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

Report of the AAN Guideline Subcommittee

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Abstract

Objective
To update the 2011 American Academy of Neurology (AAN) guideline on the treatment of painful diabetic neuropathy (PDN) with a focus on topical and oral medications and medical class effects.

Methods
The authors systematically searched the literature from January 2008 to April 2020 using a structured review process to classify the evidence and develop practice recommendations using the AAN 2017 Clinical Practice Guideline Process Manual.

Results
Gabapentinoids (standardized mean difference [SMD] 0.44; 95% confidence interval [CI], 0.21–0.67), serotonin-norepinephrine reuptake inhibitors (SNRIs) (SMD 0.47; 95% CI, 0.34–0.60), sodium channel blockers (SMD 0.56; 95% CI, 0.25–0.87), and SNRI/opioid dual mechanism agents (SMD 0.62; 95% CI, 0.38–0.86) all have comparable effect sizes just above or just below our cutoff for a medium effect size (SMD 0.5). Tricyclic antidepressants (TCAs) (SMD 0.95; 95% CI, 0.15–1.8) have a large effect size, but this result is tempered by a low confidence in the estimate.

Recommendations Summary
Clinicians should assess patients with diabetes for PDN (Level B) and those with PDN for concurrent mood and sleep disorders (Level B). In patients with PDN, clinicians should offer TCAs, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain (Level B) and consider factors other than efficacy (Level B). Clinicians should offer patients a trial of medication from a different effective class when they do not achieve meaningful improvement or experience significant adverse effects with the initial therapeutic class (Level B) and not use opioids for the treatment of PDN (Level B).

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Glossary

AAN = American Academy of Neurology; **CBT** = cognitive behavioral therapy; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **COI** = conflict of interest; **DEA** = Drug Enforcement Administration; **FDA** = Food and Drug Administration; **GS** = Guidelines Subcommittee; **PDN** = painful diabetic neuropathy; **SMD** = standardized mean difference; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **TCA** = tricyclic antidepressant.

Diabetes is the most common cause of peripheral neuropathy, accounting for 32%–53% of cases.[1-4] Painful diabetic neuropathy (PDN) occurs in more than 16% of patients with diabetes, but physicians do not always discuss this important symptom with patients; therefore, pain often goes untreated.[5] PDN, even compared with painless neuropathy, negatively affects physical and mental quality of life.[6]

A large, nationally representative health care claims study found that the most common prescriptions for pain associated with peripheral neuropathy were opioids, followed by gabapentin, pregabalin, duloxetine, amitriptyline, and venlafaxine.[7] The high use of opioids in people with painful neuropathy occurs despite a position statement from the American Academy of Neurology (AAN) and a guideline from the Centers for Disease Control and Prevention (CDC) recommending caution with opioid use in people with chronic noncancer pain.[8,9] According to the CDC, opioid overdose deaths have accelerated during the pandemic, highlighting the importance of appropriate prescribing.[10] We aimed to update a 2011 AAN guideline on the treatment of PDN[11] and perform meta-analyses of individual medications as well as commonly used medication classes. An update was needed to review a large number of new randomized controlled trials of the treatment of pain in people with PDN and to highlight the alternatives to opioid use in this population. Furthermore, we aimed to evaluate the effects of different medication classes on PDN, whereas most previous guidelines and systematic reviews have focused solely on individual medications.[11-14] 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. We chose to focus this guideline on oral and topical medications for PDN, but it is important to note that other interventions are also available. Specifically, this guideline seeks to answer the following question: In people with painful diabetic polyneuropathy, what is the efficacy of using oral or topical pharmacologic interventions to reduce pain compared with placebo or an active comparator?

Description of the Analytic Process

In November 2017, the Guidelines Subcommittee (GS) of the AAN convened a panel of clinicians with expertise in painful diabetic polyneuropathy. The panel included content experts, methodology experts, AAN GS members, and patient advocates/representatives. Individuals with a clear financial conflict and those whose professional and intellectual bias would diminish the credibility of the review were excluded. A majority (82%) of the members of the development panel and the lead author are free of conflicts of interest (COIs) relevant to the subject matter of this practice guideline. Three of the guideline developers (V.B., L.B.H., B.A.P.) were determined to have COIs, but the COIs were judged to be not significant enough to preclude them from authorship. These 3 developers were not permitted to review or rate the evidence, but they did serve in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles, and they participated in the recommendation development process.

The panel searched the MEDLINE, Cochrane, EMBASE, and ClinicalTrials.gov databases from January 2008 to September 2018 for relevant peer-reviewed articles that met inclusion criteria and were in English. The 2011 AAN PDN guideline included articles published prior to August 2008, and we included Class I and II studies from the 2011 guideline in the meta-analyses. The initial search yielded 1,044 articles. The panelists reviewed the article titles and abstracts for potential relevance. Of the reviewed abstracts, 155 were identified as potentially relevant and corresponding articles were obtained for full-text review. Each of the 155 articles was reviewed by 2 panel members working independently of each other. The panelists selected 95 articles for inclusion in the analysis, all of which were selected for evidence rating. The selected articles were required to be randomized controlled trials with more than 20 participants. An updated literature search completed in April 2020 identified an additional 20 potentially relevant articles published since September 2018. From the 2011 guideline, 34 articles were germane to the treatments discussed in this guideline and had been previously rated as Class I or Class II studies.

Risk of bias for each of the 149 (95 + 20 + 34) articles was assessed independently by 2 authors who used the 2017 AAN Clinical Practice Guideline Process Manual criteria.[15] Any disagreements were reconciled to achieve a final classification. Sixteen of the 149 articles were rejected during the risk of bias classification or because they were deemed not pertinent to our clinical questions or our inclusion/exclusion criteria.

We included only Class I and Class II studies. Where possible, we used outcomes and outcome measures that were prespecified in the articles as the primary outcomes of interest. Otherwise, we used outcomes and outcome measures in the same domain as the prespecified primary outcome. When articles reported outcomes at multiple time points, we used the final time point. When articles reported outcomes for different doses of a medication, we pooled the outcomes for all doses into a single measure because no significant differences were observed for lower compared with higher doses of a medication within the same trial. All effect sizes were converted to a standardized mean difference (SMD). We considered an absolute value of 0.2, 0.5, and 0.8 as thresholds for small, medium, and large effect sizes, respectively.

These effect size values were entered into AAN's synthesis tool to calculate a random-effects meta-analysis. The tool also automates implementation of a modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. Because the presence of a robust placebo response is expected in randomized placebo-controlled trials with pain outcomes, we systematically reviewed the placebo response for all included trials. We manually downgraded the directness rating by 1 level for articles in which the group that received placebo showed pain improvement of <10% but >5% and by 2 levels for pain improvement of ≤5%.

For each analysis performed, the synthesis tool generates a clinically relevant conclusion, along with a level of confidence about the conclusion. These conclusions were used to inform our final conclusions and recommendations, which were harmonized via a modified Delphi process to achieve at least an 80% consensus.

We prespecified 5 oral medication classes to evaluate: gabapentinoids (such as gabapentin and pregabalin), serotonin-norepinephrine reuptake inhibitors (SNRIs) (such as duloxetine, venlafaxine, and desvenlafaxine), tricyclic antidepressants (TCAs) (such as amitriptyline, nortriptyline, imipramine), sodium channel blockers (such as carbamazepine, oxcarbazepine, lamotrigine, valproic acid, lacosamide), and SNRI/opioid dual mechanism agents (such as tramadol and tapentadol). Of note, defining sodium channel blockers as a class is more difficult than other medication classes. The medications above were chosen a priori by the author panel. Topiramate was not included as a sodium channel blocker because it has several mechanisms of action. Of note, no new studies of topiramate were identified since the 2011 guideline.

The panel formulated a rationale for recommendations based on the evidence systematically reviewed and stipulated axiomatic principles of care. This rationale is an explanatory section that precedes each recommendation statement or set of recommendation statements. From this rationale, corresponding actionable recommendation statements were developed. The level of obligation of the recommendations was assigned using a modified Delphi process. "Must" corresponds to Level A, very strong recommendations; "should" to Level B, strong recommendations; and "may" to Level C, weak recommendations.

Analysis of Evidence

A summary of the analysis is provided in the following. The full-length update, including a more detailed description of the analytic process, can be viewed at aan.com/Guidelines/home/GuidelineDetail/1038.

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?

Tables 1–3 include study dosage and duration data, individual medication efficacy data, and efficacy data by drug class (Figure).

Gabapentinoids

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).

Gabapentinoid Class Effect

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%.

Serotonin-Norepinephrine Reuptake Inhibitors

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).

SNRI Class Effect

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%.

Tricyclic Antidepressants

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).

Table 1 Medication Dosage and Duration Information

Medication class	Medication	Dosage, mg/d	Duration, wk
SNRI	Duloxetine	40–60	12
SNRI	Venlafaxine	150–225	6
SNRI	Desvenlafaxine	200	13
Gabapentinoid	Gabapentin	900–3,600	4–8
Gabapentinoid	Pregabalin	300–600	5–12
Gabapentinoid	Mirogabalin	15–30	5
Sodium channel antagonist	Oxcarbazepine	1,400–1,800	16
Sodium channel antagonist	Lamotrigine	200–400	6
Sodium channel Antagonist	Lacosamide	400	12
Sodium channel blocker	Valproic acid	1,000–1,200 or 20 mg/kg/d	4–12
TCA	Amitriptyline	75–150	6
Capsaicin	Capsaicin	8% for 30 min/ application or 0.075% 4 times per day	12

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

TCA Class Effect

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%.

Sodium Channel Blockers

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).

Sodium Channel Blocker Class Effect

Five Class II studies were included for medications 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%.

SNRI/Opioid Dual Mechanism Agents

Tapentadol is possibly more likely than placebo to improve pain (SMD 0.78; 95% CI, 0.54–1.03; medium effect, low confidence; 1 Class II study).

SNRI/Opioid Class Effect

Four Class II studies[30-33] were identified for medications of this class, including 3 tramadol studies from the systematic review of the 2011 guideline.[11] SNRI/opioid dual mechanism agents are probably more likely than placebo to improve pain (SMD 0.62; 95% CI, 0.38–0.86; medium effect, moderate confidence; 4 Class II studies). The I^2 value for heterogeneity was 59%.

Class Effect Sizes

Gabapentinoids (SMD 0.44; 95% CI, 0.21–0.67), SNRIs (SMD 0.47; 95% CI, 0.34–0.60), sodium channel blockers (SMD 0.56; 95% CI, 0.25–0.87), and SNRI/opioid dual mechanism agents (SMD 0.62; 95% CI, 0.38–0.86) all have comparable effect sizes just above or just below our cutoff for a medium effect size (SMD 0.5) (Figure). Although TCAs (SMD 0.95; 95% CI, 0.15–1.5) may have a large effect size, this result is tempered by a low confidence in the estimate.

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).

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).

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-5′-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

Table 2 Efficacy of Oral and Topical Medications

Comparison	SMD[a]	LCL	UCL	Number of articles	Class
ABT 639/placebo	−0.04	−0.41	0.32	1	I
ABT 894/placebo	−0.06	−0.24	0.13	1	I
Amitriptyline/ gabapentin	0.33	−0.32	0.98	1	II
Amitriptyline/ placebo[b]	0.95	0.15	1.76	4	I and II
ASP8477/placebo	0.01	−0.47	0.48	1	II
AZD2423/placebo[b,c]	−0.45	−0.87	−0.04	1	II
Buprenorphine/ placebo	0.23	−0.09	0.55	1	II
Capsaicin/placebo[b]	0.30	0.14	0.47	2	I and II
***Citrullus colocynthis*/ placebo[b]**	0.91	0.36	1.45	1	II
Desvenlafaxine/ placebo[b]	0.25	0.07	0.43	1	II
Dextromethorphan + quinidine/placebo	0.69	−0.03	1.41	1	II
Duloxetine/ nortriptyline[b]	1.64	0.63	2.65	1	II
Duloxetine/placebo[b]	0.50	0.26	0.74	7	I and II
Epalrestat sustained release/epalrestat immediate release	0.25	−0.14	0.64	1	II
Filorexant/placebo	0.21	−0.36	0.79	1	II
Gabapentin/placebo[b]	0.53	0.22	0.84	1	I
γ-Linolenic acid/ α-lipoic acid	0.34	−0.12	0.80	1	II
***Gingko biloba*/placebo[b]**	0.83	0.48	1.18	1	II
Glyceryl trinitrate + valproate/placebo[b]	1.14	0.52	1.77	1	II
Glyceryl trinitrate/ placebo[b]	1.19	0.55	1.83	1	II
Pregabalin or duloxetine/ combination of both drugs	−0.10	−0.33	0.13	1	II
Lacosamide/placebo[b]	0.28	0.15	0.41	2	II
Metanx/placebo	−0.43	−0.86	0.001	1	II
Mirogabalin/placebo[b]	0.31	0.07	0.55	1	II
Mirogabalin/ pregabalin[b]	0.40	0.08	0.72	1	II
Nabilone/placebo[b]	1.32	0.52	2.13	1	I
Nitrosense/placebo[b]	0.59	0.03	1.15	1	II
Nutmeg extract/ placebo	−0.01	−0.46	0.44	1	II
PF-05089771/ placebo	0.34	−0.10	0.77	1	I
Pregabalin/placebo[b]	0.32	0.14	0.50	14	I and II
Pregabalin/ venlafaxine[b]	0.84	0.48	1.20	1	I
Pregabalin/ carbamazepine[b]	0.86	0.50	1.21	1	I
Pregabalin and N-acetylcysteine/ pregabalin alone[b]	1.00	0.56	1.44	1	II
Tanezumab/placebo[b]	0.47	0.001	0.93	1	II
Tapentadol/placebo[b]	0.78	0.54	1.03	1	II
Tocotrienols/placebo	0.09	−0.14	0.32	1	II
Clonidine/placebo	0.29	−0.01	0.58	1	II
Valproic acid/placebo[b]	0.86	0.38	1.33	3	II
Venlafaxine/ carbamazepine	−0.02	−0.32	0.35	1	I

Abbreviations: LCL = lower confidence limit; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants; UCL = upper confidence limit.
[a] SMD >0 indicates intervention is clinically better than comparator.
[b] $p < 0.05$.
[c] Placebo more efficacious.

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).

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 whether mirogabalin 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).

Table 3 Efficacy of Oral Medications for Painful Diabetic Neuropathy by Class Effect

Medication class	SMD[a]	LCL	UCL	Number of articles	Number of patients	Conclusion	Confidence
Gabapentinoids	0.44	0.25	0.63	16	3,550	Probably more likely than placebo to improve pain	Moderate
Sodium channel blocker	0.56	0.25	0.87	5	566	Probably more likely than placebo to improve pain	Moderate
SNRI	0.47	0.34	0.60	9	1,884	Probably more likely than placebo to improve pain	Moderate
SNRI-opioid	0.62	0.38	0.86	4	775	Probably more likely than placebo to improve pain	Moderate
TCA	0.95	0.15	1.75	3	139	Possibly more likely than placebo to improve pain	Low

Abbreviations: LCL = lower confidence limit; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants; UCL = upper confidence limit.
[a] SMD >0 indicates intervention is clinically better than placebo.

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).

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).

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?

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).

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

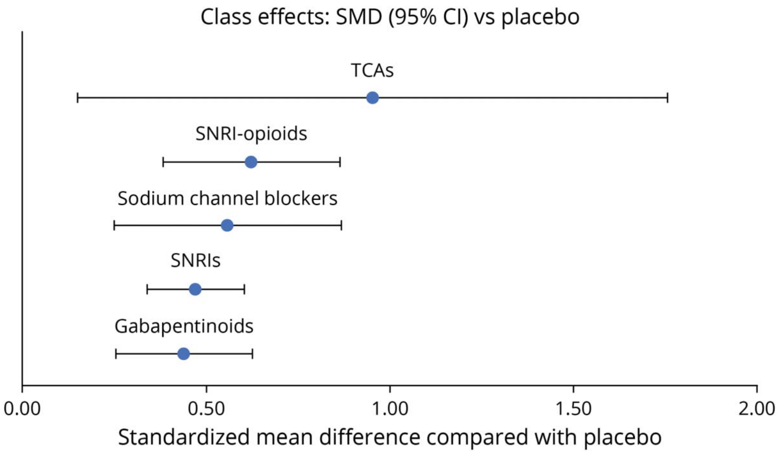
Metaregression revealed no significant association between sex and pain reduction (slope for proportion male sex; SMD 0.01; 95% CI, −0.02 to 0.05).

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,

Figure Class Effects for the Most Well-Studied Oral Treatments of Painful Diabetic Polyneuropathy



The effects of different oral medication classes on painful diabetic neuropathy including gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, SNRI/opioid dual mechanism agents, and tricyclic antidepressants (TCAs). CI = confidence interval; SMD = standardized mean difference.

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.

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).

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.

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).

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.

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).

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.

Recommendation Statement 4

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

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]

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).

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.

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).

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.

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).

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]

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).

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 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.

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.

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Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships is conducted in compliance with the 2017 AAN process manual section titled "Implementing the AAN Conflict of Interest Policy for Guidelines and Case Definitions," which can be viewed at aan.com.

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Don Smith, MD	Department of Neurology, University of Colorado, Aurora	Study concept and design; acquisition of data; analysis or interpretation of data; drafting/revising the manuscript; and critical revision of the manuscript for important intellectual content
Gary Franklin, MD, MPH	Department of Neurology, University of Washington, Seattle	Acquisition of data; analysis or interpretation of data; and critical revision of the manuscript for important intellectual content
Gary Gronseth, MD	Department of Neurology, University of Kansas Medical Center, Kansas City	Analysis or interpretation of data; and critical revision of the manuscript for important intellectual content
Michael Pignone, MD, MPH	Department of Internal Medicine, The University of Texas at Austin Dell Medical School	Study concept and design; analysis or interpretation of data; and critical revision of the manuscript for important intellectual content
William S. David, MD, PhD	Department of Neurology, Massachusetts General Hospital, Boston	Study concept and design; analysis or interpretation of data; and critical revision of the manuscript for important intellectual content
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Vera Bril, MD	Division of Neurology, Department of Medicine, Toronto General Hospital, Canada	Study concept and design; analysis or interpretation of data; and critical revision of the manuscript for important intellectual content
Alexander Rae-Grant, MD	Professor Emeritus, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, OH	Analysis or interpretation of data; and critical revision of the manuscript for important intellectual content

Continued

Appendix (continued)

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