Pharmacological treatment of painful neuropathy in adults with diabetes

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Key words

- Diabetic neuroarthropathy
- Neuropathic pain
- Pharmacological therapy

Article points

1. Painful diabetic neuropathy is common in people with diabetes and is difficult to manage clinically.
2. Guidelines recommend amitriptyline, duloxetine, gabapentin or pregabalin as initial pain management options.
3. Patients often do not respond to monotherapy, so combination pharmacotherapy may be required.

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Diabetic neuropathy is one of the most prevalent chronic complications in people living with diabetes and painful diabetic neuropathy is difficult to manage clinically. Guidelines recommend offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain. It is recommended that pharmacotherapy is offered in a stepwise approach to ensure tolerability and effectiveness of individual medications. Patients often do not respond to monotherapy and, therefore, combination pharmacotherapy may be required. The aim of treatment is to improve quality of life for patients living with painful diabetic neuropathy by reducing pain and promoting increased participation in all aspects of daily living.

Diabetes is one of the most common long-term health conditions in the UK (National Institute for Health and Care Excellence [NICE], 2015). It is estimated that over 4.3 million people in the UK have a diabetes diagnosis in 2021/22 (Diabetes UK, 2023). Diabetic neuropathy is one of the most prevalent chronic complications in people living with diabetes, with an estimated lifetime prevalence exceeding 50% (Pop-Busui et al, 2022).

Diabetic neuropathy covers a wide range of neuropathic conditions, with the most common being diabetic peripheral neuropathy (DPN), which also has the largest evidence base for therapeutic treatments. Approximately 30% of all individuals with DPN will experience painful symptoms that will require pharmacological and other treatments (Pop-Busui et al, 2022). The pain associated with DPN is often described as tingling, burning, shooting or stabbing, and can be associated with paresthesias, dysesthesias, sensory ataxia or numbness (Pop-Busui et al, 2017). Neuropathic pain is typically worse at night and may be accompanied by hyperalgesia and allodynia and can lead to reduced quality of life, sleep disturbance, increased morbidity and mortality (Pop-Busui et al, 2017; 2022).

Painful diabetic neuropathy is difficult to manage clinically, and there are a variety of pharmacological and non-pharmacological options that are available. This article will consider the pharmacological approaches.

The aim of treatment should be to improve quality of life for people living with painful diabetic neuropathy by reducing pain and promoting increased participation in all aspects of daily living.

NICE (2013) recommends offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain. The American Diabetes Association guidelines also recommend gabapentinoids and serotonin-norepinephrine reuptake inhibitors (SNRI) as first-line treatments (Pop-Busui et al, 2022) While acknowledging the effectiveness of tricyclic antidepressants, these guidelines are more cautious of their use, due to anticholinergic side-effects and increased risks for those with ischaemic heart disease and glaucoma (Pop-Busui et al, 2022).

Prescribing guidance for neuropathic analgesia in painful diabetic neuropathy.

Drug	Initial dosing	Titration	Max dose	Contraindications and cautions	Duration of trial
Amitriptyline	10–25 mg daily 2 hours before bed (to reduce hangover effect)	Increase in increments of 10–25 mg every 3–7 days	100 mg at night (in two divided doses if >75 mg) **NB:** Limited benefit >50 mg, but increased side-effects	**Contraindications:** Arrhythmias; Recent MI; Manic phase of bipolar disorder; Heart block **Cautions:** Significant mental health history (e.g. psychosis, bipolar disorder, suicidal ideation); age >75 years (due to cardiac and psychotropic adverse effects); susceptibility to glaucoma; BPH; chronic constipation; cardiovascular disease; epilepsy; phaeochromocytoma Glycaemic control may be affected: adjust glucose-lowering therapy accordingly	If no response in 4–6 weeks (at least 2 weeks at maximum tolerated dose), withdraw slowly (over a minimum of 4 weeks; usually, reduce by 10 mg per week) to avoid withdrawal effects
Gabapentin	300 mg daily (100 mg daily in frail/elderly)	Increase by 300 mg every 2–3 days **Rapid titration:** Day 1: 300 mg o.n. Day 2: 300 mg b.d. Day 3: 300 mg t.d.s.	3,600 mg/day in three divided doses Dose reductions required for renal impairment **CrCl (ml/min):** 50–79 = 600–1800 mg 30–49 = 300–900 mg 15–29 = 150–600 mg <15 = 150–300 mg If side-effects occur, remain at highest tolerated dose for 4 weeks before reassessment and further titration if required	**Cautions:** Substance misuse history (potential for dependence and abuse); low body weight; elderly; suicidal ideation; respiratory depression Seizure exacerbation in patients with absence, myoclonic, tonic or atonic seizures	3–8 weeks with at least 2 weeks at maximum tolerated dose If no benefit, gradually wean down over at least 1 week
Pregabalin	75 mg b.d. (25 mg b.d. in frail/elderly) **CrCl (ml/min):** 30–59: 75 mg o.d. 15–29: 25–50 mg o.d. <15: 25 mg o.d.	Increase by 75 mg b.d. after 3–7 days and can increase by a further 150 mg b.d. after another 7 days. 25 mg increments in frail elderly	300 mg b.d. **CrCl (ml/min):** 30–59: 150 mg b.d. or 100 mg t.d.s. 15–29: 150 mg o.d. or 75 mg b.d. <15: 75 mg o.d.	**Cautions:** Substance misuse history (potential for dependence and abuse); suicidal ideation; respiratory depression; severe congestive heart failure; elderly; those at risk of encephalopathy Seizure exacerbation in patients with absence, myoclonic, tonic or atonic seizures	If no benefit after 8 weeks at maximum tolerated dose, reduce and gradually titrate down as titrated up
Duloxetine	60 mg daily	30 mg increments	120 mg (two divided doses)	**Contraindications:** Severe liver disease; Severe renal impairment (CrCl <30 ml/min). Do not use in combination with fluvoxamine, ciprofloxacin, enoxacin or MAOIs. **Cautions:** Bleeding disorders; cardiac disease; elderly; history of mania; history of seizures; hypertension (uncontrolled); raised interocular pressure; susceptibility to closed-angle glaucoma	Stop after 8 weeks if providing no benefit
Capsaicin 0.075% cream	Apply 3–4 times daily	No titration	Apply 3–4 times daily sparingly, leave at least 4 hours between applications	**Contraindications:** Do not use on broken or irritated skin **Cautions:** Pain, burning sensation and erythema at application site	For period of 8 weeks then reassess

Dosing abbreviations: o.d. = once daily; o.n. = once nightly; b.d. = twice daily; t.d.s. = three times daily; PRN = when required. CrCl = creatinine clearance; BPH = benign prostatic hyperplasia; MAOI = monoamine oxidase inhibitor; MI = myocardial infarction. **Note:** Tramadol should be used as rescue therapy only when awaiting specialist pain services. Use 50–100 mg PRN up to four times a day. See SmPC for common side-effects, cautions and contraindications. **Always consult the electronic BNF or Summaries of Product Characteristics (SmPCs) prior to prescribing any drug.** Information correct on 9 March 2023.

Box 1. Common adverse events.

Amitriptyline
Anticholinergic syndromes (dry mouth, blurry vision, constipation, drowsiness, sedation, urine retention, confusion), tremor, dizziness, headache, speech disorder, palpitations, tachycardia, orthostatic hypotension, weight gain, QT interval prolongation.

Gabapentin
Fatigue, fever, dizziness, ataxia, drowsiness, confusion, memory loss, emotional lability, gastrointestinal disturbance, infections.

Pregabalin
Gastrointestinal disturbance, dizziness, drowsiness, headache, dry mouth, memory loss, altered mood.

Duloxetine
Anxiety, headache, dizziness, dry mouth, nausea, flushing.

Capsaicin 0.075% cream
Nil.

Tramadol
Nausea, dizziness, confusion, constipation, hallucinations.

Table 2. Switching from gabapentin to pregabalin.

- Offer pregabalin if gabapentin is not tolerated or the person has not responded fully.
- One option is to gradually decrease and stop gabapentin over 1 week before starting pregabalin titration.
- If stopping gabapentin and switching immediately to pregabalin, see dosing advice below:

Daily dose of gabapentin pre-switch	Daily dose of pregabalin post-switch	Dosing schedule of pregabalin
0–900 mg	150 mg	75 mg twice daily
901–1,500 mg	225 mg	75 mg in the morning and 150 mg in the evening
1,501–2,100 mg	300 mg	150 mg twice daily
2,101–2,700 mg	450 mg	150 mg in the morning and 300 mg in the evening
>2,700 mg	600 mg	300 mg twice daily

Adapted from UK Medicines Information (2017).

When choosing which medication to select first line, consider the patient's current symptoms and other comorbidities. Contra-indications and cautions to using each of the different types of medication are listed in *Table 1*.

Pregabalin is a gabapentinoid and has been shown in many studies to be effective for painful neuropathy and evidence suggests a dose-dependent response, with weaker effect at lower doses (Pop-Busui et al, 2022). However, up-titration of the dose is recommended to reduce adverse effects. Because pregabalin additionally has anxiolytic activity, it may be particularly helpful in individuals with marked anxiety, which is not uncommon among people experiencing neuropathic pain (Pop-Busui et al, 2022).

Gabapentin has also been shown to be effective in painful neuropathy. It does have a shorter half-life and, therefore, needs to be given more frequently (Pop-Busui et al, 2017). Gabapentin has similar adverse effects to pregabalin (*Box 1*). Gabapentin is not always well tolerated and pregabalin may then be considered. Down-titration of gabapentin followed by initiation of pregabalin can be considered, but a conversion for immediate switching is shown in *Table 2*.

Duloxetine is a SNRI and several randomised controlled trials have confirmed that duloxetine reduces neuropathic pain effectively and to a clinically meaningful degree (Ziegler et al, 2022). As duloxetine is an antidepressant it may also be beneficial to use in patients who have symptoms of depression, which can be a frequent comorbidity in patients with painful diabetic neuropathy. Duloxetine has well-documented adverse effects (*Box 1*) .

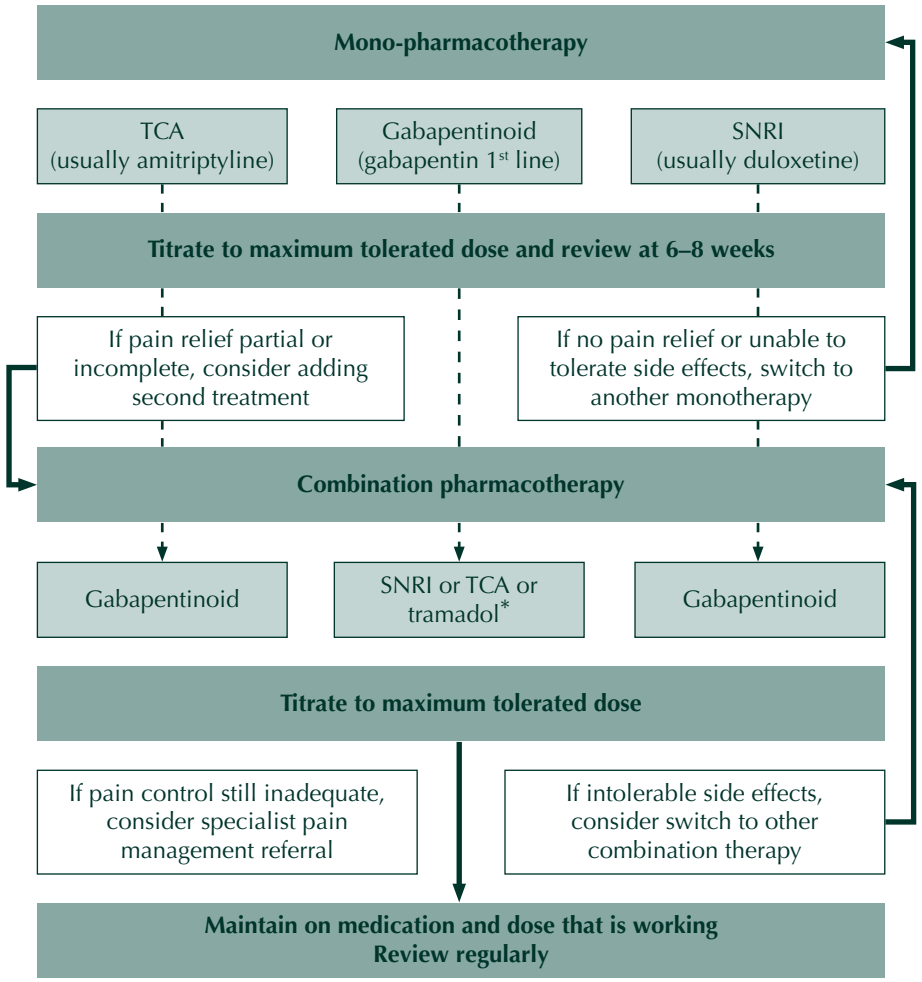
Amitriptyline is the most commonly used tricyclic antidepressant (TCA) for painful neuropathy. It is also the TCA recommended by NICE, while others, such as nortriptyline, are also used for pain management (NICE, 2013). Amitriptyline and other TCAs have been used for many years to manage neuropathic pain and studies have proven it to be more efficacious than placebo (NICE, 2013). Given amitriptyline's side-effect profile (*Box 1*), it is not always well-tolerated and must be avoided in certain conditions (*Table* 1).

It is recommended that if the initial treatment offered is not effective or is not tolerated, then one of the remaining three drugs is offered, and consider switching again if the second and third drugs tried are also not effective or not tolerated. Overall, only 50% of subjects with painful diabetic neuropathy respond to monotherapy. Therefore, combination pharmacotherapy maybe required in patients who have only partial response or in whom the drug cannot be further titrated due to intolerable side effects (Ziegler et al, 2022). *Figure 1* shows how this stepwise approach should be conducted.

Other pharmacotherapies to consider are opiates and topical treatments. NICE recommends that tramadol is only considered if acute rescue therapy is needed. Although tramadol has some efficacy in the management of neuropathic pain (NICE, 2013), the associated risks of addiction, abuse and side-effects have meant it has been recommended for short-term use only.

Capsaicin cream can be considered for people with localised neuropathic pain who wish to avoid, or who

Figure 1. Neuropathic pain treatment pharmacological treatment pathway.



*Tramadol should only be used as acute rescue therapy.
SNRI=serotonin–norepinephrine reuptake inhibitor; TCA= tricyclic antidepressant.
Adapted from Ziegler et al (2022).

cannot tolerate, oral treatments and has been shown to have some efficacy (NICE, 2013).

Pharmacological treatment is only one aspect of the treatment of painful diabetic neuropathy and should always be considered alongside non-pharmacological treatments to gain the best outcomes for patients. Diabetes prevalence is increasing and other than slowing progression through glucose management and lifestyle advice we only have symptomatic treatments available to use currently. It is imperative that we use the evidence base available to us when both diagnosing and treating the symptoms of painful diabetic neuropathy, given the significant impact it can have on quality of life. ■

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