

Evidence-based Pharmacy Practice (EBPP): NEUROPATHIC PAIN

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Abstract

Neuropathic pain (NP) is the most difficult type of pain to treat. The management of patients with chronic NP is complex and the response to existing treatments is often inadequate and subject to inter-patient variability. Even with medications that have been well established in the treatment of NP, effectiveness is unpredictable, dosing can be complicated, analgesic effect is delayed and side effects are common.¹ Evidence based recommendations recommend a stepwise approach to the management of NP. However as existing literature shows that no one drug appears to be more effective than another, an individualised patient approach is necessary. A choice of agent must be based on a comprehensive patient assessment that takes into account individual risk factors for adverse effects, co-morbidities, cost to the patient and the healthcare system, patient response and acceptance of the fact that combinations of medications ‘polypharmacy’ may be necessary. Non-pharmacological interventions also play an important role in the management of NP and should not be disregarded.

Definitions

Pain is a complex subjective sensation reflecting real or potential tissue damage and the affective response to it.²

Physiological pain is caused by normal activation of primary afferent neurons known as nociceptors and a subsequent inflammatory response in the peripheral nervous system after tissue damage.³

Neuropathic pain (NP) (also known as pathophysiologic pain) can be defined as pain caused by a lesion of the peripheral (PNS) or central nervous system (CNS) or both manifesting with sensory symptoms or signs.⁴ It is thought to arise from abnormal physiology of the peripheral and central nervous systems and may be unrelated to ongoing tissue damage or inflammation.³

Pain is a normal biological process that can serve to protect us by providing a warning of imminent or actual tissue damage.⁵ In contrast NP is maladaptive, pathophysiologic and serves no purpose except to cause suffering and distress.⁵

NP is especially problematic because of its severity, chronicity and resistance to simple analgesics.⁷

It is often experienced in parts of the body that otherwise appear normal.⁷ It is generally chronic, severe and resistant to OTC (over the counter) analgesics.⁷ It is further aggravated by allodynia (touch-evoked pain).⁷ Allodynia can be caused by the lightest stimulation, such as skin contact with clothing or a light breeze.⁷

Epidemiology

The prevalence of NP is still unknown. It has been estimated to be that 1.5% of individuals of the USA and 1% of those of the UK experience some form of neuropathic pain.^{6,8} These rates can be considered underestimates because NP is often unrecognised or unreported in relation to many disease conditions.⁶ Certain disease conditions are more associated with NP such as diabetes, herpes zoster and spinal cord injury.⁶ Post herpetic neuralgia (PHN) and painful diabetic neuropathy (PDN) are two types of NP commonly seen in the elderly population.⁶ Although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy which is probably

Table 1: Characteristics of physiologic and neuropathic pain⁶

Physiologic pain	Neuropathic pain
Caused by activation of nociceptors e.g. thermal, chemical, mechanical or inflammatory stimuli	Caused by damage to the CNS or PNS or both
Warns and protects individual against injury	Serves no useful purpose
Subsides with time	Is usually sustained and chronic

the most common type of NP.¹ Evidence indicates that NP impairs patient's mood, quality of life, activities of daily living and performance at work.⁷

Aetiology/pathophysiology

The pathophysiology of NP is complex.⁹ Current research indicates that NP results from cellular changes that occur both in the peripheral and central nervous systems, which results in sensitisation to the transmission of pain signals.⁶ Possible mechanisms of NP include the following:⁶

Peripheral mechanisms⁶

- Peripheral sensitisation initiated by release of chemicals such as bradykinin, prostaglandins, serotonin, nor-adrenaline, leukotrienes and cytokines from damaged cells and inflammatory cells.
- Number and location of ion channels are altered (e.g. sodium and calcium channels)
 - lowered threshold for depolarisation
 - ectopic and spontaneous discharges occur
 - increased responsiveness to mechanical and chemical stimuli
- Collateral sprouting of primary afferent neurons.
- Recruitment of 'silent' nociceptors.
- Coupling between the sympathetic nervous system and sensory nervous system.
- Clinical symptoms include hyperalgesia, burning pain, dyesthesias and paresthesias.

Central mechanisms⁶

- Initiated by tachykinin and neurotransmitter release from peripheral nociceptors (e.g. substance P, neurokinin A, glutamate, calcium gene-related peptide, gamma-aminobutyric acid) – NMDA receptor is activated.
- Intracellular calcium is increased.
- "Wind-up" occurs (an increased excitability and sensitivity of spinal dorsal horn neurons)
 - lower activation threshold
 - increased response to stimuli
 - larger receptive field
- Ephaptic conduction ("cross excitation" or "cross talk") occurs between neurons.
- Neuronal reorganisation occurs (sprouting of spinal cord neurons into new locations).
- Central disinhibition (occurs when control mechanisms along inhibitory pathways are lost or suppressed which causes abnormal excitability of central neurons).

Normally, peripheral and central sensitisation phenomena dissipate as tissue heals and inflammation subsides.⁶ These processes may continue when changes in primary afferent function persist after disease or injury of the nervous system and result in NP.⁶

Underlying causes of NP include exposure to toxins, infection, viruses, trauma, metabolic abnormalities, nutritional deficiencies, ischaemia, chemotherapy, surgery, irradiation,

neurotoxins, inherited neurodegeneration, nerve compression, inflammation, tumour infiltration and stroke.^{3,6}

NP in a clinical setting never occurs in isolation, but rather as a part of a disease or injury that alerts other tissues and initiates other mechanisms, such as inflammation.⁴ In general most patients with NP have other types of pain, most frequently musculoskeletal related.⁴

Diagnosis

There is no single diagnostic test for NP or pain in general.⁹ There may be a high degree of interpatient variability in presentation.¹⁰ Not all patients with nerve damage will experience NP, some may only experience sensory loss.¹⁰ In patients whose pain is not well controlled by conventional analgesics, NP should be suspected.⁹ The qualitative words used by patients to describe their pain are often indicative of NP e.g. 'burning', 'stabbing' and 'shooting'.⁹

Diagnosis of NP is based primarily on history (e.g. underlying disorder and distinct pain qualities) and the findings on physical examination (e.g. pattern of sensory disturbances).⁷ Clinical evaluation rather than diagnostic tests is one of the best available tools for diagnosis.¹⁰ Physical and neurological examination remains a critical element for patient evaluation.¹⁰

A basic neurological examination may identify features associated with NP:⁹

- i. *Allodynia*: pain produced by a normally non-painful stimulus
- ii. *Hyperalgesia*: an increased response to a standard pain stimulus
- iii. *Alteration of skin sensation*: a change in pin-prick threshold
- iv. *Dysesthesia*: an unpleasant abnormal sensation (whether spontaneous or evoked)

In NP both positive and negative symptoms and signs are observed and these correlate with clinical assessments on physical examination of normal, decreased or increased sensations.¹⁰ Positive sensory phenomena include spontaneous and evoked pain (including allodynia and hyperalgesia) and parathesias.¹⁰ Negative sensory symptoms and signs include reduced sensitivities to touch, pinprick, cold/warm sensations, or vibration.¹⁰

Classification of NP is not easy and may be based either on the presumed neurophysiological changes or on the underlying cause.⁹

Clinical approaches to neuropathic pain for the pharmacist

A thorough review of all a patient's current medications is warranted before prescribing any drugs for NP.⁷ A pharmacist is in an ideal position to check what other medication the patient has had prescribed before from the patients prescrip-

Table 2: Conditions associated with neuropathic pain⁷

Diagnosis	Cause
Painful diabetic neuropathy	Diabetes-hyperglycaemia
Lumbosacral radiculopathy	Herniated intervertebral disc
Postherpetic neuralgia	Varicella zoster virus infection
HIV-related neuropathy	HIV
Postsurgical neuropathic pain	Phantom pain; amputation, mastectomy

tion records. The prescriber may not be aware of other medications (both allopathic and complementary) that the patient may have had from other prescribers.

If the pharmacist identifies any possible interactions the prescriber should be informed. Due to the potential for overdose and toxicity with opioids and TCAs, suicide risk should be evaluated before prescribing.⁷ If the pharmacist is aware of any possible risk they could suggest to the prescriber that the medication be dispensed on a weekly basis. Some patients need reassurance that analgesia with antidepressants and anticonvulsants does not necessarily imply a diagnosis of depression or epilepsy.⁷ The pharmacist is best placed to advise the patient at the time of dispensing to advise and counsel patients regarding their medication. With certain medications used to treat NP a gradual dose titration is necessary so the onset of pain relief will be gradual. The pharmacist can advise the patient on this and if the medication is repeated weekly there will be regular patient contact to guide the dose titration.

Other non-pharmacological methods that can help the patient with managing their pain include keeping a pain diary so they can evaluate the effectiveness of drug and non-drug pain relief strategies.¹¹ Pacing of activities could be suggested to the patient. This helps patients limit pain and prevent exacerbations.¹¹ Pacing often requires finding new ways to perform normal activities that were not painful before the onset of chronic pain.¹¹ Relaxation, imagery and hypnosis are other methods of helping a patient deal with chronic pain.¹¹ Maintaining a healthy lifestyle by paying attention to diet and exercise is always something a pharmacist can advocate and give advice on to patients. Pharmacists can also give advice on plans to manage flare-ups and when to use different treatments especially opioids for breakthrough pain. Pharmacists should always advise patients on when and how to take their medications correctly, how to deal with side effects and when to contact the doctor and how to safely store their medications so that they are out of the reach of children and are at the right temperature.

Available treatment options

Treatments are generally palliative and include conservative non-pharmacological therapies (which include psychological

interventions), drugs and more invasive physical interventions.⁷ Initial treatment is usually pharmacological and ideally should be paired with psychological interventions which help the patient cope with and manage their problem.⁹ This provides a holistic approach to improving a patient's quality of life.⁹ Complex invasive physical interventions tend to be reserved for those who are unresponsive to simple pharmacological treatment.⁹ This is due to the fact that specialist skills are required to perform the likes of electrical spinal cord stimulation and implanted drug delivery systems are invasive and expensive.⁹

Therapeutic objectives

Early intervention, diagnosis and treatment results in improved patient outcomes.⁹ For the successful management of neuropathic pain, patient education and support are critical components.¹ Careful explanation of the cause of neuropathic pain and the treatment plan are essential.¹ A patient centred approach involves both the prescriber and the patient discussing realistic treatment goals.¹ The patient may have specific goals e.g.¹⁰

- Sleeping through the night
- Improving ability to eat or participate in physical therapy
- Resuming a hobby or social activity
- Returning to work

The prescriber needs to explain to the patient that complete relief of pain is not always possible and that multiple drug therapies may need to be trialled before one is found to give any relief. Also multiple drug therapy 'polypharmacy' may need to be employed to maximise therapy for NP in a patient. When evaluating a patient with NP and taking a history all information about prior treatments and their efficacy needs to be ascertained.¹⁰ Current and past medication use should be fully evaluated.¹⁰ It is critically important to ascertain whether prior treatments were titrated until pain relief or unacceptable side effects occurred.¹⁰ Clinical surveys have shown that a large majority of patients with NP received the wrong type of drug or the right type of drug in doses that were too low.¹⁰

Non-pharmacological management

These include non-drug treatment, psychological and physical interventions.

Non-drug interventions¹⁰

- Physical or occupational therapy
- Active exercise
- Stretching
- Massage
- Myofascial release
- Craniosacral manipulation

Psychological interventions

- Cognitive behavioural therapy⁷
- Supportive psychotherapy⁷
- Relaxation/diversion⁹
- Counselling and education⁹

- Stress reduction¹
- Good sleep hygiene¹

Physical interventions

- Acupuncture⁹
- Transcutaneous electrical nerve stimulation (TENS)⁷
- Percutaneous electrical nerve stimulation⁷
- Nerve blocks⁹
- Spinal cord stimulation⁹
- Epidural or intrathecal drug delivery systems^{7,9}
- Epidural or perineural injections of local anaesthetics or corticosteroids⁷
- Neural ablative procedures (Gasserian ganglion glycerol injection or gamma knife surgery)⁷

Pharmacological treatment

Antidepressants

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake inhibitors (SSNRIs) are used in the management of NP.

The first medication category that proved effective for neuropathic pain in placebo-controlled trials was TCAs.³

They are still the most commonly prescribed group of drugs for the management of NP.⁹ Their analgesic actions may be attributable to the blockade of serotonin and noradrenaline re-uptake in the CNS thereby increasing the activity of the descending inhibitory pathways,⁹ NMDA antagonism and sodium channel blockade.⁷ TCAs are inexpensive and usually administered once daily.¹ The presence of depression is not required for the analgesic effects of TCAs, although they may be useful in patients with inadequately treated depression.¹ The most common side effects of TCAs include sedation, anticholinergic effects (e.g. dry mouth, constipation and urinary retention), weight gain and orthostatic hypotension.^{1,3} TCAs must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy.³ Amitriptyline is

the most commonly used TCA in the management of NP.⁹ The use of nortriptyline and desipramine which are secondary amines is preferred over the tertiary amines amitriptyline and imipramine because they are better tolerated and they have comparable analgesic efficacy.¹ Amitriptyline is not recommended in elderly patients because of the risk of significant adverse effects.³ They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls.¹ Due to the possibility of cardiac toxicity and the increased risk of sudden cardiac death at dosages of 100mg per day or higher the lowest effective dosage of a TCA should be used in all patients with NP.¹ TCAs should be avoided in patients who have ischaemic heart disease or an increased risk of sudden

cardiac death.¹ A screening electrocardiogram (ECG) to check for cardiac conduction abnormalities is recommended before beginning treatment with TCAs in patients over 40 years of age.^{1,3} TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose.^{1,3} Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P4502D6, such as the SSRIs (selective serotonin reuptake inhibitors).¹ Caution must be undertaken when TCAs and SSRIs are administered together and when switching from one drug class to the other.³ To decrease adverse effects and increase patient adherence to treatment starting doses of TCAs should be low-10 to 25 mg in a single dose at bedtime, and the dosage titrated slowly, every three to seven days by 10 to 25 mg

per day as tolerated until pain is adequately controlled or side effects limit continued titration.^{1,3} TCAs should be titrated to dosages of 75 to 150 mg daily. Monitoring medication levels is not usually necessary unless dosages are greater than 150 mg daily where it may reduce the risk of cardiac toxicity.^{1,3} An adequate trial of a TCA in the management of NP would last six to eight weeks with at least one to two weeks at the maximum tolerated dosage.³

SSRIs and SSNRIs have fewer adverse effects and are generally better tolerated than TCAs.³ However they do not appear to be as effective as TCAs.⁷ SSRIs and SSNRIs are safer to use than TCAs and are a better option in patients with cardiac disease.¹² Paroxetine and citalopram have been associated with statistically significant pain relief compared with placebo in randomised controlled trials (RCTs) in patients with PDN, whereas fluoxetine has been shown to be no more effective than placebo.³ Sustained release bupropion hydrochloride was found to provide statistically significant pain relief compared with placebo in a controlled trial of patients with different peripheral and central neuropathic pain syndromes.¹³

Table 3: Drug classes used in the treatment of neuropathic pain^{1,3,7,15}

- Antidepressants
- Anticonvulsants
- Opioids
- Topical local anaesthetics and analgesics
- NMDA (N-methyl-D-aspartate) antagonists
- Cannabinoids
- α - 2 agonists
- Skeletal muscle relaxants
- Corticosteroids

Duloxetine is a SSNRI that inhibits both the reuptake of both noradrenaline and serotonin.¹ It has a favourable side effect profile with nausea being the most common side effect.¹ This can be minimised if the starting dose is 30mg daily and titrated after one week to 60mg daily.¹ This is an effective dosage at which pain relief can occur within one week.¹ Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and noradrenaline reuptake at higher dosages.¹ It has been shown to cause ECG changes so monitoring is recommended in patients with cardiovascular risk factors.¹ Two to four weeks is often required to titrate to an effective dosage with a starting dose of 37.5 mg once or twice daily increasing by 75 mg each week to a maximum dosage of 225 mg.¹ Patients should be tapered gradually from venlafaxine due to the risk of discontinuation syndrome.¹⁴

Anticonvulsants

Older anticonvulsants such as carbamazepine, phenytoin, and sodium valproate have significant adverse effects, so are not considered first-line treatment for NP.⁷ Although carbamazepine is considered first-line treatment for trigeminal neuralgia.⁷ Some anticonvulsants achieve their analgesic effects through blockade of voltage dependent sodium channels in peripheral neurons.⁹ Lamotrigene has actions on glutamate secretion.⁹ The differing sites of action of anticonvulsants could suggest that 'rational polypharmacy' may be of value in patients resistant to standard regimens of therapy in the management of NP.⁹

Gabapentin and pregabalin both bind to the α 2- δ subunit of voltage-gated calcium channels in the dorsal horn of the spinal cord, decreasing the release of glutamate, noradrenaline, and substance P.¹⁹ Gabapentin has repeatedly demonstrated analgesic efficacy in many different NP syndromes and has also shown improvements in mood and sleep.¹ Since gabapentin is not bound to plasma proteins it has no clinically important drug interactions which is a valuable advantage as NP patients are usually taking a large number of other medications.¹⁵ It is now available in generic formulations which makes it a lot more affordable for patients. The main dose-limiting side effects are somnolence and dizziness.¹ These can be reduced by gradual dose titration. In the elderly gabapentin may cause or exacerbate cognitive or gait impairment.¹ An effective dose of between 1800 and 3600mg daily can take several weeks to achieve. This is administered in three divided doses with the night-time dose being the dose that is preferentially increased.¹ In patients with renal impairment the dose will need to be decreased.¹ The onset of activity can be seen in the second week when titration is rapid but the peak effect usually occurs two weeks after a therapeutic dosage is achieved.¹ A trial of at least two months is therefore required.¹

Pregabalin is structurally related to gabapentin and has a similar mechanism of action but with greater affinity for the calcium channel and better bioavailability.² The potential for twice daily dosing and the linear pharmacokinetics of

pregabalin make it easier to use than gabapentin.¹ The overall efficacy and tolerability of these two medications appear similar.¹ Pregabalin also has no clinically important drug interactions.¹ The onset of pain relief can be more rapid than with gabapentin because its starting dose of 150 mg daily is effective.¹ Upward dosage titration can reach 300 mg daily within one to two weeks.¹ Maximum benefits usually occur after two weeks of treatment at dosages of 300–600 mg daily.¹

Opioids

Opioid analgesics and tramadol have demonstrated efficacy in multiple RCTs in patients with NP.¹ They are recommended when patients do not have a satisfactory response to the first-line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications.¹ In certain clinical circumstances opioid analgesics and tramadol can be considered for first-line treatment.¹ These circumstances include: when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, for episodic exacerbations of severe pain, acute NP, and neuropathic cancer pain.¹ Opioids are generally considered second-line due to them producing more side effects than TCAs and gabapentin which can persist throughout long-term treatment; long-term use has been associated with development of immunological changes and hypogonadism; and they have been associated with hyperalgesia.¹ The most common side effects are nausea, constipation and sedation.¹ Nausea and sedation typically decrease after a few weeks constipation does not and needs to be managed.¹ Of the existing medications that are efficacious in NP, opioids are the most likely to provide prompt pain relief.¹ Opioids should be used cautiously in patients at risk of suicide or accidental death from overdose.¹ In elderly patients opioids can cause or exacerbate cognitive impairment and gait disturbances which increases the risk of falls.¹ Physical dependence develops in all patients treated chronically with opioid analgesics so patients must be advised not to discontinue these medications abruptly.¹

Tramadol is a noradrenaline and serotonin reuptake inhibitor with a major metabolite that is a weak μ opioid agonist.^{1,3} Tramadol is less efficacious than stronger opioid analgesics in patients with NP.¹ It is recommended like the opioids for patients who have not responded to the first-line medications but can also be considered first-line in certain circumstances.¹ The side effects of tramadol include somnolence, constipation, dizziness, nausea and orthostatic hypotension.^{1,3} Tramadol can cause or exacerbate cognitive impairment and gait disturbances in the elderly.¹ There is an increased risk of seizures in patients with a history of seizures or who are also receiving antidepressants, opioids, neuroleptics, or other drugs that can reduce the seizure threshold.³ Abuse of tramadol is considered rare but has been observed.³ Concurrent use of other serotonergic medications (including SSRIs, SSNRIs and MAOIs-monoamine oxidase inhibitors) may increase the risk of serotonin syndrome.^{1,3} To

decrease the likelihood of adverse effects and increase patient adherence the starting dose should be low; 50 mg once or twice daily and then titrated every three to seven days by 50 to 100 mg daily as tolerated.³ The maximum daily dosage of tramadol is 100 mg four times daily (100 mg three times daily in the elderly).³ Dosage adjustment is necessary in patients with renal or hepatic disease.^{1,3}

Topical local anaesthetics and analgesics

Locally acting analgesics are attractive because they deliver medication locally with minimal side effects.^{7,15} The 5% lidocaine patch is recommended for patients with localised peripheral NP but not for patients with central NP.¹ When used as recommended the only side effects that occur with the lidocaine 5% patch are mild skin reactions which include erythema and localised rash.¹ When a patch is either applied three times in 12 hours or four times in 18 hours blood levels are minimal.¹ Caution should still be exercised in patients on Class I antiarrhythmic medications and in patients with severe hepatic dysfunction.¹

Lidocaine gel has also shown to be effective and can be considered when the lidocaine 5% patch is not available.¹

A eutectic mixture of local anaesthetics Emla[®] cream is another topical treatment. Emla[®] contains lidocaine 2% with prilocaine 2.5%. Unlike the lidocaine patch Emla[®] produces numbness in the skin over which it is applied.¹⁵ It has been found to be effective in reducing the incidence and intensity of chronic pain when used perioperatively in women with breast cancer undergoing surgery.¹⁵

Capsaicin is a vanilloid compound isolated from chilli peppers.¹⁵ It enhances the release of substance P from nerves and prevents its reaccumulation and this is how it is thought to elevate the pain threshold.¹⁵ After application, there is a burning sensation with heat hyperalgesia.¹⁵ It has shown mixed results in RCTs of patients with NP.⁷ Some patients with PHN have reported pain exacerbation with its use.⁷ One RCT evaluating the use of doxepin, capsaicin and their combination demonstrated significant analgesia with all three of these medications.¹⁶

NMDA (N-methyl-D-aspartate) antagonists

Activation of the NMDA receptor found in the spinal cord dorsal horn causes the spinal cord neuron to become responsive to all types of inputs, including nociception and touch, which results in central sensitisation.¹⁵ Blocking the NMDA receptor can reduce spontaneous pain and hyperalgesia.¹⁵ Ketamine is a NMDA antagonist. In addition to its general anaesthetic properties it is known to be useful in

nociceptive pain in both acute pain and palliative care.⁹ It has been successfully used in NP.⁹

However it is associated with dose limiting psychomimetic side effects which limit its use.⁹

Methadone is believed to have some action at the NMDA receptor.⁹ It is not easy to titrate its dosage but it has the advantage of having a long duration of action.⁹ It may be difficult to get patients to use this drug because of the social stigma associated with its use in opioid abuse and withdrawal.⁹

Dextromethorphan a cough suppressant and the antiviral drug memantine (also used in Parkinson's disease) are also NMDA antagonists.⁹ They have both been used in PHN and PDN but results from published RCT's are poor and they are not commonly used.⁷

Cannabinoids

Nabilone and dronabinol (both unavailable in South Africa) are synthetic forms of tetrahydrocannabinol.⁹ Dronabinol has shown a modest analgesic benefit in central pain in Multiple sclerosis.⁷

α -2 agonists

Clonidine which is an α -2 agonist sympathetic blocker has been found to be effective in a subset of patients with peripheral neuropathy.¹⁷ It can be administered intrathecally or epidurally to minimise systemic side effects.¹⁵ It is also available as a transdermal patch.

Skeletal muscle relaxants

Baclofen is a GABA-B receptor agonist and has proven effective for trigeminal neuralgia¹⁵ and can be considered second line when carbamazepine is ineffective or not tolerated.⁷

Corticosteroids

Methylprednisolone has been injected intrathecally along with lidocaine in the treatment of PHN refractory to other treatment.¹⁵

Simple analgesics such as NSAIDs (non-steroidal anti-inflammatories) and paracetamol are usually ineffective in pure neuropathic pain but may help with co-existing nociceptive conditions (e.g. sciatica with musculoskeletal low-back pain).⁷

No single drug works for all neuropathic pain states and treatment must be individualised.⁷ This is due to the presence of comorbid conditions, psychosocial issues and interpatient variability.¹⁰ Side effects and whether prompt onset of pain relief is necessary also need to be considered when selecting medication.¹

Table 4: Medications used to treat NP^{1,3,7}

Drug	Dosage	Effective and maximum dosage	Other factors to consider
First-line medications			
Topical lidocaine 5%	1–3 patches in 12 hr or 1–4 patches in 18 hr	3 patches in 12 hr or 4 patches in 18 hr	Patch must be applied to painful area
TCA's			
Amitriptyline, imipramine, nortriptyline, desipramine	10–25 mg/d at night or in divided doses every 12 hr Increase dose weekly by 10–25 mg/d	50–150 mg/d Average dose 50–75 mg/d	More ADRs with amitriptyline, imipramine Contraindicated in patients with glaucoma and those taking MAOIs
SSRNI's			
Duloxetine	60 mg/d 60 mg Q12hr also safe and effective	60 mg/d Maximum of 120 mg/d	Contraindicated in patients with glaucoma and those taking MAOI's
Venlafaxine	37.5 mg/d increase dose weekly by 37.5 mg	150–225 mg/d Maximum dose 375 mg/d	Adjust dose in renal impairment Contraindicated in those patients taking MAOIs
Calcium α 2-δ ligands			
Gabapentin	300–900 mg/d in divided doses every 8 hr Increase dose weekly by 300 mg/d	1200–2400 mg/d Maximum dose 3600 mg/d	Adjust dose in renal impairment
Pregabalin	50–150 mg/d in divided doses every 8–12 hr Increase dose weekly by 50–150 mg/d	300–600 mg/d Maximum dose 600 mg/d	Adjust dose in renal impairment
Second-line medications			
Opioids			
Tramadol	50 mg/d in divided doses every 12 hr Increase dose weekly by 50 mg/d	200–400 mg/d Maximum dose 800 mg/d	Use with caution in patients with epilepsy
Morphine (or equivalent)	5–15 mg (short-acting) every 4hr as needed; after 1–2 weeks convert to long-acting preparation and continue dose titration as needed	Benefits of > 180 mg/d not established	Screen patients for alcohol/substance abuse, co-administer stool softeners to help with constipation and antiemetics for nausea
Third-line medications			
Antiepileptics			
Carbamazepine (CBZ)	100–200 mg/d in divided doses every 6–8hr Increase dose weekly by 100–200 mg/d	600–1200 mg/d Maximum 1600 mg/d For trigeminal neuralgia CR CBZ every 8–12 hr with short-acting CBZ every 4 hr for "rescue"	First-line therapy for trigeminal neuralgia Contraindicated in patients with porphyria or AV block and in those taking MAOIs
Oxcarbazepine	Initially 600 mg/d in two divided doses Increase dose by 600 mg/d at weekly intervals	Usual range 900–1200 mg/d Maximum dose 2400 mg/d	Enzyme induction minimal and no auto induction occurs
Lamotrigene	25–500 mg/d in 2 divided doses Start low at 25 mg and go very slow	Usual maintenance dose 100–200 mg/d as a single dose or in 2 divided doses Maximum dose 500 mg/d	Can cause Stevens-Johnsons syndrome
Antidepressants			
Bupropion	100–150 mg 2–3 times daily	Maximum dose 300 mg/d Maximum single dose 150 mg, and interval between doses at least 8 hours	Insomnia common, avoid taking at bedtime
Paroxetine	20–50 mg/d increase by 10 mg/d every week	Maximum dose 50mg/d	
Citalopram	20–40 mg/d	Maximum dose 60 mg/d	Maximum dose 30 mg/d in the elderly. Dose should be halved in hepatic impairment.
Locally acting analgesics			
Capsaicin	Topical cream, apply 2–4 times daily	Can take up to four weeks to have an effect	Causes burning, stinging and erythema

Drug-related adverse effects are common in the treatment of NP, not only because of the specific medications used, but also because many patients with NP are older, take other medications, and have co-morbid illnesses.³

Evidence based recommendations

Recommended first-line treatments include certain anti-depressants (TCAs and SSNRIs), calcium α 2- δ ligands (gabapentin and pregabalin) and topical lidocaine.¹

Opioid analgesics and tramadol are recommended as second-line treatments that can be considered for first-line use in select clinical circumstances.¹ Generally opioids should be reserved for patients who have failed to respond to or cannot tolerate the first-line medications.¹

Other medications that can be considered third-line that could be used as second-line in certain circumstances include certain antiepileptic (carbamazepine, lamotrigene, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine (no longer available in South Africa), NMDA receptor antagonists and topical capsaicin.¹

The overall approach to treating a patient with NP should be recognised as a stepwise process intended to identify the medication or medication combination that provides the greatest pain relief and fewest side effects.¹ If an adequate trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment with that medication should be discontinued and another medication should be selected.¹ If a medication is found to be well tolerated and provides partial pain relief, it should be continued and a second medication with a different mechanism of action added to the treatment regimen.¹ Combination therapy has potentially additive analgesia and it also may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved.¹ It may result in improved results at lower dosages with fewer side effects.⁷ Disadvantages include the possibility of additive adverse effects, drug interactions, increased cost and reduced adherence to a more complex treatment regimen.¹

Table 5: Factors to be considered when selecting medication for a patient with NP¹

1. The potential for adverse outcomes associated with medication-related side effects
2. Potential drug interactions
3. Co-morbidities that also may be relieved by the non-analgesic effects of the medication (e.g. sleep disturbance, depression, anxiety)
4. Costs associated with therapy
5. The potential risks of medication abuse
6. The risks of intentional and unintentional overdose

There is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety.¹ Given these limitations, clinicians must consider several other factors when selecting a specific medication for a patient with NP including:¹

Conclusion

NP is best managed with a multidisciplinary approach consisting of pharmacological and non-pharmacological treatments. Existing pharmacological treatments for NP are limited with no more than 40-60% of patients obtaining partial relief of their pain.¹ Treatment with the lowest risk of adverse effects should be tried first and then a stepwise approach employed to either discontinue or add further treatment. Even though evidence supporting conservative non-pharmacological treatment is limited it should be considered whenever appropriate. An alternative way to look at managing NP would be prevention as it is always better than cure. Preventative interventions for patients who are at risk for chronic NP including patients who are undergoing breast cancer surgery, those with herpes zoster, those with diabetes and those with HIV could negate the need for pain relief for chronic NP altogether.¹ □

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