Oral and topical treatment of painful diabetic polyneuropathy practice guideline update

Report of the Guideline Subcommittee of the American Academy of Neurology

Authors

Raymond Price, MD[1], Don Smith, MD[2], Gary Franklin, MD, MPH[3], Gary Gronseth, MD[4], Michael Pignone, MD, MPH[5], William S. David, MD, PhD[6], Carmel Armon, MD, MSc, MHS[7], Bruce A. Perkins, MD, MPH[8], Vera Bril, MD[9], Alexander Rae-Grant, MD[10], John Halperin, MD[11], Nicole Licking, DO[12], Mary Dolan O'Brien, MLIS[13], Scott R. Wessels, MPS, ELS[13], Leslie C. MacGregor, PhD, VMD, JD[14], Kenneth Fink, MD, MPH[15], Lawrence B. Harkless, DPM[16], Lindsay Colbert, MA[17], Brian C. Callaghan, MD, MS[18]

1. Department of Neurology, University of Pennsylvania, Philadelphia
2. Department of Neurology, University of Colorado, Aurora
3. Department of Neurology, University of Washington, Seattle
4. Department of Neurology, University of Kansas Medical Center, Kansas City
5. Department of Internal Medicine, The University of Texas at Austin Dell Medical School
6. Department of Neurology, Massachusetts General Hospital, Boston
7. Department of Neurology, Tel Aviv University Sackler School of Medicine and Shamir (Assaf Harofeh) Medical Center, Israel
8. Leadership Sinai Centre for Diabetes, Sinai Health System, University of Toronto, ON, Canada
9. Division of Neurology, Department of Medicine, Toronto General Hospital, ON, Canada
10. Professor Emeritus, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, OH
11. Department of Neurosciences, Overlook Medical Center, Summit, NJ
12. New West Physicians, Golden, CO
13. American Academy of Neurology, Minneapolis, MN

14. Neuropathy Action Foundation, Santa Ana, CA

15. Kamehameha Schools, Honolulu, HI

16. University of Texas Rio Grande Valley School of Podiatric Medicine, Edinburg

17. The Foundation for Peripheral Neuropathy, Buffalo Grove, IL

18. Department of Neurology, University of Michigan, Ann Arbor

Address correspondence and reprint requests to

American Academy of Neurology:

guidelines@aan.com

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DISCLOSURE

R. Price has received honoraria for a collaboration between Critical Thinking and Grifols; serves as codirector of and has received honoraria for organization and lecturing for a Penn Neurology Board Review Course; and has given expert testimony in 2 cases regarding etiology, diagnosis, and management of foot pain, sensory loss, and weakness.

D. Smith is a paid evidence-based medicine consultant for the American Academy of Neurology (AAN).

G. Franklin serves on a scientific advisory board for Workers' Compensation Research Institute, serves as an editorial board member for Neuroepidemiology, serves as a reviewer for Neurology, serves on the editorial board for Evidence Review, and has received research funding from Centers for Disease Control and Prevention (CDC), Patient-Centered Outcomes Research Institute (PCORI), Washington State Department of Labor, and Mathematica.

G. Gronseth has received travel funding from the AAN to attend Guideline Subcommittee meetings, serves as an associate editor for *Neurology*, has served as chief evidence-based medicine consultant for the AAN, and serves as an editorial advisory board member of *Brain & Life*.

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W. David has received royalties for a continuing medical education (CME) video course on EMG/neuromuscular medicine, performs EMG in practice, and has served as a consultant for Flex Pharma.

C. Armon serves as associate editor for the *Journal of the Neurological Sciences*; has received royalties from publishing from UpToDate and Medscape; has provided expert testimony in personal injury and medical-legal cases; and has acted as a neurology consultant for Inbal, Inc. (the Israeli Government Insurance Agency).

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V. Bril serves on scientific advisory boards for CSL Behring, USB, and Pfizer; has received honoraria from CSL Behring, USB, and Pfizer; has received research support from UCB, Grifols, CSL Behring, Octapharma, Argenx, Muscular Dystrophy Canada, CIDP/GBS Foundation, Myasthenia Gravis Foundation of America, and the NIDDK; and has participated in the development of an American Diabetes Association position statement on painful diabetic neuropathy and of a Canadian Diabetes Association clinical practice guideline on diabetic neuropathy.

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M. Dolan O'Brien is an employee of the AAN.

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K. Fink serves on the American Academy of Family Physician's Commission on Health of the Public & Science (AAFP CHPS), has received funding for travel to attend AAFP CHPS meetings, and has received compensation for consulting services that are typically related to Medicaid.

L. Harkless has served on scientific advisory boards for Genetech and Next Science; has received honoraria from Genentech, NextScience, and the Texas Podiatric Medical Society; holds stock in Metric Medical, and Mr3Health; has received funding from the International Diabetes Foundation, and honoraria from Mississippi Podiatric Medical Society, and North Carolina Podiatric Medical Society; has given expert deposition on a nonhealing wound; and has given expert opinion on a medical record regarding diabetes.

L. Colbert reports no disclosures relevant to the manuscript.

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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

CV: curriculum vitae

DEA: Drug Enforcement Administration

FDA: Food and Drug Administration

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

GS: Guideline Subcommittee

SMD: standardized mean difference

SNRI: serotonin-norepinephrine reuptake inhibitor

TCA: tricyclic antidepressants

ABSTRACT

Objective: To update the 2011 AAN guideline on the treatment of painful diabetic neuropathy 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 American Academy of Neurology 2017 Clinical Practice Guideline Process Manual.

Results: Gabapentinoids (standardized mean difference [SMD] 0.44; 95% confidence interval [CI], 0.25–0.63), 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). While tricyclic antidepressants [TCAs] (SMD 0.95; 95% CI, 0.15–1.8) may have a large effect size, this result is tempered by a low confidence in the estimate.

Recommendations summary: Clinicians should assess patients with diabetes for peripheral neuropathic pain (Level B) and those with painful diabetic neuropathy for concurrent mood and sleep disorders (Level B). In patients with painful diabetic neuropathy, 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 painful diabetic neuropathy (Level B).

INTRODUCTION

Peripheral neuropathy affects 2–7% of the general population and has an even higher prevalence in people older than 40 years.[1, 2] Diabetes is the most common cause in the United States, accounting for 32–53% of cases.[3-6]

The prevalence of neuropathy in people with type 1 and type 2 diabetes is 8–34%.[7] Painful diabetic neuropathy 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.[8] Painful diabetic neuropathy, even compared with painless neuropathy, negatively affects physical and mental quality of life.[9]

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.[10] Out of 14,426 patients with peripheral neuropathy, 66% received at least 1 opioid prescription, and 9% received long-term opioid therapy. Only 12% of patients received prescriptions for more than 1 neuropathic pain medication other than opioids. 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.[11,12] According to the CDC, opioid overdose deaths have accelerated during the pandemic, highlighting the importance of appropriate prescribing.[13] The purpose of this guideline is to systematically review all randomized controlled trials of oral and topical medications for painful diabetic neuropathy. We aimed to update a 2011 AAN guideline on the treatment of painful diabetic neuropathy[14] 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 painful diabetic neuropathy and to highlight the alternatives to opioid use in this population. Furthermore, we aimed to evaluate the effects of different medication classes on painful diabetic neuropathy, whereas most previous guidelines and systematic reviews have focused solely on individual medications.[14-17] 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. Overall, the goal of this systematic review is to provide physicians and patients with information on the

evidence for and against different neuropathic pain medications to inform shared decision making. We chose to focus this guideline on oral and topical medications for painful diabetic neuropathy, but it is important to note that other interventions are also available. Specifically, this guideline seeks to answer the following questions: 1) 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? and 2) 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?

DESCRIPTION OF THE ANALYTIC PROCESS

In November 2017, the Guideline Subcommittee (GS) of the AAN convened a panel of clinicians with expertise in painful diabetic polyneuropathy (see appendices 1 and 2 for a listing of the mission and members of the AAN GS). The panel included content experts (C.A., V.B., L.C., W.S.D., K.F., L.B.H., L.C. M., B.A.P., M.P., R.P.), methodology experts (G.G., D.S.), AAN GS members (B.C.C., J.H., N.L., A.R.G.), and patient advocates/representatives (L.C., L.C.M.). Each potential author was required to submit an AAN relationship disclosure form and a copy of his or her curriculum vitae (CV). The panel leadership, consisting of the lead developer (B.C.C.), the AAN methodologists (G.G., D.S.), the AAN staff person (M.D.O.), and Guideline Subcommittee leadership reviewed the relationship disclosure forms and CVs for financial and intellectual conflicts of interest (COI). These documents were specifically screened to exclude those individuals with a clear financial conflict and those whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended users. As required by the AAN, a majority (82%) of the members (C.A., L.C., W.S.D., K.F., G.F., G.G., J.H., L.C.M., N.L., M.P., R.P., A.R.G., D.S.) of the development panel and the lead author (B.C.C.) are free of COI 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. Rather, these 3 developers were not permitted to review or

rate the evidence. These individuals served 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 to validate the literature search. The panel members with COI were allowed to participate in the recommendation development process. This author panel was solely responsible for the final decisions about the design, analysis, and reporting of the systematic review and subsequent practice guideline based on that systematic review.

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 (see appendix 3 for search strategies). The 2011 AAN painful diabetic neuropathy guideline searched 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. Cohort studies, case series, and case-control studies were excluded, as were studies with 20 or fewer participants. Also excluded were studies not relevant to the clinical questions, studies including participants who had unrelated diseases or were outside of the study population, and articles that were not peer reviewed.

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.[18] 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.

Of these 149 articles, 133 were found to have quantifiable data pertinent to 1 or more of our PICO questions. From these 133 articles, 351 effect sizes were abstracted by 1 methodologist (D.S.) into data rows of a spreadsheet. These data rows were defined by a unique combination of article, PICO question, intervention, comparator, outcome measure, and timing of the outcome measure. Of the 351 effect sizes, 89 were used in the data synthesis. Each of these data rows were checked for error by 1 of 4 authors (B.C., J.H., N.L., and A.R.G.). We used prespecified rules for selecting data rows for data synthesis from the 351 available data rows. 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. We decided to pool outcomes rather than split them out individually because no significant differences were observed for lower compared with higher doses of a medication within the same trial, and this allowed our meta-analysis to only use 1 data point for each 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. It incorporates consideration of various parameters of risk of bias, consistency, directness, precision, and publication bias. Since 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%. For articles that showed pain

improvement in the group that received placebo to be ≤5%, directness was downgraded 2 levels. Effect sizes, measures, and internal/external validity are included in the evidence tables in appendices 4.

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.

Our prespecified rules for deciding which data should be included in computing the SMD between an intervention and a comparator treatment were designed to assure that we used the highest class of evidence that provided the conclusion with the highest level of confidence, at the greatest precision of the effect size estimate. Following these rules, 89 effect sizes, from 58 articles, were used in the data synthesis.

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.

A modified form of the GRADE process was used to develop conclusions. In this process, the evidence is analyzed on the basis of various parameters of risk of bias (multiple types), consistency, directness, precision, and publication bias. This process permits transparency in the upgrading or downgrading of evidence classification.

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 that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of benefit to harm. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments regarding the importance of outcomes, cost of compliance with the recommendation in relation to benefit, the availability of the intervention, and anticipated variations in patients' preferences. The level of obligation was indicated using standard modal operators. "Must" corresponds to Level A, very strong recommendations; "should" to Level B, strong recommendations; and "may" to Level C, weak recommendations (appendix 5).

ANALYSIS OF EVIDENCE

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, 2, and 3 include study dosage and duration data, individual medication efficacy data, and efficacy data by drug class (figure 1).

Gabapentinoids

Gabapentin

One Class I[19] and 4 Class II studies[20-23] were identified, including 2 new studies since the systematic review for the 2011 guideline[14] was performed. In the Class I study, participants were randomized to gabapentin (n = 82) titrated from 900 to 3,600 mg/d or maximum tolerated dose vs placebo (n = 80).[19] At 8 weeks, a significant medium reduction in pain was observed compared with placebo (SMD 0.53; 95% confidence interval [CI], 0.22–0.84). Adverse events reported in these 5 studies include dizziness, somnolence, abdominal pain, asthenia, body odor, headache, diarrhea, abnormal thinking, nausea, confusion, hypesthesia, drowsiness, fatigue, and

imbalance. Including the Class II studies in a meta-analysis decreased the precision of the estimate; therefore, the conclusion was based solely on the 1 Class I study.

Conclusion: gabapentin is probably more likely than placebo to improve pain (SMD 0.53; 95% CI, 0.22–0.84; medium effect, moderate confidence; 1 Class I study).

Pregabalin

Eight Class I[24-31] and 7 Class II studies[22, 32-37] were identified, including 11 new studies since the systematic review for the 2011 guideline[14] was performed. In the 15 studies, participants were randomized to a range of pregabalin doses from 150 to 600 mg/d (n = 2,076) compared with placebo (n =1,682) and followed for a range of 4–13 weeks. Adverse events included dizziness, somnolence, peripheral edema, weight gain, and balance disorder. Including Class I and Class II studies, 6 studies revealed a SMD CI that did not include 0, whereas the other 9 studies did include 0. Overall, a significant small reduction in pain was observed when combining all studies (SMD 0.29; 95% CI, 0.13–0.45).

Conclusion: 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

Two new Class II studies included 557 participants randomized to mirogabalin and 200 to placebo.[36,37] Doses from 5 to 30 mg/d were used, and pain was measured at 5 and 7 weeks, respectively. A significant small reduction in pain was observed (SMD 0.21; 95% CI, 0.02–0.40). Adverse events included dizziness and somnolence.

Conclusion: 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

8 Class I[19,24, 26-31] and 8 Class II[21-23, 32,33, 35-37] studies were included for medications of this class. Four studies used gabapentin, 2 used mirogabalin, and 10 used pregabalin (some studies evaluated more than 1 intervention). The meta-analysis of these studies showed that this class of medication provided a reduction in pain, as compared to placebo: SMD 0.44; 95% CI, 0.25–0.63).

Conclusion: 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%.

SNRIs

Duloxetine

Two Class I[38, 39] and 5 Class II studies[32, 40-43] were identified, including 4 new studies since the systematic review for the 2011 guideline[14] was performed. In the 7 studies, participants were randomized to duloxetine doses from 40 to 120 mg/d (n = 978) compared with placebo (n = 699) and followed for a range of 4–12 weeks. Adverse events included nausea, somnolence, anorexia, dysuria, dizziness, and fatigue. Five studies revealed a SMD CI that did not include 0, whereas the other 2 studies did include 0. Overall, a significant moderate reduction in pain was observed when combining all studies (SMD 0.50; 95% CI, 0.26–0.74).

Conclusion: 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

One new Class II study reported 318 participants randomized to desvenlafaxine and 90 to placebo.[44] Doses from 50 to 400 mg/d were used, and pain was measured at 13 weeks. A significant small reduction in pain was observed (SMD 0.25; 95% CI, 0.07–0.43). Adverse events included nausea and dizziness.

Conclusion: 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[38, 39, 45] and 6 Class II studies[32, 40-44] were included for medications of this class, including 1 venlafaxine, 1 for desvenlafaxine, and 7 for duloxetine. For the class, there was a significant small reduction in pain (SMD 0.47; 95% CI, 0.34–0.60).

Conclusion: 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%.

TCAs

Amitriptyline

One Class I[46] and 2 Class II studies[32, 47] were identified, including 1 new Class II study. In the new Class II study, participants were randomized to amitriptyline (n = 23) 75 mg/d vs placebo (n = 24).[32] At 4 weeks, no significant reduction in pain was observed compared with placebo (SMD 0.45; 95% CI, -0.11 to 1.02). Inclusion of all studies (amitriptyline n = 71, placebo n = 72) revealed a significant large reduction in pain (SMD 0.95; 95% CI, 0.15–1.8). Adverse events reported in these 4 studies include dry mouth, sedation,

dizziness, constipation, depression, tinnitus, urinary hesitancy, urinary frequency, jitteriness, leg weakness, muscle cramps, unsteadiness, and itching.

Conclusion: 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).

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.

Conclusion: 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

Three Class II studies[48-50] were identified, including 1 new Class II study.[48] In the most recently published Class II study, participants were randomized to valproic acid (n = 20) 20 mg/kg/d vs placebo (n = 21). At 3 months, no significant reduction in pain was observed compared with placebo (SMD 0.59; 95% CI, -0.02 to 1.19). Inclusion of all studies (valproic acid n = 69, placebo n = 63) revealed a significant large reduction in pain (SMD 0.86; 95% CI, 0.38–1.33). Of note, all 3 studies were downgraded secondary to lack of a robust placebo response (2 severe and 1 moderate problems with indirectness rating). Adverse events reported in these 3 studies include elevated aspartate aminotransferase/alanine aminotransferase levels.

Conclusion: 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,[51] 2 lacosamide,[52, 53] 1 oxcarbazepine[54] and 1 valproic acid.[49] For this class, there was a medium-sized reduction in pain (SMD 0.56; 95% CI, 0.25–0.87).

Conclusion: 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

One new Class II study reported on 133 participants randomized to tapentadol and 131 to placebo.[55] Doses from 100 to 250 mg twice per day were used, and pain was measured at 12 weeks. A significant medium reduction in pain was observed (SMD 0.78; 95% CI, 0.54–1.03). Adverse events included nausea, anxiety, diarrhea, and dizziness.

Conclusion: 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[55-58] were identified for medications of this class including 3 tramadol studies from the systematic review of the 2011 guideline.[14] Including all studies revealed a significant medium reduction in pain (SMD 0.62; 95% CI, 0.38–0.86).

Conclusion: 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, 0.25 to 0.63), SNRIs (SMD 0.47; 95% CI, 0.34 to 0.60), sodium channel blockers (SMD 0.56; 95% CI, 0.25 to 0.87), and SNRI/opioid dual mechanism agents (SMD 0.62; 95% CI, 0.38 to 0.86) all have comparable effect sizes just above or just below our cutoff for a medium effect size (SMD 0.5) (figure 1). Although TCAs (SMD 0.95; 95% CI, 0.15 to 1.75) may have a large effect size, this result is tempered by a low confidence in the estimate.

Other oral medications

Nabilone (synthetic cannabinoid)

One new Class I study randomized 13 participants to nabilone and 13 to placebo.[59] Doses up to 2 mg twice per day were used, and pain was measured at 5 weeks. A significant large reduction in pain was observed (SMD 1.32; 95% CI, 0.52–2.13). Adverse events included dizziness, dry mouth, drowsiness, confusion, impaired memory, lethargy, euphoria, headache, and increased appetite.

Conclusion: nabilone 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

One new Class II study randomized 62 participants to ginkgo biloba and 72 to placebo.[60] The dose was 120 mg/d, and pain was measured at 6 months. A significant large reduction in pain was observed (SMD 0.83; 95% CI, 0.48–1.18). No adverse events of clinical significance were reported.

Conclusion: 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 (selective voltage-dependent T-type calcium channel blocker, not available)

One new Class I study[31] was identified. In this Class I study, participants were randomized to ABT 639 (n = 57) 50 mg 2 times per day vs placebo (n = 108).[31] At 6 weeks, a significant reduction in pain was not observed (SMD -0.04; 95% CI, -0.41 to 0.32). There were no significant safety issues reported.

Conclusion: ABT 639 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 (nicotinic acetylcholine receptor agonist that is not available)

One new Class I study[39] was conducted. In this Class I study, participants were randomized to ABT 894 (n = 228) at doses of 1 mg, 2 mg, 4 mg, and 6 mg two times per day vs placebo (n = 214).[39] At 8 weeks, a significant reduction in pain was not observed at any of the 4 doses (SMD CIs for all doses included zero). There were no significant safety issues.

Conclusion: ABT 894 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 (orexin antagonist, not available)

One new Class II study was identified that included 87 participants randomized to filorexant and 83 to placebo.[61] A dose of 10 mg per night was used, and pain was measured at 4 weeks. A significant reduction in pain was not observed (SMD 0.21; 95% CI, -0.36 to 0.79). Adverse events included dizziness, depressed mood, nausea, palpitations, chest pain, somnolence, and fatigue.

Conclusion: filorexant 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 (vitamin E family)

One new Class II study reported on 150 participants randomized to tocotrienols and 150 randomized to placebo.[62] A dose of 200 mg twice per day was used, and pain was measured at 52 weeks. No reduction in pain was observed (SMD 0.09; 95% CI, -0.14 to 0.32). Adverse events reported were similar to those for placebo.

Conclusion: tocotrienols 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

One new Class II study[63] was identified. In this Class II study, participants were randomized to nutmeg extract (n = 37) 4 sprays, 3 times per day vs placebo (n = 37).[63] At 4 weeks, no reduction in pain was observed (SMD -0.01; 95% CI, -0.46 to 0.44). The rate of adverse events reported was comparable with placebo.

Conclusion: 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 (L-methylfolate calcium, algae-S powder, pyridoxal-5´-phosphate and methylcobalamin)

One new Class II study[64] was completed. In this Class II study, participants were randomized to Metanx (n = 106) 2 times per day vs placebo (n = 108).[64] At 24 weeks, a significant reduction in pain was not observed (SMD -0.43; 95% CI, -0.86 to 0.001). The rate of adverse events reported was comparable with placebo.

Conclusion: Metanx 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 ($Na_v1.7$ and $Na_v1.8$ voltage-gated sodium channel blocker, not available)

One new Class I study[65] was identified. In this Class I study, participants were randomized to PF-05089771 (n = 41) 150 mg two times per day vs placebo (n = 39).[65] At 4 weeks, a significant reduction in pain was not observed (SMD 0.34; 95% CI, -0.10 to 0.78). Adverse events included constipation, urinary tract infection, back pain, muscle spasms, headache, and polyuria.

Conclusion: PF-05089771 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).

ASP8477 (fatty acid amide hydrolase inhibitor, not available)

One new Class II study[66] was found. In this Class II study, participants were randomized to ASP8477 (n = 33) at doses up to 30 mg two times per day vs placebo (n = 33).[66] At 3 weeks, a significant reduction in pain was not observed (SMD 0.01; 95% CI, -0.47 to 0.48). ASP8477 was well tolerated and had a good safety profile. Of note, there was a lack of a robust placebo response (extreme problem with indirectness rating).

Conclusion: there is insufficient data as to whether ASP8477 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).

Dextromethorphan/quinidine

One new Class II study was identified that included 256 participants randomized to dextromethorphan/quinidine and 123 to placebo.[67] Doses of 30 mg/30 mg and 45 mg/30 mg twice per day were used, and pain was measured at 13 weeks. A significant reduction in pain was not observed (SMD 0.69; 95% CI, -0.03 to 1.41). Adverse events included dizziness, nausea, diarrhea, headache, fatigue, somnolence, and insomnia.

Conclusion: 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

One new Class II study[68] was completed. In this Class II study, participants were randomized to AZD2423 (n = 90) either 20 mg daily or 150 mg daily vs placebo (n = 90).[68] At 4 weeks, a significant reduction in pain was not observed at either dose (SMD -0.45; 95% CI, -0.87 to 0.04). Adverse events included headaches, dizziness, nausea, and pyrexia.

Conclusion: 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 vs carbamazepine

One new Class I study[69] was identified. In this Class I study, participants were randomized to pregabalin (n = 86) 150 mg/d vs carbamazepine (n = 85) 400 mg daily.[69] At 5 weeks, a significant large difference in the reduction of pain with pregabalin compared with carbamazepine was observed (SMD 0.86; 95% CI, 0.50–1.21).

Conclusion: 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 vs carbamazepine

One Class I[69] and 1 Class II study[70] were completed, including 1 new Class I study. In the new Class I study, participants were randomized to venlafaxine (n = 86) 150 mg/d vs carbamazepine (n = 85) 400 mg daily.[69] At 5 weeks, no difference in reduction in pain between agents was observed (SMD -0.02; 95% CI, -0.32 to 0.35). Similarly, including both studies (venlafaxine n=150, carbamazepine n=150) a significant difference in the reduction of pain was also not observed (SMD 0.29; 95% CI, -0.26 to 0.85).

Conclusion: 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).

Mirogabalin vs Pregabalin

Two new Class II studies[36,37] were identified. In these 2 studies, participants were randomized to mirogabalin (n = 557) at doses from 5 to 30 mg/d vs pregabalin (n = 141) 300 mg daily.[36,37] These 2 studies demonstrated that no significant reduction in pain comparing mirogabalin with pregabalin was observed after 5–7 weeks (SMD 0.23; 95% CI, -0.05 to 0.52).

Conclusion: 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 vs venlafaxine

One new Class I study[69] was found. In this Class I study, participants were randomized to pregabalin (n = 86) 150 mg daily or venlafaxine (n = 69) 150 mg daily.[69] At 5 weeks, a significant large reduction in pain favoring pregabalin compared with venlafaxine was observed (SMD 0.84; 95% CI, 0.48–1.20).

Conclusion: 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 vs gabapentin

One Class II study[71] was identified from the previous systematic review. In this Class II study, participants were randomized to amitriptyline (n = 21) up to 75 mg daily vs gabapentin (n = 21) up to 1,800 mg daily.[71] At 6 weeks, a significant difference in the reduction in pain was not observed (SMD 0.33; 95% CI, -0.32 to 0.98).

Conclusion: 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).

Pregabalin or duloxetine vs a combination of both drugs

One new Class II study[72] was completed. In this Class II study, participants were randomized to duloxetine 120 mg/d or pregabalin 600 mg/d (n = 149) vs the combination of pregabalin 300 mg/d and duloxetine 60 /d (n = 141).[72] At 8 weeks, a significant reduction in pain was not observed (SMD -0.10; 95% CI, -0.33 to 0.13).

Conclusion: 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 vs nortriptyline

One new Class II study[73] was identified. In this Class II study, participants were randomized to duloxetine (n = 61) 30–60 mg daily vs nortriptyline (n = 57) 25–75 mg/d.[73] At 6 weeks, a significant large reduction in pain favoring duloxetine compared with nortriptyline was observed (SMD 1.64; 95% CI, 0.63–2.65).

Conclusion: 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 vs pregabalin alone

One new Class II study[74] was identified. In this Class II study, participants were randomized to pregabalin (150 mg/d) and N-acetylcysteine (600 mg twice per day) (n = 43) vs pregabalin alone (n = 47) 150 mg/d. At 8 weeks, a significant large reduction in pain favoring pregabalin and N-acetylcysteine compared with pregabalin alone was observed (SMD 1.00; 95% CI, 0.56–1.44).

Conclusion: 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 vs α-lipoic acid

One new Class II study[75] was identified. In this Class II study, participants were randomized to γ-linolenic acid (n = 35) 320 mg daily vs α-lipoic acid (n = 38) 600 mg/d. At 12 weeks, a significant difference in pain reduction was not observed (SMD 0.34; 95% CI, -0.12 to 0.80).

Conclusion: 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 vs epalrestat immediate release

One new Class II study[76] was identified. In this Class II study, participants were randomized to epalrestat sustained release (n = 50) 150 mg daily vs epalrestat immediate release (n = 50) 50 mg three times per day. At 12 weeks, no significant difference in pain reduction was observed (SMD 0.25; 95% CI, -0.14 to 0.64).

Conclusion: 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

Glyceryl trinitrate spray and valproic acid

One new Class II study[48] was identified. In this Class II study, participants were randomized to valproic acid 20 mg/kg/d and glyceryl trinitrate spray 0.4 mg/d (n = 22) vs placebo (n = 21).[48] At 3 months, a significant large reduction in pain was observed compared with placebo (SMD 1.14; 95% CI, 0.52–1.77).

Conclusion: 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).

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

One Class I[77] and 1 Class II study[78] were identified, including 1 new Class I study. In the new Class I study, participants were randomized to capsaicin (n = 186) 8% applied for 30 minutes for 1 application versus placebo (n = 183).[77] At 12 weeks, a significant small reduction in pain was observed compared with placebo (SMD 0.25; 95% CI, 0.05–0.45). Inclusion of all studies (capsaicin n = 277, placebo n = 294) revealed a significant small reduction in pain (SMD 0.30; 95% CI, 0.14–0.47). The only adverse events reported in these 2 studies were application site reactions.

Conclusion: topical 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

One new Class II study[79] was completed. In this Class II study, participants were randomized to 1 nitrosense patch (n = 24) applied every other day vs placebo (n = 24).[79] At 3 weeks, a significant medium reduction in pain was observed compared with placebo (SMD 0.59; 95% CI, 0.03–1.15). The only adverse events reported in this study were application site skin reactions.

Conclusion: 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

One new Class II study was identified that included 28 participants randomized to *Citrullus colocynthis* and 27 randomized to placebo.[80] The intervention was applied to the feet twice daily and pain was measured at 12 weeks. A significant large reduction in pain was observed compared with placebo (SMD 0.91; 95% CI, 0.36–1.45). No adverse events of clinical significance were reported.

Conclusion: *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

One new Class II study[48] was found. In this Class II study, participants were randomized to glyceryl trinitrate spray 0.4 mg/d (n = 20) vs placebo (n = 21).[48] At 3 months, a significant large reduction in pain was observed compared with placebo (SMD 1.19; 95% CI, 0.55–1.83).

Conclusion: 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

One new Class II study[81] was identified. In this Class II study, participants were randomized to 1 pump from the mechanical dispensing bottle of clonidine (n = 89) applied three times per day vs placebo (n = 90).[81] At 12 weeks, a significant reduction in pain was not observed (SMD 0.29; 95% CI, -0.01 to 0.58). There were no significant adverse events reported.

Conclusion: 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 patch

One new Class II study randomized 89 participants to buprenorphine transdermal patches and 92 to placebo.[82] Patches delivering up to 40 µg/h were used, and pain was measured at 12 weeks. A significant reduction in pain

was not observed (SMD 0.23; 95% CI, -0.09 to 0.55). Adverse events included nausea, vomiting, and constipation.

Conclusion: 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

Meta regression revealed no significant association between age and pain reduction (slope for age; SMD 0.001; 95% CI, -0.10 to 0.11[see figure 2]).

Sex

Meta regression revealed no significant association between sex and pain reduction (slope for proportion male sex; SMD 0.01; 95% CI, -0.02 to 0.05 [see figure 3]).

PRACTICE 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.[83-85] 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)[86] or effects on quality of life (Norfolk QOL-DN)[87] 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 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.[88] 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 painful diabetic neuropathy, 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 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.[89,90] Mood and sleep can both influence pain perception.[91,92] 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 painful diabetic neuropathy for the presence of concurrent mood and sleep disorders and treat them as appropriate (Level B).

Recommendation 4 rationale

Painful diabetic neuropathy is a highly prevalent condition that greatly affects quality of life.[9] 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 painful diabetic neuropathy, 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,[11,12] 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).[93] Furthermore, there is moderate and consistent evidence for the use of cognitive behavioral therapy (CBT) for many types of chronic pain.[94,95] 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.[96,97]

Recommendation statement 5a

Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for painful diabetic neuropathy (Level C).

Recommendation statement 5b

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) (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 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.[98] 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 painful diabetic neuropathy (Level B).

Recommendation statement 6b

In patients of child-bearing potential with painful diabetic neuropathy, clinicians should not offer valproic acid (Level B).

Recommendation statement 6c

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 (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 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 (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 painful diabetic neuropathy (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.[11,12] 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."[99] 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.[100] 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.[11,12,95,101] Data from the CDC suggests that it is likely that dependence may set in within days to weeks of starting opioids.[102] 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.[103] 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.[99]

Recommendation statement 8a

Clinicians should not use opioids for the treatment of painful diabetic neuropathy (Level B).

Recommendation statement 8b

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 (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 very poor, with

respiratory depression, addiction, and overdose reflected in a Food and Drug Administration (FDA) "black box" warning.[104] A recent study reported an increase in all-cause mortality among patients taking tramadol for osteoarthritis.[105] Although true prevalence is unknown, serotonin syndrome has also been associated with tramadol.[106] The abuse liability in terms of reported abuse events per population are substantial and greater than that for morphine.[107]

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.[108] 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.[107] The efficacy of tramadol and tapentadol for painful neuropathy is only reported in studies of short duration.[109] 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 painful diabetic neuropathy (Level C).

Recommendation statement 9b

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 (Level C).

SUGGESTIONS FOR FUTURE RESEARCH

The current systematic review and guideline provide data on multiple interventions that are effective for the treatment of painful diabetic neuropathy. However, our review has also highlighted 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 1 other intervention; therefore, there are limited data to support 1 therapeutic intervention over another. One exception is the PAIN-CONTRoLS study, which compared 4 active medications for patients with cryptogenic neuropathy.[110] The study found that duloxetine and nortriptyline outperformed pregabalin and mexiletine. Comparable studies in painful diabetic neuropathy are also needed. Similarly, the evidence for combination therapy compared with monotherapy and for the best titration schedule is also 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 if there is any role for these medications in this population. Additionally, 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 currently 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 1 class together, but it is possible that certain medications within a class are better than others. Patients with painful diabetic neuropathy have multiple effective interventions available to them, but hopefully new studies can address our current gaps in knowledge to enable even better treatments for the future.

DISCLAIMER

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AUTHOR CONTRIBUTIONS

Name	Location	Contribution
Raymond Price, MD	Department of Neurology, University of Pennsylvania, Philadelphia	Study concept and design; analysis or interpretation of data; drafting/revising the manuscript; and critical revision of the manuscript for important intellectual content.
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	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	Acquisition of data; 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.
Carmel Armon, MD, MSc, MHS	Department of Neurology, Tel Aviv University Sackler School of Medicine and Shamir (Assaf Harofeh) Medical Center, Israel	Study concept and design; analysis or interpretation of data; and critical revision of the manuscript

		for important intellectual content.
Bruce A. Perkins, MD, MPH	Leadership Sinai Centre for Diabetes, Sinai Health System, University of Toronto, ON, Canada	Study concept and design; analysis or interpretation of data; and critical revision of the manuscript for important intellectual content.
Vera Bril, MD	Division of Neurology, Department of Medicine, Toronto General Hospital, ON, 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.
John Halperin, MD	Department of Neurosciences, Overlook Medical Center, Summit, NJ	Analysis or interpretation of data; and critical revision of the manuscript

		for important intellectual content.
Nicole Licking, DO	New West Physicians, Golden, CO	Analysis or interpretation of data; and critical revision of the manuscript for important intellectual content.
Mary Dolan O'Brien, MLIS	American Academy of Neurology, Minneapolis, MN	Critical revision of the manuscript for important intellectual content.
Scott R. Wessels, MPS, ELS	American Academy of Neurology, Minneapolis, MN	Critical revision of the manuscript for important intellectual content.
Leslie C. MacGregor, PhD, VMD, JD	Neuropathy Action Foundation, Santa Ana, CA	Analysis or interpretation of data; critical revision of the manuscript for important intellectual content.
Kenneth Fink, MD, MPH	Kamehameha Schools, Honolulu, HI	Analysis or interpretation of data; critical revision of the manuscript for important intellectual content.

Lawrence B. Harkless, DPM	University of Texas Rio Grande Valley School of Podiatric Medicine, Edinburg	Analysis or interpretation of data; critical revision of the manuscript for important intellectual content.
Lindsay Colbert, MA	The Foundation for Peripheral Neuropathy, Buffalo Grove, IL	Analysis or interpretation of data; critical revision of the manuscript for important intellectual content.
Brian C. Callaghan, MD, MS	Department of Neurology, University of Michigan, Ann Arbor	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.

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Table 1. Medication dosage and duration information

Medication Class	**Medication**	**Dosage**	**Duration**
SNRI	duloxetine	40–60 mg/d	12 weeks
SNRI	venlafaxine	150–225 mg/d	6 weeks
SNRI	desvenlafaxine	200 mg/d	13 weeks
Gabapentinoid	gabapentin	900–3,600 mg/d	4–8 weeks
Gabapentinoid	pregabalin	300–600 mg/d	5–12 weeks
Gabapentinoid	mirogabalin	15–30 mg/d	5 weeks
Sodium channel antagonist	oxcarbazepine	1,400–1,800 mg/d	16 weeks
Sodium channel antagonist	lamotrigine	200–400 mg/d	6 weeks
Sodium channel Antagonist	lacosamide	400 mg/d	12 weeks
Sodium channel blocker	valproic acid	1,000–1,200 mg/d or 20 mg/kg/d	4–12 weeks
TCA	amitriptyline	75–150 mg/d	6 weeks
Capsaicin	capsaicin	8% for 30 min/application OR	12 weeks

		0.075% 4 times per day	

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

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	0.95	0.15	1.76	4	I & II
ASP8477 | placebo	0.01	-0.47	0.48	1	II
AZD2423 | placebo	-0.45	-0.87	-0.04	1	II
buprenorphine | placebo	0.23	-0.09	0.55	1	II
capsaicin | placebo	0.30	0.14	0.47	2	I & II
Citrullus colocynthis | placebo	0.91	0.36	1.45	1	II
desvenlafaxine | placebo	0.25	0.07	0.43	1	II
dextromethorphan + quinidine | placebo	0.69	-0.03	1.41	1	II
duloxetine | nortriptyline	1.64	0.63	2.65	1	II
duloxetine | placebo	0.50	0.26	0.74	7	I & 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	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	0.83	0.48	1.18	1	II
glyceryl trinitrate + valproate | placebo	1.14	0.52	1.77	1	II
glyceryl trinitrate | placebo	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	0.28	0.15	0.41	2	II
Metanx | placebo	-0.43	-0.86	0.001	1	II
mirogabalin | placebo	0.31	0.07	0.55	1	II
mirogabalin | pregabalin	0.40	0.08	0.72	1	II
nabilone | placebo	1.32	0.52	2.13	1	I
nitrosense | placebo	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	0.32	0.14	0.50	14	I & II
pregabalin | venlafaxine	0.84	0.48	1.20	1	I
pregabalin | carbamazepine	0.86	0.50	1.21	1	I
pregabalin and N-acetylcysteine | pregabalin alone	1.00	0.56	1.44	1	II
tanezumab | placebo	0.47	0.001	0.93	1	II
tapentadol | placebo	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	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; UCL = upper confidence limit; TCA = tricyclic antidepressants

[a] SMD >0 indicates intervention is clinically better than comparator

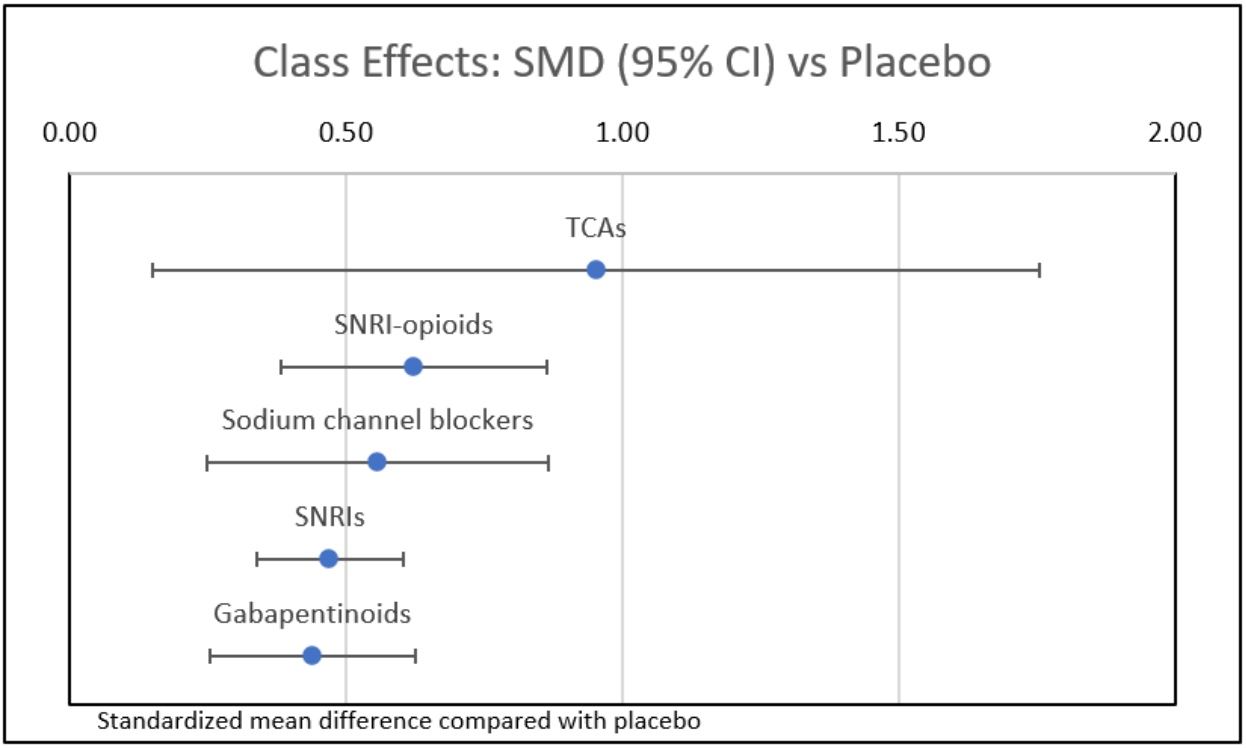
Table 3. Efficacy of oral medications for painful diabetic neuropathy by class effect

Medication Class	SMD[a]	LCL	UCL	Number of Articles	Number of Patients	Conclusion	Confidence
Gabapentin	0.44	0.25	0.63	16	3550	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	1884	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; UCL = upper confidence limit; TCA = tricyclic antidepressants

[a] SMD >0 indicates intervention is clinically better than placebo

Figure 1. 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).

Figure 2.

Meta regression **Pain Reduction by Male%**

Random Effects (DL) Scale: Linear

Study	SMD	LCL	UCL	Male%	Weight
98	0.143	-0.077	0.364	59	6.5%
103	1.893	1.490	2.296	55	4.3%
154	0.573	0.259	0.887	60	5.2%
155	0.946	0.292	1.600	78	3.0%
166	0.253	-0.551	1.056	51	2.5%
8	0.575	0.266	0.885	62	5.2%
17	0.391	-0.216	0.999	69	3.1%
58	-0.188	-0.389	0.013	65	6.8%
84	0.133	-0.025	0.290	47	7.8%
96	0.105	-0.124	0.334	53	6.3%
97	0.055	-0.171	0.281	55	6.4%
98	-0.224	-0.525	0.077	59	5.3%
129	0.323	0.092	0.554	55	6.3%
134	-0.093	-0.414	0.228	54	5.1%
149	-0.066	-0.422	0.290	52	4.7%
150	0.800	0.539	1.061	60	5.8%
151	0.623	0.310	0.937	61	5.2%
152	0.673	0.337	1.009	56	4.9%
153	0.688	0.413	0.964	54	5.6%
	1.441	**1.172**	**1.771**	**58**	**100.0%**

Model: Random Effects (DL), Z Distribution				DF	17
Parameter	SMD	LCL	UCL	Q	25
Intercept	-0.404	-2.460	1.651	T^2	0.074
Beta (Slope)	0.013	-0.022	0.049	Z	1.960

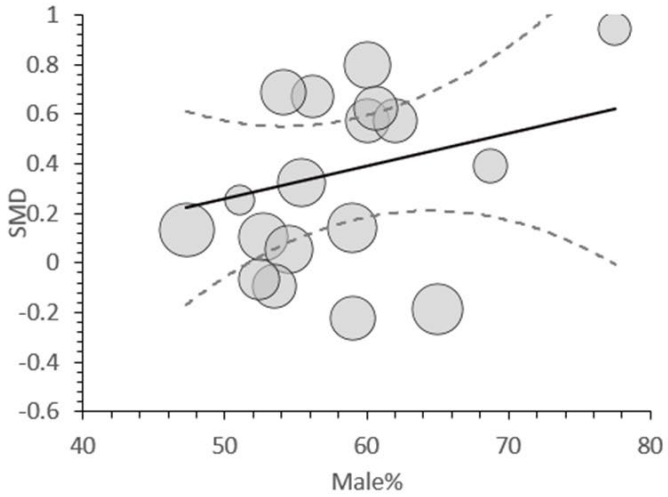


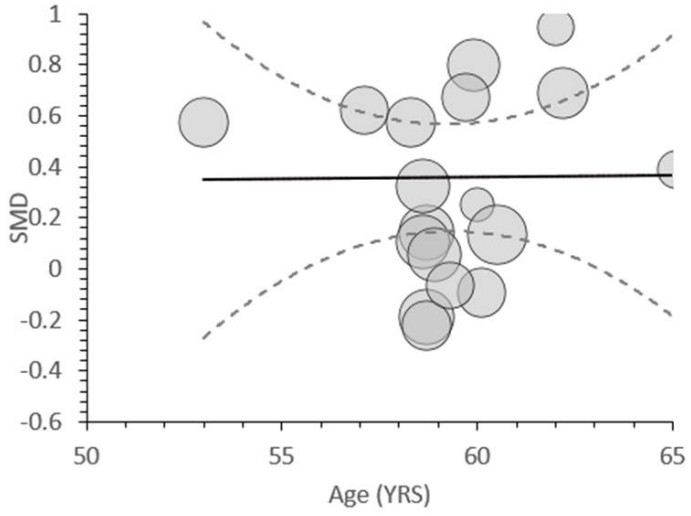
Figure 3.

Meta regression **Pain Reduction by Age**

Random Effects (DL) Scale: Linear

Study	SMD	LCL	UCL	Age (YRS)	Weight
98	0.143	-0.077	0.364	58.7	6.4%
103	1.893	1.49	2.296	58.7	4.3%
154	0.573	0.259	0.887	53	5.2%
155	0.946	0.292	1.6	62	3.0%
166	0.253	-0.551	1.056	60	2.5%
8	0.575	0.266	0.885	58.3	5.2%
17	0.391	-0.216	0.999	65.1	3.2%
58	-0.188	-0.389	0.013	58.7	6.8%
84	0.133	-0.025	0.29	60.5	7.7%
96	0.105	-0.124	0.334	58.6	6.3%
97	0.055	-0.171	0.281	58.9	6.4%
98	-0.224	-0.525	0.077	58.7	5.3%
129	0.323	0.092	0.554	58.6	6.3%
134	-0.093	-0.414	0.228	60.1	5.1%
149	-0.066	-0.422	0.29	59.3	4.7%
150	0.8	0.539	1.061	59.9	5.8%
151	0.623	0.31	0.937	57.1	5.2%
152	0.673	0.337	1.009	59.7	4.9%
153	0.688	0.413	0.964	62.2	5.6%
	1.429	**1.159**	**1.763**	**59**	**100.0%**

Model: Random Effects (DL), Z Distribution				DF	17
Parameter	SMD	LCL	UCL	Q	26
Intercept	0.277	-5.848	6.401	T^2	0.079
Beta (Slope)	0.001	-0.102	0.105	Z	1.960



Appendix 1. AAN Guideline Subcommittee mission

The mission of the Guideline Subcommittee is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The Guideline Subcommittee is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix 2. AAN Guideline Subcommittee members 2019–2021

Alexander Rae-Grant, MD (Chair), John J. Halperin, MD (Vice-Chair), Lori L. Billinghurst, MD, Brian Callaghan, MD, Anne Constantino, MD, Jeremy K. Cutsforth-Gregory, MD, Wendy S. Edlund, MD, Scott A. Heller, MD, Koto Ishida, MD, Mark Douglas Johnson, MD, Mark Robert Keezer, MD, Benzi Kluger, MD, Shaheen E. Lakhan, MD, PhD, MEd, Nicole J. Licking, DO, Mia T. Minen, MD, Asma Moheet, MD, Pushpa Narayanaswami, MBBS, MD, Alison M. Pack, MD, Sonja Potrebic, MD, PhD, Vishwanath Sagi, MD, Navdeep Sangha, MD, Nicolaos Scarmeas, MD, Kelly Sullivan, PhD, Sarah Tanveer, Benjamin D. Tolchin, MD, Shawniqua T. Williams, MD,

Appendix 3. Complete search strategy

Search history sorted by search number ascending

#	Searches	Results	Type
1	exp diabetic neuropathies/dt, th	6009	Advanced
2	(diabet* and neuralg*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word,	1100	Advanced

	keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
3	exp *diabetic neuropathies/ or ((diabet* or pain*) adj3 (neuropath* or polyneuropath*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	42415 Advanced
4	exp anticonvulsants/ or antiepileptic*.mp. or (anti adj (epileptic* or convulsant*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	141524 Advanced
5	(gabapentin* or pregabalin or neurotin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8453 Advanced
6	exp Sodium Channel Blockers/ or nortriptyline.mp. or desipramine.mp. or amitriptyline.mp. or clomipramine.mp. or imipramine.mp. or duloxetine.mp. or venlafaxine.mp. or lidocaine.mp. or capsaicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	134465 Advanced
7	("sodium channel" or carbamazepine or lamotrigine or oxcarbazepine or phenytoin or topiramate or valproate or valproic acid or amiodarone or amiloride or disopyramine or encainide or flecainide or lidocaine or mexiletine or procainamide or quinidine or ranolazine or tocainide or triamterene).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	128960 Advanced
8	(1 or 2 or 3) and (6 or 7 or lipoic*.mp. or thioctic acid/) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3419 Advanced
9	(1 or 2 or 3) and (4 or 5)	2761 Advanced

10	exp antidepressive agents/ or "tricyclic antidepress*".mp. or ssri.mp. or ssris.mp. or "selective serotonin reuptake inhibitor*".mp. or snri.mp. or "selective norepinephrine reuptake inhibitor*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	144162	Advanced
11	exp Serotonin Uptake Inhibitors/	35260	Advanced
12	exp neurotransmitter uptake inhibitors/ or "serotonin and noradrenaline reuptake inhibitors"/	135288	Advanced
13	exp Analgesics, Opioid/	105720	Advanced
14	(opiod* or opiate* or tapentadol or tramadol or oxycodone or methadone or morphine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	90216	Advanced
15	(1 or 2 or 3) and (10 or 11 or 12 or 13 or 14)	3291	Advanced
16	exp anti-arrhythmia agents/ or exp vitamins/ or exp dietary supplements/ or acetyl-l-carnitine.mp. or exp protein kinase inhibitors/ or "alpha lipoic acid".mp. or thioctic acid/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	632189	Advanced
17	exp Aldehyde Reductase/ai [Antagonists & Inhibitors]	1970	Advanced
18	("aldose reductase" adj3 (block* or antagonist* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2073	Advanced
19	(q10.mp. or 16 or 17 or 18) and (1 or 2 or 3) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2074	Advanced
20	8 or 9 or 15 or 19	8054	Advanced
21	limit 20 to (english language and yr="2008 -Current")	4465	Advanced

22	21 and (random* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	937	Advanced
23	21 and meta-analy*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	159	Advanced
24	21 and (review.pt. or review.ti.)	872	Advanced
25	or/22-24	1567	Advanced
26	25 and (quality of life/ or qol.mp. or euroqol.mp. or scale*.mp. or inventory.mp. or "visual analog*".mp. or vas.mp. or pain*.mp. or sleep*.mp. or depress*.mp. or neuroqol.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1460	Advanced
27	pain measurement/ or "life activit*".mp. or discomfort*.mp. or distress*.mp. or anxiety.mp. or depression.mp. or iadl.mp. or "daily life".mp. or "mental health".mp.	835055	Advanced
28	25 and 27	533	Advanced
29	26 or 28	1460	Advanced
30	1 or 2 or 3	42817	Advanced
31	30 and (topical*.mp. or administration, topical/ or transderm*.mp. or patch*.mp. or cream*.mp. or lotion*.mp. or spray*.mp. or ointment*.mp. or cutaneous*.mp. or gel.mp. or gels.mp. or oral*.mp. or administration, oral/) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4238	Advanced
32	31 and (randomized controlled trial.pt. or random*.mp. or blind*.mp. or meta-analysis.mp. or systematic*.mp. or placebo*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	939	Advanced

33	limit 32 to (english language and yr="2008 -Current")	574	Advanced
34	29 or 33	1758	

CENTRAL – 451

Embase <1988 to 2018 Week 41>

Search history sorted by search number ascending

#	Searches	Results	Type
1	diabetic neuropathy/ or exp polyneuropathy/	50570	Advanced
2	exp anticonvulsive agent/	304786	Advanced
3	exp analgesic agent/	692481	Advanced
4	gabapentin/	27397	Advanced
5	pregabalin/	12079	Advanced
6	exp sodium channel blocking agent/	222006	Advanced
7	exp antidepressant agent/	346133	Advanced
8	exp serotonin uptake inhibitor/	207886	Advanced
9	exp serotonin noradrenalin reuptake inhibitor/	133063	Advanced
10	opiate/	67019	Advanced
11	tapentadol/ or exp narcotic analgesic agent/	250368	Advanced
12	exp antiarrhythmic agent/	233802	Advanced
13	exp vitamin/	500040	Advanced
14	exp dietary supplement/	7195	Advanced
15	levacecarnine/	1487	Advanced
16	exp aldose reductase inhibitor/	5580	Advanced
17	thioctic acid/	7225	Advanced
18	ubidecarenone/	7647	Advanced

19	exp protein kinase C inhibitor/	32527	Advanced
20	or/2-19	1793247	Advanced
21	1 and 20	9299	Advanced
22	exp pain intensity/ or exp pain assessment/ or exp McGill Pain Questionnaire/ or exp pain measurement/ or exp "Shoulder Pain and Disability Index"/ or exp pain/ or exp Brief Pain Inventory/ or exp neuropathic pain/ or exp Memorial Pain Assessment Card/	1150323	Advanced
23	pain*.mp.	1111282	Advanced
24	exp Pittsburgh Sleep Quality Index/ or exp sleep quality/ or exp "International Classification of Sleep Disorders"/ or exp sleep/ or sleep.mp. or exp sleep disorder assessment/ or exp Leeds Sleep Evaluation Questionnaire/	297070	Advanced
25	exp "quality of life"/ or inventor*.mp. or "visual analog*".mp. or vas.mp. or pain*.mp. or sleep*.mp. or depress*.mp. or "life activit*".mp. or discomfort*.mp. or distress*.mp. or anxiety.mp. or iadl.mp. or "daily life".mp. or "mental health".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2682200	Advanced
26	(qol or hqol or hrqol or euroqol or neuroqol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	84491	Advanced
27	or/22-26	2922348	Advanced
28	21 and 27	5513	Advanced
29	randomized controlled trial/ or meta-analysis/ or systematic review/	744144	Advanced
30	28 and 29	660	Advanced

31	limit 30 to (english language and yr="2008 - Current")	362	Advanced
32	28 and review/	1807	Advanced
33	limit 32 to (english language and yr="2008 - Current")	988	Advanced
34	(*diabetic neuropathy/dt or exp *polyneuropathy/dt) and 33	161	Advanced
35	31 or 34	491	Advanced
36	remove duplicates from 35	488	Advanced
37	topical drug administration/ or cutaneous drug administration/ or transdermal drug administration/ or oral drug administraction/	52359	Advanced
38	(diabetic neuropathy/ or exp polyneuropathy/) and ((oral* or topical*).mp. or administration, topical/ or transderm*.mp. or patch*.mp. or cream*.mp. or lotion*.mp. or spray*.mp. or ointment*.mp. or cutaneous*.mp. or gel.mp. or gels.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	7450	Advanced
39	1 and 37	117	Advanced
40	38 or 39	7450	Advanced
41	limit 40 to (english language and yr="2008 - Current")	4263	Advanced
42	29 and 41	334	Advanced
43	41 and review.pt.	1101	Advanced
44	43 and *diabetic neuropathy/	115	Advanced
45	(42 or 44) not 36	221	Advanced
46	36 or 42 or 45	709	

Appendix 4. Evidence tables

The evidence profile tables are available from the AAN, by request.

Appendix 5. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

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 (RELA).[79-81] Patients with diabetes should be assessed for the presence of peripheral neuropathy and neuropathic pain periodically (PRIN), 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 (EVID). Such scales are commonly used in practice, but they do not provide insight into the effect of pain on patients' functioning

and well-being (PRIN). Other scales that assess pain interference or effects on quality of life may provide more relevant information to assess the need for treatment and success of such treatment (INFER).

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 5	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 8	Yes
Feasible	Rarely 1	Occasionally 0	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2 rationale

Several classes of pharmacologic agents have been demonstrated to reduce pain in patients with painful diabetic neuropathy (EVID). However, complete resolution of symptoms is often not achieved (EVID). Patients expect a high degree of pain relief, and many expect complete pain resolution (RELA).[82] 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 (PRIN).

Recommendation statement 2

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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 6	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 7	Yes
Feasible	Rarely 1	Occasionally 0	Usually 1	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

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 (PRIN). 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 (RELA).[83,84] Mood and sleep can both influence pain perception (RELA).[85,86] 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 (INFER). 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 (INFER).

Recommendation statement 3

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 8	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 4 rationale

Painful diabetic neuropathy is a highly prevalent condition that greatly affects quality of life (RELA).[9] Four classes of oral medications have demonstrated evidence of pain reduction in meta-analyses: TCAs, SNRIs, gabapentinoids, and sodium channel blockers (EVID). 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 (EVID).

Recommendation statement 4

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 3	Modest 6	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 6	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

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 (PRIN). Furthermore, given the downsides of opioid therapy (RELA),[11,12] the ability to offer effective nonopioid interventions to reduce pain in patients failing initial therapies is important (PRIN). TCAs, SNRIs, gabapentinoids, and sodium channel blockers have all been shown to improve pain in patients with diabetic neuropathy (EVID). 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) (EVID), nontraditional interventions (ginkgo biloba) (EVID), and nonpharmacologic approaches (exercise, cognitive behavioral therapy, mindfulness) (RELA).[87] Furthermore, there is moderate and consistent evidence for the use of cognitive behavioral therapy (CBT) for many types of chronic pain[88,89] (RELA). 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[90,91] (RELA).

Recommendation statement 5a

Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for painful diabetic neuropathy (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 9	Critically important 2	Yes
Variation in preferences	Large 3	Moderate 2	Modest 3	Minimal 5	No
Feasible	Rarely 0	Occasionally 3	Usually 4	Always 6	No
Cost relative to net benefit	Very large 1	Large 2	Moderate 5	Small 5	No
Strength of recommendation	R/U	C	B	A	

Recommendation statement 5b

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) (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 2	Benefit >> harm 6	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 3	Very important 8	Critically important 2	Yes
Variation in preferences	Large 2	Moderate 2	Modest 4	Minimal 5	No
Feasible	Rarely 0	Occasionally 3	Usually 7	Always 3	No
Cost relative to net benefit	Very large 0	Large 4	Moderate 5	Small 4	No
Strength of recommendation	R/U	C	B	A	

Recommendation 6 rationale

Individual pharmacologic agents from the TCA, SNRI, gabapentinoid, and sodium channel blocker classes have similar efficacy on neuropathic pain outcomes (EVID). However, class and agent-specific differences exist in the potential for and nature of adverse effects (EVID). For example, the potential anticholinergic side effects of TCAs may be less tolerated in patients with preexisting constipation, urinary retention, or orthostatic hypotension (PRIN). 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 (PRIN). 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 (PRIN). Valproic acid has potential teratogenic effects such as neural tube defects as well as hepatotoxicity, pancreatitis, hyponatremia, pancytopenia, and many other serious adverse events (RELA).[92] Dose adjustment for the level of renal function is required for many of these agents and must be reviewed before prescribing (PRIN). Discussion of cost and patient preference should be made (PRIN). 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 (PRIN).

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 painful diabetic neuropathy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 2	Modest 6	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 4	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 6b

In patients of child-bearing potential with painful diabetic neuropathy, clinicians should not offer valproic acid (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 0	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 0	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 6c

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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 2	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

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 (PRIN). 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 (EVID). The typical duration of treatment in which efficacy is demonstrated is approximately 12 weeks, with a range from 4 to 16 weeks (EVID). 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 (PRIN). 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 (EVID). 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 (PRIN). 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 (PRIN). 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 (INFER). 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 (INFER).

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 painful diabetic neuropathy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 1	Modest 9	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 10	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 8	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 7	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 5	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

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 experience significant adverse effects with the initial therapeutic class (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 7	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 5	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 9	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 1	Modest 7	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

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 (RELA).[11,12] 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" (RELA).[93] 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 (RELA).[94] 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 (RELA).[11,12,89,95] Data from the CDC suggests that it is likely that dependence may set in

within days to weeks of starting opioids (RELA).[96] 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 (PRIN). 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 (RELA).[97] 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 (RELA).[93]

Recommendation statement 8a

Clinicians should not use opioids for the treatment of painful diabetic neuropathy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 7	Yes
Variation in preferences	Large 1	Moderate 2	Modest 8	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 8b

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 (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 2	Moderate 4	Modest 4	Minimal 3	No
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

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 (RELA).[98] A recent study reported an increase in all-cause mortality among patients taking tramadol for osteoarthritis (RELA).[99] Although true prevalence is unknown, serotonin syndrome has also been associated with tramadol (RELA).[100] The abuse liability in terms of reported abuse events per population are substantial and greater than that for morphine (RELA).[101]

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 (RELA).[102] 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 (RELA).[101] The efficacy of tramadol and tapentadol for painful neuropathy is only reported in studies of short duration (EVID and RELA).[103] Demonstration of long-term efficacy without substantial side effects would be needed to justify the severity of potential side effects.

Recommendation statement 9a

Clinicians may not use tramadol and tapentadol (opioids/SNRI dual mechanism agents) for the treatment of painful diabetic neuropathy (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 3	Modest 7	Minimal 3	No
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation statement 9b

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 (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 1	Moderate 3	Modest 5	Minimal 4	No
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 6	Yes
Strength of recommendation	R/U	C	B	A	