Pharmacotherapy in patients with painful diabetic neuropathy: what do recent guidelines tell us?

Kathrin Doppler & Claudia Sommer*

Practice Points

- Anticonvulsants (e.g., pregabalin and gabapentin) and antidepressants (e.g., amitriptyline, duloxetine and venlafaxine) are the most recommended drugs for symptomatic treatment of painful diabetic neuropathy.
- Opioids are effective in painful diabetic neuropathy.
- Cost–effectiveness needs to be considered.
- Guidelines cannot replace treatment decisions in the individual patient.

SUMMARY Painful diabetic neuropathy is a common complication of diabetes. Pharmacological and nonpharmacological options are available for symptomatic treatment. Several guidelines have been published recently, evaluating randomized controlled trials and providing evidence-based recommendations on how to treat this condition. This article summarizes the most important recent national and international guidelines on the treatment of painful diabetic neuropathy. The main drug classes and the recommendations of the different guidelines are presented, as well as the results of economic studies on cost–effectiveness. In the different guidelines, first-line recommendations can be found for pregabalin, duloxetine, gabapentin, venlafaxine and tricyclic antidepressants. There is a consensus that treatment and care should take into account patients' needs and preferences.

Painful diabetic neuropathy

Diabetic neuropathy is one of the most common complications in diabetes [1]. Up to 50% of all patients with diabetic neuropathy develop neuropathic pain [2]. As high blood glucose levels are known to be the major risk factor for diabetic neuropathy, avoiding hyperglycemia is the most important causal treatment [3]. Every patient needs to be instructed on how to reach optimal blood glucose levels not only by oral antidiabetics and insulin therapy but also by physical activity and a healthy diet. However, as neuropathic pain often cannot be controlled by optimization of diabetic treatment alone, symptomatic therapy plays an important role. Numerous randomized controlled trials have established the

Department of Neurology, University Hospital of Würzburg, Josef-Schneider-Straße 11, 97080 Würzburg, Germany
*Author for correspondence: Tel.: +49 931 2012 3763; Fax: +49 931 2012 3697; sommer@uni-wuerzburg.de

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efficacy of a number of drugs in the treatment of this condition. Nonpharmacological treatment complements the therapeutic options. Given the variety of treatment options, it is a challenge for the physician to choose the best therapy for each patient. The choice should be evidence based and cost effective. Several national and international guidelines have been published to help clinicians approach this challenge. In this article, the most important recent national and international guidelines will be summarized and discussed.

The guidelines

■ American Academy of Neurology/American Association of Neuromuscular & Electrodiagnostic Medicine/American Academy of Physical Medicine & Rehabilitation guideline

The guideline of the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) and the American Academy of Physical Medicine and Rehabilitation (AAPMR) selectively addresses painful diabetic neuropathy. A systematic literature search of MEDLINE® and Embase from 1960 until August 2008 was performed using the Medical Subject Headings term 'diabetic neuropathies' and its text word synonyms and keywords for the therapeutic interventions of interest. The resulting 2234 citations were reviewed by at least two experts, leading to 79 relevant articles. Recommendations were based on strength of evidence and efficacy of a drug to reduce pain and improve physical function and quality of life. Trials were classified as level I in quality if they had:

- Concealed allocation;
- Clearly defined primary outcomes;
- Clearly defined inclusion and exclusion criteria;
- Adequate accounting for drop-outs, with at least 80% of enrolled subjects completing the study and crossovers with numbers sufficiently low to have minimal potential for bias.

While in the design of a study the first three points can be controlled for, it is not possible to control in advance for drop-outs. Therefore, in this guideline, many well-designed and well-performed studies were rated as class II. This is why data analysis in this guideline results in only one level A recommendation for the treatment of painful diabetic neuropathy. Level A and B recommendations are shown in **Table 1** [4].

■ NICE guideline

The guideline of NICE in the UK deals with neuropathic pain in general, but gives specific recommendations for patients with painful diabetic neuropathy. The NICE guideline specifically addresses healthcare providers in England and Wales in nonspecialist settings (i.e., it is not meant for pain specialists). In addition to the recommendations on drug treatment, the NICE guideline gives a useful summary of patient management, detailing key principles of care, for example what to discuss with the patient and what to take into account of their lifestyle. A total of 34 different pharmacological treatments for neuropathic pain were considered and a systematic literature search was performed to identify randomized placebo-controlled trials of these treatments. They all belonged to the four main drug classes consisting of antidepressants, anticonvulsants, opioid analgesics and topical treatments. Finally, 104 studies could be included. In addition, a systematic review of the economic evidence was performed. For recommendations for first- and second-line treatments from the NICE guideline see **Table 1** [5]. What distinguishes the NICE guideline from most of the others is the inclusion of a health economic statement. This is derived from a National Health Service (NHS)-sponsored work, which at the time of writing had not yet been published [101], but which the authors had access to; the Health Technology Assessment report.

■ European Federation of Neurological Societies guideline

The guideline of the European Federation of Neurological Societies (EFNS) deals with neuropathic pain in general, but most evaluated studies are about painful diabetic neuropathy [6]. The guideline is based on an initial search of the Cochrane Library from 2005. The literature search was expanded to MEDLINE and other electronic databases including web results from major unpublished company trials from 2005 until September 2009. The authors identified 64 randomized controlled trials since 2005, resulting in recommendations for first-, second- and third-line treatment **(Table 1)**. The list of level A recommendations is longer than in the AAN/AANEM/AAPMR guideline, showing that the criteria were different. In order to fulfil class I

Table 1. Summary of the most important international guidelines on the treatment of neuropathic pain.

Guideline (period of literature search)	Method of search	Number of studies included	Primary end points considered	Recommendations	Ref.
AAN/AANEM/AAPMR 2011 (1960–2008)	MEDLINE® and Embase with the search term diabetic neuropathies, citations evaluated by two reviewers	79	Reduction of pain, quality of life and improvement of physical function	Level A: pregabalin Level B: gabapentin, sodium valproate, venlafaxine, duloxetine, amitriptyline, dextromethorphan, morphine sulfate, tramadol, oxycodone, capsaicin, isosorbide dinitrate spray, electrical stimulation	[4]
NICE 2010 (1950–2009)	Numerous databases and websites, search for 34 considered treatments of neuropathic pain	104	Pain reduction, patient-reported global improvement and adverse effects	First line: duloxetine; if contraindicated: amitriptyline Second line: amitriptyline or pregabalin (monotherapy or combination)	[5]
EFNS 2010 (2005–2009)	Cochrane Library from 2005, new literature search of web and MEDLINE when no top-level study identified, chapters evaluated by two task force members according to defined criteria	64 (since 2005)	Efficacy on pain and symptoms/signs, quality of life, sleep and mood and side effects	First line: duloxetine, gabapentin, pregabalin, tricyclic antidepressants, venlafaxine Second/third line: opioids, tramadol (first choice in acute exacerbation)	[6]
IASP 2007 (1966–2007)	MEDLINE search, examination of reference lists, knowledge of authors, consensus meeting	NS	Pain reduction, safety, tolerability, drug interactions, ease of use and quality of life	Nortriptyline, desipramine, duloxetine, venlafaxine, gabapentin, pregabalin Localized pain: topical lidocaine (or combination) Acute exacerbation: opioids, tramadol	[7]

AAN: American Academy of Neurology; AANEM: American Association of Neuromuscular and Electrodiagnostic Medicine; AAPMR: American Academy of Physical Medicine and Rehabilitation; EFNS: European Federation of Neurological Societies; IASP: International Association for the Study of Pain; NS: Not specified.

criteria, in this instance a randomized controlled trial needs to have adequate accounting for drop-outs, but there is not the strict rule that 80% of participants need to complete the trial.

■ International Association for the Study of Pain guideline

The guideline of the International Association for the Study of Pain (IASP) is also about neuropathic pain in general, but again painful diabetic neuropathy is the most studied condition leading to neuropathic pain. The guideline is based on a consensus meeting where systematic literature reviews, randomized clinical trials and existing guidelines were evaluated. A number of drugs are recommended for treatment of neuropathic pain, but no specific recommendations are made for painful diabetic neuropathy [7].

The drug classes

■ Anticonvulsants

Pregabalin and gabapentin are the most frequently recommended anticonvulsants. Both drugs are structurally similar to GABA, but do not bind to GABA receptors or affect the metabolism of GABA. Their action is thought to involve binding to $\alpha_2\delta$ subunits of voltage-gated calcium channels [8,9].

According to the guideline of the AAN/AANEM/AAPMR, pregabalin receives a level A recommendation, gabapentin and sodium valproate receive a level B recommendation while topiramate, oxcarbazepine, lamotrigine and lacosamide should not be considered [4]. The EFNS and IASP guidelines suggest gabapentin and pregabalin as a first-line treatment for painful neuropathy [6], whereas the NICE guideline recommends pregabalin as a second-line therapy if duloxetine and amitriptyline are not effective [5]. The recommended dose of pregabalin is 150–600 mg/day [6] or 300–600 mg/day [4,7]. The starting dose is 150 mg/day (50 mg three-times daily or 75 mg twice daily) and can be increased to 300 mg/day after 3–7 days [5,7]. For gabapentin, the recommended daily dose is 900–3600 mg/day [4] or 1200–3600 mg/day [6]. The starting dose can be 100–300 mg (at bedtime or three-times daily) with an increase by 100–300 mg every 1–7 days [7]. The recommended dosages of the drugs are listed in **Table 2**.

Antidepressants

Different antidepressive agents are known to be effective in reducing neuropathic pain. Diverse mechanisms are supposed to play a role. Reinforcement of descending inhibitory pathways by increasing the amount of norepinephrine and serotonin in the synaptic cleft at supraspinal and spinal levels is one of these mechanisms. Other mechanisms are blockage/activation of ion channels and adrenergic receptors, antagonism on *N*-methyl-D-aspartate receptors or activation of certain opioid receptors [10–12]. Antidepressants are divided into subgroups according to their molecular structure and their main mode of action. Tricyclic antidepressants (e.g., amitriptyline) have proven to be effective [13,14]. Of the newer drugs, the serotonin and norepinephrine reuptake inhibitors duloxetine and venlafaxine are effective in the treatment of neuropathic pain [15,16]. The AAN/AANEM/AAPMR guideline recommends amitriptyline, venlafaxine and duloxetine and with level B strength of recommendation [4]. In the NICE guideline, duloxetine alone is mentioned as first-line therapy. Amitriptyline is considered if duloxetine is contraindicated or as second-line therapy [5]. In the EFNS guideline duloxetine, venlafaxine and tricyclic antidepressants are all rated as first-line therapy [6]. The IASP guideline recommends nortriptyline, desipramine, duloxetine and venlafaxine [7]; however, this is not specific for diabetic neuropathy. Information on the dosage of antidepressants differs slightly between different guidelines **(Table 2)**. For amitriptyline, the effective dose is 25–100 mg/day according to the AAN/AANEM/AAPMR and EFNS guidelines [4,6], the NICE guideline recommends 10 mg/day to begin with and to increase to a maximum of 75 mg/day [5]. The IASP guideline advises to start with 25 mg at bedtime and to increase by 25 mg/day every 3–7 days with a maximum of 150 mg/day. Duloxetine can be started with 60 or 30 mg/day and increased to 120 mg [4,5,7]. The recommended dose of venlafaxine is 75–150 mg [4,5,7].

Opioids

It has long been under dispute whether opioids are effective in neuropathic pain [17,18]. In several studies, opioids have proved to be efficacious [19–21], but all guidelines agree that opioids should not be considered a first-line therapy. The AAN/AANEM/AAPMR guideline rate dextromethorphan, morphine sulfate, tramadol and oxycodone equally with a level B strength of recommendation [4]. In the NICE guideline, tramadol is recommended as third-line treatment instead of or in combination with the second-line treatment (amitriptyline or pregabalin) [5]. In the EFNS guideline, oxycodone and tramadol achieved evidence class I, dextromethorphan

Table 2. Recommended doses of the most frequently recommended drugs.

Drug	AAN/AANEM/AAPMR 2011	NICE 2010	EFNS 2010	IASP 2007
Pregabalin	300–600 mg/day†	Start at 150 mg/day (two doses), upward titration, maximum 600 mg/day	150–600 mg/day	Start with 150 mg/day (two or three doses), increase to 300 mg/day after 3–7 days, then by 150 mg/day every 3–7 days, maximum 600 mg/day
Gabapentin	900–3600 mg/day	–	1200–3600 mg/day	Start with 100–300 mg at bedtime or three-times daily, increase each dose by 100–300 mg/day every 1–7 days, maximum 3600 mg/day
Venlafaxine	75–225 mg/day	–	150–225 mg/day	Start with 37.5 mg (1–2 doses), increase by 75 mg each week, maximum 225 mg/day
Duloxetine	60–120 mg/day	Start at 60 mg/day, upward titration, maximum 120 mg/day	60–120 mg/day	Start with 30 mg once daily, increase to 60 mg after 1 week, maximum 120 mg/day (two doses)
Amitriptyline	25–100 mg/day	Start at 10 mg/day, upward titration, maximum 75 mg/day	25–150 mg/day	Start with 25 mg at bedtime, increase by 25 mg daily every 3–7 days, maximum 150 mg/day

Doses refer to those given in the guidelines, all doses are EMA approved. Venlafaxine is not licensed for the treatment of neuropathic pain. License differs between countries and needs to be considered.
†The 600-mg dose is not US FDA approved.
AAN: American Academy of Neurology; AANEM: American Association of Neuromuscular and Electrodiagnostic Medicine; AAPMR: American Academy of Physical Medicine and Rehabilitation; EFNS: European Federation of Neurological Societies; IASP: International Association for the Study of Pain.

was rated as evidence class II for efficacy; in the final recommendation, opioids are regarded as second- or third-line therapy [9]. The IASP guideline suggest opioids as a therapy for acute exacerbations [7]. However, typical side effects such as nausea, obstipation, hypotonia and dizziness, as well as tolerance and addiction, need to be considered.

Other therapies

Local therapy with capsaicin or isosorbide dinitrate spray is assessed as effective with class II evidence in the AAN/AANEM/AAPMR guideline. The lidoderm patch is considered effective with class III evidence [4]. The IASP guideline recommends topical lidocaine alone or in combination with any other drug for cases of localized pain [6]. No sufficient evidence could be found for treatment with vitamins or α-lipoic acid [4]. As for nonpharmacological treatment, percutaneous electrical nerve stimulation is evaluated as effective with class II evidence [4]. Electromagnetic field treatment, low-intensity laser treatment and Reiki therapy should probably not be considered [4]. Placebo effect has to be taken into account with up to 50% of pain reduction [4].

Cost–effectiveness of different treatments

Although most studies account for pharmacological efficacy in the first line, cost–effectiveness of treatment becomes more and more important for clinicians in their daily life. Only a few studies have so far concentrated on this issue [22–25]. The AAN/AANEM/AAPMR guideline notes that cost–effectiveness studies of different treatments should be done, without further addressing the topic [4]. In the IASP guideline, the relative costs of the different treatment options are listed, marking tricyclic antidepressants as the therapy with the lowest cost [7]. The NICE guideline includes a health economic statement, a systematic review of economic evidence on the pharmacological evidence of neuropathic pain [5]. A simulation of a cohort of 2000 people was performed. Pain was categorized as reduced (at least 50%) or unimproved. Health outcomes were measured in terms of quality-adjusted life years and costs were taken from established sources. The results of the analysis are listed in **Box 1**. Duloxetine was concluded to be the most cost-effective treatment option [5]. However, cost–effectiveness varies among different countries and is influenced by individual factors. Studies on cost–effectiveness give us a survey on economic aspects but cannot replace individual calculation of costs.

Algorithms in the different guidelines

The aim of a guideline is to provide unequivocal recommendations how to treat a patient under certain conditions. Of course, individual needs and contraindications have to be considered, but algorithms are still what most clinicians expect from a good guideline. The existence of a number of different guidelines on the same topic raises the question of which guideline should be considered first. A patient with painful diabetic neuropathy consulting his doctor for a first treatment of neuropathic pain without presenting any contraindications will be recommended different treatments, depending on the guideline considered. According to the AAN/AANEM/AAPMR guideline, pregabalin will be prescribed; considering the NICE guideline, duloxetine will be chosen; the EFNS guideline leaves the choice between duloxetine, gabapentin, pregabalin, tricyclic antidepressants and venlafaxine; and the IASP guideline recommends nortriptyline, desipramine, duloxetine, venlafaxine, gabapentin or pregabalin. The existence of different well-accepted treatment options reflects the fact that there are a number of effective drugs to treat neuropathic pain and there are only slight differences concerning effectiveness and evidence of these treatments. Thus, physicians have the possibility to choose the drug that fits best with the patient's needs (when side effects, contraindications and interactions are considered) and to try different treatments if the first is not sufficient.

Conclusion & future perspective

The panel of drugs discussed and recommended in the different guidelines is more or less the

Box 1. Hierarchy of cost–effectiveness from most to least cost effective in terms of mean net benefit according to the NICE guideline.

- Duloxetine 60 mg/day
- Duloxetine 20 mg/day
- Amitriptyline 75 mg/day
- Duloxetine 120 mg/day
- Pregabalin 600 mg/day
- Oxcarbazepine 1200 mg/day
- Pregabalin 300 mg/day

Data taken from [5].

same and judgment of evidence is very similar; however, recommendations differ. Classification as first- or second-line treatment differs between the guidelines owing to differences in the period of time that was reviewed, criteria for levels of evidence, expert opinions and the inclusion of economic issues. All guidelines agree that treatment and care should take into account patients' needs and preferences and that people with neuropathic pain ought to have the opportunity to make informed decisions about their care and treatment in partnership with their healthcare professionals. Therefore, good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care and the information patients are given about it should be tailored to each patient's needs.

All of the guidelines present useful pathways and algorithms to help physicians to provide up-to-date evidence-based medicine. Nevertheless, guidelines cannot replace knowledge on pharmacological interactions, adverse effects and contraindications, as well as communication between physician and patient, to determine the appropriate therapy for each patient. The optimal treatment, which has not yet been uncovered, would at the same time alleviate pain and causally improve the diabetic neuropathy. Guidelines will have to be updated when new knowledge from clinical trials accumulates, when new drugs become available and when, hopefully, our knowledge on the pathogenesis of pain in diabetic neuropathy advances.

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References

Papers of special note have been highlighted as:

- ▪ of interest

1 Dyck PJ, Kratz KM, Karnes JL *et al.* The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 43(4), 817–824 (1993).

2 Tesfaye S, Vileikyte L, Rayman G *et al.* Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab. Res. Rev.* doi:10.1002/dmrr.1225 (2011) (Epub ahead of print).

3 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N. Engl. J. Med.* 329(14), 977–986 (1993).

4 Bril V, England J, Franklin GM *et al.* 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. *Neurology* 76(20), 1758–1765 (2011).

▪ **The North American guideline on the subject.**

5 NICE. *Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings.* NICE, London, UK (2010).

▪ **The UK guideline on the subject.**

6 Dworkin RH, O'Connor AB, Backonja M *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132(3), 237–251 (2007).

▪ **The International Association for the Study of Pain (IASP) guideline on the subject.**

7 Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin. Ther.* 29(1), 26–48 (2007).

8 Gale JD, Houghton LA. Alpha 2 delta ($\alpha(2)\delta$) ligands, gabapentin and pregabalin: what is the evidence for potential use of these ligands in irritable bowel syndrome. *Front. Pharmacol.* 2, 28 (2011).

9 Attal N, Cruccu G, Baron R *et al.* EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur. J. Neurol.* 17(9), 1113–e88 (2010).

▪ **The European Federation of Neurological Societies (EFNS) guideline on the subject.**

10 Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. *J. Clin. Pharmacol.* 52(1), 6–17 (2012).

11 Benbouzid M, Gaveriaux-Ruff C, Yalcin I *et al.* Delta-opioid receptors are critical for tricyclic antidepressant treatment of neuropathic allodynia. *Biol. Psychiatry* 63(6), 633–636 (2008).

12 Yalcin I, Choucair-Jaafar N, Benbouzid M *et al.* Beta(2)-adrenoceptors are critical for antidepressant treatment of neuropathic pain. *Ann. Neurol.* 65(2), 218–225 (2009).

13 Davis JL, Lewis SB, Gerich JE, Kaplan RA, Schultz TA, Wallin JD. Peripheral diabetic neuropathy treated with amitriptyline and fluphenazine. *JAMA* 238(21), 2291–2292 (1977).

14 Max MB, Culnane M, Schafer SC *et al.* Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 37(4), 589–596 (1987).

15 Smith T, Nicholson RA. Review of duloxetine in the management of diabetic peripheral neuropathic pain. *Vasc. Health Risk Manag.* 3(6), 833–844 (2007).

16 Kajdasz DK, Iyengar S, Desaiah D *et al.* Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from *post hoc* analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin. Ther.* 29(11 Suppl. 1), 2536–2546 (2007).

17 Dellemijn P. Are opioids effective in relieving neuropathic pain? *Pain* 80(3), 453–462 (1999).

18 Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 33(1), 11–23 (1988).

19 Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* 43(3), 273–286 (1990).

20 Jadad AR, Carroll D, Glynn CJ, Moore RA, McQuay HJ. Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia. *Lancet* 339(8806), 1367–1371 (1992).

21 Mcquay HJ, Jadad AR, Carroll D *et al.* Opioid sensitivity of chronic pain: a patient-controlled analgesia method. *Anaesthesia* 47(9), 757–767 (1992).

22 O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics* 27(2), 95–112 (2009).

23 Beard SM, McCrink L, Le TK, Garcia-Cebrian A, Monz B, Malik RA. Cost effectiveness of duloxetine in the treatment of diabetic peripheral neuropathic pain in the UK. *Curr. Med. Res. Opin* 24(2), 385–399 (2008).

24 Rodriguez MJ, Diaz S, Vera-Llonch M, Dukes E, Rejas J. Cost–effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia. *Curr. Med. Res. Opin* 23(10), 2585–2596 (2007).

25 Tarride JE, Gordon A, Vera-Llonch M, Dukes E, Rousseau C. Cost–effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Canadian perspective. *Clin. Ther.* 28(11), 1922–1934 (2006).

Website

101 National Institute for Health Research (NIHR) Health Technology Assessment Programme. www.hta.ac.uk/1527