Neuropathic pain - Current concepts

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Abstract

Neuropathic pain (NP) represents a common and diverse group of disorders with peripheral and/or central nervous system damage or dysfunction. Many patients report intractable and severe pain that is resistant to simple analgesics. The diagnosis of NP is primarily based on clinical evaluation rather than diagnostic tests. Distinct pain qualities in the patient's history and findings on clinical examination, such as hyperalgesia and other sensory findings in an area correlating with the patient's pain pattern are important in diagnosis. Various screening tools may assist in the diagnosis of NP.

A number of pathophysiological mechanisms have been identified in NP, including sodium- and calcium-channel upregulation and spinal cord hyperexcitability (central sensitisation).Appropriate management includes evaluation of the functional impact of NP, patient education and reassurance. A multi-model biopsychosocial approach that includes various nonpharmacological modalities is recommended. Appropriate pharmacological management is based on evidence-based recommendations that provide guidance for selecting first-, second- and third-line medications, alone or in combination. It is hoped that future treatment advances will improve the care of patients who live with NP.

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Introduction

The description of pain as a result of peripheral nerve lesions by Dr Weir-Mitchell in casualties of the American Civil War in 1864 is widely regarded as the start of the scientific approach to the features of neuropathic pain (NP).[1] Various ideas regarding the mechanisms of NP were proposed by scientists in the early 1900s. However, the special nature of NP and its terminology only started to appear in the medical literature in the late 1970s.[2]

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Neuropathic pain is initiated or caused by a lesion or dysfunction of the nervous system and is maintained by a number of mechanisms.[3,4] Injury or insult to the nervous system may lead to long-term structural and functional changes, resulting in altered processing of sensory input (central sensitisation) and hyperalgesia. Neuropathic pain may therefore persist long after healing of the original stimulus (e.g. injury) and may thus be regarded as an abnormal activation of pain pathways.

While most acute pain is nociceptive (i.e. a response to noxious stimuli), chronic pain may be nociceptive, neuropathic or of mixed origin. The severity of nociceptive pain (e.g. osteoarthritis) often correlates with the extent of tissue damage. Neuropathic pain, however, may be initiated by a relatively minor physical insult and patients may have severe pain not correlating with the extent of tissue damage or with significant neurological deficits. On the other hand, patients with clear evidence of lesions in the nervous system (e.g. neuropathy) may have no associated NP.[5]

It is estimated that as many as one in five adults with chronic pain will have symptoms of NP. Compared with other types of pain NP is generally more difficult to treat and often has a more profound impact on quality of life. Patients with NP often present repeatedly before an accurate diagnosis is made and appropriate management instituted.[2,5] The personal impact of NP is often devastating and patients mostly generate high health costs. In the USA, costs associated with chronic pain have in recent years been estimated at $150 billion annually, of which almost $40 billion is attributable to neuropathic pain.[6]

Most patients with NP respond poorly to traditional analgesics and many require a multidisciplinary approach. With current available treatments, only 30–50% of patients with NP experience meaningful improvement in pain and function, and a long-term commitment from the patient and physician are required to ensure compliance and appropriate outcomes.[2] Viewing NP as a disease in its own right, rather than a symptom, is the first step towards its appropriate management. The aim of treatment is to assist the patient in managing the pain and to improve function and coping mechanisms, rather than to eliminate the pain.[7,8]

Aetiology and epidemiology

Neuropathic pain may present as a specific neuropathic pain disorder such as in painful diabetic polyneuropathy and postherpetic neuralgia.

However, NP is often not a binary phenomenon (present or absent), but both neuropathic and nociceptive elements may contribute to the patient's pain.[2] The view that chronic pain may be "more or less neuropathic" is supported by current opinion regarding chronic pain mechanisms. Clinical disorders in this category include chronic pain associated with HIV/AIDS, as well as chronic cancer pain and chronic pain of spinal origin.[9] The diagnosis of pain of predominantly neuropathic origin (POPNO) may be simplified with the use of various recently developed screening tools.[9–13]

Neuropathic pain may also be classified as peripheral or central, depending on where the nerve lesion is anatomically located [2,14,15] (see Table I).

Table I: Common causes of neuropathic pain

Peripheral	Central
• Painful diabetic polyneuropathy • Postherpetic neuralgia • Trigeminal neuralgia • HIV-associated neuropathic pain • Cancer-related pain • Metabolic causes, e.g. Alcoholic polyneuropathy Nutritional deficiency neuropathy • Mechanical (nerve compression), e.g. Carpal tunnel syndrome Disc herniation • Postsurgical pain, e.g. Postmastectomy pain Postherniorrhaphy pain Phantom limb pain Failed back surgery syndrome • Toxic exposure neuropathy, e.g. Chemotherapeutic agents Antiretrovirals, e.g. ddC, d4T Antituberculosis drugs, e.g. isoniazid • Complex regional pain syndrome • Idiopathic	• Posttraumatic spinal cord injury pain • Multiple sclerosis – related pain • Poststroke pain • Transverse myelitis • Postradiation myelopathy • HIV myelopathy

Diabetic polyneuropathy is one of the most common complications of diabetes, with a prevalence of 30–50%.[16] Painful diabetic polyneuropathy (PDPN) has a prevalence of 16–26%, and up to 80% of patients may have moderate or severe pain.[17] Quality of life is significantly reduced in these patients, with restriction in daily activities and an association with depression and sleep disturbances.[16,18] In a United Kingdom population study almost 40% of patients with PDPN had never received any treatment for pain and almost a third had been prescribed medication with no known efficacy in NP, e.g. nonsteroidal anti-inflammatory agents (NSAIDs) and paracetamol.[19]

Postherpetic neuralgia (PHN) is defined as pain at least one month after rash onset.[2,7] It occurs in 9–24% of patients who have had herpes zoster infection. In persons older than 60 years 27–68% develop PHN following herpes zoster infection which may lead to disability, depression, sleep disturbance and social withdrawal.[14] Risk factors for the development of PHN include older age, female gender, severity of acute shingles and associated acute pain, HIV infection and chronic corticosteroid use.[7]

Trigeminal neuralgia, also known as "tic douloureux", is a NP disorder in the facial area. It is defined by the IASP as "a sudden, unilateral, severe, brief, stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve."[20] It is usually associated with vascular compression of the trigeminal nerve, but may rarely be secondary to a brain tumour or multiple sclerosis. The pain is an extremely severe "electric shock" shooting pain lasting from seconds to two minutes, and it does not cross the midline. It displays a paroxysmal pattern triggered by non-noxious stimuli such as talking, chewing and teeth brushing.[22] Trigeminal neuralgia has a higher prevalence in females, it increases with age and peaks at around 70 years. When the condition is diagnosed in younger individuals, it should raise the suspicion of secondary trigeminal neuralgia, e.g. multiple sclerosis.[21,22]

HIV-associated distal symmetrical polyneuropathy (DSP) is the most frequent neurological complication associated with HIV infection; it occurs in over one-third of HIV-infected patients. The most disabling feature of DSP is pain and it may cause severe morbidity.[23] The combined effect of potentially neurotoxic antiretroviral drugs, e.g. d4T and ddI, and isoniazid used for tuberculosis, may worsen DSP, possibly due to the combined effect of vitamin B_6 deficiency and direct neurotoxicity. Other neurotoxic drugs used in HIV-infected individuals may include metronidazole and antineoplastic agents such as vincristine and vinblastine.[23] In a recent study at a large regional hospital in Tshwane, on 354 ambulatory patients with confirmed AIDS before commencing antiretroviral therapy, 20,9% had pain of predominantly neuropathic origin. The pain was significantly more prevalent in males who had a lower CD_4 count and higher viral load levels, and in those using antituberculosis treatment.[24] Eighty per cent of these patients experienced moderate to severe pain (pain severity ≥ 5 out of 10 on a numerical rating scale). Neuropathic pain is an often under-recognised and under-treated complication of HIV infection. Other forms of NP in HIV-infected patients may include postherpetic neuralgia, mononeuropathy multiplex and progressive polyradiculopathy.[14,23]

Iatrogenic neuropathic pain is probably the most important cause of chronic postsurgical pain.[25] If nerves are injured during surgery NP may develop early and persist long-term in the absence of ongoing peripheral stimuli. Chronic pain after surgery persists in 10–50% of patients after common operations such as inguinal hernia repair, breast and thoracic surgery, and leg amputation.[25,26] Early aggressive management of perioperative pain and surgical techniques that avoid nerve damage are probably important to prevent chronic postoperative pain. A multimodal analgesic regimen using regional blockade, NSAIDs, coxibs, paracetamol and other analgesics throughout the perioperative period may be the most effective approach.[26] Other factors that may contribute to this phenomenon include levels of pain before the surgery, and genetic and psychosocial factors.[25,27]

Neuropathic pain is a common and important source of pain also in cancer patients. Common aetiologies of NP in patients with cancer include neural compression or infiltration, as well as neuropathies due to chemotherapy or radiation.[14]

Low back and neck pain are very common disorders, but the prevalence of NP contributing to low back and neck pain is unknown. Patients with pain of spinal origin may have both elements of nociceptive and neuropathic pain. A variety of nerve-damaging stimuli may contribute to the NP component of patients with neck and low back pain. Neurological symptoms and signs may escape routine

clinical evaluation and these patients should be examined carefully and comprehensively.[14,28,29] In two research studies in cohorts of patients with low back pain where different screening tools were used, 37% and 54,7% of patients had scores that suggested pain of predominantly neuropathic origin.[28,29]

Complex regional pain syndrome (CRPS) is indeed a complex disorder characterised by the development of NP after tissue trauma, e.g. surgery or a fracture (CRPS type 1) or after a nerve injury (CRPS type 2). It was previously known as reflex sympathetic dystrophy and causalgia. This form of NP is considered to be sympathetically maintained. Symptoms include skin colour changes, sweating asymmetry and trophic changes in the nails and skin in the presence of the features of NP.[14,30] The health and quality of life of patients with NP has been shown to be severely impaired. The Health Related Quality of Life (SF-36) questionnaire was used in a population based sample of patients with chronic pain and results demonstrated poor health in all dimensions (physical, psychological and social) in chronic pain patients, in particular in individuals with NP.[31] The SF-36 in patients with chronic NP was as low as that observed in patients with serious organic disease, including coronary artery disease, recent myocardial infarction and poorly controlled diabetes mellitus.[31,32]

Diagnosing neuropathic pain

There are currently no specific objective criteria to diagnose NP and even questionnaires are subjective. An objective neuropathy with pathological changes in a nerve and even a nerve injury does not necessarily cause pain. It should be remembered that NP may present long after the initial nerve injury and that genetic, psychosocial and other factors are relevant in the pathogenesis.[2,6,33,34]

Neuropathic pain is diagnosed clinically and the patient's report of specific pain qualities is important. Neuropathic pain is commonly associated with sleep disorders, anxiety and depression, which may have a significant effect on morbidity. The psychosocial history should include concurrent mood disorder and the impact of pain on the patient's ability to work and on family life. The patient's belief about the pain and maladaptive thinking patterns (e.g. "I will never get better" or "The situation is hopeless") is often a reliable predictor of disability. A focused neurological examination should include the anatomic distribution of abnormal sensory signs.

Symptoms[2,6,8,33]

- Assessing pain quality is important in diagnosing NP. Most patients have more than one pain and the following sensory descriptions are often used by patients with NP: "burning", "electric shock", "tingling", "cold", "pricking" and "lancinating".
- Neuropathic pain may be spontaneous (continuous or intermittent) or evoked in response to various stimuli. Neuropathic pain often worsens towards the end of day and after dark.
- Neuropathic pain often occurs in a distribution that matches the level of a nerve lesion and a dermatome chart is useful in recognising referral patterns.
- Common non-painful symptoms that may occur in patients with NP include "itching", "crawling", numbness" and "pins-and-needles" (paraesthesiae).

Signs[2,3,6,7,8,33,34]

- Neuropathic pain may be present in the absence of objective neurological findings.
- The neurological examination focuses on the somato-sensory function in the area identified through the pain history. If sensory abnormalities are detected in an area of nerve innervation correlating with the patient's pain, it is a strong predictor for the diagnosis of NP.[2,33]
- The sensory examination evaluates the patient's response to multiple stimuli, e.g. touch, pressure, pin-prick, cold, hot and vibration. Sensory abnormalities may be limited to one or two of the above when compared at the site of pain and a control site.[6,33]
- Positive sensory signs include allodynia and hyperalgesia. Allodynia is pain due to a stimulus that does not normally provoke pain; hyperalgesia is an increased response to a normally painful stimulus. Dynamic allodynia is when movement of a cotton swab or paint brush causes pain; static allodynia is when light blunt pressure (e.g. with a finger) causes pain; thermal allodynia is when cold or mildly hot stimuli are painful. Hyperalgesia often coexists with allodynia and these phenomena, in a patient with chronic pain, are strongly indicative of a neuropathic aetiology.[2,35]
- Negative sensory signs are absent or diminished light touch, vibration, thermal or pin-prick sensations in the involved nerve distribution, which may also extend beyond the involved dermatome.[6]
- Other clinical signs may include:
  - Signs of autonomic dysfunction such as skin colour changes, cold skin temperature and trophic changes in nails and hairs (indicative of sympathically maintained pain in patients with complex regional pain syndrome).
  - Motor weakness around the involved nerves and diminished or absent tendon reflexes.[6]
  - Residual scars revealed after skin examination (due to previous herpes zoster infection) or the skin changes associated with diabetes mellitus.
  - Localised muscle tenderness and myofascial trigger points (indicative of secondary myofascial pain syndrome).[6,33,36]

A common clinical presentation of NP is allodynia, combined with tingling and numbness (sensory loss) at the site of pain.[2,7,36] Patients may be confused by their sensory experiences – a patient may be both numb to a pinprick but very sensitive to light touch (allodynia) in the same nerve distribution.[33] Abnormal sensory findings in a pattern consistent with proposed nervous system disease or injury strongly supports a diagnosis of NP.[9]

Special investigations

Laboratory studies are mostly not diagnostic but may assist in detecting a treatable lesion, e.g. nerve compression. Detailed diagnostic testing is mostly inappropriate and too expensive for routine clinical use.[2,6,7,33] Special investigations include nerve conduction velocity testing (NCV), electromyography (EMG), magnetic resonance imaging (MRI) and quantitative sensory testing (QST). Although these investigations may rarely confirm or exclude a nerve lesion they are often normal in patients with NP, while many patients with abnormal studies have no pain. EMG and NCV studies assess only large nerve fibres that have very little involvement in pain transmission.[2,3,6,7,33] It is therefore wrong to label a patient with NP as "malingering" or "psychogenic" in the absence of positive neurophysiological or imaging studies.

Screening tools

Primary care physicians often have time constraints that preclude a meticulous neurological examination in patients with NP, and

hence it may be difficult to detect the presence of a nerve lesion. In this scenario, screening tools have been used to distinguish between neuropathic and nociceptive pain. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale was the first of these scales; it consisted of five symptoms and two clinical examination items.[10,29] The LANSS scale has been tested and validated in several clinical settings with around 80–85% accuracy when compared with expert clinical evaluation.[2,9,38,39] Other scales that have since been developed and validated include the Neuropathic Pain Questionnaire (NPQ) and the Douleur Neuropathique (DN4) (see Table II). These questionnaires enable the clinician to decide if NP is the "dominant pain mechanism" in a patient with chronic pain. Screening tools are a useful indicator of possible NP but fail to identify 10–20% of patients with NP, and therefore cannot replace clinical assessment.[10]

Table II: DN4 questionnaire[12]

DN4 questionnaire		
Complete this questionnaire by ticking one answer for each item in the four questions below:		
PATIENT INTERVIEW		
Question 1: Does the pain have one or more of the following characteristics?		
	Yes	No
1 – Burning		
2 – Painful cold		
3 – Electric shocks		
Question 2: Is the pain associated with one or more of the following symptoms in the same area?		
	Yes	No
4 – Tingling		
5 – Pins and needles		
6 – Numbness		
7 – Itching		
EXAMINATION OF THE PATIENT		
Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?		
	Yes	***No***
8 – Hypoaesthesia to touch		
9 – Hypoaesthesia to prick		
Question 4: In the painful area, can the pain be caused or increased by:		
	Yes	***No***
10 – Brushing		

Mechanisms of neuropathic pain

The underlying feature in NP is the presence of damage or a lesion to some component of the sensory nervous system. This may be the consequence of inflammation, ischaemia, tumour invasion, nutritional deficits, nerve trauma or compression, metabolic disturbance or cytotoxic agents. These neuropathic pain syndromes share various overlapping pathogenetic mechanisms.[41]

Normal transmission of pain impulses is through the Aδ- and C-afferent fibres to the dorsal horn in the spinal cord. In the dorsal horn, neurotransmitters such as substance P and glutamate are activated to transfer pain impulses to the postsynaptic neuron. The dorsal horn can modulate this input, allowing excitation or inhibition, and the net result is transmitted via the ascending tract to higher brain centres where the pain experience is constructed in the pain matrix. Inhibitory signals are sent from the brain to the dorsal horn in the spinal cord (descending pathways) to modulate the pain experience. The descending pathways release various neurotransmitters such as norepinephrine (NE), serotonin (5-HT) and gamma-aminobutyric acid (GABA), which ultimately inhibit the transmission of excitatory pain impulses.[2,42,43]

The hyperalgesia, allodynia and other features associated with neuropathic pain disorders may be explained by the following changes that occur in the nervous system following nerve damage:

1. Peripheral sensitisation. Chemical medicators such as substance P, bradykinin and histamine may sensitise nociceptors to transmit stimuli perceived as painful, although the stimulus may be much lower than the original pain activation threshold.[43]
2. Ectopic discharges. An accumulation of sodium channels at the site of nerve injury causes repetitive firing of injured axons, which may be perceived as spontaneous pain.[2,43]
3. Central sensitisation.[41,44] Central sensitisation is a state of increased sensitivity of dorsal horn neurons so that their activation threshold is reduced. It follows the activation of the N-methyl D-aspartate (NMDA) receptor by the neurotransmitter glutamate and the subsequent influx of calcium through the voltage-gated calcium channels into the neuron. A complex set of intracellular events following this calcium influx lead to altered gene expression and long-term neuronal changes, and a more sensitive nervous system.[42,44] Expression of the voltage-gated calcium channels is increased following nerve injury.[6,45] Clinical support for this phenomenon arises from the analgesic efficacy of α2-δ voltage-gated calcium channels antagonists (see later) in patients with NP disorders.[46] The pain may also spread beyond the dermatome of an affected nerve to adjacent segments as a result of central sensitisation, previously thought to be an indication of "hysteria".[8]
4. Central reorganisation. After nerve injury, pain fibres in the spinal cord may reorganise, such that sections that normally receive only painful stimuli from the peripherary via C fibres now receive non-painful stimuli from the Aß-fibres (due to "sprouting" of Aß-terminals into the superficial lamina of the dorsal horn). Thus, even light touch may now be perceived as painful, explaining the clinical phenomenon of allodynia.[4,8,41]
5. Loss of inhibitory control. Peripheral nerve injury may also cause a reduction in the activity of the spinal inhibitory pathways which contributes to abnormal pain sensitivity in patients with NP.[41,42,43] Together with the other mechanisms, it is associated with increased excitability in the flow of pain impulses through the central nervous system, and may manifest as spontaneous pain.
6. Nerve injury may, in some individuals, be associated with an increased expression of α-adreno-receptors in injured axons. This phenomenon, together with sprouting of sympathetic axons onto the dorsal root ganglion, give rise to sympathetically maintained pain, e.g. as in complex regional pain syndrome.

Management of neuropathic pain

Management of neuropathic pain is symptomatic when the underlying condition causing the pain cannot be removed.[6,8,34,47–51] In this scenario, chronic NP becomes a disease in its own right and which is managed accordingly, rather than cured (similar to other chronic disorders such as hypertension and diabetes mellitus).[52] Clinicians must remain aware of the high rate of comorbidity of NP with sleep disorders, anxiety and mood disorders.[37] NP may also be present with other types of pain requiring particular management, e.g. a patient with chronic neck pain with both osteoarthritis and a radiculopathy.

The comprehensive management of a patient with NP is based on the biopsychosocial approach and may include conservative modalities such as physiotherapy, exercise, sleep hygiene, transcutaneous electrical nerve stimulation (TENS), etc. Rigorous evidence supporting the efficacy of these modalities is limited, but they should be considered when appropriate.

Patient education, support and reassurance is a critical component of optimal management. It also includes the setting of realistic treatment goals.

Cognitive behavioural therapy (CBT) assists patients to identify maladaptive thinking patterns and to develop the ability to challenge errors of thinking. Objectives in a CBT programme include:

- change view of pain from overwhelming to manageable
- engage in pleasurable distracting activities
- teach specific coping skills

Since non-pharmacological treatment is often not sufficient, rational pharmacotherapy is usually indicated, although it is also limited in its efficacy (only ± 40–50% of patients obtain partial pain relief).[3,47–49] A reduction of 30% in pain intensity (on an 11-point numerical rating scale) is regarded as clinically relevant and equivalent to ratings of "moderate relief" and "much improved". Drug-related adverse effects are common because many patients are older and take other medications for comorbid illnesses. Simple analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs and coxibs) are ineffective in pure NP.[6]

Currently five medications have been approved by the US Food and Drug Administration (FDA) for the treatment of NP, namely:

- *Postherpetic neuralgia:* lidocaine patch (5%), gabapentin, pregabalin
- *Painful diabetic polyneuropathy:* pregabalin and duloxetine
- *Trigeminal neuralgia:* carbamazepine

The majority of randomised controlled trials (RCTs) have investigated patients with postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (PDPN), mostly only for a period of three months or shorter. The applicability of these results to other NP disorders is difficult to determine, and some types of NP patients may respond differently. However, the first-line medications have been tested with different types of NP, and extrapolation of efficacy to other types of NP is probably reasonable and often clinically necessary.[34,47,48]

Treatment efficacy can be expressed in the number-needed-to-treat (NNT) to obtain at least 50% pain relief in one patient. The NNT approach has various limitations, such as lacking other important outcomes, e.g. improvement in function and quality of life. Most RCTs are short-term studies, and there may be methodological differences between different RCTs that may influence NNT calculations, which are done retrospectively with often different cut-off points for defining pain relief.[48] It should be remembered that the NNT does not focus on intolerable side effects, and that the numbers needed to harm (NNH) necessitating withdrawal from a trial is also important in evaluating and comparing medication efficacy.[2] The available studies evaluating adjuvant analgesics in NP are mostly placebo-controlled and do not compare specific agents. The following guidelines are based on the most recent recommendations of the IASP Neuropathic Pain Special Interest Group.[47]

First-line medications:

- ***Tricyclic antidepressants (TCAs):***
  The analgesic effect of TCAs is independent of its antidepressive effect and has repeatedly been shown to reduce NP.[53] TCAs (NNT = 3) are more effective than SSRIs (NNT = 6, 7) and their analgesic action may be due to noradrenaline and serotonin reuptake inhibition (enhancing descending inhibition) and NMDA receptor blockade.[54] The main problem with TCAs is their adverse effects, including anticholinergic effects (e.g. constipation, blurred vision, dry mouth and urinary retention), sedation and orthostatic hypotension. Cognitive impairment and gait disturbances may predispose to falls in older patients and cardiotoxicity necessitates a screening electrocardiogram in patients over 40 years of age, and avoidance in patients with ischaemic heart disease.[6,47] TCAs must be used cautiously when there is a risk for suicide.

- ***Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs):***
  Duloxetine is a SSNRI and has demonstrated significant pain relief compared with placebo in RCTs, (also in an open-label study over 52 weeks) in patients with PDPN.[55] Duloxetine has a more favourable side effect profile in comparison with TCAs. Fewer studies have been done on Venlafaxine (another SSNRI). The NNT of the SSNRIs is regarded as 4– 5.5.[6,48]

- ***Calcium channel $\alpha 2$-δ ligands:***
  Both gabapentin and pregabalin have a unique mechanism of action that differs from other anticonvulsants. They bind to the α_2-δ subunit of the voltage-gated calcium channels, resulting in the inhibition of glutamate and substance P release in the spinal dorsal horn.[56] The α_2-δ subunits of the voltage-gated calcium channels are widely distributed throughout the peripheral and central nervous system, and upregulation of the α_2-δ subunits are thought to play an important role in the central sensitisation process after damage to the nervous system.[57] Both gabapentin and pregabalin have proven efficacy in RCTs of various neuropathic pain disorders. Most of the larger studies were done on patients with PHN and PDPN.[3,47,48,57] Pregabalin has a higher binding affinity for the α_2-δ subunit than gabapentin, and the twice daily dosing and linear pharmacokinetic profile makes it more convenient for prescriber and user.[47,57] However, the overall efficacy and tolerability of gabapentin and pregabalin are very similar. More common side effects include somnolence, dizziness and mild peripheral oedema.[34] The NNT for gabapentin is comparable to that of pregabalin, and mostly ranges from 3.1 to 5.4 depending on the dosages used in the particular study.[48]

- ***5% lidocaine patch*** (not available in South Africa):
  It has proven efficacy in patients with focal PHN and allodynia, and has been FDA approved for this indication.[58]

Second-line medications:

- ***Opioid analgesics and tramadol*** have demonstrated efficacy in NP patients in a recent meta-analysis.[59] They may be used as second-line treatment, alone or in combination with first-line medication(s) in patients with an inadequate response to first-line pharmacotherapy. They may also be used as first-line medications in patients with severe acute neuropathic pain when prompt pain relief is required and in patients with severe neuropathic cancer pain.[47]

Tramadol is a weak opioid and a mixed serotonin/noradrenaline reuptake inhibitor. Three RCTs of tramadol for neuropathic pain have yielded significant evidence for its use in NP with an overall NNT of 3,9.[6,48] There is an increased risk of seizures in patients treated with tramadol who have a history of seizures, or who are also receiving antidepressants.[34] The role of strong opioids in NP has been controversial, but a recent meta-analysis provided convincing evidence of benefit, with the NNT ranging from 2.5 to 2.6.[6,48,59] Current evidence supports the use of strong opioids in a carefully selected subset of patients with chronic and resistant NP. A detailed assessment by an experienced pain clinician is necessary and only sustained-release opioids, e.g. transdermal fentanyl, and sustained release oral morphine, should be used.[60,61] Short-acting and injectable opioids may predispose to tolerance and dependence. Effective pain relief should be accompanied by improved physical and psychosocial functioning.

The incidence of true addiction to strong opioids in the management of chronic pain is low if the medication is appropriately prescribed and monitored by the prescribing physician. Opioids should not be prescribed to patients with a personal or family history of substance abuse, with comorbid psychiatric comorbidity, or where the pain is "psychologically maintained".[60–62] Therapy with strong opioids in chronic NP is not regarded as lifelong. There is evolving data on the potential immunological, endocrine and other effects of long-term treatment with opioids and the line between appropriate caution and excessive "opio-phobia" is a fine and evolving one.[63]

Third-line medications:

These are medications for which there is much less evidence of efficacy than for first- and second-line medications.[2,47,48] Such medications include the following:

- *Anticonvulsants*: carbamazepine, oxcarbazepine, valproic acid, phenytoin, lamotrigine
- *Antidepressants*: paroxetine, citalopram, bupropion
- *NMDA receptor antagonists*: ketamine
- *Capsaici.*

Carbamazepine is considered first-line therapy for trigeminal neuralgia with a NNT of 1,7.[48] Although it has been recommended for patients with other types of NP who do not respond to gabapentin or pregabalin, it has yielded inconsistent results in RCTs of other NP conditions.[34,47,48] Carbamazepine is associated with ataxia and cognitive impairment, and induces various cytochrome-P_{450} liver enzymes, accelerating the metabolism of coadministered drugs and resulting in many drug interactions.[51]

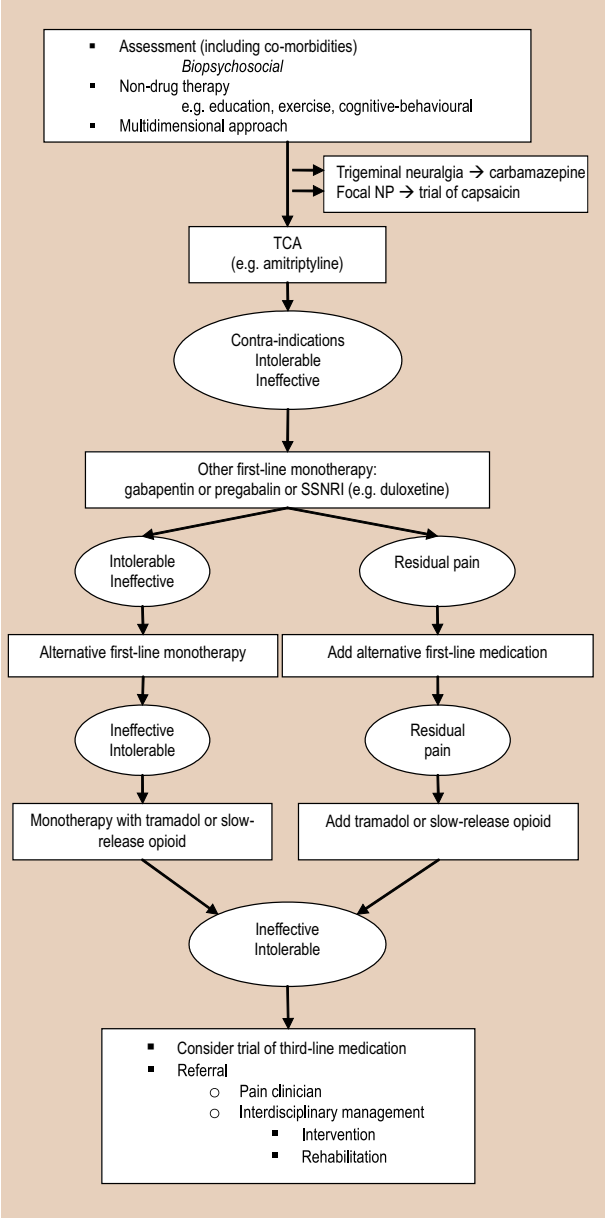
Lamotrigine is a third-line anticonvulsant which has shown modest efficacy for HIV-associated sensory neuropathy.[64]

Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and citalopram are not as effective as SSNRIs and TCAs. They have a NNT of 6.7 [6]

NMDA antagonists such as ketamine have thus far shown limited efficacy and often have intolerable side effects.

Capsaicin, an ingredient of hot peppers, has shown mixed results in RCTs. It is applied topically and has shown efficacy in PHN, PDPN and in mixed NP conditions, with a NNT ranging from 4.6 to 12 (average 6.7).[48] Capsaicin inhibits the release of substance-P from nerve endings, with a gradual analgesic effect, which may take effect only after 2–4 weeks with consistent application. The most common side effect is burning at the site of application, which may have a significant impact on patient compliance.

Figure 1: Proposed algorithm for management of neuropathic pain in primary care[4,6,34,41,42,47,48,50]



Rational polypharmacy is often appropriate in patients with NP. More than one mechanism is often involved in NP and the use of multiple medications with different mechanisms may be of substantial benefit to some patients.[50]

Interventional pain management

Existing pharmacologic treatments are of limited efficacy. Despite the best care and trials of therapy, NP will remain inadequately relieved for 40–60% of patients, and 10–15% of NP patients are regarded as truly refractory to all forms of pharmacotherapy.[44,47,51,65]

Nerve block procedures may, in selected patients, be of value earlier in the course of NP, e.g. sympathetic nerve blocks in early complex regional pain syndrome, to facilitate physiotherapy and rehabilitation.

There is little controlled evidence to confirm the efficacy of other nerve blocks in NP.[6,65]

Pulsed radiofrequency is a nondestructive procedure that may relieve chronic NP in carefully selected patients, but more evidence is needed before official recommendations for this procedure in guidelines will be appropriate.[66]

More invasive therapy may be considered for patients with refractory and intractable NP without surgically treatable pathology. These include augmentative neuromodulation therapy, e.g. peripheral, spinal cord and motor cortex stimulation, intrathecal drug delivery systems and ablative neurosurgical procedures.[44] The best success rates in this category are for trigeminal ganglion balloon decompression and microvascular decompression, both procedures for trigeminal neuralgia.[6,67]

Conclusion

Neuropathic pain is an important cause of intractable and severe pain. It remains however an underdiagnosed and undertreated entity in primary and other levels of care. Due to its multifactorial aetiology involving different mechanisms and a high prevalence of comorbidities, various medications from different classes may be necessary to manage NP. The proposed algorithm provides the primary care practitioner with appropriate pharmacological guidelines as part of a multidimensional biopsychosocial approach.

Neuropathic pain research and management is an evolving science. Future strategies should include identification of treatments most effective for a particular clinical profile and an increased emphasis on prevention. Further validated tools for the diagnosis of NP are necessary to increase awareness and improve management of a difficult but relevant health care problem.[6,34,51]

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