

Clinical practice guidelines for management of neuropathic pain: expert panel recommendations for South Africa

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Abstract

Neuropathic pain (NeuP) is challenging to diagnose and manage, despite ongoing improved understanding of the underlying mechanisms. Many patients do not respond satisfactorily to existing treatments. There are no published guidelines for diagnosis or management of NeuP in South Africa. A multidisciplinary expert panel critically reviewed available evidence to provide consensus recommendations for diagnosis and management of NeuP in South Africa. Following accurate diagnosis of NeuP, pregabalin, gabapentin, low-dose tricyclic antidepressants (e.g. amitriptyline) and serotonin norepinephrine reuptake inhibitors (duloxetine and venlafaxine) are all recommended as first-line options for the treatment of peripheral NeuP. If the response is insufficient after 2 - 4 weeks, the recommended next step is to switch to a different class, or combine different classes of agent. Opioids should be reserved for use later in the treatment pathway, if switching drugs and combination therapy fails. For central NeuP, pregabalin or amitriptyline are recommended as first-line agents. Companion treatments (cognitive behavioural therapy and physical therapy) should be administered as part of a multidisciplinary approach. Dorsal root entry zone rhizotomy (DREZ) is not recommended to treat NeuP. Given the large population of HIV/AIDS patients in South Africa, and the paucity of positive efficacy data for its management, research in the form of randomised controlled trials in painful HIV-associated sensory neuropathy (HIV-SN) must be prioritised in this country.

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1. Introduction

Neuropathic pain (NeuP) is defined as pain that arises as a 'direct consequence of a lesion or disease affecting the somatosensory system'.¹ Importantly, NeuP differs from nociceptive pain in respect of causes, mechanisms, symptomatology and different therapeutic approaches required for successful management.

The burden of NeuP for the patient is substantial. NeuP is associated with psychological distress, physical disability and reduced overall quality of life.²⁻⁵ A systematic review and meta-analysis by Doth *et al.*⁶ showed lower health-utility scores in patients with NeuP than the general population and in people with other chronic conditions like Parkinson's

disease, heart failure, motor neurone disease, cancer, and stroke. Patients with peripheral NeuP are generally affected by difficulty in sleeping, lack of energy, drowsiness, and difficulty in concentrating.⁷

The problem is further compounded by the fact that globally, and in South Africa, NeuP is often underdiagnosed and inappropriately treated, exacerbating the burden of this already debilitating condition. The costs of NeuP are considerable,^{3,8} with misdiagnosis, mistreatment, and mental and physical comorbidities such as depression and nerve damage contributing to the cost, in addition to usual diagnostic and treatment costs. Indeed, it has been reported that patients with NeuP have annual healthcare

costs threefold higher than the costs for matched control populations.⁹

Reduced work ability of patients and carers, and medical expenses also contribute to the overall cost of NeuP.¹⁰ A survey in the USA revealed that almost 65% of working patients with painful diabetic neuropathy reported absence from work or decreased work productivity due to pain.¹¹ Another study reported that the employment status was reduced, owing to pain, in 52% of patients with peripheral NeuP.⁷

In South Africa there are a number of specific challenges to evaluating and treating NeuP. Lack of education and awareness among physicians, including specialists, was noted as a problem in South Africa, leading to suboptimal identification, assessment and management of NeuP. For example, inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids as first-line treatment is widespread, and inappropriate back surgery is common. Referrals to pain clinicians often come too late, and even in specialist centres a multidisciplinary approach is not always taken.

Patient access to care varies widely in South Africa, from rural to urban areas and across socioeconomic divides. But access to care does not guarantee access to the most appropriate drugs, as financial and supply-chain constraints, and restricted formulary in the public sector and restricted reimbursement in the private sector limit access to appropriate medications.¹² Along with access issues, lack of trained personnel is also a problem.^{13,14} Added to these challenges, which are not necessarily unique to South Africa, is the high rate of HIV in this country and the paucity of evidence for treating painful HIV-related neuropathy.¹⁵ To improve NeuP management in South Africa, regional guidelines for NeuP management, which take local settings into account, are vital. The consensus recommendations described here aim to help healthcare practitioners in South Africa become more aware of NeuP, better skilled at its diagnosis, and equipped to select appropriate treatment options for patients suffering from NeuP.

2. Methods

2.1 Expert panel

A panel with special expertise in diagnosis and management of NeuP met in Johannesburg, South Africa on 9 July 2011. The panel included specialists from the fields of psychiatry, neurology, neurosurgery, anaesthesiology, family medicine and basic science. The panel collaborated with a French NeuP specialist to critically analyse available randomised controlled trials (RCTs) and evidence-based international and regional guidelines for the evaluation and treatment of NeuP. The objective of the meeting was to develop clear clinical practice guidelines to aid the diagnosis and medical management of NeuP in South Africa.

2.2 Evidence evaluation

Recommendations from recent international and regional guidelines were reviewed in addition to discussion of recent systematic reviews, meta-analyses, and peer-reviewed randomised, double-blind, placebo-controlled studies;¹⁵⁻³⁰ a number of Cochrane reviews were also referred to.³¹⁻⁴⁰ The validity, clinical relevance, and applicability of the evidence for peripheral and central NeuP in South Africa were discussed. The main sources of evidence were the 2010 guidelines from the European Federation of Neurological Societies (EFNS)²⁶ and recommendations from both the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP)^{27,41} and the French Pain Society,¹⁶ all based on systematic reviews of available evidence. A systematic review of evidence by Danish pain experts,¹⁷ consensus recommendations from the Canadian Pain Society¹⁹ and consensus recommendations from experts in Latin America,¹⁸ the Middle-East region (MER)²¹ and the Maghreb region²² were also consulted. Reference was also made to the American Academy of Neurology (AAN) guidelines for management of painful diabetic peripheral neuropathy (DPN);²⁰ postherpetic neuralgia (PHN)²⁴ and trigeminal neuralgia (TN)²³ were also referred to. It was decided against using number-needed-to-treat (NNT) as the sole measure of efficacy in making recommendations for South Africa, since NNT does not provide a complete picture of the quality of a study, particularly as the studies assessed vary widely in number of participants and quality of study design. After considering the evidence, the panel achieved consensus on a number of recommendations that are supported by best scientific evidence. The recommendations include some agents that may not be indicated for use in NeuP. Similarly, some agents that are supported by best scientific evidence are not available in South Africa (e.g. the topical lidocaine patch), so are mentioned here but have been excluded from the final recommendations. The levels of evidence stated in this review follow the levels attributed in the formal systematic reviews from which the data were sourced (refer to Appendix A available online at www.safpj.co.za).

2.3 Guideline development

The discussions and consensus statements were recorded at the meeting and written up as a full manuscript draft by a professional medical writer. The panel reviewed, edited, and provided comments on the outline and drafts of the manuscript until a final version was reached that was approved by all members.

3. Results

3.1 Epidemiology and burden of NeuP

Estimating the prevalence of NeuP is notoriously difficult – a recent systematic review by Smith and Torrence⁴² found that estimates vary widely, confounded by underreporting and inconsistent definitions and diagnostic criteria. They suggest a prevalence of 6 - 8% in the general population.

Table 1: Aetiology-based classification of painful peripheral neuropathies

Focal or multifocal lesions of the peripheral nervous system	Generalised lesions of the peripheral nervous system (polyneuropathies)	Lesions of the CNS	Complex neuropathic disorders
Common/important			
Post-traumatic neuralgia, Phantom limb and stump pain, PHN	Diabetes mellitus (leading to DPN), Alcohol HIV (leading to HIV-SN), Antiretroviral agents, Chemotherapy	SCI Stroke	Complex regional pain syndromes types I (controversial) and II
Others/miscellaneous			
Diabetic proximal mononeuropathy Entrapment syndromes Ischaemic neuropathy	Heavy metals, e.g. thallium, arsenic Drugs, e.g. metronidazole, isoniazid, vinca alkaloids Metabolic/genetic, e.g. amyloid, uraemia, Fabry disease, Nutritional, e.g. vitamin B deficiencies	MS Syringomyelia Spinal infarction	

Modified from Baron *et al.*⁵⁶ CNS – central nervous system, PHN - postherpetic neuralgia, DPN - diabetic peripheral neuropathy, HIV-SN - HIV-associated sensory neuropathy; SCI - spinal cord injury; MS - multiple sclerosis.

They estimate that approximately 20% of patients with diabetes and 8% of people who have had herpes zoster suffer from NeuP. There are no published estimates of NeuP prevalence in South Africa. The prevalence of NeuP resulting from common aetiologies (see Table 1) is likely to be similar to other countries, but with a large additional component resulting from the high rate of HIV in this country.

Low back pain is a major contributor to NeuP prevalence globally, and there may be a neuropathic component in nearly 50% of black Africans with lower back pain.⁴³ A similar rate of neuropathic pain (55%) was reported in adults with lower back pain in an outpatient setting in the Arabian Gulf region.⁴⁴ PHN and DPN are also leading causes of NeuP, but data on the prevalence of these causes in South Africa are limited. The International Diabetes Federation (IDF) Diabetes Atlas estimates the prevalence of type II diabetes in the Africa region in 2010 to be 3.8%,⁴⁵ which is below the global average but expected to rise disproportionately in the developing world in the coming decades.⁴⁶ In diabetes patients attending outpatient clinics in the Middle East, 54% met the criteria for painful DPN.⁴⁷ The reported occurrence of peripheral neuropathy in patients with diabetes varies widely in sub-Saharan African countries, from 4% in Zimbabwe to 69% in Nigeria,⁴⁸ and was estimated at 28% among black African diabetes patients in a 1997 audit of public-sector diabetes care in South Africa.⁴⁹ While not all diabetes-related neuropathy is painful, as many as 20% of diabetes patients could suffer from NeuP related to DPN,⁴² and this clearly represents a large, and growing, cause of NeuP, in South Africa.

According to the 2010 global report by the United Nations Program on HIV/AIDS (UNAIDS), 5.6 million people in South Africa are living with HIV.⁵⁰ HIV-associated sensory neuropathy (HIV-SN), a frequent complication of both HIV and neurotoxic antiretroviral medications such as stavudine, is therefore a major concern in South Africa. Prevalence of NeuP was reported to be 20.9% among South African AIDS patients who had not received prior antiretroviral treatment.⁵¹ The prevalence of symptomatic HIV-SN was 57% in 395

HIV-positive black South Africans exposed to stavudine, with 76% of affected individuals experiencing pain as their primary symptom.⁵² In 598 HIV-infected individuals in South Africa, the frequency of HIV-SN was 37% in individuals never exposed to antiretroviral drugs, increasing to 60% in individuals receiving antiretroviral therapy. In both groups of patients, the neuropathy was symptomatic in approximately 60% of individuals, with almost all these individuals reporting pain and/or paraesthesias.⁵³ A recent study conducted in a South African hospital revealed that although 71% of the patients with HIV/AIDS had pain documented in their medical charts, only 34% of the patients reported adequate pain management.⁵⁴ HIV-positive outpatients are no better off, with over 40% of ambulatory patients in pain not receiving any treatment, and of those patients who received treatment, less than 3% received drugs recommended for the treatment of NeuP, despite over a third of the patients having symptoms consistent with HIV-SN.⁵⁵ These studies highlight that the neuropathic component of HIV-related pain is probably poorly recognised and undertreated in South Africa.

3.2 Pathophysiology of NeuP

NeuP, by definition, arises as a 'direct consequence of a lesion or disease affecting the somatosensory system'.¹ While the detailed mechanisms that underlie NeuP are not fully understood, they are thought to operate at both central and peripheral levels (Fig. 1): (A) at the level of peripheral nerves, there is sensitisation, ectopic transmission and spontaneous discharges; (B) changes in central modulatory systems, predominantly in spinal neurones, lead to central sensitisation. The relationship between these mechanisms and the resulting symptoms is not straightforward – one mechanism may give rise to more than one symptom and one individual symptom may result from multiple mechanisms.⁵⁶ Knowledge of the possible mechanisms underlying NeuP is helpful in understanding and improving treatment of NeuP. An overview of the basic mechanisms and targets for disease is given in Fig. 1.

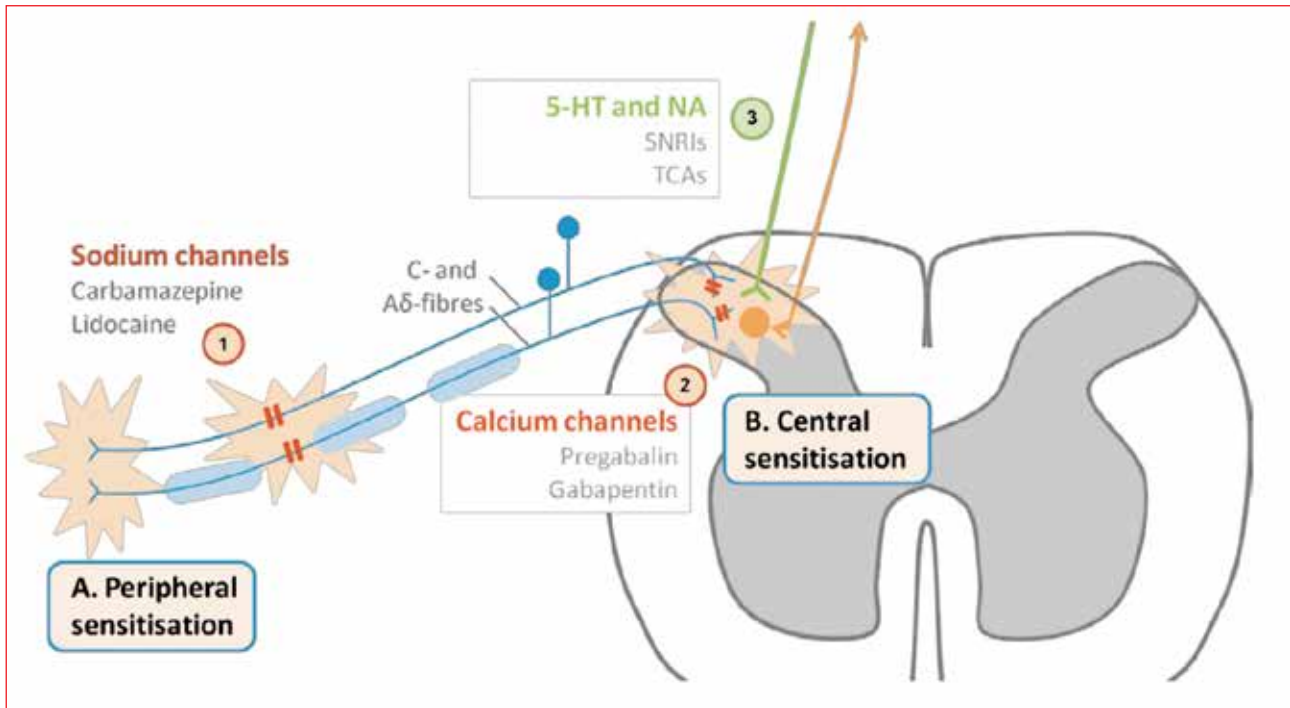


Figure 1: Lesion of peripheral nerves results in peripheral sensitisation (A), via a number of mechanisms. For example, increased expression of sodium and calcium channels, in unmyelinated (C-fibre) and thinly myelinated (A δ - fibre) primary afferent neurones can lead to spontaneous discharges, reduced thresholds for activation, enhanced responses to stimuli and abnormal neuronal sprouting (e.g. neuroma formation). This peripheral sensitisation can drive dramatic secondary changes in the spinal cord dorsal horn, leading to central sensitisation (B) – an increase in the general excitability of multireceptive spinal cord neurones. The glutamate NMDA receptor plays a central role in these changes, which are manifested by increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields and spread of spinal hyperexcitability to other segments. Dorsal horn neurones receive a powerful descending modulatory control from the brain and brainstem, and dysfunction of the descending inhibitory serotonergic and noradrenergic pathways may contribute to central sensitisation. Each of these malfunctioning systems represents a target for drugs used to treat NeuP: 1. carbamazepine and lidocaine target sodium channel; 2. gabapentin and pregabalin target calcium channels (the $\alpha_2\delta$ subunit) on terminals in spinal neuronal circuits; and 3. serotonin/noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) target descending serotonergic and noradrenergic pathways.

3.3 Aetiology of NeuP

Currently there is no universally accepted classification for NeuP types. However, four broad classes of diseases are recognised based on aetiology and anatomy (Table 1).

3.4 Clinical features of NeuP

Patients with NeuP experience symptoms arising in an area of altered sensation (numbness/loss of sensation and/or hyperexcitability) and exhibit a number of typical observable signs.⁵⁷ The painful symptoms include both spontaneous pain (i.e. occurs with no apparent stimulation), which can be continuous or paroxysmal, and evoked pain. Terms commonly used to describe painful and unpleasant sensations (dysaesthesias) include burning, shooting, and electric shock-like pain. A number of altered, but not unpleasant, sensations (paraesthesias) – tingling, ants crawling, and pins and needles – are also common. Stimulus-evoked pain is described as allodynia if normally non-painful stimuli (e.g. light breeze, skin contact with clothing, temperature change) evoke pain, and as hyperalgesia when a normally painful stimulus (e.g. pinprick) evokes a heightened pain sensation.⁵⁸

3.5 Diagnosis and evaluation of NeuP

NeuP is distinct from other chronic pain types that have an intact nociceptive system (nociceptive pain). For the differential diagnosis of NeuP it is helpful to analyse the exact quality of somatosensory abnormalities in the affected area as well in the areas adjacent to the sensory deficit.⁵⁶ Clinical tools, such as questionnaires for screening and assessment, focus on the presence and quality of neuropathic pain, and can be used to alert a clinician to the likelihood of NeuP and the need for a careful examination. It is important to note that screening tools fail to identify about 10 - 20% of patients with clinician-diagnosed NeuP,⁵⁹ and they should be used as a guide for further diagnostic evaluation and pain management but cannot replace clinical judgment.

3.5.1 Screening tools

In recent years, several standardised screening tools have been developed to aid the identification and classification of NeuP on the basis of patient-reported verbal descriptors of pain qualities.⁵⁹

These include (among others) painDetect, ID-Pain, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ) and

Douleur Neuropathique en 4 questions (DN4). Most of these questionnaires include questions about burning pain, paraesthesias, pain attacks, mechanical and thermal hypersensitivity, and numbness.^{60,61} They are attractive because of their ease of use by both professionals and patients, in clinic or via telephone or Internet, and because they provide immediate information.⁶¹

The painDetect questionnaire was developed and validated in Germany to identify NeuP components in back pain, whereas ID-Pain, DN4 and LANSS were developed to help differentiate nociceptive pain and NeuP.^{62,63}

The DN4 scale is based on the patient's description, and physician examination, of sensory dysfunction – it has a sensitivity of 82.9% and specificity of 89.9%.⁶⁴ The 10-item questionnaire includes 7 items related to symptoms and 3 related to clinical examination. A total score of 4 or higher suggests NeuP. The 7 sensory descriptors can be used as a self-report questionnaire with similar results. The DN4 has validated translations in 15 languages (in addition to its original French), and while it is not validated in South African languages, the DN4 questionnaire (Fig. 2) is recommended as it is short, quick and easy to follow in regular clinical practice.

3.5.2 Clinical assessment

A simple examination-based way to identify NeuP and differentiate from nociceptive pain is the '3L' approach: Listen, Locate and Look (Table 2).⁶⁵

Listen to the verbal description of pain and any non-painful symptoms in the same area as the pain.

Locate the region of pain and document with a pain drawing, created either by the patient or by the physician. Any abnormal sensations may also be highlighted on the same illustration.

Look for sensory abnormalities and recognise the distribution pattern. A careful inspection of the painful bodyarea should be carried out and any differences in colour, texture, temperature, etc. should be noted. A simple bedside examination of somatosensory functions is recommended, including touch, cold, warmth and pain sensibility (Table 3).⁵⁹ The aim is to identify altered sensation in the painful area, and hence responses should be compared with a non-painful adjacent area.

Physicians need to consider a holistic approach to diagnose and treat the underlying condition and comorbid conditions. This will lead to improvement of patients' overall quality of life, physical functioning and sleep quality, along with a reduction of the psychological distress associated with NeuP conditions. Where the underlying pathology is understood, it is recommended that both symptomatic treatment (pain management) and treatment of the aetiology should be initiated. Where the underlying pathology is not clear, symptomatic treatment should be initiated while further testing is done to clarify the pathology.

3.5.3 Recommendations

- Apply screening tools and careful clinical examination and screening tools to help identify and evaluate NeuP.
- Use simple screening tools such as DN4 to help identify likely NeuP.
- Employ the 3L approach to differentiate NeuP from nociceptive pain: **listen** to the verbal description of pain, **locate** the region of pain and **look** for somatosensory deficits with the help of simple bedside tests.

3.6 Pharmacological treatments

Despite a reported 66% increase in published randomised, placebo-controlled trials (RCTs) for NeuP in the past 5 years,¹⁷ there are several gaps in the evidence for NeuP treatments. Although many types of peripheral and central NeuP occur in clinical practice, most RCTs have included patients with either PHN or painful DPN. Importantly, there are very few head-to-head trials comparing different treatments, making direct comparisons of efficacy and tolerability difficult or impossible. HIV neuropathy and chronic radiculopathy seem less responsive to drugs generally found useful in other NeuP conditions based on large-scale trials, particularly tricyclic antidepressants (TCAs), pregabalin, and gabapentin.^{15,66} Central NeuP is also difficult to treat, and while it appears to respond to the same drug treatments as peripheral NeuP, the response is generally less robust.⁶⁶

DN4 Questionnaire PATIENT INTERVIEW

Question 1. Does the pain have any of the following characteristics?

1. Burning
2. Painful sensation of cold
3. Electric shocks

Question 2. Is the pain associated with any of the following symptoms in the same area?

4. Tingling
5. Pins and needles
6. Numbness
7. Itching

PATIENT EXAMINATION

Question 3. Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

8. Hypoaesthesia to touch
9. Hypoaesthesia to prick

Question 4. In the painful area, can the pain be caused or increased by:

10. Brushing

YES = 1 point
NO = 0 points

Patient's score: ___/10

If the patient's score is ≥ 4 , the test is positive. (sensitivity 82.9%; specificity 89.9%)

Figure 2 : DN4 questionnaire.

Reprinted from Bouhassira D, *et al.*⁶⁴ This questionnaire has been reproduced with permission of the International Association for the Study of Pain® (IASP®). The questionnaire may not be reproduced for any other purpose without permission.

Table 2: 3L approach to differential diagnosis of NeuP⁵⁹

	Listen	Locate	Look
Neuropathic pain	Common descriptors: shooting, electric shock, burning, tingling, itching, numbness	The painful region may not necessarily be the same as the site of injury. Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain)	Apply bedside sensory tests Conduct aetiology-specific tests if appropriate
Nociceptive pain	Common descriptors: aching, throbbing, stiffness	Painful region is typically localised at the site of injury	Physical manipulation causes pain at site of injury

Modified from Haanpaa *et al.*⁵⁹

Table 3. Bedside assessment of negative and positive sensory symptoms and signs in patients with NeuP

Signs and symptoms	Bedside assessment
Negative symptoms and signs	
Tactile hypoaesthesia/numbness	Touch skin with a painter's brush, cotton swab, or gauze
Hypoalgesia	Single pin-prick with a safety pin or sharp stick (e.g. cocktail stick/toothpick)
Thermal hypoaesthesia	Cold (10°C): calibrated metal roller or glass with water, acetone Hot (40°C): calibrated metal roller or glass with water
Evoked pain	
Mechanical allodynia (dynamic)	Stroke skin with a painter's brush, cotton swab, or gauze
Mechanical hyperalgesia (static)	Firm pressure applied with the finger
Mechanical hyperalgesia (punctuate/pin-prick)	Prick with a safety pin, sharp stick, or stiff von Frey hair
Temporal summation	Prick with safety pin or sharp stick at intervals of <3 s for 30 s duration
Cold hyperalgesia (20°C)	Calibrated metal roller, glass with water, acetone Control: objects at skin temperature
Heat hyperalgesia (40°C)	Calibrated metal roller, glass with water Control: objects at skin temperature
Mechanical deep hyperalgesia (somatic)	Apply manual light pressure at joints or muscles

Adapted from Baron *et al.*⁵⁶

Table 4a: Recommended first- and second-line agents for peripheral NeuP by international and national/regional guidelines

	IASP, 2010 ²⁷	EFNS 2010 ²⁶	Latin America, 2009 ¹⁸	MER, 2010 ²¹	FAR, 2011 ²²	CPS, 2007 ¹⁹	French, 2010 ¹⁶	Danish, 2010 ¹⁷
First line	Pregabalin Gabapentin SNRIs TCAs Topical lidocaine (localised peripheral NeuP) Tramadol and opioids*	Pregabalin Gabapentin SNRIs (for DPN) TCAs Topical lidocaine (for PHN)	TCAs Topical lidocaine (localised peripheral NeuP)	Pregabalin Topical lidocaine TCAs	Pregabalin Gabapentin Topical lidocaine TCAs	Pregabalin Gabapentin TCAs	Pregabalin Gabapentin SNRI† (duloxetine) TCAs Tramadol (for mixed pain) Topical lidocaine (for PHN with allodynia)	Pregabalin Gabapentin SNRIs TCAs Topical lidocaine (PHN or focal neuropathy with allodynia)
Second line	Opioids Tramadol	For poly-neuropathy: tramadol followed by strong opioids For PHN: opioids and capsaicin	Pregabalin Gabapentin Tramadol (for mixed pain)	SNRIs Opioids (tramadol, oxycodone or others)	SNRI (duloxetine)	SNRIs Topical lidocaine	TCA (maprotiline) SNRI† (venlafaxine) Opioids Tramadol	Tramadol Opioids Combination therapy

* For patients with acute NeuP, NeuP due to cancer, and episodic exacerbations of severe NeuP, as well as when titrating one of the first-line medications if prompt relief of pain is required.

† Venlafaxine is not proposed as first line given the absence of marketing authorisation in France.

IASP – International Association for Study of Pain; EFNS – European Federation of Neurological Societies; MER – Middle East Region; FAR – French-speaking Magreb region; CPS – Canadian Pain Society; SNRIs – serotonin-noradrenalin reuptake inhibitors; TCAs – tricyclic antidepressants; DPN – diabetic peripheral neuropathy; PHN – postherpetic neuralgia.

Table 4b: Recommended agents for specific peripheral NeuP aetiologies (painful DPN and PHN)

	AAN, 2010 (for painful DPN) ²⁰	AAN, 2004 (for PHN) ²⁴
Level A/group 1*	Pregabalin	Pregabalin Gabapentin Lidocaine patch Oxycodone or morphine sulphate, controlled release TCAs
Level B/group 2†	Gabapentin Sodium valproate, SNRIs TCA (amitriptyline) Opioids (dextromethorphan, morphine sulfate, tramadol, oxycodone) Capsaicin (topical) Isosorbide dinitrate spray	Aspirin (cream/ointment) Capsaicin (topical) Methylprednisolone (intrathecal)

AAN – American Academy of Neurology; DPN - diabetic peripheral neuropathy; PHN – postherpetic neuralgia; SNRIs – serotonin-noradrenalin reuptake inhibitors; TCAs – tricyclic antidepressants

*Level A recommendation: established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population (level A rating requires at least two consistent class I studies) (in exceptional cases, one convincing class I study may suffice for an 'A' recommendation if: (i) all criteria are met; and (ii) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

†Group 1. Medium to high efficacy, good strength of evidence, and low level of side-effects.

‡Level B recommendation: probably effective for the given condition in the specified population (level B rating requires at least one class I study or two consistent class II studies.)

§Group 2. Lower evidence than those listed in group 1, or limited strength of evidence, or side-effect concerns.

3.6.1 Treatment recommendations by international guidelines

In the past few years, several national, regional and international guidelines, systematic reviews and expert panel recommendations have been published for the treatment of NeuP,^{16-19,21,22,26,27,41} and for specific aetiologies;^{20,23,24} these are summarised in Table 4a and 4b. The first-line treatments recommended by most of the guidelines are TCAs, $\alpha_2\delta$ -ligands or gabapentinoids (pregabalin and gabapentin), and topical lidocaine (for localised NeuP), with selective serotonin/noradrenaline reuptake inhibitors (SNRIs) sometimes included as first-line, sometimes second-line therapy. All guidelines recommend reserving tramadol and stronger opioid analgesics for second- or third-line treatment (Table 4a). The EFNS²⁶ and the French¹⁶ publications provide recommendations separately for specific NeuP aetiologies, while the others make general recommendations for peripheral (and central) NeuP.

3.6.2 Treatment framework

The initial approach to treatment of NeuP should include a thorough investigation and treatment of underlying pathology. The treatment choice should address the possible pain mechanisms as well as comorbid conditions (anxiety, depression, sleep disorders) associated with pain. Other considerations for treatment selection include potential for adverse effects, drug interactions, contraindications, risks of misuse and abuse, patients' response to prior therapy, and cost. Patient education is a vital aspect of NeuP management. It is important to clearly explain the mechanisms of NeuP as well as the goals of treatment to the patient in order to maximise treatment benefits and manage treatment expectations. The patient should be informed that the onset of analgesic effect will take time and reduction of pain is not achieved quickly, in most cases. Non-pharmacological methods of coping with pain should be discussed, including the importance of stress reduction and good sleep hygiene, and access to physical therapy and psychotherapy should be recommended or arranged.

3.6.3 Peripheral NeuP

Four classes of drugs have good evidence of efficacy in the treatment of non-localised NeuP: $\alpha_2\delta$ -ligands (pregabalin and gabapentin), TCAs (low-dose amitriptyline or other TCA), SNRIs (duloxetine and venlafaxine), and opioids (tramadol, methadone and morphine). The efficacy and safety of these agents are briefly discussed below and also summarised in Table 5.

3.6.3.1 $\alpha_2\delta$ -ligands (pregabalin and gabapentin)

Pregabalin and gabapentin are recommended (grade A) as first-line therapy by IASP, EFNS, and French guidelines, based on high-quality evidence of efficacy established in multiple RCTs.^{16,26,27} The AAN guidelines for painful DPN recommend pregabalin (level A) because of the availability of strong evidence and gabapentin (level B evidence).²⁰ A systematic review by Danish pain experts¹⁷ and several Cochrane reviews^{32,35,67} confirm the efficacy of these $\alpha_2\delta$ -ligands for the treatment of NeuP. Although pregabalin and gabapentin appear to have similar efficacy, there are minor differences in the pharmacokinetic profile of these two drugs.²⁷ Gabapentin pharmacokinetics are nonlinear (due to saturable absorption), and dosing requires careful titration. Treatment should be initiated at low dosages with gradual increases until pain relief, dose-limiting adverse effects, or a dose of 3 600 mg/day in 3 divided doses is/are reached. Pregabalin has linear pharmacokinetics and dosing is more straightforward. Dosing can start at 25 mg/day (at night), and be titrated slowly up to a maximum dose of 300 - 450 mg/day (in 2 divided doses). Because of its shorter titration period and potentially efficacious starting dosage, pregabalin may provide analgesia more quickly than gabapentin.^{27,68} Thus, pregabalin has pharmacokinetic advantages compared to gabapentin. The IASP NeuPSIG guidelines¹⁶ acknowledge the additional efficacy of gabapentin and pregabalin in sleep disorders, and pregabalin in anxiety disorders associated with pain. Although gabapentin and pregabalin have few drug interactions, both can produce dose-

dependent dizziness and sedation, which can be reduced by starting with lower dosages and titrating cautiously. It is also important to note that both these medications require dosage reduction in patients with renal insufficiency.^{69,70}

3.6.3.2 SNRIs (duloxetine and venlafaxine)

SNRIs are considered a first-line treatment option by most of the international guidelines, including the NeuPSIG guidelines²⁷ (grade A) and the EFNS guidelines²⁶ (level A for DPN), thus highlighting the efficacy of SNRIs for management of NeuP. Although the French guidelines¹⁶

recommend SNRIs for second-line therapy because of the lack of marketing authorisation, duloxetine and venlafaxine have grade A recommendations for DPN and sensory polyneuropathy respectively. Danish pain experts¹⁷ state in their review that duloxetine and venlafaxine have a well-documented efficacy in painful polyneuropathy.

Although both duloxetine and venlafaxine have been studied in peripheral NeuP, especially in painful DPN, more evidence of efficacy is available for duloxetine.^{28,30,34,71} Venlafaxine has shown efficacy in painful polyneuropathies

Table 5: Summary of recommended therapeutic agents for peripheral NeuP in South Africa

Drug	Dosage	Side-effects	Contraindications/ precautions/drug interactions	Other benefits	Benefits in symptoms of NeuP
α₂δ-ligands					
Pregabalin	Start: 25 mg nocte Titrate: Increase in 25 mg increments every 2 - 3 days (as tolerated) until the patient is taking 75 mg twice daily. The dose can then be increased by 75 mg/day every 3 - 7 days if necessary Maximum dose: 300 - 450 mg/day in 2 divided doses	Dizziness, sedation, peripheral oedema, dry mouth, asthenia	No significant drug interactions Linear pharmacokinetics Dose reduction required in renal insufficiency	Improvement of sleep disturbance Anxiolytic	Effective in continuous pain ¹⁶ and mechanical allodynia ^{16,26}
Gabapentin	Start: 100 - 300 mg at bedtime or 100 - 300 mg 3 times daily Titrate: Requires careful titration Increase by 100 - 300 mg 3 times daily every 1 - 7 days as tolerated Maximum dose: 3 600 mg/day (1 200 mg 3 times daily)	Dizziness, sedation, peripheral oedema, dry mouth, asthenia	Dosage reduction required in renal insufficiency No clinically significant drug interactions	Improvement of sleep disturbance	Effective in continuous pain ¹⁶
SNRIs					
Duloxetine	Start: 30 mg once daily Titrate: Increase to 60 mg once daily after 1 week. Maximum dose: 60 mg twice daily	Nausea/vomiting, constipation, anorexia, dry mouth, dizziness	Contraindicated in severe hepatic impairment, end-stage renal disease, alcohol abuse, concomitant use of tramadol and MAOIs Low initial doses for mild to moderate hepatic and renal impairment Caution required in patients with history of mania, seizures, acute narrow-angle glaucoma Glucose monitoring required as worsening glycaemic control seen in diabetic patients Drug interactions with tramadol, TCAs, SSRIs and SNRIs. Inhibition of metabolism of drugs metabolised by CYP2D6 Suicide risk (black-box warning, in line with other antidepressants)	Improvement of MDD and GAD	
Venlafaxine	Start: 37.5 mg once or twice daily Titrate: Increase by 75 mg each week Maximum dose: 225 mg/day To discontinue treatment, venlafaxine should be tapered instead of abrupt discontinuation to avoid withdrawal syndrome	Nausea	Caution required in patients with cardiac disease. Risk of hypertension, hence regular blood pressure monitoring required Lower dose may be necessary in patients with renal impairment (GFR = 10 to 70 ml/min) or cirrhosis of the liver Use with caution in patients with history of seizures and history of mania Drug interactions with tramadol, TCAs, SSRIs and SNRIs. Inhibition of metabolism of drugs metabolised by CYP2D6 Suicide risk (black-box warning, in line with other antidepressants)		

of different origins.^{31,72} Both duloxetine and venlafaxine are approved for the treatment of major depression disorder (MDD) and generalised anxiety disorder (GAD)^{73,74} and hence are the treatment of choice in NeuP patients with these co-morbid conditions. Nausea, the most frequent side-effect with duloxetine, occurs less frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day.⁷⁵ According to the IASP NeuPSIG guidelines,⁴¹ duloxetine 60 mg once daily appears to be as efficacious as 60 mg twice daily and is associated with fewer side-effects in painful DPN. SNRIs in general and duloxetine in particular pose a minor to moderate hepatic risk; the use of duloxetine is contraindicated in patients with severe hepatic impairment.⁷³ Elevated blood pressure and clinically significant electrocardiogram (ECG) changes are associated with patients treated with venlafaxine.⁷⁴ Therefore, venlafaxine should be prescribed with caution in patients with cardiac disease and with regular BP monitoring. Venlafaxine should be tapered when treatment is being discontinued as a withdrawal syndrome has been described.⁷⁶ Antidepressants are generally associated with increased risk of suicide; hence patients should be closely monitored (refer to Table 5 for additional considerations). An additional consideration, when using relatively high doses (120 mg duloxetine, 225 mg venlafaxine), is the risk of precipitating manic episodes in vulnerable individuals.

3.6.3.3 Low-dose TCAs (amitriptyline, imipramine, nortriptyline)

Published international guidelines including the EFNS²⁶ (level A evidence for DPN and PHN), IASP NeuPSIG²⁷ (grade A), French guidelines (grade A scientific evidence in several aetiologies) as well as the systematic review by Danish experts¹⁷ have documented the efficacy of TCAs for treating a variety of types of NeuP. A Cochrane review³⁴ that considered data from 17 studies validated the efficacy of TCAs in NeuP. TCAs are an attractive option mainly because they are inexpensive and have a convenient once-daily dosing. Although TCAs are approved to treat MDD, the analgesic effect is independent of the antidepressant effect, and occurs at a lower dose.²⁷ Therefore, low-dose TCAs are not the NeuP treatment of choice in patients with comorbid depression. Starting doses of amitriptyline should be low (10 - 25 mg/day), and titrated slowly until pain is adequately controlled or side-effects limit continued titration.

It is important to take into account the potential for drug interactions, especially when amitriptyline is co-administered with drugs that inhibit CYP2D6 enzyme. TCAs are associated with cardiac toxicity and hence amitriptyline is contraindicated in patients who have ischaemic heart disease or an increased risk of sudden cardiac death.^{77,78} The MER guidelines²¹ recommend a screening ECG before beginning treatment with TCAs in patients over 40 years of age. Amitriptyline should be avoided in elderly patients. Please refer to Table 5 for additional safety considerations.

3.6.3.4 Opioids (tramadol, morphine and methadone)

The IASP NeuPSIG guidelines²⁷ reviewed several high-quality RCTs that showed the efficacy of opioid analgesics

including tramadol in patients with different types of NeuP and recommend them as second-line agents (grade A), except in certain specific clinical situations in which first-line use could be considered. The EFNS guidelines²⁶ recommend opioids as second- or third-line agents with level A evidence for DPN and PHN. A systematic review by Danish pain experts¹⁷ also acknowledged the consistent efficacy of opioids in NeuP.

Tramadol is a weak μ -opioid agonist that inhibits the reuptake of noradrenalin and serotonin. It has been shown to reduce pain in DPN and sensory polyneuropathies; although it may be less efficacious than strong μ -agonists.⁷⁹ The risk of abuse with tramadol appears considerably less compared with opioid analgesics.⁷⁵ The EFNS guidelines²⁶ cautions the use of tramadol in elderly patients because of risk of confusion and does not recommend tramadol with drugs acting on serotonin reuptake such as selective serotonin reuptake inhibitors (SSRIs). The French guidelines¹⁶ recommend tramadol for treatment of mixed pain (pain with nociceptive and neuropathic components) as it is effective in nociceptive pain.

Cochrane reviews have demonstrated the effectiveness of strong opioids (oxycodone, morphine, and methadone) in different types of NeuP, providing greater pain relief than placebo.^{38,80} In head-to-head comparisons, opioids provided at least as much analgesia as TCAs and gabapentin.^{81,82} Despite strong evidence of efficacy, most of the international guidelines reserve opioid analgesics as second- or third-line agents mainly because of risk of long-term side-effects and possible opioid misuse and addiction. The IASP NeuPSIG guidelines estimate that the frequency of these problems associated with opioid analgesics ranges widely from less than 5% to as much as 50%. Hence, prior to initiating opioids, clinicians should take into account the risk factors for abuse, which include active or previous substance abuse and family history of substance abuse.⁷⁵

3.6.4 Recommendations for peripheral NeuP

The panel reviewed the evidence and constructed a treatment algorithm (Fig. 3) to aid step-wise management of non-localised NeuP.

3.6.4.1 First-line treatment

Three classes of drugs are recommended for first-line monotherapy: $\alpha_2\delta$ -ligands (pregabalin or gabapentin), TCAs (low-dose amitriptyline or other TCA) and SNRIs (duloxetine or venlafaxine). Pregabalin is the preferred first-line option because of its simple pharmacokinetics and good tolerability. The choice of drug also depends on additional factors summarised in Table 5.

Patients should be evaluated at 2 - 4 weeks after initiating therapy to determine response to treatment. If the response is good, the current treatment should be maintained, and if the response is sustained for 3 months, slow down-titration can be attempted. If symptoms return, treatment should be titrated back to an effective dose. If a partial response is seen at 2 - 4 weeks, consider increasing the dose of the

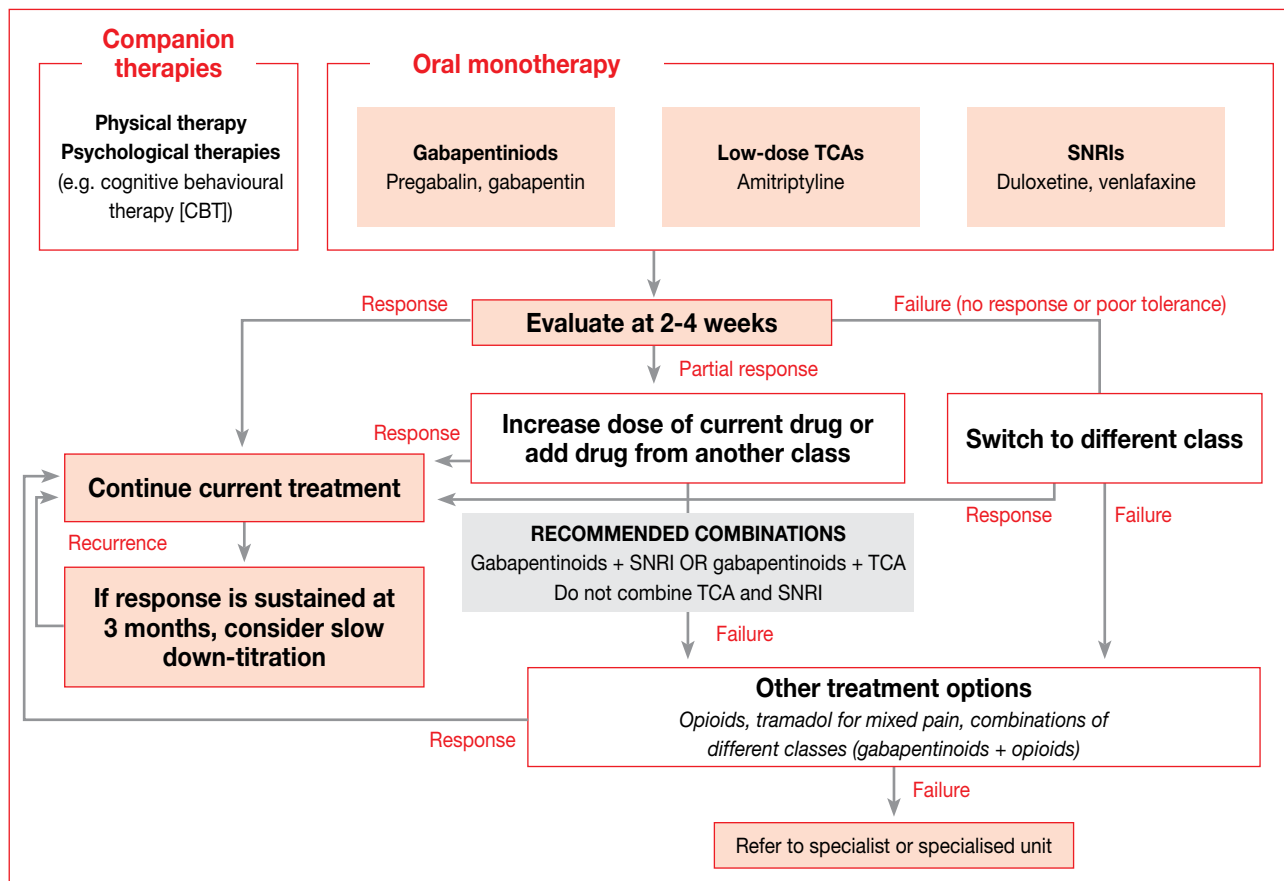


Figure 3: Algorithm for the treatment of non-localised peripheral neuropathic pain.

current agent. If the response is poor, or the drug is not tolerated, move to second-line approaches.

3.6.4.2 Second-line therapy – combination

In case of partial response to first-line therapy, recommendations include either increasing the dose of the current drug or adding a drug from a different class. In case of complete failure to first-line therapy, the patient should be switched to a drug from a different class.

For combination treatment, pregabalin with either an SNRI or amitriptyline is recommended. It is important to note that although TCA and SNRI are different classes of antidepressant they target the same mechanism, so a combination of SNRI and TCA is not recommended.

Combination therapy may offer additional analgesic benefits and benefits on associated symptoms,⁸³ but potential advantages must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen.⁴¹

3.6.4.3 Third-line treatment

If the patient does not respond to combination therapy or the switch strategy, tramadol is recommended (especially in NeuP with a nociceptive component) followed by strong opioids (e.g. morphine, oxycodone, hydromorphone), or a combination of first-line options with opioids.

Evidence for these combinations is limited, but the combination of morphine and gabapentin seems to provide better pain relief than each drug given alone.⁸² In another study, a combination of gabapentin and an opioid was associated with significant pain relief and improved sleep, without an exacerbation of opioid-induced adverse events.⁸⁴

3.6.4.4 Follow-up

The tools and scales used for diagnosis may be useful for clinical monitoring (though not all are validated for this use) to establish a baseline and assess the patient's response. Monitoring for potential drug interactions, adverse events, co-morbidities, need for dose titration, etc., should be part of the follow-up plan. If a patient does not show a satisfactory therapeutic response, he/she should be referred to a pain specialist centre.

3.6.5 Aetiology-based recommendations

3.6.5.1 Polyneuropathy

Painful DPN: The EFNS guidelines²⁶ recommend the use of TCAs, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) as first-line treatment in painful polyneuropathy (notably related to diabetes), tramadol as second-line therapy and strong opioids as third-line agents.

Recommendations: The panel recommends use of pregabalin or gabapentin, low-dose amitriptyline (or other TCA), duloxetine or venlafaxine (SNRIs) for treatment of

painful polyneuropathies, including painful DPN. If response to treatment is poor, patients should be switched to, or have added, a drug from a different class. Tramadol and opioids are recommended after failure of second-line or combination therapy.

Painful HIV-SN: A recent systematic review of pharmacological treatment of HIV-associated neuropathy¹⁵ identified only 3 agents with good evidence of efficacy (v. placebo): smoked cannabis (1 - 8% δ -9-tetrahydrocannabinol), high-dose topical capsaicin (8%), and recombinant human nerve growth factor (rhNGF). Lamotrigine had limited efficacy in one trial, demonstrating superiority over placebo in a secondary endpoint and only in patients exposed to neurotoxic ARVs.¹⁵ Drugs that are generally effective for peripheral neuropathic pain of other aetiologies (amitriptyline, pregabalin, and gabapentin) have been studied but with no evidence of efficacy, and there have been no RCTs of SNRIs in HIV-associated neuropathy.

Recommendations: Because of the lack of evidence for treatment of HIV-SN, the panel recommends following the framework outlined for other polyneuropathies and the step-wise management as illustrated in Fig 3. In addition, if the onset of the neuropathy is associated with starting antiretroviral therapy (even if it is a tenofovir-based regimen), then an alternative regimen should be considered, where possible.

3.6.5.2 Postherpetic neuralgia

Systematic reviews including a review by the AAN concur that gabapentin, pregabalin, TCAs, lidocaine patches and strong opioids have strong evidence of efficacy in PHN.^{24,29,34} Opioids have similar or slightly better efficacy compared with TCA but are associated with more frequent discontinuation because of side-effects.^{26,29} Because of the lack of RCTs, the efficacy of SNRIs duloxetine and venlafaxine for the treatment of PHN is not known. The EFNS guidelines²⁶ state that although topical lidocaine patches are effective for the treatment of PHN with brush-induced allodynia, the level of evidence is lower compared with systemic agents.⁸⁵ Topical capsaicin has also reported modest benefits in patients with PHN.²⁹

Recommendations: The panel recommends pregabalin, gabapentin or amitriptyline for first-line treatment of PHN, and to combine drugs from different classes as a second-line approach. Opioids (tramadol, then stronger opioids) should be reserved for third-line treatment.

As a topical lidocaine patch is not available in South Africa, the panel could not recommend its use despite strong supporting evidence. Topical capsaicin is also not available in South Africa, so it cannot be recommended. The panel suggests that the regulatory authorities in South Africa consider approval of these agents for use in neuropathic pain.

3.6.5.3 Trigeminal neuralgia (TN)

The AAN-EFNS guidelines for TN²³ recommend carbamazepine (200 -1 200 mg/day) as the drug of choice

in classic TN because of its robust treatment response; however, its efficacy may be compromised by poor tolerability and pharmacokinetic interactions.^{23,37} Oxcarbazepine has shown similar efficacy to carbamazepine for controlling pain in TN,^{23,26} but with fewer drug-drug interactions. The AAN-EFNS guidelines also comment on the lack of evidence for treatment of TN following failure of first-line therapy and acknowledge some evidence supporting add-on therapy with lamotrigine or a switch to baclofen, but recent Cochrane reviews conclude that there is insufficient evidence to recommend them in TN.^{36,39}

Recommendations: The panel recommends the use of carbamazepine and oxcarbazepine for the treatment of TN.

3.6.6 Central NeuP (CP)

Relatively few RCTs have been conducted in patients with CP, but results and clinical experience suggest that such conditions may be relatively more refractory to treatment than peripheral NeuP.²⁷ The EFNS guidelines,²⁶ IASP NeuPSIG group recommendations,²⁷ and a systematic review by Danish pain experts¹⁷ assessed the available data and agreed that the use of pregabalin, gabapentin, and TCAs (specifically amitriptyline) is best supported for CP states, specifically spinal cord injury (SCI) and poststroke pain. The EFNS guidelines²⁶ recommend these three agents as first-line options for CP, with tramadol or stronger opioids as second-line. Cannabinoids are suggested in multiple sclerosis (MS) if other treatments fail,^{26,27} although poor availability and concerns about risk of abuse and precipitation of psychosis limit use. There is some mixed evidence for lamotrigine in SCI and post-stroke pain.^{26, 27}

A systematic review of evidence by Danish pain experts did not include any RCTs with SNRIs in CP.¹⁷ A recent RCT which evaluated the effects of duloxetine on pain relief concluded that there is insufficient evidence for the efficacy of duloxetine in treatment of CP.⁸⁶

Recommendations: Based on the scientific evidence and added benefit in treating comorbidities (depression, insomnia, anxiety), the panel recommends using pregabalin or amitriptyline for first-line treatment of CP (Fig. 4). As a result of the consistent clinical experience, fewer contraindications and better risk/benefit ratio compared with TCAs, the panel agrees that pregabalin should be the preferred option. Treatment trials should be approached as for peripheral NeuP; switching to other first-line agent or combining drugs if treatment fails. Tramadol should be considered next, followed by stronger opioids. As cannabinoids are not available in South Africa they cannot be recommended.

3.7 Non-pharmacological treatments

3.7.1 Companion treatments

A recent review of the evidence supporting the potential complementary role of psychosocial treatments of patients with chronic pain suggest that a combination of

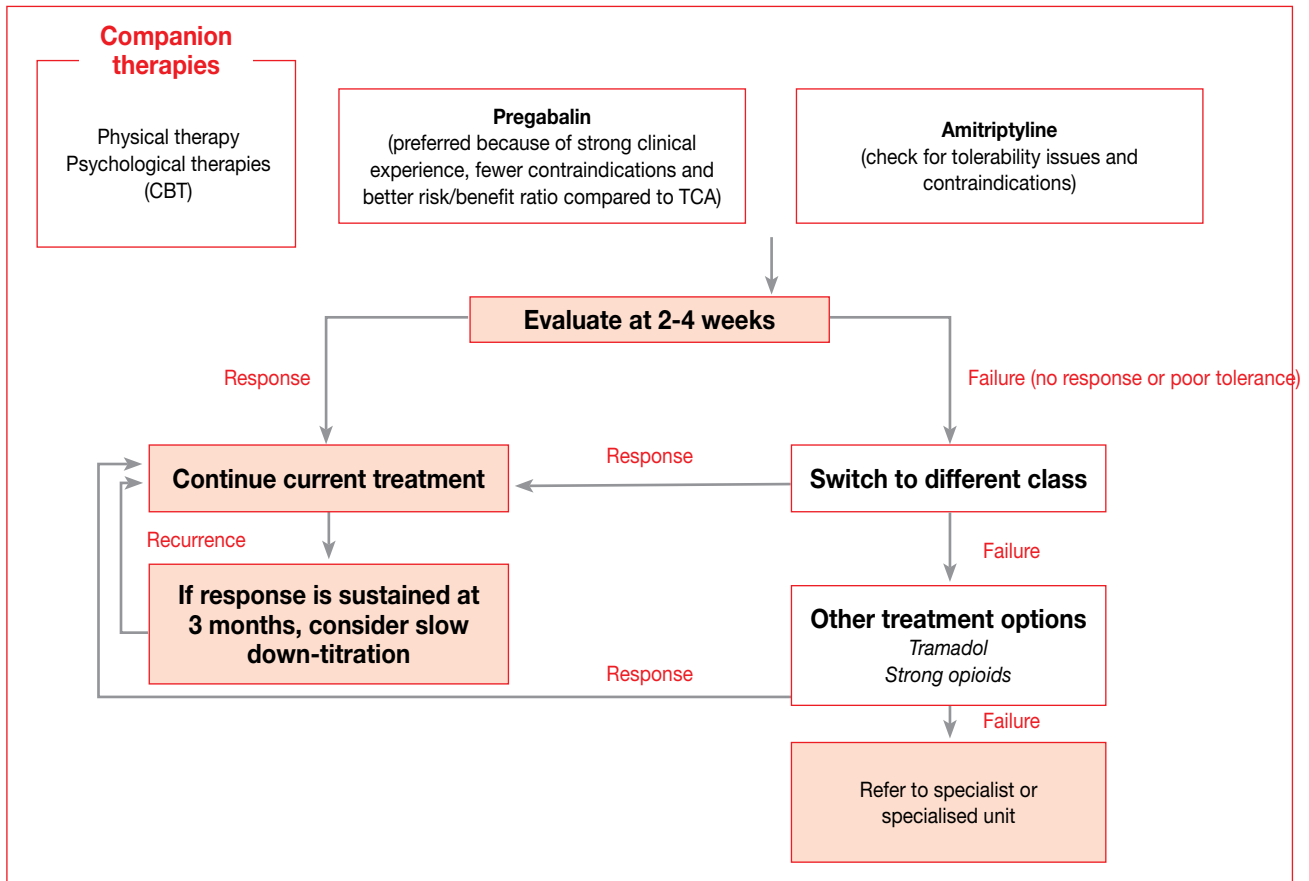


Figure 4: Recommendations for management of central neuropathic pain.

psychological, pharmacological and physical therapies, tailored to the needs of the individual patient, may be the best approach.⁸⁷ Transcutaneous electrical nerve stimulation (TENS) is widely used for NeuP and nociceptive pain, and while it lacks robust efficacy data,⁸⁸ it is recommended by EFNS Task Force⁸⁹ as a preliminary or as an adjunct to analgesic therapy as it is inexpensive, non-invasive, safe, and can be self-administered. A review of non-pharmacological treatment approaches by Guastella *et al.*,⁹⁰ indicate TENS in focal neuropathic pain when upstream stimulation is possible for a superficial sensitive nerve trunk. There are no good data supporting the use of acupuncture in NeuP.

Recommendation: The panel recommends the use of psychotherapy, particularly cognitive behavioural therapy, and TENS alongside appropriate physiotherapy and pharmacological treatment, for the management of NeuP. Comprehensive patient education can also help improve treatment outcomes.

3.7.2 Stimulatory treatments and surgical management (non- invasive and invasive)

Non-invasive electrical stimulation of the brain, using a variety of methods, has been studied in some chronic pain conditions with very limited evidence of efficacy.⁹¹ Spinal cord stimulation, via electrodes implanted into the spinal cord, has limited evidence of efficacy in failed back surgery

syndrome and complex regional pain syndrome type I,⁹⁰ the EFNS Task Force identified level B evidence of efficacy in several systematic reviews, as well as primary studies for spinal cord stimulation in these two conditions.⁸⁹ Guastella *et al.*⁹⁰ suggest the use of spinal cord stimulation in segmental mononeuropathies refractory to drug treatment. Dorsal root entry zone lesioning (DREZotomy) involves destruction of nociceptive fibres and the dorsal root entry zones in an aim to destroy the neurones that sustain the painful state. Guastella *et al.*⁹⁰ suggest its use in refractory pain due to plexus avulsion.

Recommendations: The panel did not discuss these non-pharmacological treatment approaches extensively, but recommends spinal cord stimulation in cases of pain that cannot be managed by pharmacological and companion treatments. The panel does not recommend DREZotomy for management of any NeuP, because of limited evidence and risk of worsening of NeuP after this invasive procedure.

4. Discussion

The management of NeuP is challenging, and even when NeuP is diagnosed and treated according to the best evidence available, not all patients can achieve a satisfactory response. This article provides recommendations for the management of NeuP in South Africa, with the aim of raising awareness of NeuP and improving its diagnosis and

treatment in this country. These recommendations apply published, international, evidence-based guidelines for NeuP management to the South African setting.

NeuP is widely underdiagnosed in South Africa, and the panel recommends the use of simple questionnaires, such as DN4, to identify NeuP. A raised awareness of common signs and symptoms of NeuP, and of the descriptors used by patients, will also help clinicians to better identify those patients who have neuropathic aspects to their pain. For management of peripheral NeuP, the $\alpha\delta$ -ligands pregabalin and gabapentin, low-dose TCAs, and the SNRIs duloxetine and venlafaxine are recommended as first-line options. Pregabalin is the preferred option, based on tolerability and pharmacokinetics. Opioids should be reserved for later use, and only after switching to another monotherapy or combination therapy with multiple first-line agents fails.

For painful DPN, recommendations are as for peripheral NeuP in general; for PHN, first-line recommendations are pregabalin (preferred), gabapentin and low-dose amitriptyline; and for TN, oxcarbazepine (preferred) and carbamazepine. Some agents with good evidence, recommended in guidelines from other regions, are not available in South Africa. The panel requests that the South African regulatory authorities evaluate the evidence for the lidocaine patch and topical capsaicin in localised peripheral NeuP and consider approval of these agents in South Africa.

Based on current international recommendations, the committee cannot recommend specific therapy for the management of HIV-associated neuropathy. Currently these patients should be managed following the same recommendations used for the management of peripheral neuropathic pain.

Evidence in CP is less consistent than for peripheral NeuP, but first-line recommendations are pregabalin (preferred) and amitriptyline. Companion therapies, such as cognitive-behavioural therapy (and other psychotherapy) and physical therapy are recommended to accompany pharmacological management. Invasive options like DREzotomy are not currently recommended. The recommendations presented here have several limitations. Evidence is still lacking for the relative efficacy of agents for NeuP, as there are very few head-to-head trials. There are also limited data available for pain due to specific aetiologies other than painful DPN, PHN, and TN. In particular, the paucity of evidence for treatment of painful HIV-SN makes it impossible to provide an evidence-based recommendation for this problem that

is so common in South Africa. This must be a priority area of future research. In addition, because there are few placebo-controlled RCTs in South African populations, the recommendations given here have to assume that results in other populations can be extrapolated to the various ethnic groups represented in South Africa.

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Appendix A. Evidence classification scheme, and levels of recommendation used by Attal *et al.*⁹²

Class I: An adequately powered prospective, randomised, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomised controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- (a) randomisation concealment
- (b) primary outcome(s) is/are clearly defined
- (c) exclusion/inclusion criteria are clearly defined
- (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets

- (a) - (e) above or a randomised, controlled trial in a representative population that lacks one criterion (a) - (e).

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a

representative population, where outcome assessment is independent of patient treatment **Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion **Rating of recommendations**

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence

Level C rating (possibly effective, ineffective, or harmful) rating requires at least two convincing class III studies