

A Literature Review on Treatment of Neuropathic Pain

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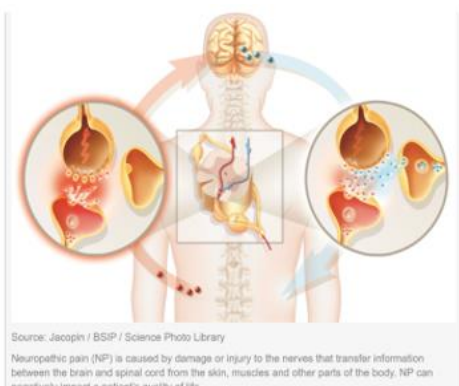
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Abstract: Neuropathic pain is a chronic condition representing a significant burden for patients, society, and healthcare systems. The prevalence of neuropathic pain in the general population has been estimated at 7–8% and is expected to increase in the future. Neuropathic pain differs from nociceptive pain and requires a different therapeutic approach; and the management of neuropathic pain is complicated and challenging. This chapter discusses clinical practice guidelines for neuropathic pain and their usefulness in clinical practice.

Keywords: Enter key words or phrases in alphabetical order, separated by commas.

1. Introduction

Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7–8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain. The management of neuropathic pain can be challenging and, as with all pain, should be approached with a biopsychosocial framework. There are several options for drug treatment as part of an overall approach to improve patients' quality of life and function. International guidelines have clarified the definition of neuropathic pain and updated their recommendations for drug treatment based on evidence from a systematic review and meta-analysis. Being aware of these changes is important in the clinical assessment and treatment.



2. Sources and selection criteria

Information for this narrative review was collected based on a search of the literature in the following areas: evidence-based guidelines for the treatment of NP, Cochrane reviews and meta-analyses of the use of different classes of medications used to treat NP. The following databases were also searched for relevant information: Embase (January 1990–May 2017), PubMed/Medline (January 1990–May 2017) and Cochrane Database of Systematic Reviews (January 2009–August 2017). Key terms used to search these databases include “neuropathic pain” and “neuropathy”. References of retrieved articles were scanned for additional relevant studies.

A. Symptoms, assessment and diagnosis

Peripheral NP is the result of injury to nerve fibres due to various aetiologies including toxic, traumatic, ischaemic, metabolic, infectious or compressive damage. Positive symptoms are typically altered or painful sensations such as tingling, prickling, or pain described as shooting, stabbing, burning, or having an electric shock sensation. Negative symptoms are described as diminished sensations due to loss of sensory function. Patients may also experience allodynia (pain caused by a stimulus that usually does not cause pain), hyperalgesia (increased pain from a stimulus that normally provokes pain), and anaesthesia dolorosa (pain in an area that is anaesthetic or numb).

The diagnosis of NP is primarily based on patient history and physical examination. The Special Interest Group on Neuropathic Pain (NeuPSIG) recently updated a grading system to assist with determining the level of certainty that the pain is neuropathic in nature and not related to other.

For patients to be classified at the possible level, pain distribution must be consistent with suspected lesion or disease, and patient history must be assessed and associated with NP using validated screening tools (Table 1). The next level of probable NP is obtained through clinical examination, particularly focusing on negative sensory signs. “Definite” NP requires an objective diagnostic test to confirm a lesion or disease that affects the somatosensory nervous system. If a patient is classified with probable or definite NP, consideration

Table 1
Screening and assessment tools to help differentiate neuropathic pain (NP) from non-NP

Tool	Components	Additional information
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	Patient symptom self-assessment Physical exam signs measured by healthcare professional	Translated and validated in several languages Not quantitative S-LANSS (self-report LANSS test) is a modified version that allows patient to perform physical exam
Neuropathic Pain Questionnaire (NPQ)	Self-reported assessment	Translated and validated in several languages Only tool to incorporate symptoms related to weather changes Not quantitative NPQ-SF is a short-form version
Douleur Neuropathique 4 Questions (DN4)	Symptoms and physical exam signs	Translated and validated in several languages Not quantitative One of the few to incorporate itch
painDETECT	Patient symptom self-assessment	Translated and validated in several languages Includes radiation of pain in the assessment Not quantitative Not as predictive of NP in certain painful conditions
ID Pain	Patient symptom self-assessment	Translated and validated in several languages Available to use for free Short and easy to use Not quantitative

should be given to pharmacologic treatment using clinical guidelines

B. Common neuropathic pain conditions

NP has multiple aetiologies. Some of the more common underlying conditions that are associated with NP include diabetic peripheral neuropathy, HIV-associated neuropathy, chemotherapy-induced peripheral neuropathy (CIPN), postherpetic neuralgia (PHN) and trigeminal neuralgia. Although the aetiologies may vary, the signs and symptoms of NP that patients experience can be similar.

C. Primary disease management:

The primary disease management of neuropathic pain needs to consider the individual as a whole. For instance, in patients with diabetic neuropathy, erratic glycaemic control worsens symptoms and improving glycaemic control may reduce progression of neuropathy. However, there is increased mortality with intensive insulin regimens in patients with established diabetic neuropathy compared to patients without neuropathy. HIV-associated neuropathy presents an even more complex picture – starting antiretrovirals may initially improve symptoms although nerve damage may progress. Some antiretrovirals can cause neuropathy, and neurotoxicity may be a feature of concomitant medicines such as isoniazid for tuberculosis.

3. Drugs for neuropathic pain

The IASP’s Neuropathic Pain Special Interest Group (NeuPSIG) has recently undertaken a systematic review of medicines for neuropathic pain Fibromyalgia, atypical facial pain, complex regional pain syndrome and chronic low back pain without radiculopathy were not included in the review as they do not meet the current criteria for the definition of neuropathic pain.

Drug treatment for neuropathic pain – updated recommendations from the International Association for the

SNRI serotonin noradrenaline reuptake inhibitors.

Table 2
Drug treatment for neuropathic pain – updated recommendations from the International Association for the Study of Pain

Recommendation	Drugs
First-line	SNRI – duloxetine, venlafaxine
	Tricyclic antidepressants
	Gabapentin, pregabalin
Second-line	Capsaicin 8% patches
	Lidocaine (lignocaine) patches
	Tramadol
Third-line	Strong opioids

Adapted from reference

The review included tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs, opioids, topical lidocaine (lignocaine), capsaicin high-concentration patches and oromucosal cannabinoids. A number of overarching themes were identified:

- Most studies were conducted in diabetic neuropathy or postherpetic neuralgia
- Publication bias accounted for approximately 10% of the treatment effect
- Placebo effect was large
- Drug effects were modest
- Data did not identify that one particular drug or drug class was Superior in any particular neuropathic pain syndrome
- The majority of studies were for 12 weeks or less data were limited to non-cancer pain in adults.
- *Antidepressants:* Tricyclic antidepressants and SNRIs were effective in reducing pain. Amitriptyline was the most studied tricyclic antidepressant (daily doses 25–150 mg) and did not show a dose-response effect. Seven of nine studies with duloxetine 20–120 mg were positive, while two of four studies identified efficacy with venlafaxine 150–225 mg daily. The negative venlafaxine studies were at lower doses.
- *Antiepileptics:* Most trials with pregabalin (18/25)

showed improvement in neuropathic pain, and the effect was greater with larger doses. Pregabalin in HIV neuropathy was no better than placebo. However, the placebo was very effective. Gabapentin was also found to be effective, although no dose response was identified. The number needed to harm was 13.9 for pregabalin and 25.6 for gabapentin. Other antiepileptic drugs had minimal evidence of efficacy, and topiramate, carbamazepine and oxcarbazepine had a poor safety profile.

- *Tramadol, tapentadol and opioids:* Tramadol consistently showed efficacy, while tapentadol had very limited supporting data. With morphine or oxycodone, 10 of 13 trials showed benefit, with no benefit in increasing the dose beyond 180 mg daily oral morphine equivalents.
- *Topical treatments:* There were some limited data suggesting the efficacy of lidocaine (lignocaine) 5% patches, with good safety and tolerability. Although registered, this product is not available on the Pharmaceutical Benefits Scheme (PBS) so may be prohibitively expensive for patients.
- For postherpetic neuralgia and HIV neuropathy, a high-concentration (8%) capsaicin patch demonstrated efficacy over a low-dose (0.04%) patch. Unfortunately, the high-dose patch is not available in Australia.
- *Oromucosal cannabinoids:* The meta-analysis identified mostly negative data for a fixed-dose combination of cannabidiol and 9-tetrahydrocannabinol (nabiximols) in reducing pain in multiple sclerosis. A statement by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists on medicinal cannabis identifies no role for the use of cannabinoids in neuropathic pain, but notes pain and spasticity related to multiple sclerosis may be an exception.

4. Guidelines for NP treatment

Guidelines and recommendations presented by key organisations around the world focus on NP in general or on specific types of NP. The following recommendations from each organisation are designed to help healthcare practitioners select appropriate pharmacologic treatment for patients with NP. In addition to the recommendations listed in this article, there are also local guidelines available to help guide therapy for NP.

National Institute for Health and Care Excellence (NICE): NICE provided recommendations for treating patients with NP in non-specialist settings in 2013, which were updated in February 2017. In September 2017, it was decided that these guidelines did not require updating further at this time.

First-line treatments for NP include a choice of monotherapy with amitriptyline, duloxetine, gabapentin or pregabalin. If a

patient does not experience effective results, or if the medications cannot be tolerated, then it is recommended to choose one of the three remaining first-line therapies. If a patient does not respond, then trials with the other first-line agents should be initiated. Tramadol may be considered for short-term, acute rescue therapy, but long-term use is not recommended unless advised by a pain specialist. For patients with painful diabetic neuropathy, the first-line choice is duloxetine, unless contraindicated (see Table 4). Capsaicin cream may be used for localised NP if a patient cannot tolerate the oral first-line agents. NICE also recommends carbamazepine for the first-line treatment of trigeminal neuralgia. These recommendations are based on high- or moderate-quality RCTs and cost-effectiveness.

A. Trigeminal neuralgia

Trigeminal neuralgia is the only condition in which a specific drug class has shown superior efficacy. Carbamazepine and oxcarbazepine are first line for pharmacological pain management. It is currently recommended that Asian people of non-Japanese origin are tested for the HLA-B*1502 allele as this confers an increased risk of cutaneous drug reactions with carbamazepine.

5. Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain

This special interest group provides guidelines that cover the assessment, the interventional management and the pharmacological management of NP. In 2015, NeuPSIG revised its recommendations for the pharmacotherapy of NP after performing a systematic review and meta-analysis of RCTs in patients with this condition. For general NP, NeuPSIG strongly recommends the use of duloxetine, extended-release gabapentin, gabapentin, pregabalin, venlafaxine and TCAs as options for first-line therapies. Duloxetine has been studied more, and is the preferred choice of SNRIs. NeuPSIG also recommends that TCAs not be used in doses greater than 75mg in patients aged 65 years and older because of the adverse effect profile and the potential risk for falls in this patient population.

- *Interventional modalities:* Local nerve blocks, spinal or epidural medicines, and neuro-ablative, neuromodulatory and neurosurgical procedures are also used for neuropathic pain.
- *Updated recommendations for treatment:* As a result of the meta-analysis, NeuPSIG has updated its recommendations for the treatment of non-cancer associated neuropathic pain in adults. With the exception of trigeminal neuralgia, there were no data identifying that any particular drug was superior to another in any particular disease state.

The guidelines recommend tricyclic antidepressants, gabapentin or pregabalin, and the SNRIs venlafaxine or duloxetine as first line. Second-line treatments include tramadol. Topical lidocaine (lignocaine) or high-concentration

capsaicin may be considered for neuropathic pain when there is a presumed local generator. The consensus is that opioids can no longer be recommended as first-line treatment, and there is general agreement that they should only be considered as third line, with appropriate monitoring for safety and efficacy. It is increasingly recognised that the harms of opioids, in particular addiction, cannot be adequately identified in short-term studies. Also, these short-term studies could not identify if any benefit persists or is lost as tolerance develops.

6. A pragmatic approach to drug therapy:

Choose a tricyclic antidepressant or SNRI with consideration of the patient's comorbidities, potential drug interactions and adverse effects, and consider pregabalin or gabapentin next before tramadol. There is a paucity of guidance on duration of treatment. Again, a pragmatic approach may be to try a therapy for 12 weeks as this is the maximum duration of most of the trials. Monitor for efficacy (using multidimensional tools for pain intensity, quality of life and patient function) and safety, and stop if the treatment is not working.

The PBS listing for pregabalin in neuropathic pain is that 'the condition must be refractory to treatment with other drugs'. Cost of treatment is significant. In 2016–17, more than 3.5 million PBS scripts for pregabalin were issued at a cost of over \$190 million. neurocognitive adverse effects, can cause weight gain and are associated with an increased risk of falls. They are anxiolytic, and there is emerging evidence of significant pregabalin abuse.

Any consideration of psychotropic drugs including opioids (tramadol or stronger opioids) should involve:

- Assessing the risk of abuse, including history of psychiatric, personality or substance use disorder
- Ongoing monitoring for development of abuse
- Multidimensional assessment of efficacy.

A plan to stop therapy should be discussed with the patient before treatment starts, and daily opioid doses should not exceed 60 mg oral morphine equivalents without specialist review.¹⁷

7. Antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline, nortriptyline and desipramine, achieve their effects by inhibiting norepinephrine reuptake in the spinal dorsal synapses and have secondary activity at sodium channels. Because of the fewer side effects, nortriptyline and desipramine are preferred in older patients or in those likely to experience adverse effects, however, neither are recommended for use in the UK. Adverse effects are the main limitations of this class of medications and include somnolence and anticholinergic effects. There is also concern about TCAs causing possible cardiotoxicity, therefore, caution should be used in patients with known or suspected cardiac disease. TCAs should be started at low doses (10mg to 25mg/day), at bedtime and can be titrated up to 75mg/day. Patients will usually see the analgesic effect after two to four

weeks of therapy.

The review and meta-analysis by Finnerup et al. found that the quality of evidence for the effectiveness of amitriptyline in NP was moderate. The NNT for amitriptyline was reported as 3.6. A Cochrane review in 2015 by Moore et al. could not provide good-quality, unbiased evidence to support the use of amitriptyline in the treatment of NP. The review did not find any lack of efficacy, but the concern was that there may be an overestimation of treatment effect. It was emphasised that amitriptyline should continue to be used as part of the treatment for NP, but only a minority of people will experience good pain relief.

Serotonin norepinephrine reuptake inhibitors (SNRIs) work to block the presynaptic serotonin and norepinephrine transporter proteins, which inhibits the reuptake of these neurotransmitters. Duloxetine inhibits the neurotransmitters equally, whereas venlafaxine inhibits only serotonin at doses less than 150mg/day, but inhibits both serotonin and norepinephrine at higher doses. The combined NNT for both SNRIs was reported as 6.4 (quality of evidence was high). Both medications are associated with increasing blood pressure and cardiac conduction abnormalities so should be used cautiously in patients with cardiac disease. Duloxetine is usually dosed at 60–120mg but the incidence of nausea, its most common adverse effect, may be reduced if patients start at 30mg/day.

One of duloxetine's adverse effects, anorexia, may cause weight loss that could be advantageous in certain populations. Older patients may experience more severe adverse effects so it is recommended to start at a low dose and titrate slowly. In painful diabetic neuropathy, duloxetine had a higher level of evidence of pain reduction compared with venlafaxine. Venlafaxine is dosed between 150 and 225mg/day, and can lower the seizure threshold. An adequate trial of venlafaxine is four to six weeks. When discontinuing either duloxetine or venlafaxine, doses should be tapered down gradually to prevent withdrawal symptoms.

A. Opioid or opioid-like drugs

Overall, these medications are not recommended as first-line therapy because of concerns about diversion, misuse, opioid-associated overdose, morbidity and death. These medications should be avoided in those with a history of substance abuse. Tramadol and tapentadol are more specifically discussed in recent guidelines, however, other agents evaluated include oxycodone and morphine. Tramadol, a centrally acting analgesic, has weak mu-opioid receptor agonist activity and inhibits norepinephrine and serotonin reuptake. Tramadol was found to be effective (NNT: 4.7), but the quality of evidence is moderate. Tramadol is limited by its potential for abuse as mentioned above, even though the risk is lower compared with other opioids.

Tapentadol is another centrally acting opioid analgesic that is a mu-opioid agonist, but also inhibits noradrenaline reuptake. Finnerup et al. determined that the effectiveness of tapentadol was inconclusive owing to both negative and positive findings

with potential biases. The abuse potential of tapentadol may be similar to other opioids, although because of its low use compared with other opioids, the risk for addiction is currently unknown. At this time, tapentadol is not a recommended treatment for NP in the UK.

Cochrane reviews have reported low or very low-quality evidence related to the use of strong opioids in the treatment of NP. A 2016 review by Gaskell et al. reported that three out of the five studies showed a 30% reduction in pain, and no study reported a 50% reduction in pain with oxycodone. Additional Cochrane reviews reported that there is no evidence for the use of or against hydromorphone, fentanyl, morphine or buprenorphine in the treatment of NP. These reviews do not provide much evidence because of the limited number of studies that focus on these medications as treatment for NP, limited participants in the studies, bias and the potential mishandling of dropout information.

B. Topical therapies

For peripheral NP, the meta-analysis by Finnerup et al. emphasised utilising topical treatments as second- or third-line therapies. These include capsaicin, lidocaine and botulinum toxin type A. Topical therapies are recommended in patients with local NP (e.g. postherpetic neuralgia) and may be considered first-line therapies for populations such as elderly patients who may have differences in their drug distribution, metabolism and elimination. Advantages of topical or local therapies include lower systemic drug levels, fewer adverse effects and fewer drug interactions. Unlike systemic therapies, titration is unnecessary with targeted topical therapies.

Capsaicin 8% patches are single application patches that can reduce pain for up to 12 weeks, but must be applied by a healthcare provider in a clinic with either local anaesthesia or short-acting opioids to reduce pain associated with application. Capsaicin is derived from hot chili peppers and desensitises TRPV-1 sensory axons over several days to decrease depolarisation, initiation of an action potential and pain signal transmission. Repeated applications can result in “defunctionalisation” or a long-lasting effect due to reversible degeneration of nerve terminals. The NNT for the Capsaicin 8% patch was reported to be 10.6, but was also identified as susceptible to publication bias. The long-term safety of repeated applications of these patches has not been established. Creams are of limited use because they must be applied multiple times per day and can cause pain for the first few weeks of therapy.

Lidocaine, either in 5% patches or gel, acts locally to reduce spontaneous ectopic nerve discharge by antagonising sodium channels. Lidocaine plasters or patches are licensed in the UK, Europe and US for the treatment of post-herpetic neuralgia only. It is also listed on PrescQIPP DROP-List, as there are cheaper and safer alternatives. Patches can be cut if needed and should be applied to painful sites. Minimal absorption occurs if hepatic function is normal, but if patients take a Class I arrhythmic medication, systemic absorption should be considered. Titration is not necessary but patients should allow

two to four weeks for an adequate trial. Skin reactions at the site of application can be seen. Evidence for the efficacy in the treatment of postherpetic neuralgia is limited.

Subcutaneous injections of botulinum toxin type A has shown efficacy for the treatment of peripheral NP. The NNT found with a single administration of this therapy compared with placebo was 1.9; however, the strength of the recommendation to use this therapy is weak because of the limited quantity of evidence. Botulinum toxin type A is a neurotoxin that treats focal muscle hyperactivity with repeated administration locally over six months. Several small trials have studied its use in patients with postherpetic neuralgia, trigeminal neuralgia and diabetic neuropathy with positive results.

8. Other treatments

There are other medications (e.g. selective serotonin receptor inhibitors, other antiepileptics, mexiletine, clonidine and sodium valproate) that have been evaluated and have shown inconsistent, weak or negative results; had study limitations; or unacceptable adverse effects. Cannabinoid use for NP has been recommended as a third-line agent in a few select guidelines, but the use of this product is not recommended in the UK for the treatment of NP pain. It is associated with dizziness, sedation, dry mouth, oral discomfort and gastrointestinal adverse effects. Additionally, cannabinoids should not be used in patients with a history of heart disease or psychiatric disorders. There is concern and controversy about their long-term use.

Interventional therapies may be considered in select patients with refractory NP if medications fail to provide relief. Spinal cord stimulation is recommended by the National Institute for Health and Care Excellence (NICE) guidelines as a therapy for patients who experience chronic NP for greater than six months despite standard treatments and have had successful trials with spinal cord stimulation by a specialist. Other interventional therapies include transcutaneous electrical nerve stimulation, sympathetic nerve blocks and steroid injections.

Nonpharmacological treatments have also been suggested to help patients suffering from NP. In general, nonpharmacological treatments are considered safe and may decrease pain, decrease the use of medications and help increase function. They may also aid in improving the patient’s overall quality of life. A Cochrane review did not find sufficient evidence to evaluate the effectiveness of exercise in NP. However, it did state that there were several small trials that have shown exercise may help patients with muscle strength, functional ability and fatigue. Recommendations for exercise in patients with NP include both aerobic and strengthening exercises.

Psychotherapy is another nonpharmacological treatment that has received attention for helping patients with NP. Cognitive behavioural therapy is a type of psychotherapy that uses methods to assess biases associated with pain and avoiding unpleasant thoughts. A Cochrane review focused on

psychotherapy as a treatment for NP found insufficient evidence on the efficacy or safety of psychotherapy. Other nonpharmacological treatments include physical therapy and occupational therapy.

9. Combination treatments

Combination therapies are often used in patients with NP who have either failed to have a response, or only had a partial response to monotherapy. In theory, utilising lower doses of different classes of drugs may help alleviate or prevent adverse drug effects that are seen with higher doses of monotherapy. Studies have focused on the use of combination therapies and have found mixed results. A meta-analysis of two studies did find that a combination of gabapentin with an opioid were superior to monotherapy (or placebo), but the combination of the two medications were associated with higher drop-out rates due to adverse effects. A large study that focused on comparing duloxetine and pregabalin at high doses as monotherapy to lower doses in combination did not show any difference in efficacy or side effects. Owing to the limited number of studies, there is not much available evidence that supports specific combinations of medications for NP.

10. Future treatments

Researchers continue to seek new treatments for NP. There are new voltage-gated sodium channel blockers that are receptor specific and may have less risk of cardiac, motor and central nervous system adverse effects. A new selective angiotensin type 2-receptor antagonist, EMA401, has been used in trials including one that focused on treating patients with postherpetic neuralgia. Additional medications that are being evaluated include acetyl-L-carnitine and alpha-lipoic-acid. A review of stem cell therapy focused on preclinical data suggested that adult stem cell therapy in patients with NP showed positive effects, with peripheral appearing to be more responsive than central NP.

Personalised pain therapy is another approach that can provide patients with the most effective treatment for NP. The phenotype-based classification system focuses on categorising patients by mechanisms responsible for NP rather than aetiology. By focusing on patients' profiles of signs and symptoms, researchers can identify treatment responders. Several phenotypes have been identified and are associated with a positive response to various treatments. Studies that focus on genetics and subgrouping patients based on their phenotypes may play an important role in the future of personalised pain management for NP.

11. Guidelines for NP treatment

Guidelines and recommendations presented by key organisations around the world focus on NP in general or on specific types of NP. The following recommendations from each organisation are designed to help healthcare practitioners

select appropriate pharmacologic treatment for patients with NP. In addition to the recommendations listed in this article, there are also local guidelines available to help guide therapy for NP.

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12. Conclusion

A well-conducted meta-analysis reviewing drug treatment of neuropathic pain provides clear recommendations. Tricyclic antidepressants and SNRIs should be trialled first. If they are ineffective, consider a trial of a gabapentinoid then tramadol. This should be accompanied by multidimensional assessment of efficacy, review for harms associated with treatment and a plan for stopping treatment if there is no benefit.

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