Guidelines for the treatment of neuropathic pain in South Africa

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Abstract

Neuropathic pain is defined as pain that originates due to a lesion, dysfunction or disease, e.g. diabetes, HIV infection, herpes zoster, chemotherapy or surgery, and which affects the peripheral or central nervous system. This results in abnormal neural function, often presenting in an individual as sensory pain-related symptoms which are either positive, i.e. hyperaesthesia or hyperalgesia; or negative, i.e. hypoaesthesia or anaesthesia. The quality of life of patients with neuropathic pain is often compromised as many have difficulty sleeping, lack energy, and experience drowsiness and altered concentration, and this can potentially progress to a stage in which the patient is physically and psychologically distressed. In 2012, an expert panel proposed clinical guidelines for the treatment of neuropathic pain in the South African context. These guidelines shifted from traditional pain management, primarily comprised of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, to alternative therapeutic agents including pregabalin, gabapentin, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (SNRIs) and opioids. Recent studies have suggested that melatonin, a neurohormone responsible for regulating the circadian rhythm, may be a potential therapeutic agent for symptoms associated with neuropathic pain. The guidelines reviewed in this article offer healthcare providers with a concise step-wise approach with which to diagnose and treat neuropathic pain.

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Introduction

Neuropathic pain is defined as the pain that originates due to a lesion, dysfunction or disease, e.g. diabetes, HIV infection, herpes zoster, chemotherapy or surgery, and which affects the peripheral or central nervous system.[1] This results in abnormal neural function, often presenting in an individual as sensory pain-related symptoms that are either positive, i.e. hyperaesthesia or hyperalgesia; or negative, i.e. hypoaesthesia or anaesthesia.[2] Patients often describe neuropathic pain as a shooting, stabbing, burning, electric, tingling, numbness or "pins and needles" sensation.[3] The quality of life of patients with neuropathic pain is often compromised as many have difficulty sleeping, lack energy, and experience drowsiness and altered concentration, and this can potentially progress to a stage where a patient is physically and psychologically distressed.[3]

Limited data are available on the prevalence of neuropathic pain in South Africa.[3] Some studies have identified the prevalence of neuropathic pain associated with a specific disease. For example, a cross-sectional study on diabetic peripheral neuropathic pain found a 30% prevalence thereof in type 1 and type 2 diabetic patients attending private outpatient clinics in South Africa.[4] Several factors exacerbate the burden of neuropathic pain.[3] Firstly, the burden of HIV/AIDS is extremely high in South Africa, and as a result, a considerable number of patients may experience HIV-associated neuropathy or present with neuropathic pain as a side-effect of antiretroviral therapy.[3] The second major factor is the lack of knowledge and awareness about neuropathic pain amongst healthcare providers.[3] This gap in knowledge often results in underdiagnosis, inappropriate management and poor prescribing patterns.[3]

An expert panel has formulated clinical practice guidelines for healthcare providers in order to standardise the approach to diagnosing and managing neuropathic pain in South Africa.[3] These 2012 guidelines were developed based on evidence obtained through reviewing both international and regional neuropathic pain management guidelines, systematic reviews, meta-analyses and peer-reviewed, randomised, double-blind, placebo-controlled studies.[3] The guidelines presented in this article are based on these expert recommendations which were published in the South African Medical Journal in 2012.[3]

Diagnosis

Several standardised screening tools have been developed to identify neuropathic pain based on verbal descriptions of the

symptoms thereof. These include tools such as painDETECT questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale, the Neuropathic Pain Questionnaire and *Douleur Neuropathique en 4 Questions*.[3] The South African guidelines recommend the use of *Douleur Neuropathique en 4 Questions*, which consists of seven items related to symptoms, and three items related to clinical examination, to help identify and evaluate patients with neuropathic pain.[3] Additionally, the guidelines suggest that diagnosis should not solely rely on screening tools, but should include a combination of clinical evaluation and a screening tool.[3] The use of the "3L" approach (listen, locate and look) to differentiate neuropathic pain from nociceptive pain is recommended for clinical assessment. This includes listening to the patient's verbal account of pain, locating painful regions and assessing the presence of somatosensory problems.[3]

Treatment

When treating neuropathic pain, it is crucial that a holistic approach is adapted whereby the healthcare provider first identifies the underlying aetiology, then treats the primary cause of pain, and thereafter initiates the appropriate neuropathic pain therapy.[3,5] Many agents that are used in the treatment of neuropathic pain provide additional benefits for coexisting conditions, such as

Table I. A summary of recommended therapeutic agents used in the treatment of neuropathic pain in South Africa[3]

Therapeutic agent	Other benefits	Side-effects	Contraindications, precautions and drug interactions
α2δ-ligands			
Pregabalin	• Reduced sleep disturbance • An anxiolytic	Dizziness, sedation, peripheral oedema, a dry mouth and asthenia	• No significant drug interactions • Dose reduction in renal insufficiency
Gabapentin	Reduced sleep disturbance	Dizziness, sedation, peripheral oedema, a dry mouth and asthenia	• No significant drug interactions • Dose reduction in renal insufficiency
SNRIs			
Duloxetine	Improved MDD and GAD	Nausea and vomiting, constipation, anorexia, a dry mouth and dizziness	• Low initial doses for mild to moderate hepatic and renal impairment. • Contraindicated in severe hepatic impairment, end-stage renal disease, alcohol abuse and the concomitant use of tramadol and MAOIs. • Caution is required in patients with history of mania, seizures and acute narrow-angle glaucoma. • Glucose monitoring required as worsening glycaemic control is seen in diabetic patients. • Drug interactions occur with tramadol, TCAs, SSRIs and SNRIs. • There is inhibition of metabolism of drugs metabolised by CYP2D6. • Those at risk of suicide ("black-box" warning, in line with other antidepressants).
Venlafaxine		Nausea	• Caution required in patients with cardiac disease. • There is a risk of hypertension, hence regular blood pressure monitoring required. • A lower dose may be necessary in patients with renal impairment (GFR of 10–70 ml/minute) or cirrhosis of the liver. • Use with caution in patients with a history of seizures and a history of mania. • Drug interactions occur with tramadol, the TCAs, SSRIs and SNRIs. • There is inhibition of the metabolism of drugs metabolised by CYP2D6. • Those at risk of suicide ("black-box" warning, in line with other antidepressants).
TCAs			
Amitriptyline	Improved MDD	Sedation, a dry mouth, blurred vision, weight gain, urinary retention and dizziness	• Contraindicated with MAOI use, antihypertensive medication, in patients with myocardial infarction and heart block, and those with untreated narrow-angle glaucoma. • Use with caution in patients with glaucoma, cardiovascular disease, (especially in elderly patients), hyperthyroidism, impaired liver function, epilepsy, urinary retention, prostatic hypertrophy, constipation and mania.
Opioids			
Tramadol (weak) **Morphine (strong)**	Rapid onset of analgesia	Nausea and vomiting, constipation, drowsiness and dizziness	• There is risk of addiction and abuse. • Psychomotor impairment is possible. • Use with caution in patients with history of substance abuse, suicide risk, seizure disorder and in elderly patients because of the risk of confusion. • Contraindicated with the concomitant use of SSRI, SNRI, TCAs.

α2δ ligands: alpha-2-delta ligands, CYP: cytochrome P450 (CYP), GAD: generalised anxiety disorder, GFR: glomerular filtration rate, MAOIs: monoamine oxidase inhibitors, MDD: major depressive disorder, SNRIs: serotonin noradrenaline reuptake inhibitors, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants

sleep disorders, anxiety and depression. The choice of therapy should take into consideration the efficacy, side-effect profile and the relief of coexisting conditions.[3]

Four classes of therapeutic agents are recommended for use in the treatment of neuropathic pain in South Africa, i.e. alpha-2-delta ligands (pregabalin and gabapentin), tricyclic antidepressants (TCAs) (low-dose amitriptyline and others), serotonin and noradrenaline reuptake inhibitors (SNRIs) (duloxetine and venlafaxine), and opioids.[3] These have been summarised in Table I, including the additional benefits and safety profile.[3]

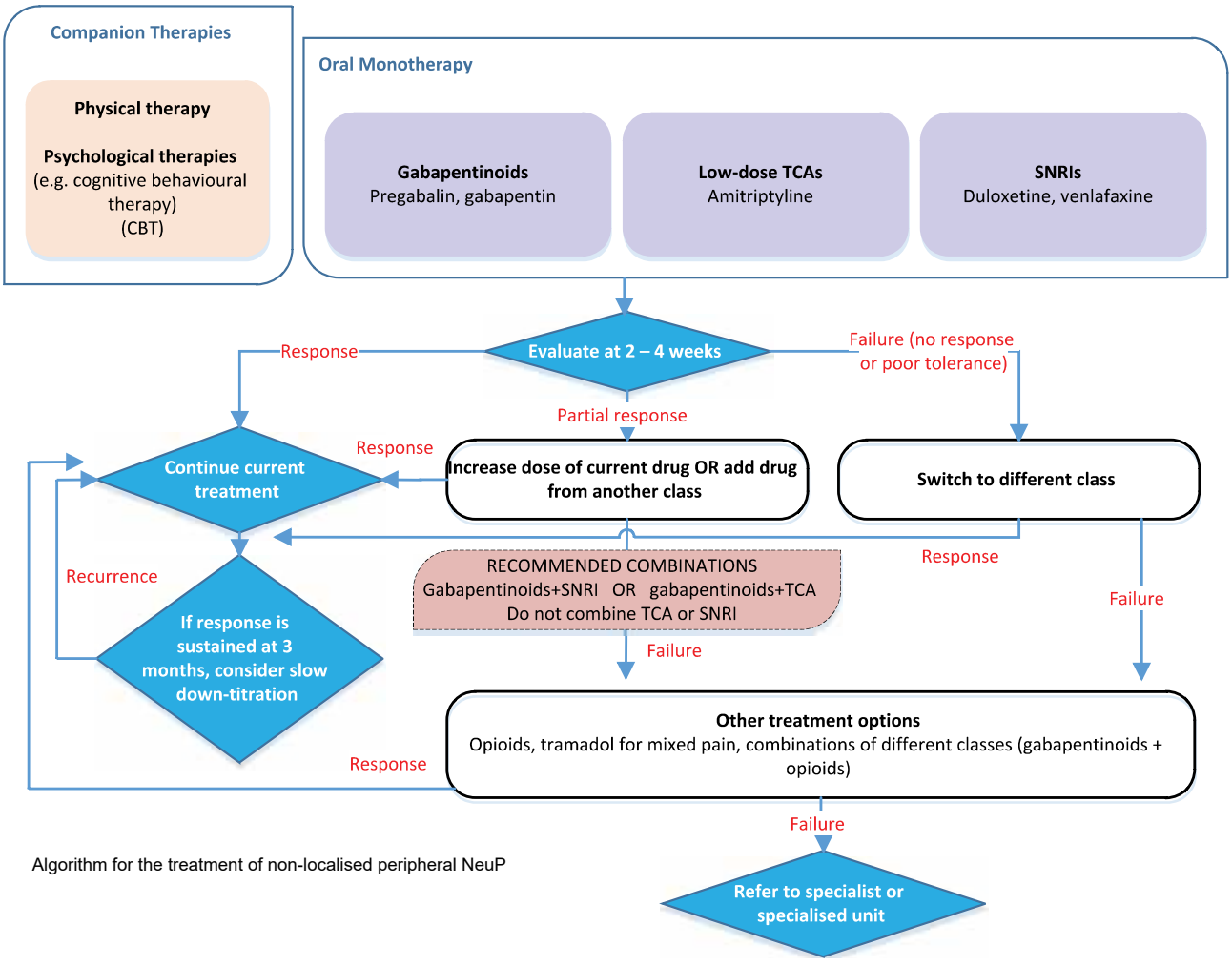
Current research studies have suggested that melatonin, a neurohormone responsible for regulating the circadian rhythm, may be a potential therapeutic agent for symptoms associated with neuropathic pain.[6] The precise pathway of melatonin in pain modulation is not fully understood; however, some evidence suggests melatonin exerts a pain modulation effect along the opioid system and nitric oxide pathways.[6] Melatonin has a high degree of lipid solubility and it is able to penetrate the blood brain barrier, thus increasing the potential therapeutic activity in patients with central neuropathic pain.[6] However, further research is required to determine the efficacy of melatonin in neuropathic pain relief.

Recommendations for the treatment of peripheral neuropathic pain

The expert panel constructed the following algorithm (Figure 1) which highlights a stepwise approach to the management of peripheral neuropathic pain.[3]

First-line therapy consists of oral monotherapy using a gabapentinoid (pregabalin or gabapentin), a low-dose TCA (amitriptyline) or an SNRI (duloxetine or venlafaxine).[3] Pregabalin is usually the agent of choice. Companion therapies such as physical therapy and psychological therapy, may be used in conjunction with oral monotherapy.[3]

Evaluation should be carried out two to four weeks after the initiation of therapy. If the patient is stable on first-line monotherapy, the treatment should be continued.[3] Some patients may experience only a partial response to therapy. In these cases, effective treatment can be achieved by either increasing the dose of the first-line agent or by combining two first-line agents, i.e. an SNRI and gabapentinoid, or a gabapentinoid and a TCA. If a patient shows no response or poor tolerance to a first-line agent, the medicine should be switched to an agent from a different therapeutic class.[3]



Algorithm for the treatment of non-localised peripheral NeuP

Figure 1. Recommendations for management of peripheral neuropathic pain[3]

If the patient does not respond to second-line therapy (a combination or a switch), third-line therapy, consisting of a weak opioid (tramadol) may be recommended.[3] If the patient still does not respond, a stronger opioid, i.e. morphine, oxycodone, hydromorphone, or a combination of first-line options with an opioid is recommended. Evidence of good pain relief has been observed with the use of a combination of morphine and gabapentin.[3]

Recommendations for the treatment of central neuropathic pain

In comparison to peripheral neuropathic pain, central neuropathic pain is often difficult to treat, but responds to similar treatment.[3] A stepwise algorithm has been proposed (Figure 2) for the treatment of central neuropathic pain.[3] Pregabalin or amitriptyline are recommended as first-line agents. Pregabalin is the preferred choice as it has a better risk to benefit ratio and fewer contraindications. As with peripheral neuropathic pain, the response should be evaluated after two to four weeks. If treatment is effective and there is good tolerance, treatment should be continued. However, if the patient shows no response or poor tolerance, he or she should be switched to a different class of medicine or combination therapy. If second-line treatment fails, tramadol should be considered, followed by a stronger opioid.[3]

Aetiology-based treatment recommendations

The expert panel recommends pregabalin, gabapentin or amitriptyline as the first-line treatment for the treatment of postherpetic neuralgia, and combination therapy as a second-line strategy. It also recommends the initiation of tramadol followed by an opioid as third-line therapy.[3] Other international guidelines recommend the use of lidocaine patches. However, despite good evidence of efficacy in the treatment of postherpetic neuropathic pain, this therapeutic agent has been omitted from the guidelines as it is not available on the South African market.[3]

The panel recommends the use of carbamazepine and oxcarbazepine for the treatment of trigeminal neuralgia.[3]

Conclusion

Neuropathic pain is a condition that can result in severe suffering, disability and reduced quality of life. It is important to diagnose the condition at an early stage, and to provide appropriate and effective therapy to reduce the burden experienced. The guidelines reviewed in this article are evidence-based and offer healthcare providers with a concise stepwise approach with which to diagnosis and treat neuropathic pain. Nonpharmacological treatment options should also be considered, and include advising the patient on the importance of stress reduction and

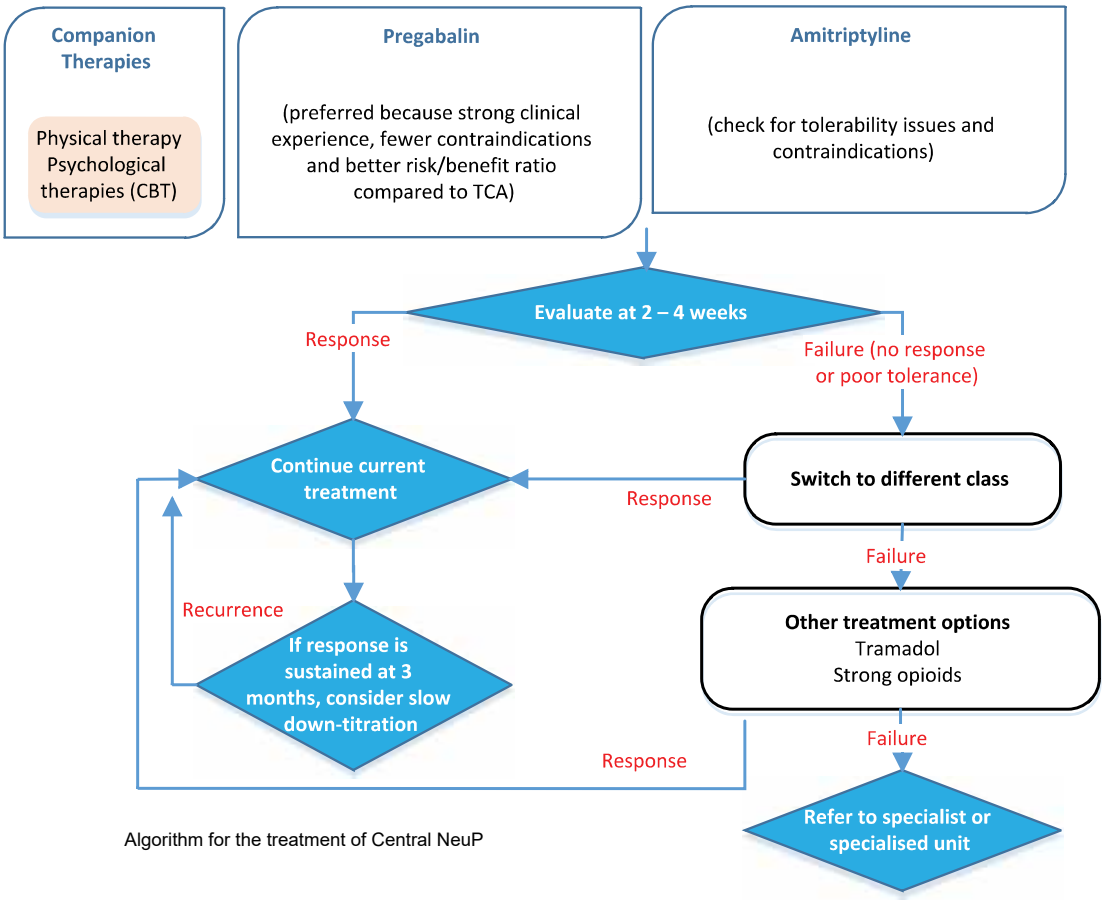


Figure 2. Recommendations for management of central neuropathic pain[3]

sleep hygiene. To ensure the best treatment outcome for patients, pharmacists have a crucial role to play in ensuring that the strategies used to treat neuropathic pain are rational, effective and in agreement with the recommended guidelines for South Africa.

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