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Neuropathic pain: diagnosis and treatment today

Key points:

- The updated, narrower definition of neuropathic pain emphasises its association with a lesion or disease of the somatosensory nervous system.
- Neuropathic and nociceptive pain have different treatments. A targeted history and a physical examination are important diagnostic prerequisites to medicine selection for effective pain management.
- Low-dose amitriptyline remains a first-line contender in the treatment of neuropathic pain.

Updated guidelines, familiar medicines

The efficacy of neuropathic and other chronic pain medicines is partial at best, which makes helping patients with chronic pain very challenging. People have asked me to amputate their leg, just to get rid of the fire that never goes away. With this desperation and distress, it is tempting to try anything in the hope that it will give relief. Being as sure as possible of the diagnosis is important in order to best help the patient.

Philip Siddall

Professor Philip Siddall, Director of the Pain Management Service at Greenwich Hospital, has over 25 years of clinical experience in the field of pain management.

Despite the many challenges of caring for patients with neuropathic pain, careful clinical assessment and use of first-line medicines remain the cornerstones of diagnosis and pharmacological treatment.

The clinical assessment

The latest guidelines use the updated definition of neuropathic pain.[1] A targeted history and a physical examination continue to underpin diagnosis – demonstrating a neurological lesion or disease of the somatosensory system as part of the diagnosis of neuropathic pain.

The first-line medicines

Australian and international guidelines[2-5] recommend four first-line medicines for the treatment of neuropathic pain: amitriptyline, duloxetine, gabapentin and pregabalin.a Medicine selection should be done on a case-by-case basis, taking into account the patient's profile, contraindications and comorbidities.[2,3] Amitriptyline may not be uppermost in the minds of GPs when they are considering first-line treatment of neuropathic pain. It has, however, been effectively used (in low doses) for many years, is still one of the most efficacious medicines for this type of pain, and remains relevant today.

a Some guidelines recommend the tricyclic antidepressant (TCA) drug class first-line, of which amitriptyline has the most evidence, as well as the serotonin and norepinephrine reuptake inhibitor (SNRI) drug class, of which duloxetine is uniformly recommended.

What is neuropathic pain in 2018?

'The main change in the new definition is the removal of the word "dysfunction"', says Professor Siddall.

Narrowing the definition excludes nervous system changes, such as central sensitisation, as well as conditions such as fibromyalgia or irritable bowel syndrome where there is little to find in terms of nerve damage.

Philip Siddall

The current definition of neuropathic pain used by the International Association for the Study of Pain (IASP) is 'pain caused by a lesion or disease of the somatosensory system'.[1] The definition was updated to distinguish neuropathic pain from pain that is either clearly nociceptive or pain that is not clearly nociceptive or neuropathic and seems to be associated with nervous system changes such as central sensitisation (as in fibromyalgia,b and chronic regional pain syndrome type 1).[6,7]

b Although fibromyalgia is not classified as neuropathic pain, Australian Therapeutic Guidelines recommend TCAs, gabapentinoids or SNRIs for pharmacological treatment.[8]

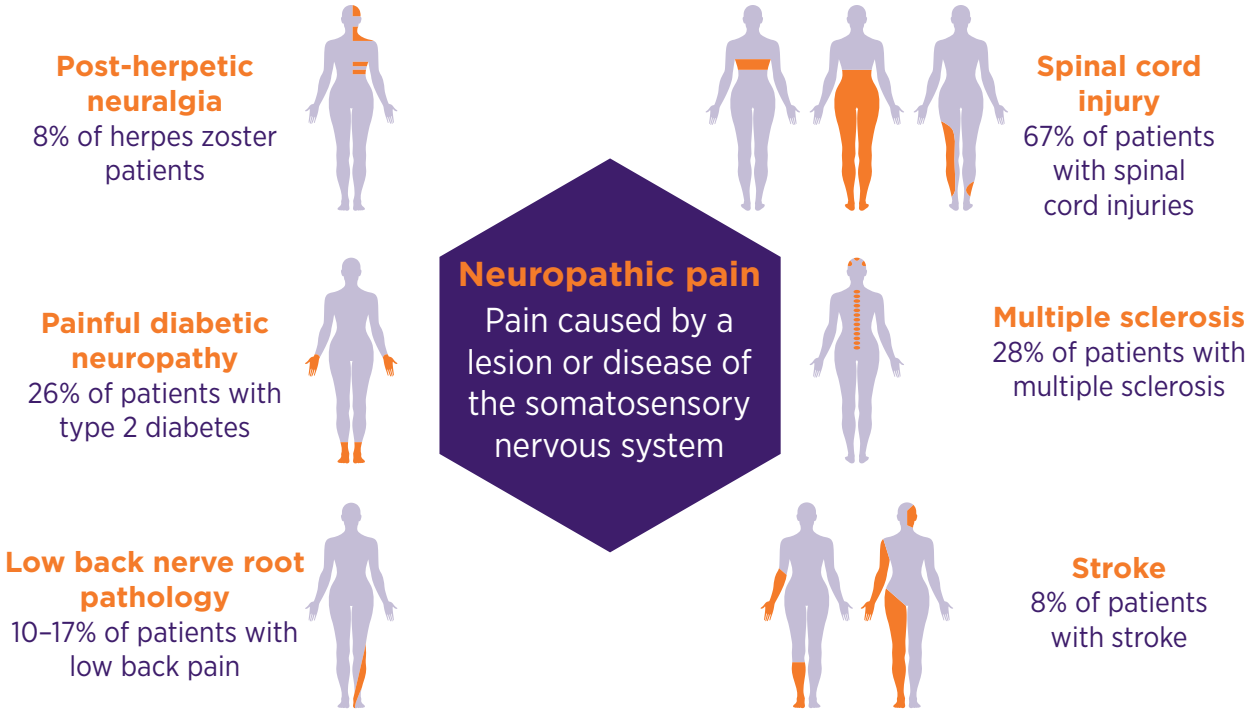


Figure 1: Examples of neuropathic pain[9–12]

With the updated definition of neuropathic pain, a physical examination is important to establish the link between the pain and a lesion or disease in the somatosensory system.[13–15] Australian guidelines from 2011,[2] which are consistent with more recent international guidelines and recommendations,[2,13–15] use a stepwise approach to build evidence for a possible, probable or definite neuropathic pain diagnosis. Pain descriptors that include prickling, burning or tingling can contribute towards the diagnosis.[9,13–15]

Some patients may have mixed pain, but it is not true that all pain types have a neuropathic component.[7,16] Understanding the pain and underlying pathology (neuropathic or otherwise) is important to be able to address the pain with appropriate treatment strategies. Studies have shown that medicines for neuropathic pain may be prescribed in situations where they are not indicated.[17–19]

Neuropathic pain medicines have demonstrated limited efficacy, especially when a neuropathic component was not clearly established or absent.[20–22] Pain due to radiculopathy seems more refractory than other types of pain.[5] Additionally, non-effective medicines may be prescribed for the treatment of neuropathic pain.[23,24]

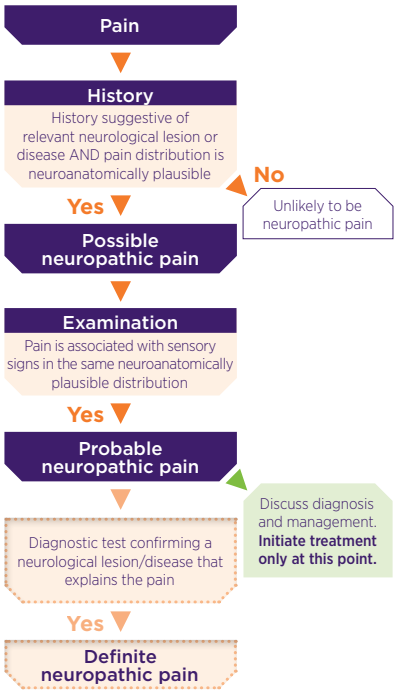
The neuropathic stroke of a brush and the prick of a toothpick

'Although often not black and white, I think the difficulty in diagnosing neuropathic pain is often overstated', says Professor Siddall.

Burning, shooting and pins and needles descriptors can alert us to the possibility of neuropathic pain. Then the clinical history and examination helps to confirm that the location of the pain is anatomically consistent with a neurological lesion.

Philip Siddall

Guidelines[2,13–15] recommend a structured approach, with patient history and clinical examination being the most important parts of the diagnosis. Neuropathic pain can be graded as possible, probable or definite based on the built-up evidence. Treatment can be commenced once probable neuropathic pain has been diagnosed,[14] with further investigations only considered if these tests would inform treatment.



History is needed to reach a 'possible' level of certainty.[14]

A history suggestive of a relevant neurological lesion (like herpes zoster or a traumatic nerve injury), pain descriptors (burning, shooting, pricking and pins and needles) or the presence of non-painful sensations like numbness or tingling are suggestive of neuropathic pain.[14] Furthermore, the pain distribution should be explainable by a lesion or disease in the somatosensory system, or be typical of an underlying neuropathic disorder[14] (see Figure 1). Validated assessment tools[14,15,25–30] have been created to help in this assessment, but should not be used alone.[14]

A **clinical examination** is needed to reach a 'probable' level of certainty.[14]

Once the history suggests a possible diagnosis of neuropathic pain, tools such as toothpicks, brushes or cotton wool can be used in a clinical examination to detect clinically consistent sensory changes that help further differentiate neuropathic from non-neuropathic pain.[2,13–5] Hypoalgesia to pinprick, hypoesthesia to tactile stimuli and allodynia to brush and cold are particularly discriminant.[13,31] Sensory changes should also lie within a plausible neurological distribution (see Figure 1).

Confirmatory tests can be considered in order to reach a 'definite' level of certainty[14] if these tests would inform treatment. A 'definite' level of certainty is commonly not required in primary care.

Tests must confirm that a lesion or disease of the somatosensory system can explain the pain.[2,13–15] These include magnetic resonance imaging (MRI) to confirm a stroke, multiple sclerosis or spinal cord injury and a skin biopsy showing reduced nerve fibre density.[14]

Medicines as part of a pain management plan

The treatment of neuropathic pain remains challenging – partial pain relief is usually considered a good result.[2] Pharmaceutical pain relief is part of a total plan for living with pain, which focuses on improving the patient's quality of life and ability to function.[32]

Non-pharmacological treatment such as physical exercise, cognitive behavioural therapy (CBT) and meditation can help in accepting and coping with the pain.[33–35]

Neuropathic pain medicines – the options

'There is little evidence to support the use of specific drugs in specific neuropathic pain conditions', says Professor Siddall.

'Usually the choice is determined by the general evidence in neuropathic pain as well as the likelihood of side effects in a particular person and the cost.'

Australian and international guidelines[2–5,36] are based on or agree with the latest systematic review and meta-analysis of relevant drug studies.[5] Common among these guidelines is that four medicines are strongly recommended for treatment of neuropathic pain: amitriptyline (a TCA), duloxetine (an SNRI), and two antiepileptics, gabapentin and pregabalin. Australian guidelines[2,37] recommend amitriptyline first-line, pregabalin and gabapentin second-line, and duloxetine as a second- or third-line consideration.

Other medicines recommended as second- or third-line options include tramadol, lignocaine, capsaicin and botulinum toxin A.[2–5,36]

There is a limited role for strong opioids in the treatment of neuropathic pain because of safety concerns and poor evidence of long-term efficacy.[5] There is little evidence that paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are effective.[38–39]

Neuropathic pain medicines – the evidence

Cumulative number-needed-to-treat (NNT) over the many trials can give an indication of the efficacy of the medicines.[5] For these medicines, NNTs are TCAs 3.6, gabapentin 6.3,[c] SNRIs 6.4, and pregabalin 7.7. Antidepressants (like amitriptyline) have the best numbers, but treatment preferences cannot be based on these numbers because of the differences in study design and quality. The quality of evidence is high for pregabalin, gabapentin and SNRIs (including duloxetine), and moderate for TCAs (including amitriptyline).[5]

Cumulative number-needed-to-harm (NNH) indicates that gabapentin has fewer tolerability issues than the others (which are approximately equal): NNHs are gabapentin 25.6,[c] pregabalin 13.9, TCAs 13.4, SNRIs 11.8.[5]

'Many physicians with less experience using TCAs think that they have to use the large doses normally used to treat depression. The tricyclic amitriptyline is almost always my first-line recommendation, used at the low doses where the side effects are far less problematic.'

Tony Hall

Tony Hall is a clinical pharmacist with 30 years of experience in persistent pain, and a senior lecturer at the Queensland University of Technology.

A recent systematic review confirmed the tolerability of low-dose amitriptyline (and other antidepressants) for the treatment of chronic pain. It reveals specific profiles of adverse effects that differ from those caused by higher doses of the same drugs prescribed for depression.[40]

There have been a number of small head-to-head studies comparing the different neuropathic pain medicines, but as they have small sample sizes, their findings need to be treated cautiously. Overall, no significant differences in efficacy or safety were found between the first-line treatments.[5]

Studies have examined the use of different neuropathic pain medicines for different conditions with neuropathic pain. Overall, all of the four first-line options can be considered, regardless of the cause or underlying disorder.[5] Australian guidelines recommend that first-line choice should be made on a case-by-case basis, according to efficacy, contraindications, adverse effect profile, cost and other indications.[2]

c Excludes gabapentin extended release or gabapentin enacarbil as these are not available in Australia.

The right dose, tested slowly, for the maximum benefit

'Some clinicians try to hurry the process by giving higher and higher doses, and the patients stop taking the medication due to adverse effects,' says Hall.

Evidence suggests that not all patients are receiving effective doses of recommended neuropathic pain medicines.[41] Studies have also demonstrated that low doses at initiation, followed by a gradual increase until maximum benefit is obtained, helps with tolerability.[32]

It may help to work with the patient to develop a plan for trialling the agreed medicine. Such a plan should include a careful up-titration, and a treatment response review after a 3–8 week treatment trial.[2,3,32] If the initial medicine is not effective or not tolerated, one or more of the other agents could be tried.[3] It may be necessary to use more than one medicine concurrently, although the evidence for benefit of combination therapy is limited.[2]

Most patients' expectations of an analgesic medicine is something that does or doesn't work almost immediately, This is not the case with the neuropathic pain analgesics, and may explain a desire for quick titrations to high doses. Much of my time is spent persuading patients to have a second 'audition' after they have stopped. Start low, go slow is my motto. Starting the patients on a very small dose and gradually increasing it is the best way to find the balance between the analgesic benefit and the side effect burden.

Tony Hall

Living with neuropathic pain

It is horrible living with neuropathic pain.

Tony Hall describes it as 'increased neural sensation'.

'Imagine listening to your favourite, beautiful piece of music playing softly on the radio. Then imagine the volume being turned up, louder and louder. It becomes irritating and eventually painful to the ear. The body becomes over-sensitive to the 'music' being sent from the body to the brain.'

Tony Hall

Unfortunately, only partial relief is possible in many cases, and people will need support and strategies to help them understand, accept, and live with their pain. A clear and targeted diagnosis, tackling the source of the pain where possible, and a considered treatment plan, including both pharmacological and non-pharmacological components, remain the best approaches to help people living with neuropathic pain.

Useful resources

Amitriptyline for nerve pain: fact sheet for patients
Provides information about what to expect when starting amitriptyline for neuropathic pain. It also helps address some of the barriers associated with starting this medicine.

Helping patients live with neuropathic pain: patient action plan
Designed to give patients with neuropathic pain a better understanding of their condition and help manage their expectations of pharmacological treatment.

Download these resources from the NPS MedicineWise website or access through clinical software (Best Practice, Medical Director, Genie and MedTech32).

Expert reviewers

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References

1. Jensen TS, Baron R, Haanpää M, et al. A new definition of neuropathic pain. Pain 2011;152:2204-5.
2. Neurology Expert Group. Therapeutic guidelines: Neuropathic pain: version 4. West Melbourne: Therapeutic Guidelines Ltd, 2011 (accessed 4 October 2017).
3. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in nonspecialist settings. Clinical guidance (CG) 173. UK, 2013 (updated 2014) (accessed 4 October 2017).
4. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from Canadian Pain Society. Pain Res Manag 2014;19:328-35.
5. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162-73.
6. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630-5.
7. Magrinelli F, Zanette G, Tamburin S. Neuropathic pain: diagnosis and treatment. Pract Neurol 2013;13:292-307.
8. Rheumatology Expert Group. Therapeutic guidelines: Rheumatology. West Melbourne: Therapeutic Guidelines Ltd, 2017 (accessed 19 October 2017).
9. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. Nat Rev Dis Primers 2017;3:17002.
10. Haanpää ML, Backonja MM, Bennett MI, et al. Assessment of neuropathic pain in primary care. Am J Med 2009;122:S13-21.
11. Bardin LD, King P, Maher CG. Diagnostic triage for low back pain: a practical approach for primary care. Med J Aust 2017;206:268-73.
12. Hush JM, Marcuzzi A. Prevalence of neuropathic features of back pain in clinical populations: implications for the diagnostic triage paradigm. Pain Manag 2012;2:363-72.
13. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152:14-27.
14. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016;157:1599-606.
15. Haanpää M, Treede R. Diagnosis and classification of neuropathic pain. Pain Clinical Updates 2010; 18 (accessed 5 October 2017).
16. Wright ME, Rizzolo D. An update on the pharmacologic management and treatment of neuropathic pain. JAAPA 2017;30:13-7.
17. Wettermark B, Brandt L, Kieler H, et al. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. Int J Clin Pract 2014;68:104-10.
18. Drug Utilisation Sub-Committee. Pregabalin: 24 month predicted versus actual analysis (October 2015). Canberra: DUSC, 2015 (accessed 4 October 2017).
19. Goodman CW, Brett AS. Gabapentin and pregabalin for pain – is increased prescribing a cause for concern? N Engl J Med 2017;377:411-4.
20. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of pregabalin for acute and chronic sciatica. N Engl J Med 2017;376:1111-20.
21. Romano CL, Romano D, Bonora C, et al. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. J Orthop Traumatol 2009;10:185-91.
22. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 2017;14:e1002369.
23. Martinez V, Attal N, Vanzo B, et al. Adherence of French GPs to chronic neuropathic pain clinical guidelines: results of a cross-sectional, randomized,
24. Hall GC, Morant SV, Carroll D, et al. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. BMC Fam Pract 2013;14:28.
25. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain 2001;92.
26. Bennett M, Smith B, Torrance N, et al. The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinical and postal research. J Pain 2005;6.
27. Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22.
28. Backonja MM, Krause SJ. Neuropathic pain questionnaire--short form. Clin J Pain 2003;19:315-6.
29. Attal N, Perrot S, Fermanian J, et al. The neuropathic components of chronic low back pain: a prospective multicenter study using the DN4 Questionnaire. J Pain 2011;12:1080-7.
30. Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. Pain 2011;152:S74-83.
31. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.
32. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51
33. Analgesic Expert Group. Therapeutic guidelines: Analgesic version 6. West Melbourne: Therapeutic Guidelines Ltd, 2012 (accessed 5 October 2017).
34. Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med 2014;44:1289-304.
35. Dimitrova A, Murchison C, Oken B. Acupuncture for the treatment of peripheral neuropathy: A systematic review and meta-analysis. J Altern Complement Med 2017;23:164-79.
36. National Institute for Health and Care Excellence. Neuropathic pain overview. UK, 2015 (accessed 4 October 2017).
37. Endocrinology Expert Group. Therapeutic guidelines: Endocrinology version 5. West Melbourne: Therapeutic Guidelines Ltd, 2014. (accessed 5 October 2017).
38. Wiffen PJ, Knaggs R, Derry S, et al. Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults. Cochrane Database Syst Rev 2016;12:CD012227.
39. Moore RA, Chi CC, Wiffen PJ, et al. Oral nonsteroidal anti-inflammatory drugs for neuropathic pain. Cochrane Database Syst Rev 2015:CD010902.
40. Riediger C, Schuster T, Barlinn K, et al. Adverse effects of antidepressants for chronic pain: A systematic review and meta-analysis. Front Neurol 2017;8:307.
41. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2009;27:95-112.

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