Special Feature

Evidence-based Guideline: Treatment of Painful Diabetic Neuropathy

Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation

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Objective: To develop a scientifically sound and clinically relevant evidence-based guideline for the treatment of painful diabetic neuropathy (PDN).

Methods: We performed a systematic review of the literature from 1960 to August 2008 and classified the studies according to the American Academy of Neurology classification of evidence scheme for a therapeutic article, and recommendations were linked to the strength of the evidence. The basic question asked was: "What is the efficacy of a given treatment (pharmacological: anticonvulsants, antidepressants, opioids, others; and non-pharmacological: electrical stimulation, magnetic field treatment, low-intensity laser treatment, Reiki massage, others) to reduce pain and improve physical function and quality of life (QOL) in patients with PDN?"

Results and Recommendations: Pregabalin is established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulphate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence or the evidence is negative. Effective treatments for PDN are available, but many have side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and QOL.

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Diabetic sensorimotor polyneuropathy represents a diffuse symmetrical and length-dependent injury to peripheral nerves that has major implications on quality of life (QOL), morbidity, and costs from a public health perspective [1,2]. Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%) [3]. PDN presents an ongoing management problem for patients, caregivers, and physicians. There are many treatment options available, and a rational approach to treating the patient with PDN requires an understanding of the evidence for each intervention.

This guideline addresses the efficacy of pharmacological and nonpharmacological treatments to reduce pain and improve physical function and QOL in patients with PDN. The pharmacological agents reviewed include anticonvulsants, antidepressants, opioids, antiarrhythmics, cannabinoids, aldose reductase inhibitors, protein kinase C beta inhibitors, antioxidants (alpha lipoic acid), transketolase activators (thiamines and allithiamines), topical medications (analgesic patches, anesthetic patches, capsaicin cream, clonidine), and others. The nonpharmacological modalities include infrared therapy, shoe magnets, exercise, acupuncture, external stimulation (TENS), spinal cord stimulation, biofeedback and behavioral therapy, surgical decompression, and intrathecal baclofen.

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DESCRIPTION OF THE ANALYTIC PROCESS

In January of 2007 the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation convened an expert panel from the United States and Canada, selected to represent a broad range of relevant expertise. In August 2008 a literature search of MEDLINE and EMBASE was performed in all languages using the MeSH term diabetic neuropathies and its text word synonyms and key words for the therapeutic interventions of interest (see appendix e-1 for a full list of search terms). The search identified 2,234 citations, the titles and abstracts of which were reviewed by at least 2 authors for relevance, resulting in 463 articles. All of these articles were reviewed in their entirety, and of these, the panel identified 79 relevant articles. Each of these articles was rated by at least 2 authors according to the AAN criteria for the classification of therapeutic articles (appendix e-2), and recommendations were linked to the strength of evidence (appendix e-3) and to effect size of the intervention. Disagreements regarding classification were arbitrated by a third reviewer.

Articles were included if they dealt with the treatment of PDN, described the intervention clearly, reported the completion rate of the study, and defined the outcome measures clearly. The panel also considered the side effects of the treatment and measures of function and QOL, if any. Case reports and review papers were excluded.

We anticipated that studies would use varying measures for quantifying pain reduction. For the purposes of this guideline we preferred the following outcome measures, listed in order of preference:

1) The difference in the proportion of patients reporting a greater than 30% to 50% change from baseline on a Likert or visual analog pain scale (VAS) as compared to no treatment (placebo) or the comparative treatment. The Likert scale is an 11-point linear scale ranging from 0 (no pain) to 10 (maximum pain), and the patient rates his/her pain level on this scale [4-6].
2) The percent change from baseline on a Likert or VAS as compared to no treatment (placebo) or the comparative treatment [6].
3) Any other quantitative measure of pain reduction provided by the investigators.

For studies reporting the difference in the proportion of patients reporting a greater than 30% to 50% reduction in pain, we considered a risk difference of >20% a large effect (number needed to treat [NNT] <5), a risk difference of >10% to 20% (NNT >5 to 10) a moderate effect, and a risk difference of ≤10% (NNT >10) a small effect, where risk difference is the reduction in pain in the active treatment group minus the reduction in the control group. For studies using a mean reduction from baseline on a Likert scale or VAS as compared to no treatment (placebo) or a comparative treatment, we considered a reduction difference of >30% a large effect, >15% to 30% a moderate effect, and ≤15% a small effect. For any other quantitative measure of pain reduction, we considered a reduction of >30% a large effect, >15% to 30% a moderate effect, and ≤ 15% a small effect.

The panel recognized that older studies generally lacked measures of QOL and function compared to more recent studies. Furthermore, the panel was aware that a standardized QOL measure for PDN or a standardized assessment of function is not available, and multiple instruments were used to measure QOL, such as the SF-36® Health Survey, subsections of the SF-36, and function (such as sleep interference).

Studies with the highest levels of evidence for each intervention are discussed in the text, and data from other studies are shown in the tables. Details of Class I, II, and III studies are presented in the evidence tables.

ANALYSIS OF EVIDENCE

In Patients With PDN, What is the Efficacy of Pharmacological Agents to Reduce Pain and Improve Physical Function and QOL?

Anticonvulsants. We identified 20 articles relevant to anticonvulsants graded higher than Class IV (table e-1). Most of the randomized controlled trials (RCTs) rated as Class II instead of Class I had completion rates of less than 80% or the completion rate was not identified.

Four studies (3 Class I and 1 Class II) evaluated the efficacy of pregabalin [7-10]. All of the studies found that pregabalin relieved pain, but the effect size was small relative to placebo, reducing pain by 11-13% on the 11-point Likert scale in the Class I studies. A large dose-dependent effect (24-50% reduction in Likert pain scores compared to placebo) was observed in the Class II study [10]. The NNT for a 50% reduction in pain was 4 at 600 g/d [7-10] In the QOL measures, social functioning, mental health, bodily pain, and vitality improved, and sleep interference decreased, all changes with $P < 0.05$.

Two studies (1 Class I and 1 Class II) evaluated the efficacy of gabapentin [11,12] In the Class I study [11], gabapentin had a small effect of net pain reduction from baseline of 11% on the 11-point Likert scale compared to the change in placebo-treated patients, while a Class II gabapentin study showed no effect [12]. Gabapentin had no effect on overall QOL in the single study reporting this measure, but did show an improvement in subsets of mental health and vitality [11].

Two Class I trials evaluated the efficacy of lamotrigine [13,14]. There was no difference in the primary outcome measures in the lamotrigine and placebo groups.

Two studies (both Class II) evaluated the efficacy of sodium valproate [15,16]. Both showed a 27-30% pain reduction (moderate) in the Short Form-McGill Pain Question-

naire (SF-MPQ) with sodium valproate compared to placebo, and QOL was not measured. Both studies were conducted by the same principal investigator at the same center in separate populations with small numbers of patients; each study was remarkable for the lack of any change in placebo patients and for the lack of side effects typically attributed to sodium valproate. Treatment allocation concealment was not described.

One Class II study evaluated the efficacy of topiramate [17]. The study reported a small effect compared to placebo, 7% net pain reduction on the VAS, and an NNT of 6.6 for >30% pain reduction.

Three Class II studies evaluated the efficacy of oxcarbazepine [18-20]. Two studies showed no benefit [18,20], but a third showed a moderate benefit—17% more patients on oxcarbazepine had a >50% pain reduction compared to that of placebo, with an NNT of 6.023 [19]. The study showing a positive response had a slightly higher completion rate (73% [19] compared to 67%) [20]. Short Form-Quality of Life (SF-QOL) scores were not improved.

Three Class III studies evaluated the efficacy of lacosamide [21-23]. All the studies showed a small reduction in pain with 400 mg/d of lacosamide (3%, 6%, and 6% compared to placebo), but in 2 studies no significant differences compared to placebo were observed with 600 mg/d of lacosamide [22,23]. In one study, benefits on general activity and sleep interference QOL measures were observed [21].

Conclusions. Based on consistent Class I evidence, pregabalin is established as effective in lessening the pain of PDN. Pregabalin also improves QOL and lessens sleep interference, though the effect size is small. Based on 1 Class I study, gabapentin is probably effective in lessening the pain of PDN. Based on 2 Class II studies, sodium valproate is probably effective in treating PDN. Lamotrigine is probably not effective in treating PDN. Based on Class II evidence, oxcarbazepine is probably not effective in treating PDN. There is conflicting Class III evidence for the effectiveness of topiramate in treating PDN. Based on Class III evidence, lacosamide is possibly not effective in treating PDN. The degree of pain relief afforded by anticonvulsant agents is not associated with improved physical function.

Recommendations.

1. If clinically appropriate, pregabalin should be offered for the treatment of PDN (Level A).
2. Gabapentin and sodium valproate should be considered for the treatment of PDN (Level B).
3. There is insufficient evidence to support or refute the use of topiramate for the treatment of PDN (Level U).
4. Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for the treatment of PDN (Level B).

Clinical Context. Although sodium valproate may be effective in treating PDN, it is potentially teratogenic and should be avoided in diabetic women of childbearing age. Due to potential adverse effects such as weight gain and potential worsening of glycemic control, this drug is unlikely to be the first treatment choice for PDN.

Antidepressants. We identified 14 articles relevant to antidepressants rated higher than Class IV (table e-2). Seventeen articles were excluded. Most of the RCTs rated as Class II instead of Class I had completion rates of less than 80%.

Two studies (1 Class I and 1 Class II) evaluated the efficacy of venlafaxine [24,25]. The Class I study reported a moderate effect of venlafaxine, with 23% more pain relief than with placebo on the VAS-PI (0-100) scale and an NNT of 5 [24]. In the Class II study, venlafaxine plus gabapentin showed a moderate effect in relieving pain on the 11-point Likert scale in PDN, with 18% more relief than with placebo plus gabapentin [25]. The QOL measures of bodily pain, mental health, and vitality improved on the SF-36.

Three studies (1 Class I and 2 Class II) evaluated the efficacy of duloxetine in PDN [26-28]. The Class I study showed that duloxetine had a small effect compared to placebo, reducing pain by 8% on the 11-point Likert scale [26]; QOL was not assessed. In 2 Class II studies, duloxetine reduced pain (measured by VAS) 13% more than placebo [27,28], but in 1 study, a moderate effect was shown in responder analysis, with 26% more responders on duloxetine 120 mg/d (total 52%) than placebo (26%) (responders defined as those patients having 50% reduction in their 24-hour average pain score) [27]. The completion rate in both studies was about 75% [27,28]. Duloxetine reduced interference with general activity and improved SF-36 and EQ-5D™ scores [27,28].

Three studies (1 Class I and 2 Class II) evaluated the efficacy of amitriptyline [29-31]. The Class I study showed a large responder effect with amitriptyline, with 43% more responders with amitriptyline than with placebo (requiring at least 20% pain reduction for responder status). A third group in this study that was treated with maprotiline had 18% more responders than the placebo group [29]. In 2 Class II studies amitriptyline had a large effect, reducing pain by 63% and 58% more than placebo on a verbal 13-item descriptor list converted to a numeric 5-point scale [30,31]. In one of these Class II studies an active placebo was used [30].

Two Class III trials evaluated other tricyclic antidepressants (imipramine and nortriptyline) [32,33]. One Class III study showed that 47% more subjects on imipramine improved on a global evaluation compared to the placebo group, but there was no difference on a 6-point symptom scale [32]. Another Class III study showed a large effect with the combination of nortriptyline plus fluphenazine compared to placebo; 63% more patients had a 50% or greater VAS reduction in the combination group [33]. One Class III study compared desipramine, amitriptyline, fluoxetine, and

placebo and found a small effect (6% pain reduction) for amitriptyline and desipramine, but not for fluoxetine on a 13-word scale converted to 5 points [34].

Conclusions. Based on 3 Class I and 5 Class II studies, the antidepressants amitriptyline, venlafaxine, and duloxetine are probably effective in lessening the pain of PDN. Venlafaxine and duloxetine also improve QOL. Venlafaxine is superior to placebo in relieving pain when added to gabapentin. There is insufficient evidence to determine whether desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine are effective for the treatment of PDN.

Recommendations.

1. Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of PDN (Level B). Data are insufficient to recommend one of these agents over the others.
2. Venlafaxine may be added to gabapentin for a better response (Level C).
3. There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of PDN (Level U).

Opioids. We identified 9 articles relevant to opioids graded higher than Class IV (table e-3). Most of the RCTs rated as Class II instead of Class I had completion rates of less than 80%.

One Class I study showed that dextromethorphan relieved pain moderately by 16% more than placebo on a 20-point Gracely Box scale in PDN and improved SF-36 results [35]. In 1 Class II study, dextromethorphan with benztropine reduced pain by 24% more than placebo on a 6-point scale, a moderate reduction [36].

A Class II study showed that morphine sulphate had a small effect and reduced pain from baseline by 15% on the SF-MPQ and improved SF-36 and Beck Depression Inventory results [37].

In 2 Class II studies, tramadol relieved pain moderately (16% and 20% more than placebo on a Likert scale) in PDN [38,39] and improved physical function [38].

In 3 Class II studies, oxycodone controlled-release and Ultracet (tramadol + acetaminophen) relieved pain in PDN[40,e1,e2]. Oxycodone had a small effect, with 9% more pain relief on the Pain Inventory than placebo. It also improved sleep quality by 7% more than placebo, but did not change SF-36 scores [40]. Ultracet improved pain by 13% on the VAS, a small effect, and also improved SF-36 scores by 10% [e1]. Oxycodone controlled-release had a moderate effect on pain (27% reduction in the VAS compared to placebo), improved disability by 10%, and improved most SF-36 subscores [e2].

Conclusions. Based on 1 Class I study, dextromethorphan is probably effective in lessening the pain of PDN and improving QOL. Based on Class II evidence, morphine sulphate, tramadol, and oxycodone controlled-release are probably effective in lessening the pain of PDN. Dextromethorphan, tramadol, and oxycodone controlled-release have moderate effect sizes, reducing pain by 27% compared with placebo.

Recommendations. Dextromethorphan, morphine sulphate, tramadol, and oxycodone controlled release should be considered for the treatment of PDN (Level B). Data are insufficient to recommend one agent over the other.

Clinical Context. The use of opioids for chronic nonmalignant pain has gained credence over the last decade due to the studies reviewed in this paper. Both tramadol and dextromethorphan were associated with substantial adverse events (e.g., sedation in 18% on tramadol and 58% on dextromethorphan, nausea in 23% on tramadol, and constipation in 21% on tramadol). The use of opioids can be associated with the development of novel pain syndromes such as rebound headache. Chronic use of opioids leads to tolerance and frequent escalation of dose.

Other Pharmacological Agents. We identified 18 articles relevant to other pharmacological agents rated higher than Class IV (table e-4). Thirteen other articles were excluded. Most of the RCTs rated Class II instead of Class I had completion rates of less than 80%, and those rated Class III often lacked predefined endpoints.

One Class I study of 0.075% capsaicin showed a large effect, with 40% more pain reduction on the VAS compared to vehicle cream [e3]. One Class II study showed that 0.075% capsaicin reduced pain in PDN with a small effect size of 13% in VAS compared to vehicle cream [e4].

One Class I study of isosorbide dinitrate spray showed a moderate effect, with 18% more pain reduction on the VAS relative to placebo [e5].

One Class I study of clonidine and pentoxifylline compared to placebo did not show an effect of these drugs on PDN [e6].

One Class I study of mexiletine did not show an effect on PDN [e7]. Two Class II studies both showed pain reduction with mexiletine, one with a large effect (37% more pain reduction than placebo) [e8] and one with a small effect (5% difference compared to placebo) [e9]. Sleep disturbance was reduced in the first Class II study [e3], but not in the second [e9].

In a single Class I study of sorbinil, pain relief was not observed [e10].

One Class I study and 2 Class II studies showed benefit from alpha-lipoic acid in reducing pain in PDN, but pain was not a predefined endpoint in these studies [e11–e13]. The effect size in pain reduction was moderate (20%-24% superior to placebo).

In 2 Class III studies, IV lidocaine decreased pain relative to placebo infusion [e14,e15]. In one study, a transient decrease of 75% was observed in a 5-point symptom scale, compared to a decrease of 50% with placebo infusion [e14]. In the other study, the McGill Pain Questionnaire improved by a small amount (9% reduction in present pain intensity) with lignocaine, and the differences with placebo were significant due to worsening in the placebo group [e15]. The baseline values were not provided.

In 2 Class III studies, the Lidoderm patch improved pain scores with a moderate to large effect (20%-30% reduction in pain scores from baseline and 70% of patients experienced more than a 30% decrease in pain) [e16,e17].

Conclusions. Based on Class I and Class II evidence, capsaicin cream is probably effective in lessening the pain of PDN. Based on Class III studies, there is insufficient evidence to determine if IV lidocaine is effective in lessening the pain of PDN. Based on Class III evidence, the lidoderm patch is possibly effective in lessening the pain of PDN. Based on Class I evidence, clonidine and pentoxifylline are probably not effective for the treatment of PDN. The evidence for the effectiveness of mexiletine is contradictory; however, the only Class I study of this agent indicates that mexiletine is probably ineffective for the treatment of PDN. There is insufficient evidence to determine whether vitamins and alpha-lipoic acid are effective for the treatment of PDN. Based on Class I evidence, isosorbide dinitrate spray is probably effective for the treatment of PDN.

Recommendations.

1. Capsaicin and isosorbide dinitrate spray should be considered for the treatment of PDN (Level B).
2. Clonidine, pentoxifylline, and mexiletine should probably not be considered for the treatment of PDN (Level B).
3. The lidoderm patch may be considered for the treatment of PDN (Level C).
4. There is insufficient evidence to support or refute the usefulness of vitamins and alpha-lipoic acid in the treatment of PDN (Level U).

Clinical Context. Although capsaicin has been effective in reducing pain in PDN clinical trials, many patients are intolerant of the side effects, mainly burning pain on contact with warm/hot water or in hot weather.

In Patients With PDN, What is the Efficacy of Non-Pharmacological Modalities to Reduce Pain and Improve Physical Function and QOL?

We identified 11 articles relevant to non-pharmacological treatment of PDN graded higher than Class IV (table e-5). Only articles on electrical stimulation, Reiki therapy, low-intensity laser therapy, and magnetized shoe insoles reached evidence levels sufficient for discussion in the text. Surgical decompression was addressed in a previous AAN practice advisory [e18] and will not be considered further in this article.

Electrical Stimulation. One Class I study reported that percutaneous electrical nerve stimulation reduced pain in PDN by a large magnitude (42% on the VAS) compared with the reduction observed with sham treatment, and also improved sleep [e19]. One Class II study reported no effect with electrical stimulation, [e20] and 1 Class II study of frequency-modulated electromagnetic neural stimulation showed a small degree of pain relief (11% on the VAS) in a crossover design, but with no improvement in the placebo group [e21].

One Class III study showed the addition of electrotherapy to amitriptyline was more effective than amitriptyline alone [e22].

Magnetic Field Treatment. One Class I study using pulsed electromagnetic fields compared with a sham device failed to demonstrate an effect in patients with PDN [e23].

One Class II study of the use of magnetized shoe insoles in patients with PDN showed a small effect (14% VAS decrease) at 4 months compared with that from non-magnetized insoles, but the endpoint of burning pain was not predetermined [e24].

Other Interventions. One Class I study on the use of low-intensity laser treatment compared to sham treatment did not show an effect on pain [e25].

Reiki therapy is defined as the transfer of energy from the practitioner to the patient to enable the body to heal itself through balancing energy. One Class I study of Reiki therapy did not show any effect on PDN [e26].

Other interventions such as exercise and acupuncture do not have any evidence for efficacy in treating PDN.

Conclusion. Based on a Class I study, electrical stimulation is probably effective in lessening the pain of PDN and improving QOL. Based on single Class I studies, electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy are probably not effective for the treatment of PDN. There is not enough evidence to support or exclude a benefit of amitriptyline plus electrotherapy in treating PDN.

Recommendations.

1. Percutaneous electrical nerve stimulation should be considered for the treatment of PDN (Level B).
2. Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for the treatment of PDN (Level B).
3. Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment of PDN (Level U).

Table. *Summary of recommendations*

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

Comparison Studies

Studies with 2 active treatment arms and without a placebo arm were considered separately and graded using active control equivalence criteria (appendix e-2; table e-6). We identified 6 comparison studies of agents but did not find sufficient evidence to recommend one over the other [e27–e32]. The comparisons were gabapentin to amitriptyline (2), venlafaxine to carbamazepine, nortriptyline + fluphenazine to carbamazepine, capsaicin to amitriptyline, and benfothiamine + cyanocobalamine with conventional vitamin B. None of the studies defined the threshold for equivalence or noninferiority.

CLINICAL CONTEXT SUMMARY FOR ALL EVIDENCE

It is notable that the placebo effect varied from 0-50% pain reduction in these studies.

Adjuvant analgesic agents are drugs primarily developed for an indication other than treatment of PDN (eg, anticonvulsants and antidepressants) that have been found to lessen pain when given to patients with PDN. Their use in the treatment of PDN is common [e33]. The panel recognizes that PDN is a chronic disease and that there are no data on the efficacy of the chronic use of any treatment, as most trials have durations of 2-20 weeks. It is important to note that the evidence is limited, the degree of effectiveness can be minor, the side effects can be intolerable, the impact on improving physical function is limited, and the cost is high, particularly for novel agents.

A summary of Level A and B recommendations for the treatment of PDN is provided in the Table.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. A formalized process for rating pain scales for use in all clinical trials should be developed.
2. Clinical trials should be expanded to include effects on QOL and physical function when evaluating efficacy of new interventions for PDN; the measures should be standardized.
3. Future clinical trials should include head-to-head comparisons of different medications and combinations of medications.
4. Because PDN is a chronic disease, trials of longer duration should be done.
5. Standard metrics for side effects to qualify effect sizes of interventions need to be developed.
6. Cost-effectiveness studies of different treatments should be done.
7. The mechanism of action of electrical stimulation is unknown; a better understanding of its role, mode of application, and other aspects of its use should be studied.

Disclaimer

This statement is provided as an educational service of the AAN, AANEM, and AAPM&R. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN, AANEM, and AAPM&R recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Conflict of Interest

The AAN, AANEM, and AAPM&R are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN, AANEM, and AAPM&R keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN, AANEM and AAPM&R limit the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN

committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pmrj.2011.03.008.

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Footnotes Continued From Page 345.

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DISCLOSURE

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E-APPENDICES

APPENDIX E-1: SEARCH TERMS USED

Painful diabetic neuropathy OR neuropathic pain OR diabetes AND: Anticonvulsant, anti-epileptic, anti-depressant, anti-arrthymic, spinal cord stimulation, infra-red therapy, acupuncture, opioids, topical patches, lidocaine, intra-thecal baclofen, TENS, vitamins, life-style modification, metabolic control, baclofen

APPENDIX E-2: AAN CLASSIFICATION OF EVIDENCE FOR RATING OF A THERAPEUTIC ARTICLE

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation
b. primary outcome(s) clearly defined
c. exclusion/inclusion criteria clearly defined
d. adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
e. For non inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*
   1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
   2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
   3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
   4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

* Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three are missing, the class is automatically downgraded to Class III.

APPENDIX E-3: CLASSIFICATION OF RECOMMENDATIONS

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)***

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

APPENDIX E-4: QUALITY STANDARDS SUBCOMMITTEE (QSS) MEMBERS 2009-2011

Jacqueline French, MD, FAAN (Co-Chair); John D. England, MD, FAAN (Co-Chair); Eric Ashman, MD; Stephen Ashwal, MD, FAAN (Ex-Officio); Misha-Miroslav Backonja, MD; Richard L. Barbano, MD, PhD, FAAN; Michael G. Benatar, MBChB, DPhil; John J. Halperin, MD, FAAN; Deborah Hirtz, MD, FAAN (Ex-Officio); Jonathan Hosey, MD, FAAN (Ex-Officio); Andres M. Kanner, MD; Steven R. Messé, MD; Leslie A. Morrison, MD; Pushpa Narayanaswami, MD, MBBS; Dean M. Wingerchuk, MD, MSc, FRCP(C); Theresa A. Zesiewicz, MD, FAAN.

APPENDIX E-5: MISSION STATEMENT OF QSS

The mission of the QSS is to prioritize, develop, and publish evidence-based practice parameters related to the

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

*** In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

diagnosis, treatment, and prognosis of neurologic disorders. The QSS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

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TABLE LEGEND

ALA is alpha lipoic acid
BDI is Beck Depression Inventory
BPI is Brief Pain Inventory
CGI is Global Impression of Severity
EQ-5D is European Quality of Life – 5 Dimensions
GES is Global Evaluation Scale (physician's)
ITT is intention to treat
LFT is liver function tests
LOCF is last observation carried forward
NCS is nerve conduction studies
NIS-LL is neuropathy impairment score in the lower limbs
NPS is numeric pain scale
NS is not significant
NSD is no significant difference
PCB is placebo
PI is pain intensity
PGE is Physician's Global Evaluation Score
PPI is present pain intensity
Prim is primary
POMS is profile of mood state
QOL is quality of life
Sec is secondary
SF36 is Short Form 36, survey on quality of life, 8 domains of health
SF-MPQ is the short form McGill Pain Questionnaire (a questionnaire about pain)
TSS is total symptoms score
VAS is visual analogue scale; 11-point scale from 0 to 10 points
For references, see article and data supplement titled "e-References."

Evidence Table e-1. *Design characteristics and outcomes in controlled studies of patients with painful diabetic neuropathy treated with anticonvulsants*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Backonja, 1998 (11)	I	165	80%	Gabapentin up to 3600 mg/day	11 pt Likert
Lesser, 2004 (7)	I	338	89.3%	Pregabalin titrate 75/300/600 day	11 pt Likert pain intensity
Richter, 2005 (8)	I	246	89.0%	Pregabalin 150/600 mg	11 pt Likert pain intensity
Rosenstock, 2004 (9)	I	146	87.0%	Pregabalin 1300 mg/day	11 pt Likert pain intensity
Vinik, 2007 (14)	I	2 studies 360/stud	95%	Lamotrigine 200, 300, or 400 mg/d or placebo during a 19 wk treatment phase, including a 7 wk dose-escalation phase and a 12 wk fixed-dose maintenance phase	Three pain scales (11 point pain intensity scale; SF-MPQ; Neuropathy pain scale
Kochar, 2002 (15)	II	60	87%	Sodium valproate 200 mg tid vs. placebo × 1 wk, then sodium valproate 400 mg TID vs placebo × 1 m	SF-MPQ
Kochar, 2004 (16)	II	48	89.6%	Sodium Valproate 500 mg QD or placebo × 1wk, then 500 mg BID or placebo × 3m	SF-MPQ, VAS, present pain intensity (PPI); (baseline to 3 mo)
Eisenberg, 2001 (13)	II	59	78%	Lamotrigine	numeric pain scale (NPS)
Raskin, 2004 (17)	II	323	59.5%	Topiramate	VAS
Dogra, 2005 (19)	II	146	72.6%	Oxcarbazepine to 1800 mg/d	100 mm VAS
Beydoun, 2006 (20)	II	347	66.9%	Oxcarbazepine 600, 1200 or 1800 mg/d or placebo	100 mm VAS

Evidence Table e-1. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Small, 11% difference −1.2 difference from placebo CI (−1.9, −0.6) **For Moderate improvement on PGIC** OR 3.7 RR 2.0 RD 0.3 NNT 3	SF-36; no difference SF-36; 5.4 for mental health and 9.7 for vitality	Dizziness, somnolence, diarrhea	
Small, 11% and 15% diff −0.2, −1.2 and −1.6 for 75, 300 and 600mg difference from PCB **For 600mg/D** CI (−2.06, −0.85) OR: 3.1 RR 2.0 RD 0.3 NNT 4	SF-36; social functioning ($p < 0.05$) SF-36; mental health and vitality ($p < 0.05$)	Dizziness, somnolence, diarrhea	
Small, 12% diff −1.3 difference for 600mg from PCB when compared to baseline	sleep interference; −1.2 (P=0.004)	Dizziness, somnolence, peripheral edema as most common for pregabalin	
Small, 13% diff −1.5 (p=0.0001) CI (−2.2,−0.8) **For 50% reduction in pain** OR 3.9 RR 2.8 RD 0.3 NNT 4	SFMPQ; −441 (P=.0033) SF36; bodily pain improved	Dizziness, somnolence, peripheral edema as most common for pregabalin	
Small, 10% diff Neuropathy pain scale −2.7 for 400 mg Lamotrigine at 19 weeks compared to −1.6 placebo (significant); inconsistent results for other pain scales **NSD**	Sleep Interference NSD	Headache, rash, 1 patient hospitalized with fever and rash	Results between 2 studies inconsistent LOCF analysis NSD in both studies Post-hoc analysis showed some changes
Moderate, 30% diff approx 30% reduction on sodium valproate; vs 0% with PCB **Change in pain ≥5 group** RD 0.5 NNT 2	NCS; no change	One patient with elevated LFTs (?drug vs. placebo)	Strange placebo did not improve No description of treatment allocation concealment.
Moderate, 27% diff 19.5 to 9.7; VAS = 6 to 3; PPI = 2.7 to 1.3 in treatment group. No change in placebo group	NCS; no change	Elevated LFTs, nausea	Strange placebo did not improve. No description of treatment allocation concealment. **No effect size**
Moderate, 17% diff 37% reduction lamotrigine vs. 20% in controls **For 50% pain reduction** OR 3.4 RR 2.3 RD 0.3 NNT 4	none	Skin rash in 2 on lamotrigine	Used depression scale-no change; McGill pain questionnaire-no change; only 6 weeks
Small, 7% diff 68 to 46.2 points topiramate vs.69.1 to 54 placebo; topiramate better for mean worst pain severity **For >30% reduction in VAS** OR 1.9 RR 1.4 RD 0.2 NNT 7		High prevalence of side effects with treatment including diarrhea, anorexia, somnolence (topir 15.2 vs. 11% in placebo)	?blinding primary efficacy parameter NS
Moderate, 17% diff >50% reduction in 35% of tx and 18% of placebo (P=0.01) OR 2.4 RR 1.9 RD 0.2 NNT 6	Sleep questionnaire; 31% in treatment and 49% in placebo awakened from sleep (p=0.02)	Dizziness, headache, nausea, somnolence, fatigue, vomiting	
NSD P – 19.1 Oyc: 600: −25.9 1200: −29.5 1800: −26.5	SF36-QOL; not statistically significant	Dizziness, tremor, headache, somnolence, fatigue, increased as dose of OXC increased	

Evidence Table e-1. *Continued*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Freynhagen, 2005 (10)	II	338	61.8%	Pregabalin in fixed dose of 600 mg/day versus 150-600 mg/day	11 pt Likert pain intensity scores
Gorson, 1999 (12)	II	40	Not reported	Gabapentin 900 mg/day	VAS, MPQ score and PPI
Grosskopf, 2006 (18)	II	141	67.4%	Oxcarbazepine 1200 mg/d	VAS
Beydoun, 2004 (e35)	III Open label	30	66.7%	Oxcarbazepine	VAS
Gomez-Perez, 2004 (e36)	III	339	95.3%	Gabapentin	VAS
Rauck, 2007 (21)	III	119 25 drop-outs	79.0%	RCT Lacosamide 100-400 mg/d × 4 wks after titration compared to placebo	Likert 11 point pain scale
Wymer, 2009 (22)	III	370	234/370 (63%)	RCT Lacosamide 200, 400, 600 mg vs P after 6 w titration for total 18 weeks	Likert 11 point pain scale Prim: ITT-LOCF of change in Likert in last 4 weeks of maintenance. Sec: Same, but in total 12-week maintenance
Shaibani, 2009 (23)	III	468	257 (55%)	RCT same as above.	Same as above (same investigators)
Agrawal, 2009 (e37)	III	83	80/83 (96%)	2X2 design Valproic Acid (20 mg/kg/day) and Glyceryl trinitrite spray (0.4 mg/actuation per leg qhs) Placebo controlled	VAS SF-MPQ PPI (present pain intensity) 10 p Likert.

Evidence Table e-1. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Large effect, 24% and 28% at 50% reduction baseline pain of 6.7 decreased vs placebo to the difference that lead to *P*=.007 and also in 30% and 50% response which was also significant NNT for ≥50% pain reduction 3.6 (CI 2.4-6.9)	Not reported	Dizziness, peripheral edema, weight gain, somnolence	
VAS NSD MGP improved on gabapentin compared to placebo 8.9 vs 2.2	Not done	Drowsiness, fatigue, and imbalance	Lack of completion rate information ?**primary end point did not change**
NSD Pain reduction: P 27.9% Oxc 31.1% VAS; 48.3% degree of change	Components of SF-36;NS Sf-QOL; no degree of change	Dizziness, nausea, headache VES in 17% of patients who dropped out	
Large VAS; 53.6% titrated vs. 43.3% for fixed	Only sleep interference; 57% titrated vs. 37.2% for fixed		Open label study
Small, 3% diff decrease in Likert pain score by LOCF = 0.9 for placebo and 1.2 for lacosamide (*P*=0.039). By AOD, means were 0.9 and 1.7, respectively (*P*=.0022). The proportion with a 2-pt decrease was 50.8% for P and 60% for lacosamide (*P*-value not provided)	Analyzed sleep interference (Likert), interference with general activity (Likert). and SF-MPQ with statistically significant improvements in each.	Tachycardia, dizziness, nausea, constipation, back pain, anxiety, nervousness; percentages in paper; these are more frequent than in placebo group	III; greater than 20% drop-out, not well defined study population (painful polyneuropathy not well defined w/objective scale)
Small, 7% 400 mg and 4% 600 mg Prim: P: −1.6 vs −2.3 (*P*=.01) in 400 mg group; −2.02 (*P*=NS) in 600 mg group. Sec: **Small, 8% 600 mg** −1.7 in P vs –s.4 (*P*=.02) in 400; −2.6 (*P* < .01) in 600 In 400mg group, 56% got decrease of 30% as compared to 46% in P – p not given. **Small, 6% at 400 mg and 5% at 600 mg** Prim: −1.7P vs −2.3 in 400 (*P*-.05), −2.2 in 600 mg (p=0.07)		Tachycardia, dizziness, nausea, constipation, back pain, anxiety, nervousness; percentages in paper; these are more frequent than in placebo group 24.4% withdrawal on account of AE.	III – big dropout rate, inconsistency with larger dose and 400 mg dose; major sign outcomes I the observed-cases approach. III- big drop out rate, primary endpoint shows same inconsistency between 400 mg and 600 mg groups. ?Confusion re: actual loss to follow-up.
NSD on VA alone Moderate, 19% combination tx Only t and p values provided. Valproic acid vs placebo not sign. Valproic acid + GTN spray sign (p < 0.001) in which VAS dropped by 2.6 compared to P 0.5.		1 liver enzyme elevation	Small group comparisons – 20 per group. Valproic acid vs. placebo NS In the direct comparison.

Evidence Table e-2. *Design characteristics and outcomes in controlled studies of patients with painful diabetic neuropathy treated with antidepressants*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Rowbotham, 2004 (24)	I	244	83%	Venlafaxine ER 75 mg and venlafaxine 150-225 mg/day placebo 6 weeks	VAS-PI (0 to 100)
Raskin, 2005 (26)	I	348	85%	Duloxetine 60 mg QD; duloxetine 60 mg BID placebo; for 12 weeks	VAS (11 point)
Vrethem, 1997 (29)	I Sub-pop	19 with PDN of 37	89%	Double-blind, randomized, three-phase, crossover amitriptyline and maprotiline	Global 5-step scale and daily 10-step verbal scale; at least 20% reduction in pain compared with baseline
Max, 1987 (31)	II	37	78%	Amitriptyline for 6 weeks; Placebo with noticeable side effects for 6 weeks	verbal conversion (two 13-word lists) to numeric (5 point) scale
Max, 1987 (30)	II	24	86%	Amitriptyline Cross over study - 6 weeks on drug; 6 weeks on active placebo	Verbal descriptors (13 validated descriptors) converted to numerical scale
Goldstein, 2005 (27)	II	457	75.3%	Duloxetine 20, 60, 120 mg/d or placebo for 12 weeks	24-hr Average Pain Score rated on 11-point (0-10) Likert scale (VAS)
Wernicke, 2006 (28)	II	334	74.3%	Duloxetine 60 mg QD; duloxetine 60 mg BID placebo	VAS Weekly mean of 24-hour average pain score measured by 11-point Likert scale

Evidence Table e-2. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Small effect at low dose (5% diff) and moderate effect (23%) diff at high dose mean adjusted pain intensity score 18.7 (27%) for placebo; 22.4 (32%) for venlafaxine ER 75; and 33.8 (50%) for venlafaxine ER 150-225. NNT was 4.5 for venlafaxine ER 150-225	None	Nausea and somnolence. 7 patients on venlafaxine had clinically important ECG changes	
Small effect (8%) diff for both doses Mean change (SE) −2.0 (0.18) for duloxetine 60 mg QD and −2.5 (0.2) for duloxetine 60 mg BID; Between group difference (95% CI) versus placebo −0.9 (−1.4, −0.4) for duloxetine 60 mg QD and −0.9 (−1.4, −0.4) for duloxetine 60 mg BID	None	Nausea, somnolence, hyperhidrosis, and anorexia; vomiting and constipation more frequent in duloxetine 60 mg BID group.	
Large effect with amitriptyline (43% more with pain reduction) (67% ami, 24% placebo) Moderate effect with maprotiline (18% diff) With global pain rating, both amitriptyline ($P < .0001$) and maprotiline ($P < .05$) were more effective than placebo; amitriptyline slightly more effective than maprotiline ($P < .05$ by repeated measures ANOVA). NO difference between diabetics and nondiabetics ($F = 0.003$, df = 1.6, $P = .96$, ANOVA).	None	Dry mouth, urinary retention, sedation, vertigo	
Large effect (63% of pts over placebo had mod-complete relief) Amitriptyline superior to placebo at weeks 3 through 6. At 6 weeks there was a 45% difference in pain (large) compared with placebo ($P < .01$ by between-patient comparison unpaired t-test)	None	AEs equal between amitriptyline and active placebo	
Large (58% more on ami had mod-complete relief) significant at week 5 ($P < .05$) and week 6 ($P < .01$) by within-patient comparison paired t-test	None	Similar to active placebo with respect to dry mouth, sedation, constipation but orthostatic hypotension and palpitations more frequent with desipramine	
Small effect for absolute pain reduction (10% for low dose & 13% high dose) Mean difference between duloxetine 60 mg/d and placebo was −1.2 (95% CI: −1.8 to −0.50) and between duloxetine 120 mg/d and placebo was −1.5 (95% CI: −2.1 to −0.8). **Responders show moderate effect over placebo: (15% more at 20 mg/d, 23% more at 60 mg/d and 26% more at 120 mg/d)** A 50% reduction in 24-hr Average Pain Score was achieved by 29 (26%) in placebo group, 46 (41%) in duloxetine 20 mg/d group, 55 (49%) in duloxetine 60 mg/d group, and 57 (52%) in duloxetine 120 mg/d group. The number achieving a 50% reduction in pain was significantly greater for all duloxetine groups compared to placebo ($P < .05$).	Brief Pain Inventory (BPI); BPI interference general activity: duloxetine 60 mg/d improvement ($P < .05$ vs placebo); duloxetine 120 mg/d improvement ($P < .001$ vs placebo. Euro Quality of Life (EQ-5D); duloxetine 60 mg/d improvement ($P < .05$ vs placebo); duloxetine 120 mg/d improvement ($p < 0.05$ vs placebo)	Two adverse effects (somnolence and constipation) significant difference ($P < .01$) between duloxetine 60 mg/d and placebo; More frequent adverse effects (see Table 4) for duloxetine 120 mg/d	
Small (12% and 13% diff) Mean difference from placebo at endpoint was −1.3 (95% CI −2.0 to −0.7) for duloxetine 60 mg QD and −1.4 (95% CI −2.1 to −0.8) for duloxetine 60 mg BID Highly significant treatment effect for both duloxetine 60 mg QD and duloxetine 60 mg BID	SF-36; EQ-5D; BPI Interference; Significantly better for both treatment groups compared with placebo	Nausea, fatigue, somnolence, increased sweating, dry mouth	

Evidence Table e-2. *Continued*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Simpson, 2001 (25)	II for part II of study III for part III	Part II had 11 patients randomized: Part III had 42 patients	Part II 73% Part III 90%	Part II was 8 week trial comparing gabapentin + venlafaxine with gabapentin + placebo; Part III was uncontrolled 8 week trial of patients who did not improve on gabapentin monotherapy and then received venlafaxine + gabapentin	VAS 11 point Likert scale
Kvinesdal, 1984 (32)	III	15	80%	Imipramine compared to placebo Crossover; 5 weeks each treatment	6 item scale & global
Gomez-Perez, 1985 (33)	III	24	75%	Nortriptyline and fluphenazine vs placebo for 30 days; then cross over for 30 days	VAS Modification of VAS, but not numerical Likert scale; in % from 100% baseline
Mendel, 1986 (e38)	III	6	100%	Amitriptyline and fluphenazine and placebo crossover	10-cm graphic rating scale
Max, 1992 (34)	III	57	70% for amitriptyline-desipramine group; 83% for fluoxetine-placebo group	Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy 2 double-blind studies; crossover	Validated scale of 13 words converted to numerics (5 pt scale)
Raskin, 2006 (e39)	III	449	62.6%-63.8%	Duloxetine 60 mg BID or duloxetine 120 mg QD or routine care to determine rate of side effects more than efficacy	Brief Pain Inventory (BPI) and Clinical Global Impression of Severity (CGI)
Kadiroglu, 2008 (e40)	III	60 (of 294 considered)	Not reported	Venlafaxine	Short-form McGill – focused on categories of response "well, moderate and none"

Evidence Table e-2. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Moderate (18% diff with venlafaxine) Part II: Difference in mean pain score of −2.0 for gabapentin + venlafaxine group and −0.5 for gabapentin + placebo group; **Moderate (19% diff)** Part III: Mean pain score declined 2.1 from baseline ($P < .01$)	Part II SF-36 QOL Showed significant ($P < .01$) improvement in gabapentin + venlafaxine group. SF-36 in Part II; Bodily pain, mental health and vitality components significantly ($P < .01$) better for gabapentin + venlafaxine vs gabapentin + placebo	Dizziness, somnolence, nausea	Simpson, 2001[25]
Large effect on global impression with 47% more on imipramine than placebo. NSD in six-item scale ($P < .10$)	None	Dizziness, dry mouth, impaired micturition	
Large (63% diff) Drugs produced >50% reduction of pain in 16 patients ($P < .01$); placebo produced less than 50% decrease in pain with one exception	None	Somnolence in 6; dryness of mouth in 6; dizziness in 2.	
NSD No additional effect of amitriptyline and fluphenazine over placebo	None	None	
Small (5 pt scale, 6%, 6% and 4% diff) Mean +SEM decreased by 0.5 + 0.1 unit for amitriptyline; 0.5 + 0.1 unit for desipramine; 0.4 + 0.1 for fluoxetine; 0.2 +0.1 unit for placebo. Significant ($P < .05$ by one-tailed Dunnett's test) for amitriptyline and desipramine, but not fluoxetine.	None	Dry mouth, tiredness, headache, constipation, lightheadedness, confusion, orthostatic hypotension	
NSD between duloxetine & routine care Significant improvement from baseline to endpoint on all subscales ($P < .001$) for both treatment groups	Safe but 20.1% in duloxetine 60 mg BID and 27.0% in 120 mg QD group d/c because of AEs; TEAEs > 10% were nausea, somnolence, dizziness, headache, dry mouth, increased sweating, vomiting, constipation, insomnia and diarrhea		Open label
NSD No diff in Short-form McGill Questionnaire 16 in treatment "well response" vs 2 in P		Not reported	Only 30 subjects per group. Poor description of inclusion criteria, primary outcome

Evidence Table e-3. *Design characteristics and outcomes in controlled studies of patients with painful diabetic neuropathy treated with opioids*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Sang, 2002 (35)	I	23	82.60%	RCT Memantine or Dextromethorphan or placebo	20 pt Gracely Box; SF36
Gilron, 2005 (37)	II	57	71.90%	MSO4/gabapentin	BP1, BDI, SF36, SFMPQ
Gimbel, 2003 (40)	II	159	72.30%	RCT Oxycodone IR	P1, BPI, day 26-42
Freeman, 2007 (e1)	II	313	75.70%	RCT Ultracet	VAS, Sleep, SFMPQ, POMS
Harati, 1998 (38)	II	131	62.60%	RCT Tramadol (mean 210 mg/d)	Likert, 6 wks
Nelson, 1997 (36)	II	14	93.30%	Dextromethorphan w/cogentin	6 pt scale, 13 pt scale
Sindrup, 1999 (39)	II	45	75.50%	Tramadol	10 pt scale
Watson, 2003 (e2)	II	45	53.30%	Oxycontin CR mean score 40 vs cogentin (active placebo)	VAS, SF36
Harati, 2000 (e41)	III	120	72.60%	Tramadol Open label	Likert

Evidence Table e-3. *Continued*

Results Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Moderate DM decrease 16% vs placebo (−4.7, 0.9) memantine 1% vs placebo (−1.6, 1.3) no effect on allodynia Dose-response phase, high dose DM showed improvement	Improved "emotional" SF36 subtest (19% ± 8.1, p < 0.01)		
Small 15% reduction vs placebo, SFMPQ-15.6% reduction	SF36-10-18% improvement BDI - 6.8%		
Small 9% decrease vs placebo on PI, **Moderate** BPI decrease −18%	Sleep quality increased 7% no diff in SF36	95% of study pts 68% of placebo (!) reported mild AE	
Small 13.4% vs placebo on VAS ($P < .001$)	SFMPQ Improvement 10%; POMS	S5s - Nausea 11.9% vs 3.3%	
Moderate 16% decrease pain intensity vs placebo; 24% increase pain relief (measured both)	9.3% increase physical functions; 6.5% inc. social function	RX-nausea (23.1%) constipation (21.5%) HA (16.9%) Somnolence (12.3%)	
Moderate 24% reduction vs placebo (6, 42; P=.014) Global score reduced 23.3%=(0.6,−2.2, p=0.002)	N/A	18/31 Rx patients reported sedation	Allocation concealment
Moderate 20% reduction (P=.002, No CIs)			Allocation concealment
Moderate 27% reduction vs placebo, 22% relief	16-30% improved pain & disability 5-10% improvement in most SF36 subscores	No difference between groups (note active placebo)	
Moderate 22% pain relief maintained			Open label

Evidence Table e-4. *Design characteristics and outcomes in controlled studies of patients with painful diabetic neuropathy treated with clonidine, pentoxifylline, capsaicin, mexiletine, antioxidants*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Cohen, 1990 (e6)	I	37 16 clonidine 21 pentoxifylline	100%	DB placebo Clonidine 0.1 mg/d + placebo or placebo Bid × 4 wks, then single blind 0.1 mg clonidine BID × 4 wks Pentoxifylline 400 mb TID or placebo TID × 12 wks	Total symptom score 0-20 at 4 wks
Tandan, 1992 (e3)	I	22	90.9%	RCT 0.075% capsaicin QID × 8 weeks or placebo cream	VAS pain relief VAS pain severity category
Wright, 1997 (e7)	I	31 2 drop-outs	93.5%	Mexiletine 600 mg/D × 3wks	4 item symptom score VAS Global assessment
Ziegler, 2006 (e13)	I	187	92%	ALA 3 doses	TSS
Yuen, 2002 (e5)	I	24	92%	Isosorbide dinitrate spray	11 point Likert
Ziegler, 1995 (e11)	II	328	79%	Alpha lipoic acid 3 doses IV vs. placebo over 3 weeks	TSS was primary outcome (Positive in subsets)
Ziegler, 1999 (e12)	II	516	73%	ALA or placebo: IV ALA then po ALA, IV ALA then po placebo or IV placebo then po placebo	TSS Negative for primary
Anonymous, 1991 (e4)	II	277 58 drop-outs	79.1%	Capsaicin 0.075% or vehicle cream applied 4 x/D Masking incomplete	Physician's global evaluation score (PGE) VAS intensity VAS pain relief
Dejgard, 1988 (e8)	II	19 3 drop-outs	84.2%	RCT Mexiletine 150 mg/dx3d, 300mg/dx3d, then 10mg/kg daily × 10 weeks No tx × 4 wks Crossovers × 10 wks	VAS score
Oskarsson, 1997 (e9)	II	127 11 drop-outs	91.3%	RCT Mexiletine 225, 450 or 675 mg/d × 3wk, titration for 1 wk, then full dose × 1 wk or placebo	VAS
Young, 1983 (e10)	II	15 no drop-outs	100%	RCT Sorbinil 200 mg/d for weeks 5-8, crossover in weeks 9-12 Placebo for all weeks 1-4 and 13-16, and ½ randomized to placebo weeks 5-8 and crossover in weeks 9-12	Pain relief on summary symptom score from 0-3
Scheffler, 1991 (e42)	III	54	76%	RCT 0.075% capsaicin QID × 8 wks compared to placebo	VAS and investigator's GES
Ametov, 2003 (e43)	III	120	93%	IV alpha lipoic acid 14 treatments over 3 wks,	TSS (Total Symptom Score) for positive neuropathic sensory symptoms of burning & lancinating pain, asleep numbness, and prickling of feet or legs

Evidence Table e-4. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
NSD	No changes in NCS after 12 wk with pentoxifylline reported as written. No quantitative data given for this.	Dry mouth on clonidine and none with pentoxifylline	
Large VAS 60% capsaicin improved 20% placebo improved PGI 70% on capsaicin and 20% on placebo Pain intensity decreased by 16% capsaicin and 4% placebo VAS pain relief 45% capsaicin and 23% placebo	No comment	Burning, stinging, warmth in 6/11 capsaicin and 2/11 placebo	
NSD	No comment	nausea, headache, diarrhea, vomiting, itching, pain, palpitations.	
Moderate (16-20% over placebo) 48-52% with the three different doses compared to 32% in placebo; >50% reduction in TSS seen in 50-62% ALA doses vs 26% placebo; pain subscores of the TSS significantly reduced	No comment	Not reported	Pain not primary end-point
Moderate **18% diff with placebo**	None	None	
NSD on primary efficacy parameter 3.2 to 63.5% in ALA groups compared to 38.4% in placebo (significant reductions in pain and burning subsets of TSS)	NDS −1.8 for highest dose of ALA vs. −1.0 for placebo (significant)	None reported	Response was dose dependent End-point not predefined
NSD on TSS; TSS after IV NS if using scale, significant as area under curve	No comment	Not reported	High drop out rate; reported as positive, but only with different analyses than originally planned
Small (13% on VAS) PGE: 71.3% capsaicin vs 51.3% placebo VAS intensity: 40.1 capsaicin vs 27.8% vehicle; capsaicin 11% better than placebo VAS relief: 60% cap 45% placebo or 13% above placebo Not truly masked	No comment	Burning in 63% or 46% above placebo; coughing-sneezing in 12% or 11% above placebo; rash in 7% or 5% above placebo.	
Large 37% reduction in VAS with mexiletine No change with placebo	5 point symptom score including sleep disturbance. 48% reduction with mexiletine; none with placebo	3 patients with nausea, hiccup or tremor	End-point not predefined
Small (5% diff with placebo) VAS decreased 4.4 to 2.7 with 675 mg/d of mexiletine compared to placebo change of 5.0 to 3.8	Sleep interference; ns	9 patients with AE's: allergic reaction, tachycardia, enteritis, breast CA, LL thrombosis, dizziness, tiredness, lack of compliance and chest pain, and diarrhea. Also observed were nausea and gastric upset.	End-point not predefined
NSD in primary end point	No comment	4 had idiosyncratic reaction (skin rash, 3 with oropharyngeal involvement) leading to withdrawal of drug	
Large (40% over placebo) GES improved 89.5% with capsaicin and 50% with placebo VAS decreased 49.1 points with capsaicin and 16.5 points with placebo	Daily activities, walking, working, recreational activities, wearing shoes and socks, eating on 0-4 scale for each; walking and sleeping improved, but effect size not provided	17/28 capsaicin pts noted burning at site of application during first 2 wks mainly, sneezing in 1, 1 rash	
Moderate (24% diff) NSC-LL pain; 70% reduction vs. 46% placebo (from 10 points at baseline) TSS had improved by a mean of 5.7 points for the ALA group and a mean of 1.8 points for placebo group	No comment	None reported	Not directly on topic although painful symptoms improved.

Evidence Table e-4. *Continued*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Ziegler, 2004 (e44)	III	1258	88%	ALA IV for 3 weeks	TSS
Kastrup, 1986 (e14)	III	20	75%	IV Lidocaine 5 mg/day No baseline comparison	5 item symptom scale
Viola, 2006 (e15)	III	15	80%	Lignocaine IV	MPQ
Argoff, 2004 (e16)	III	41	NS	Lidoderm Patch	NPS at 2 wks
Barbano, 2004 (e17)	III	56	NS	Lidoderm Patch	BPI, BDI, SFMPQ, POMS at Wk 3

Evidence Table e-4. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Moderate 24.1% ALA over placebo; responder rates 52.7% ALA vs. 36.9% placebo	NIS-LL; 16% over placebo	Not reported	Meta-analysis
Moderate At day 1, pain decreased from 12 to 3 in lidocaine and 12 to 6 on placebo or 75% drop on lidocaine and 50% drop on placebo with 25% difference			No baseline comparison
Small PPI: +0.9 on placebo and −0.9 on lignocaine: ?9% improvement Baseline pain levels not described. Changes depend on marked worsening in placebo rather than improvement in lignocaine tx.			Pain intensity scores increase dramati-cally with placebo
Moderate 20-30% improvement in NP scores			Only pts with prev response to gabapentin studies
Large 70% had > 30% reduction in all scores ($p < 0.01$)			Dosage & frequency uncontrolled

Evidence Table e-5. *Design characteristics and outcomes in controlled studies of patients with painful diabetic neuropathy treated with non-pharmacological interventions*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Hamza, 2000 (e19)	I	50	100%	Percutaneous Electrical Nerve Stimulation (PENS) or sham treatment for 3 weeks	VAS
Weintraub, 2009 (e23)	I	225	86.2%	Pulsed electromagnetic fields or sham treatment 2h/d × 3m	VAS Neuropathy Pain Scale PGIC IENFD
Zinman, 2004 (e25)	I	50	100%	Low-intensity laser therapy vs sham treatment × 4 wk	VAS
Gillespie, 2007 (e26)	I	207 37 drop-outs	82.1%	RCT Reiki therapy 2x/wk for 1 wk then Qwk × 11 wks Mimic Reiki on same schedule No treatment	McGill Pain Questionnaire
Weintraub, 2003 (e24)	II	375	69%	Wearing magnetized (multipolar, static magnetic 450G) shoe insoles or unmagnetized insoles × 4 m	VAS burning
Oyibo, 2004 (e20)	II	30	47%	Electrical stimulation stockings	**Negative**
Bosi, 2005 (e21)	II	31	100%	frequency-modulated electromagnetic neural stimulation (FREMS) or no stimulation 3 weeks with 4 m follow-up, crossover design	VAS
Armstrong, 1997 (e34)	III	10	Not reported	Pulsed-dose electrical stimulation using a knitted silver-plated nylon/Dacron stocking electrode for 4 weeks	10 cm visual analog scale
Kumar, 1997 (e45)	III	31	100%	One month treatment with self-administered transcutaneous electrotherapy (using H-Wave machine) vs. sham therapy. Treatment was 30 min/day on each lower extremity (using 4 electrodes)	
Kumar, 1998 (e22)	III	26	88%	Electrotherapy + amitriptyline compared to sham treatment + amitriptyline	Descriptive scale from 0 to 5
Alvaro, 1999 (e46)	III	57 (studies 1 and 2) (Study 3 retrospective and grade IV)	Not reported	Transcutaneous electrical nerve stimulation w/ and w/o amitriptyline	Analog pain scale

Evidence Table e-5. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Large (42% above placebo) Pain reduction 56% vs. 14% in controls	VAS sleep; MOS SF-36; 41% vs. 11%	None	
NS	ND	None	
NS	ND	None	
NSD McGill Pain Questionnaire; same for Reiki and mimic-Reiki and no treatment group at end, NS	Epidemiology of Diabetes Intervention and Complications, Well-Being Questionnaire and the Diabetes Treatment Satisfaction Questionnaire; ns Epidemiology of Diabetes Intervention and Complications, Well-Being Questionnaire and the Diabetes Treatment Satisfaction Questionnaire; ns	1 death, 8 withdrew due to AEs not specified	
Small (14% over placebo) 30% magnetic insoles vs. 24% placebo at 4 m; exercise induced foot pain decreased 31% vs. 25% placebo	Sleep; NS; 30% decline in both groups	Allodynia from the footwear	End-point not predetermined
NSD	Sleep disturbance NS	None	
Small (11% over placebo) no change in placebo; FREMS scores from 37.1 to 26.2 daytime and 38.1 to 28.5 at night; persistent benefit at 4 m	SF36; no change at 3 wks, improved at 4 m.	None reported	Zero improvement for placebo is of concern; can this be truly double blinded-no current for placebo group-claim is that patients unlikely to feel active treatment
Large (50% reduction; no placebo) Pain decreased compared to baseline at 4 weeks ($p < 0.005$) and at 1 month after complete discontinuation of therapy ($P < .006$) on initial enrollment mean VAS = 7.0 cm, while at the end of the 4 wk evaluation/ treatment period, mean pain score = 1.5 and 1 month following discontinuation of electrical stimulation, mean pain score = 2.3	No comment	None reported	Cohort, uncontrolled
Large (50% responders) Pain improved in 83% of treatment group and 38% of control group			Single blinded; unclear if unbiased evaluation at endpoint; randomization method not given
Moderate (18% diff) Pain score reduction of 1.8 + 0.3 vs 0.9 + 0.3 for sham ($P < .03$)			
Large Study 1: treated electrotherapy group reported an overall greater reduction of sx (pain, etc), 52% w/ 2-3 wks of active treatment; Study 2: electrotherapy plus amitriptyline (12 wks) produced a 66% reduction of pain whereas amitriptyline alone (4 wks) produced only a 26% reduction of pain; Study 3: retrospective analysis found pts using electrotherapy for over 1 yr reported 44% improvement	No comment	None reported	Two single blinded trials briefly described, selection criteria not strict; Article titled "Review"; No Methods section; ?peer reviewed journal; third group retrospective

Evidence Table e-6. *Design characteristics and outcomes in comparison studies of patients with painful diabetic neuropathy treated with an active intervention without a placebo arm*

Author Year	Class	Subjects	Completion Rate	Intervention	Outcome
Dallocchio, 2000 (e27)	III	25	100%	Gabapentin 1200-2400 mg/d amitriptyline 30-90 mg/d	Pain Intensity Scale 0-4
Jia, 2006 (e28)	II	132	90%	venlafaxine + dummy compared with carbamazepine + dummy	VAS (11 point)
Morello, 1999 (e29)	II	25	76%	Gabapentin or amitriptyline in two 6-week periods with one-week washout between treatments	Pain Scale Rating System (13-word scale converted to numeric scale) and Global Rating Scale
Gomez-Perez, 1996 (e30)	III	16	87.5%	Nortriptyline-fluphenazine vs. carbamazepine, then placebo, then cross-over	VAS but not numerical; >50%
Biesbroeck, 1995 (e31)	II	235 23 drop-outs	90.2%	RCT DB, active comparator cream+amitriptyline Amitriptyline 25-125mg/d + vehicle or + capsaicin 0.075%	VAS pain relief
Simeonov, 1997 (e32)	III	45	100%	30 subjects in group 1 treated with benfothiamine and cyanocobalamine tabs and 15 in group 2 treated with conventional vitamin B x 3m	0-20 pain scale

Evidence Table e-6. *Continued*

Effect Size (95% CI)	QOL/function	Negative Outcomes	Comments
Large, 48% for GBP and 33% amit **Reduction 1.9 for GBP and 1.3 for amit**			Open label study Scales categorical and treated as continuous in analysis
venlafaxine superior to carbamazepine ($P < .05$) at days 5, 7, 10, 14	11-point Likert scale; ITT analysis showed venlafaxine better than carbamazepine at 10 and 14 days ($P < .05$)	Venlafaxine - 43.9% (GI discomfort, dizziness, somnolence). 4 patients withdrew; carbamazepine - 25.76% (dizziness, somnolence one with exfoliative dermatitis. 2 patients withdrew.	Threshold for equivalence not defined
Large (52% on GBP & 67% on Amit) **NSD between tx** Mean + SEM pain score decreased by 0.3 + 0.06 unit for GBP and 0.4 + 0.1 unit for amit	None	More weight gain with amitriptyline. Otherwise no significant difference. Prevalent AEs included sedation, dry mouth, dizziness, orthostatic hypotension, ataxia, and lethargy	
Large (−56% NF, −54% CBZ) Both nortriptyline-fluphenazine and carbamazepine better that placebo but not significantly different from one another	None	See Table 4 in paper; mild AEs more often in nortriptyline-fluphenazine group	
Large PGE: 73% better both tx VAS 42% better with capsaicin 43.5% better with amitriptyline Intensity same Relief 55% with either	Daily activities (eating, sleeping, shoes, working, walking, driving, housework, recreation). all groups improved; sleep interference was better by 56.7% with capsaicin and 58.8% with amitriptyline	44% burning with capsaicin (first week); coughing or sneezing in 7% with capsaicin; sedative in 64% with amitriptyline, other AE with amitriptyline: 44% anticholinergic, 25% CNS/NM, 13% GI	Threshold for equivalence not stated
Large (39% diff) 12 point improvement in the benfothiamine and cyanocobalamine group (significant) and 4.3 in the standard vit B (NS)	Rydel-Seiffer tuning fork; 1.8 change in the benfothiamine and cyanocobalamine tabs (significant) and 0.25 in the standard vit B (NS)		Not randomized Not controlled