of L-methylfolate calcium, algae-S powder, pyridoxal-59-phosphate, and methylcobalamin, is possibly no more likely than placebo to improve pain (SMD –0.43; 95% CI, –0.86 to 0.001; low confidence; 1 Class II study).
- PF-05089771, a $Na_V1.7$ and $Na_V1.8$ voltage-gated sodium channel blocker that is not available, is possibly no more likely than placebo to improve pain (SMD 0.34; 95% CI, –0.10 to 0.78; low confidence; 1 Class I study).
- There are insufficient data as to whether ASP8477, a fatty acid amide hydrolase inhibitor that is not available, is more or less likely than placebo to improve pain (SMD 0.01; 95% CI, –0.47 to 0.48; very low confidence; 1 Class II study).
- There is insufficient evidence to determine whether dextromethorphan/quinidine is more or less likely than placebo to improve pain (SMD 0.69; 95% CI, –0.03 to 1.41; very low confidence; 1 Class II study). The reason for insufficient evidence is that there was only 1 Class II study with a large CI.
- AZD2423 is possibly less likely than placebo to improve pain (SMD –0.45; 95% CI, –0.87 to 0.04; low confidence; 1 Class II study).

Conclusion—Comparative Effectiveness Studies: Oral Medications

- Pregabalin is probably more likely than carbamazepine to improve pain (SMD 0.86; 95% CI, 0.50–1.21; large effect, moderate confidence; 1 Class I study).
- Venlafaxine is probably no more likely than carbamazepine to improve pain (SMD –0.02; 95% CI, –0.32 to 0.35; moderate confidence; 1 Class I and 1 Class II study).
- There is insufficient evidence to determine whethermirogabalin is more or less likely than pregabalin to improve pain (SMD 0.23; 95% CI, –0.05 to 0.52; very low confidence; 1 Class II study).
- Pregabalin is probably more likely than venlafaxine to improve pain (SMD 0.84; 95% CI, 0.48–1.20; large effect, moderate confidence; 1 Class I study).
- Amitriptyline is possibly no more likely than gabapentin to improve pain (SMD 0.33; 95% CI, –0.32 to 0.98; low confidence;1 Class II study).
- The combination of duloxetine (60 mg/d) and pregabalin (300 mg/d) is possibly no more likely than either high-dose duloxetine (120 mg/d) or high-dose pregabalin (600 mg/d) to improve pain (SMD –0.10; 95% CI, –0.33 to 0.13; low confidence, 1 Class II study).
- Duloxetine is possibly more likely than nortriptyline to improve pain (SMD 1.64; 95% CI, 0.63–2.65; large effect, low confidence; 1 Class II study).
- Pregabalin and N-acetylcysteine is possibly more likely than pregabalin alone to improve pain (SMD 1.00; 95% CI, 0.56–1.44; large effect, low confidence; 1 Class II study).
- γ-linolenic acid is possibly no more likely than α-lipoic acid to improve pain (SMD 0.34; 95% CI, –0.12 to 0.80; low confidence; 1 Class II study).
- Epalrestat sustained release is possibly no more likely than epalrestat immediate release to improve pain (SMD 0.25; 95% CI, –0.14 to 0.64; low confidence; 1 Class II study).

Conclusion—Combination Studies

- The combination of valproic acid and glyceryl trinitrate is possibly more likely than placebo to improve pain (SMD 1.14; 95% CI, 0.52–1.77; large effect, low confidence; 1 Class II study).

Clinical Question: Topical Medications

In people with painful diabetic polyneuropathy, what is the efficacy of using topical pharmacologic interventions to reduce pain compared with placebo or an active comparator?

Conclusion—Combination Studies

- Capsaicin is possibly more likely than placebo to improve pain (SMD 0.30; 95% CI, 0.14–0.47; small effect, low confidence; 1 Class I study of 8% and 1 Class II study of 0.075%).
- Nitrosense patch is possibly more likely than placebo to improve pain (SMD 0.59; 95% CI, 0.03–1.15; medium effect, low confidence; 1 Class II study).
- Citrullus colocynthis is possibly more likely than placebo to improve pain (SMD 0.91; 95% CI, 0.36–1.45; large effect, low confidence; 1 Class II study).
- Glyceryl trinitrate spray is possibly more likely than placebo to improve pain (SMD 1.19; 95% CI, 0.55–1.83; large effect, low confidence; 1 Class II study).
- Topical clonidine is possibly no more likely than placebo to improve pain (SMD 0.29; 95% CI, −0.01 to 0.58); low confidence; 1 Class II study).
- Buprenorphine transdermal patches are possibly no more likely than placebo to improve pain (SMD 0.23; 95% CI, −0.09 to 0.55; low confidence; 1 Class II study).

Conclusion—Subgroup Analysis for All Medications Combined

Age

- Metaregression revealed no significant association between age and pain reduction (slope for age; SMD 0.001; 95% CI, −0.10 to 0.11).

Sex

- Metaregression revealed no significant association between sex and pain reduction (slope for proportion male sex; SMD 0.01; 95% CI, −0.02 to 0.05).

Practice Recommendations
Recommendation 1

Rationale

Painful peripheral neuropathy is a common complication of diabetes and is more common in patients with longer duration of diabetes and poor glycemic control.[34-36] 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 (Brief Pain Inventory–Diabetic Peripheral Neuropathy)[37] or effects on quality of life (Norfolk Quality of Life–Diabetic Neuropathy)[38] may provide more relevant information to assess the need for treatment and success of such treatment.

Practice Recommendations

Recommendation Statement 1:

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

Practice Recommendations

Recommendation 2

Rationale

Several classes of pharmacologic agents have been demonstrated to reduce pain in patients with PDN. However, complete resolution of symptoms is often not achieved. Patients expect a high degree of pain relief, and many expect complete pain resolution.[39] 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.

Practice Recommendations

Recommendation Statement 2:

When initiating pharmacologic intervention for PDN, clinicians should counsel patients that the goal of therapy is to reduce, and not necessarily to eliminate, pain (**Level B**).

Practice Recommendations

Recommendation 3

Rationale

In treating patients with PDN, 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.[40,41] Mood and sleep can both influence pain perception.[42,43] 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.

Practice Recommendations

Recommendation Statement 3

Clinicians should assess patients with PDN for the presence of concurrent mood and sleep disorders and treat them as appropriate **(Level B).**

Practice Recommendations
Recommendation 4

Rationale

PDN is a highly prevalent condition that greatly affects quality of life.[6] 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.

Practice Recommendations

Recommendation Statement 4

In patients with PDN, clinicians should offer TCAs, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain (**Level B**).

Practice Recommendations
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,[8,9] 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 been less well studied, at least 1 randomized controlled trial supports the use of other interventions, such as topical (capsaicin, glyceryl trinitrate spray, Citrullus colocynthis), nontraditional (Ginkgo biloba), and nonpharmacologic approaches (exercise, cognitive behavioral therapy, mindfulness).[44] Furthermore, there is moderate and consistent evidence for the use of cognitive behavioral therapy (CBT) for many types of chronic pain.[45,46] 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.[47,48]

Practice Recommendations

Recommendation Statements 5a and 5b

Recommendation Statement 5a
Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for PDN (**Level C**).

Recommendation Statement 5b
In patients preferring topical, nontraditional, or nonpharmacologic interventions, providers may offer topical (capsaicin, glyceryl trinitrate spray, Citrullus colocynthis), nontraditional (Ginkgo biloba), or nonpharmacologic interventions (CBT, exercise, Tai Chi, mindfulness) (**Level C**).

Practice Recommendations
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 preexisting 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 preexisting 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.[49] 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.

Practice Recommendations

Recommendation Statements 6a, 6b and 6c

Recommendation Statement 6a

Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when Recommending treatment for PDN (**Level B**).

Recommendation Statement 6b

In patients of childbearing potential with PDN, clinicians should not offer valproic acid (**Level B**).

Recommendation Statement 6c

In all patients with PDN, clinicians should not prescribe valproic acid given the potential for serious adverse events unless multiple other effective medications have failed (**Level B**).

Practice Recommendations
Recommendation 7

Rationale

A series of medications may need to be tried to identify the treatment that most benefits a given patient with PDN. 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 (Table 1) 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.

Practice Recommendations

Recommendation Statements 7a, 7b, 7c and 7d

Recommendation Statement 7a
Clinicians should counsel patients that a series of medications may need to be tried to identify the treatment that most benefits patients with PDN (**Level B**).

Recommendation Statement 7b
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**).

Recommendation Statement 7c
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 B**).

Recommendation Statement 7d
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 (**Level B**).

Practice Recommendations
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.[8,9] 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."[50] 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.[51] 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.[8,9,46,52] Data from the CDC suggest that it is likely that dependence may set in within days to weeks of starting opioids.[53] 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.[54] Whereas short-term pain reduction has been demonstrated in patients with PDN 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.[50]

Practice Recommendations

Recommendation Statements 8a and 8b

Recommendation Statement 8a
Clinicians should not use opioids for the treatment of PDN (**Level B**).

Recommendation Statement 8b
If patients are currently on opioids for the treatment of PDN, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies (**Level C**).

Practice Recommendations
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 ecently, it was not included in most state prescription drug monitoring programs. However, the risk profile of tramadol is also poor, with respiratory depression, addiction, and overdose reflected in a Food and Drug Administration (FDA) black box warning.[55] A recent study reported an increase in all-cause mortality among patients taking tramadol for osteoarthritis.[56] Although true prevalence is unknown, serotonin syndrome has also been associated with tramadol.[57] The abuse liability in terms of reported abuse events per population is substantial and greater than that for morphine.[58]
- 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.[59] 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.[58] The efficacy of tramadol and tapentadol for painful neuropathy is only reported in studies of short duration.[60] Demonstration of long-term efficacy without substantial side effects would be needed to justify the severity of potential side effects.

Practice Recommendations

Recommendation Statements 9a and 9b

Recommendation Statement 9a

Clinicians should not use tramadol and tapentadol (opioids/ SNRI dual mechanism agents) for the treatment of PDN (**Level C**).

Recommendation Statement 9b

If patients are currently on tramadol and tapentadol (opioids/ SNRI dual mechanism agents) for the treatment of PDN, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies (**Level C**).

Suggestions for Future Research

Our review highlights key gaps in current knowledge that should be addressed in future studies. Specifically, few studies have investigated the effect of interventions on quality of life, patient functioning, mood, or sleep. Furthermore, few comparative effectiveness studies have been performed. Those studies with an active comparator have rarely included more than one other intervention; therefore, there are limited data to support one therapeutic intervention over another. One exception is the PAIN-CONTRoLS study, which compared 4 active medications for patients with cryptogenic neuropathy.[61] The study found that duloxetine and nortriptyline outperformed pregabalin and mexiletine. Comparable studies in PDN are also needed. Similarly, evidence for combination therapy compared with monotherapy and for the best titration schedule is limited. Another limitation to the current evidence is the lack of data beyond 16 weeks for any intervention. Given the chronicity of pain in those with diabetic neuropathy and the potential for evolving side effects, long-term studies are needed to better inform the long-term pain management in this population. Specifically, future studies should focus on the long-term effects (positive and negative) of opioids in this population to determine whether there is any role for these medications in this population. In addition, few studies exist that compare different modalities of treatment, such as oral medications, topical treatments, nontraditional therapies, and nonpharmacologic interventions. Finally, no information is available to predict which patients will respond best to specific interventions. However, groups are trying to employ pain phenotyping to see if a differential response exists. The ability to target effective interventions to the right subgroup has the potential to improve pain management in those with diabetic neuropathy, but limited data are available to guide these choices. We also lumped medications within one class together, but it is possible that certain medications within a class are better than others. Patients with PDN have multiple effective interventions available to them, but new studies should address our gaps in knowledge to enable better treatments for the future.

Access Guideline and Summary Tools

- To access the complete guideline and related summary tools, visit AAN.com/guidelines.
  - Guideline main article
  - Full-length guideline version
  - Summary for clinicians
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Questions?