CLINICAL INVESTIGATION

The clinical landscape of painful diabetic neuropathy therapy: perspectives for clinicians from clinical practice guidelines

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Painful diabetic neuropathy (PDN) is highly prevalent, yet there are marked limitations in the efficacy of the multiple existing symptomatic therapies. This presents a major challenge to clinicians whose aim it is to use the best evidence in treatment choice. Evidence-based guidelines provide a better understanding of the foundations for the different treatment choices and this insight may be used to improve patient care. Guidelines at this point can only speak to efficacy in the hopes that the therapies will have sufficient adherence, generalizability and affordability to treat PDN effectively in society. Different guidelines for treating PDN have recently been published, however their content and recommendations differ. An understanding of why the guidelines differ may be useful to the practitioner in choosing the best emerging evidence for the treatment of PDN patients. This review compares the different guidelines and discusses the methodologies leading to different recommendations.

Keywords: diabetes • diabetic neuropathy • evidence • guidelines • neuropathy • pain • treatment

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Summarized guideline recommendations

The recommendations for the treatment of painful diabetic neuropathy (PDN) from the guidelines are summarized in Tables 1–3, Figure 1 & Box 1. Table 1 shows a summary of the tripartite evidence-based guidelines of the American Academy of Neurology (AAN), American Association of Electrodiagnostic and Neuromuscular Medicine and American Academy of Physical Medicine and Rehabilitation [1], for brevity referred to hereinafter as the AAN guidelines. Table 2 shows the European Federation of Neurolical Societies (EFNS) guidelines [2], and Table 3 the Canadian Diabetes Association evidence-based practice recommendations [3]. The NICE guidelines appear in Figure 1 [4], and the International Association for the Study of Pain (IASP) guidelines, published by the Mayo Clinic (MN, USA), are summarized in Box 1 [5]. All of the guidelines deal specifically with the treatment of PDN, or include the treatment of PDN, as a clearly identifiable subset in the broader topic of treatment of all forms of neuropathic pain.

A common theme across the guidelines is that all advocate for the use of anticonvulsants, antidepressants and opioids to relieve symptoms in PDN, but they differ in the details. One of the differences is that drugs in a given class, (e.g., tricyclic antidepressants [TCAs]), are not handled in the same way across guidelines. For example, the AAN guideline recommends amitriptyline, a tricyclic antidepressant, for the treatment of PDN (level B recommendation) and discusses the lack of evidence to recommend other TCAs such as imipramine and nortriptyline. In contrast, the EFNS guidelines recommend the use of TCAs as a class without specifying the drugs

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Table 1. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and The American Academy of Physical Medicine and Rehabilitation evidence-based guidelines for the treatment of painful diabetic neuropathy.

Level	Recommended	Not recommended
A	Pregabalin 300–600 mg/day	Oxcarbazepine
B	Gabapentin 900–3600 mg/day	Lamotrigine
	Valproate 500–1200 mg/day	Lacosamide
	Venlafaxine 75–225 mg/day	Clonidine
	Duloxetine 60–120 mg/day	Pentoxifylline
	Amitriptyline 25–100 mg/day	Mexiletine
	Dextromethorphan 400 mg/day	Magnetic field stimulation
	Morphine sulphate titrated to 120 mg/day	Low-intensity laser treatment
	Tramadol 210 mg/day	Reiki therapy
	Oxycodone, mean: 37 mg/day, maximum: 120 mg/day	
	Capsaicin, 0.075% four-times/day	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation x 3–4 weeks	

Adapted with permission from [1].

to use based on an assumption that all are effective for PDN. Such differences make it clear that the rules for evidence classification are not standardized across all organizations. The AAN and EFNS rules for classifying evidence differ and therefore the recommendations are not the same. The results of evidence classification are further modified by the inclusion of expert opinion in all but the AAN guidelines [2,5]. Another difference is that the EFNS, NICE and IASP guidelines provide a treatment algorithm with a particular order of drug selection for management of PDN, but the AAN guidelines do not suggest the order of treatment choice. Most of the guidelines include both oral and topical treatments. The AAN guidelines provide both positive and negative recommendations in contrast to other guidelines. All of the guidelines suggest the use of opioids, but in the EFNS and IASP versions, opioids are second/third-line treatments compared with the AAN guidelines. In the AAN guidelines, opioids have a level B recommendation similar to other drug choices, but there is additional discussion concerning opioid use in a clinical context segment.

AAN guideline methodology

The different guidelines can lead to confusion when treating patients with PDN, since there is such variation between the recommendations. In order to understand the evidence base for treatment of PDN, it is helpful to review how the guidelines were developed, starting with the most recent from the AAN. The AAN recommendations relied strictly on a standardized evaluation of the published medical-science literature and not on expert opinion. The results of this evidence-based, standardized approach are summarized in Table 1. The guideline process was transparent and incorporated input from multiple parties including: the expert author panel, the Quality Standards Subcommittee (QSS) of the AAN, the membership of the three sponsoring organizations, and peer reviewers from the relevant journals. The AAN method of evidence-based assessment has been defined by the QSS and follows the American Institute of Evaluative Science methods. The author panel included experts in the field and members of the AAN, American Association of Neuromuscular and Electrodiagnostic Medicine and American Academy of Physical Medicine and Rehabilitation. The authors committed to adhering to the AAN evidence-evaluation process and members of the QSS participated on the author panel to help ensure adherence to the AAN methodology. The QSS initiated the project by first determining that understanding the evidence for the treatment of PDN is an important matter. Furthermore, this understanding could be gained from a systematic literature review and the outcome had the potential to improve clinical care. The author panel started by determining the relevant question to be answered by the guideline; namely: 'In patients with PDN, what is the efficacy of pharmacologic agents and nonpharmacologic modalities to reduce pain, improve physical function and quality of life?' The pharmacological treatments included anticonvulsants, antidepressants, opioids, antiarrhythmics, cannabinoids, antioxidants, PKC inhibitors, aldose reductase inhibitors and topical medications (capsaicin, anesthetic and analgesic patches). The nonpharmacological treatments included improved glycemic control, exercise, surgical interventions, low-intensity laser treatment, acupuncture, Reiki therapy, electromagnetic field therapy, biofeedback, behavioral therapy and transcutaneous electrical nerve stimulation. After agreement on the question and search terms, a librarian performed a literature search from 1960 to 2008 using MEDBASE and EMBASE, identifying 2234 possibly relevant abstracts. Teams of authors reviewed the abstracts and flagged 463 papers requiring full review. Case reports and review articles were excluded. Different pairs of authors then reviewed the 463 articles and identified 79 articles relevant to the question. Each author independently classified the evidence for each paper as 1, 2, 3 or 4 and completed an evidence table. If there were any disputes in the classification of papers, these were arbitrated by a third and sometimes fourth author, a member of the QSS. Consistent results from more than one study raised the level of evidence.

Complete details of the classification system are set out in the paper and on the AAN website [101]. An important detail to highlight is that many studies failed to reach class I status because of the single requirement that 80% of patients enrolled in a study had to complete the study. Any study with less than 80% of subjects completing the trial was automatically dropped to class II. This 80% rule caused considerable consternation within the organizations as a different outcome to the evidence-based review was expected, but the QSS determined appropriately that the 80% rule would not be waived for these guidelines. The evidence tables with the class of evidence and details for each study are available as an e-appendix to the published guidelines. The recommendations followed directly from the strength of the evidence for each treatment. Consistent evidence was required for a positive recommendation. For example, a level 'A' recommendation required two consistent class I studies showing efficacy. Clinical context based on expert opinion was added to the guidelines and attempted to address information that was not available in the review process. For example, the use of opioid therapy for chronic non-malignant pain, such as PDN, has many potential pitfalls unlikely to become apparent in short-term studies. These problems include development of novel pain syndromes, such as rebound headache, tolerance and potential diversion of medication. The AAN guidelines were reviewed critically by the QSS while under development, by many members of the three sponsoring organizations and by peer reviewers at each journal prior to publication. The results of this multifaceted process are summarized in Table 1.

Table 2. Summary of the European Federation of Neurological Societies guidelines on the pharmacological treatment of neuropathic pain.

Etiology	First-line	Second/third-line
PDN	Duloxetine	Opioids
	Gabapentin	Tramadol
	Pregabalin	
	TCA	
	Venlafaxine	
PHN	Gabapentin	Capsaicin
	Pregabalin	Opioids
	TCA	
	Lidocaine Patch	
TGN	Carbamazepine	Surgery
	Oxcarbazepine	
Central pain	Gabapentin	Cannabinoids (MS)
	Pregabalin	Lamotrigine
	TCA	Opioids
		Tramadol

MS: Multiple sclerosis; PDN: Painful diabetic neurpathy; PHN: Postherpetic neuralgia; TCA: Tricyclic antidepressant; TGN: Trigeminal neuralgia.
Adapted from [2].

Comparison of guidelines

Since the guidelines are not identical, it is evident that methods used to evaluate the evidence and the standards used to formulate the recommendations differed between the guideline committees. Furthermore, although several guidelines (EFNS, NICE and IASP) present a treatment algorithm for PDN, specific algorithms have not been tested in clinical trials so all of the algorithms lack supporting evidence. Although practitioners might consider such treatment algorithms useful to direct clinical practice, the advice is not evidence based as noted in the relevant publications. The AAN guidelines do not provide a treatment algorithm for this very reason; no evidence is available to support an algorithm – this is one of the gaps in care that exists today.

■ Anticonvulsants

All of the guidelines conclude that pregabalin is an effective treatment for PDN. Some of the guidelines consider pregabalin as a first-line and others as a second-line treatment choice, despite the guideline committees having access to the same scientific literature. In fact, pregabalin had the highest level of evidence in the treatment of PDN (two consistent class I studies) and therefore achieved a level A recommendation in the AAN guidelines, a level that no other treatment achieved. Therefore, the strongest evidence available supports the use of pregabalin in the treatment of PDN. Other anticonvulsants with supportive evidence in the treatment of PDN are gabapentin and valproate, but not all anticonvulsants were found to be useful, as shown in Table 1. Bioavailability data from animal models might support the use of pregabalin instead of gabapentin, but there is no direct comparison trial in PDN patients to support this choice [6,7]. In the NICE guidelines, pregabalin is suggested as a second-line treatment and duloxetine is recommended as the treatment of choice for PDN. However, the evidence for duloxetine consists of efficacy in class II studies according to AAN guidelines. Therefore, the 'high- or moderate-quality randomized trials' evidence in the NICE guidelines indicates that the NICE committee rated evidence more leniently than the AAN. Furthermore, there is a complete lack of published evidence on the preferential order of treatments in PDN, so that the suggestions for first- and second-line treatments are based solely on expert opinion, as noted within each guideline that contains such algorithms [4]. In the Mayo Clinic guidelines, the decisions on first-, second- and

Table 3. Canadian Diabetes Association examples of commonly used oral medications for the management of neuropathic pain.

Medication	Initial dose	Titration	Side effects
Tricyclic antidepressant			
Amitriptyline	10 mg q.h.s.	Increase weekly by 10 mg/day to maximum of 150 mg/day	Dry mouth Blurry vision Constipation Urinary retention Dizziness Drowsiness Weight gain
Anticonvulsant			
Gabapentin	300 mg t.i.d.	Increase weekly by 300 mg/day to maximum of 3600 mg/day	Dizziness Somnolence Ataxia Fatigue Peripheral edema Weight gain
Pregabalin	75 mg b.i.d.	Increase weekly by 150 mg/day to maximum of 300 mg b.i.d.	Dizziness Somnolence Weight gain Peripheral edema
Opioid analgesic			
Oxycodone	10 mg b.i.d.	Increase Q3 days by 10 mg to maximum of 60 mg b.i.d.	Constipation Nausea Somnolence

b.i.d.: Twice daily; q.h.s.: At bedtime; t.i.d.: Three-times per day.
The Canadian Diabetes Association recommendation statement provides the level of evidence for the following drugs in the following statement: antidepressants (including duloxetine), anticonvulsants, opioid analgesics and topical isosorbide dinitrate should be considered alone or in combination for relief of painful peripheral neuropathy.
Adapted with permission from [3].

third-line treatment are based on Neuropathic Pain Special Interest Group guidelines and include expert opinion as to the order of the selection of agents [5].

80% rule

It may be useful here to consider the rule that separated class I from class II studies in the AAN guidelines. These guidelines awarded class I status to randomized, placebo-controlled, double-blinded studies with a list of further requirements to achieve class I status [1]. The major limiting factor for most studies was the '80% rule'; that is, at least 80% of those patients enrolled in the study had to complete the study. If all other requirements for class I were met, except the 80% rule, then the study was automatically rated as class II. One might argue that completion rates of <80% indicate patient dissatisfaction with the treatment due to inadequate pain relief or unacceptable adverse effects. Alternatively, it may be that completion rates of 80% or higher are observed only with shorter duration studies. A way to compensate for the time factor might be to normalize all studies to the same treatment interval when doing evidence-based reviews, but the risk is that imputation of an even dropout rate across drug exposure would produce erroneous data. Another way to approach this problem is to require a change in trial reporting, so that authors need to report dropout rates at regular intervals (e.g., 4, 8 and 12 weeks) to allow comparison of completion rates at uniform time points. Given the limitations in current study design, the 80% rule appears to have been waived by some groups [2] and kept by others [1].

Antidepressants

Some, but not all, antidepressants are useful in the treatment of PDN. Amitriptyline has shown efficacy in class II studies [1], and recommendations for its use appear in all the guidelines, sometimes simply included in the TCAs category and in other instances as a direct recommendation. However, the fact is that amitriptyline is the only TCA with sufficient evidence of efficacy to recommend it for use in PDN [1]. Desipramine and nortriptyline lack sufficient consistently supporting evidence, by AAN standards, so other guidelines advocating for their use (or generic TCA use) do so based on expert opinion, or a lesser evidence requirement [1,4]. Although some practitioners may prefer other specific TCA in select populations, such as the elderly, one could consider that the role of the evidence-based guidelines should not be to highlight these preferences, but rather to highlight that the use of such agents has not been specifically tested and thus represents a gap in knowledge. Duloxetine is listed in all of the guidelines as showing efficacy for the treatment of PDN. Venlafaxine also has efficacy for the treatment of PDN (level B in the AAN recommendation) [1]. Again, there is a lack of studies (and therefore evidence) of a specific sequence of antidepressants to try in PDN, although some experts advocate starting with amitriptyline as it is an older, and therefore cheaper, alternative compared with the newer medications. Most guidelines do not contain cost–effectiveness data and this type of data is not available for many interventions. However, on a practical level, it is reasonable to start with less expensive alternatives, if both have similar efficacy, as is the case for amitriptyline and duloxetine according to the level B recommendations in the AAN guidelines [1].

Opioids

All of the guidelines recommend oxycodone or the broader category of opioids as efficacious for the treatment of PDN, and opioids are usually second-/third-line choices when a treatment algorithm is suggested, although there is no evidence for a treatment algorithm. In the AAN guidelines, oxycodone controlled release has a level B recommendation for use in PDN [1]. However, a clinical context section

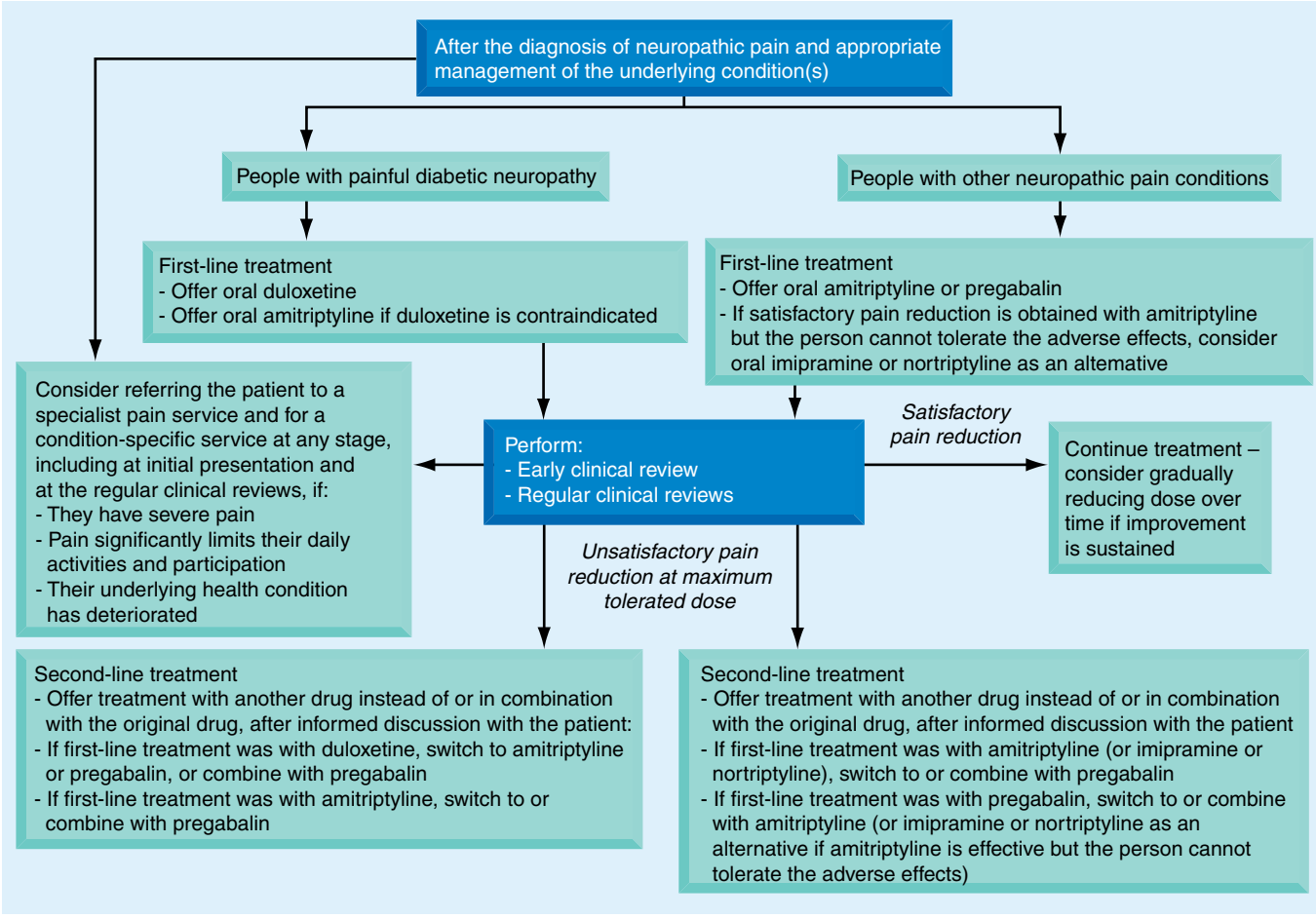

Figure 1. The pharmacological management of neuropathic pain in adults in non-specialist settings.
Addapted with permission from [4].

discusses concerns around the use of opioids in chronic, non-malignant pain conditions and this view concurs with other guidelines that place opioids as second-/third-line choices.

Summary

To summarize, there is broad consensus on some of the medications recommended as having efficacy in the treatment of PDN, if not on the order in which to try them. Pregabalin, amitriptyline, duloxetine and oxycodone are found in all recommendations (Box 2). The strictest grading of the evidence for any medication or treatment is found in the AAN guidelines, but as there is no evidence available on the order of these interventions, the AAN guidelines remain silent on this point [1]. The AAN and IASP guidelines both include oral and topical agents and the AAN guidelines consider nonpharmacological management as well as all pharmacological interventions. Of these, transcutaneous electrical nerve stimulation was the only modality showing consistent efficacy.

Gaps in care

The guidelines differ in the final recommendations because of differences in the criteria used for grading of evidence (mostly due to the 80% rule) and the need for two class I studies for a grade A recommendation in the AAN guidelines. Furthermore, the inclusion of expert interpretation and opinion in several guidelines differs from the AAN process. The AAN process is based entirely upon a systematic, evidence-based review of the literature that does include or allow expert opinion (except in clinical context sections).

The AAN and other guidelines identified important gaps in care: the chronic effects and appropriate duration of drug therapies are unknown as the studies are short-term; high-level comparative and/or combination studies are unavailable; standardized measures of pain, physical function and quality of life are lacking; cost–effectiveness is not presented; numbers needed to harm are unavailable due to limited reporting of adverse effects; the responder rate to any intervention is far from 100% and large effect sizes are not observed.

Box 1. Summary of the Mayo International Association International Association for the Study of Pain guidelines for the treatment of neuropathic pain.

First-line drugs for neuropathic pain
- Secondary amine TCA
  - Nortriptyline
  - Desipramine
  - (Tertiary: amitriptyline)
- SSNRI
  - Duloxetine
  - Venlafaxine
- Calcium channel ligand blocker
  - Gabapentin
  - Pregabalin
- Topical lidocaine

Second-line drugs for neuropathic pain
- Opioid analgesics
  - Morphine
  - Oxycodone
  - Methadone
  - Levorphanol
  - Tramadol
- These medications can be used as first-line in select circumstances such as acute neuropathic pain, neuropathic cancer pain, episodic exacerbations of severe pain or for prompt pain relief while titrating other medications

Third-line drugs for neuropathic pain
- AED
  - Carbamazepine (PHN)
  - Lamotrigine
  - Oxcarbazepoine
- ADD
  - SSRIs
  - Citalopram
  - Paroxetine
  - Bupropion
- Others
  - Mexiletine
  - NMDA-receptor antagonists
  - Topical capsaicin

ADD: Antidepresent drug; AED: Antiepileptic drug; PHN: Postherpetic neuralgia; SSNRI: Serotonin–norepinephrine reuptake inhibitor; SSRIs: Selective serotonin-reuptake inhibitor; TCA: Tricyclic antidepressant.
Reporoduced with permission from [5].

These observations have the potential to guide future research in PDN and thus to improve care of patients [1,2,5]. Furthermore, manuscript reviewers and editors need to be more vigilant in their reviews of papers for potential publication and question particularly highly atypical results, such as a zero placebo response rate in a PDN study, in order to ensure that results in the scientific literature are of the highest quality.

Limitations

All of the guidelines have limitations. Only published studies can be evaluated and unpublished studies, if any, can only lead to speculation about negative results or unacceptable drug toxicity. As requirements for outcomes become more rigorous, such as showing improved physical function and quality of life, in addition to pain relief, a bias towards novel drugs is unavoidable. Changes in physical function and quality of life have only been included in more recent studies [1,5].

Box 2. Medications universally recommended for the treatment of painful diabetic neuropathy.
- Pregabalin
- Amitriptyline
- Duloxetine
- Oxycodone

Although the treatment of PDN remains an art, the evidence provides a supportive framework for physicians in their approach to patient management. The choice of any treatment will depend on the clinical picture specific to each patient and cannot be predetermined. However, when faced with the clinical question of how to treat PDN, the AAN guidelines could be considered to provide the most objective evidence-based set of recommendations to help choose, from many options, the most suitable for that patient. The evidence to support the use of the most efficacious and effective agents in specific drug classes for all patients, as well as a specific treatment algorithm that details first-line agents remains a knowledge gap, the interpretation of which is better served in publications outside of evidence-based guidelines.

Future perspective

In the next 5–10 years, it is probable that more effective treatments for PDN will be discovered and that clinical trial design will be standardized to outcome measures, duration of treatment and trial structure. Future trials will include high-level comparison studies as a standard. Finally, our understanding of the mechanisms underlying PDN will increase substantially, thus allowing for focused therapies with fewer side effects.

Financial & competing interests disclosure

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Executive summary

Background
- Painful diabetic neuropathy (PDN) is prevalent and there are multiple treatment options.
- Several guidelines for treating PDN have been published, leading to confusion as they are not all the same.
- An examination of the guidelines will provide an understanding of the evidence-base of treatments for PDN.

Summarized guideline recommendations
- Five guidelines have been published: American Academy of Neurology (AAN), European Federation of Neurological Societies, Canadian Diabetes Association, NICE and International Association for the Study of Pain .
- All recommend the use of anticonvulsants, antidepressants and opioids.
- Specific recommendations differ.
- Expert opinion is used in some guideline recommendations.
- AAN uses strict evidence-based reviews.

AAN guideline methodology
- Evidence-based, standardized approach to evaluation of published medical scientific literature.
- Transparent process with wide input from three sponsoring organizations: AAN, the American Association of Electrodiagnostic and Neuromuscular Medicine and American Academy of Physical Medicine and Rehabilitation and oversight from the Quality Standards Subcommittee.
- Literature search for pharmacologic and nonpharmacologic treatments for PDN.
- 2234 abstracts, 463 articles and 79 relevant articles rated by independent teams.
- Class I required a double-blinded, placebo-controlled trial, with 80% of patients completing the study.
- Level A recommendation required two class I studies; that is, consistent evidence.

Comparison of guidelines
- Treatment algorithms are not evidence-based.
- Anticonvulsants: pregabalin supported in all guidelines; gabapentin and valproate have supporting evidence.
- Antidepressants: amitriptyline and duloxetine are supported in all guidelines.
- Opioids: second/third line in most guidelines, level B in AAN recommendations (oxycodone controlled release) with clinical context section.

Gaps in care
- Criteria between guidelines differ with some incorporating expert opinion to inform recommendations.
- Clinical trials in PDN need to be standardized as to measures, duration and reporting of adverse events.
- Cost–effectiveness needs to be included in evaluation of new treatments.
- Critical appraisal of studies needs to be rigorous.

Limitations
- Only published medical scientific literature informs the guidelines.
- Requirement for measures in addition to pain relief will skew the process towards novel treatments, as only newer studies incorporate these measures.
- AAN guidelines provide the most objective evidence-based set of recommendations to help physicians select treatments for patients.

manuscript.

References

Papers of special note have been highlighted as:

- **of interest**
- **Strictest evidence-based evaluation of the treatments for painful diabetic neuropathy. Practitioners who wish to rely on evidence-based treatment will find this reference the most useful.**

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