Volume 10, Issue 03, March 2024,
Publish Date: 24-03-2024
Doi https://doi.org/10.55640/ijmsdh-10-03-21

International Journal of Medical Science and Dental Health (Open Access)

MANAGEMENT OF NEUROPATHIC PAIN: A REVIEW OF CURRENT TRENDS

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ABSTRACT

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. Pain is a common symptom that knows no boundary. It differs with age, creed, sex, disease and specialty.

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Its chronic debilitating nature and unpredictive response to medication make it a challenge to most physicians and the patient they treat. The use of treatment algorithms or guidelines have found common use in the treatment of neuropathic pain. This poses a need for periodic review.

This review looked at the current trends in the management of neuropathic pain. We recommend a four-pronged approach in the evaluation and management of patients with neuropathic pain. This involved detailed review of the patient, the pain, the plan, and the pill. There is also a growing need to adopt less invasive techniques in the treatment of chronic recalcitrant pain.

KEY WORDS: Neuropathic, Pain, chronic, trend, review

BACKGROUND

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."1 Pain is a common complain across all age's disciplines, specialties and regions of the globe regardless of gender, tribe, and creed. The IASP further classified pain into two main categories: nociceptive pain and neuropathic pain.2 Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Nociceptive pain on the other hand is pain perceived from actual or threatened damage to peripheral or visceral tissues through the activation of nociceptors.2

Neuropathic pain has a diverse collection of etiologies, chronic in nature with a protracted course, variable and unpredictable response to available treatment and usually associated with other

symptoms. The insult in neuropathic pain may occur at the molecular, cellular, or tissue level resulting in sensory loss and/or increased responsiveness to stimuli.3 Associated symptoms include: allodynia (pain arising from non-painful stimuli eg pain from mild tactile stimuli), hyperalgesia (increased pain sensation beyond what is expected after painful stimuli), and hyperpathia (explosive pain that continues to exist beyond the duration of a stimulus).3 Nociceptive pain on the other hand is short-lived with specific aetiology, better response to medical/surgical treatment and in most cases an early indicator of an existing pathology or insult. This is summarized in Table 1.

NOCICEPTIVE	NEUROPATHIC
Stimulation of peripheral receptors by actual or potential tissue damage	Defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.
Primary stimuli can be identified and reversed in most cases	Spontaneous with or without stimuli
Somatic or visceral. Short lived with good response to medications	Symptoms are diffuse, chronic with limited response to medications
Pain is the main symptom	Other symptoms like allodynia, hyperalgesia and paresthesia are present
ASA, acetaminophens and NSAIDS	Gabapentinoids, Tricyclic antidepressants, SNRIs and strong opioids
Reversible by removal of originating stimulus	No identifiable stimulus

Table 1 *(Differences between neuropathic and nociceptive pain.)*

The morbidity and impact of neuropathic pain on the quality of life of patients presents a major challenge to pain practitioners. Bouhassira et al.4 reported a prevalence of 1-7% of the entire population in developed countries. Disease -specific rates may be far higher than this. Nikolajsen & Jensen5 has reported 50-80% incidence of phantom limb pain in amputees from peripheral vascular disease. Dermanovic et al6 in their study on the impact of neuropathic pain and other comorbidities on the quality of life in patients with diabetes have also clearly shown that diabetic patients with neuropathic pain have reduced sleeping time, reduced productive man-hours, increased health care expenses and overall reduction in the quality of life compared to those without neuropathic pain. When pain is not optimally controlled, the autonomic system is persistently activated, leading to further damaging effect in most physiologic functions6. Treatment of neuropathic pain can be broadly divided into pharmacological and non-pharmacological methods. Several drug classes acting along different points on the pathway with clear and occasionally uncertain mechanisms can have direct or indirect effect on neuropathic pain. Because of the wide array of available drugs and the different possible complications with their administration, the use of treatment algorithms or guidelines have found common use in the treatment of neuropathic pain.7,8 Percutaneous Surgical interventions have in recent times been fostered by the unpredictability of pharmacologic treatment. More invasive surgeries are exclusively for severe, intractable pain with poor response to other treatment options7.

PAIN PATHWAY

Understanding the physiology of pain transmission is key to appreciating all available treatment options and formulating newer ones. The Pain stimulus is primarily perceived by cutaneous and visceral receptors and transmitted by the Aδ and C afferent sensory fibers. This perceived pain message moves through the first order neurons whose cell bodies are located at the spinal cord dorsal root ganglion. Further transmission is via the second-order neurons at the dorsal horn of the spinal cord. The message then ascends the lateral spinothalamic tract to the thalamus, where the third-order neurons are dispersed from the thalamus to the cerebral cortex9.

The somatosensory cortex and the anterior cingulate cortex are mainly involved in interpreting the pain stimuli. The former main sub-serves pain intensity, pain localization and pain transmission while the latter is involved in pain-associated anxiety and fear.

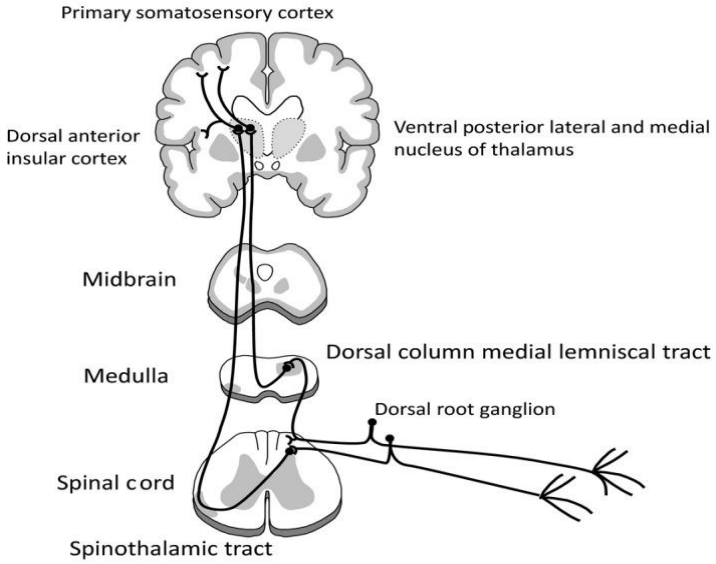

Figure 1 *(Somatosensory pathway[9])*

The micro unit of this pathway is the nerve terminal where voltage-dependent calcium channel releases several neurotransmitters which have key drug target roles. These neurotransmitters bind to post-synaptic receptors to stimulate the cascade of responses that initiate the pain transmission.

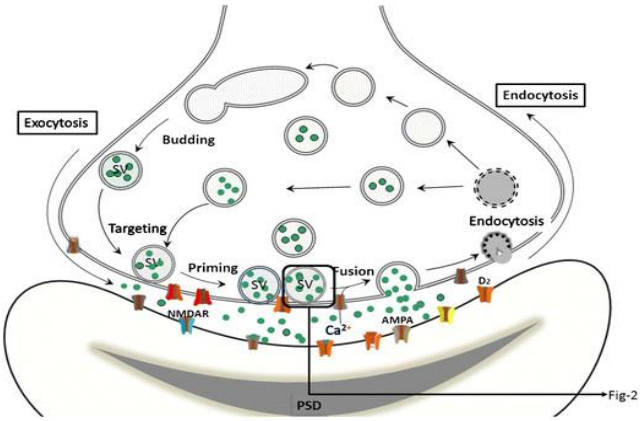

Figure 2 *(The presynaptic nerve ending[10])*

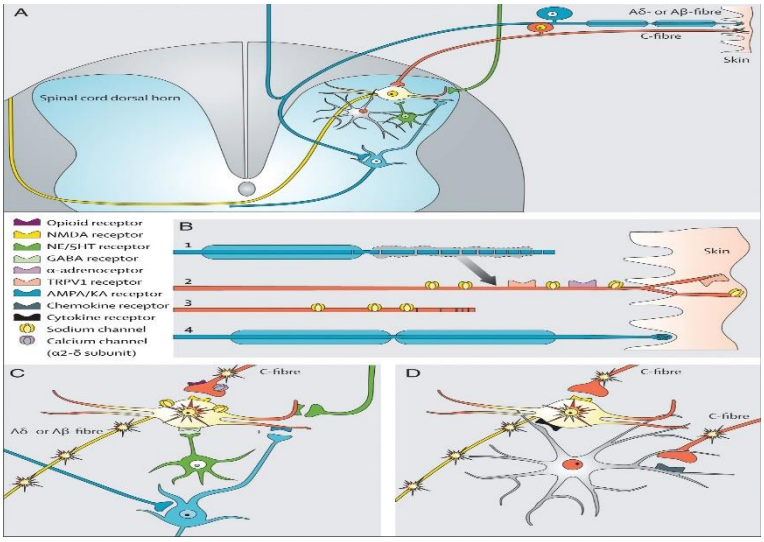

Figure 3 *(Receptors involved in neuropathic pain.[11,12,13])*

PATIENT EVALUATION

Evaluating the patient with neuropathic pain should have a four-pronged approach. Characterizing the patient, the pain, the plan, and the pill gives a holistic view of nature of the pain while respecting the peculiarities of the patient, the impact of the pain on the patient and the overall plan of treatment. Such four-pronged approach is aimed at providing long-term optimal care for patients with neuropathic pain tailored to meet each patient's peculiar needs while respecting the occupational and social variables and reducing complications that can arise1.

THE PAIN: Noriko and Mashahiro9 have opined that when dealing with a patient presenting with pain and numbness, consideration should be made of the pain characteristics in terms of the site, intensity, course, nature, occurrence pattern, known triggers, and factors worsening and relieving the pain, as well as the degree of impact that the pain has on the patient's daily and social life. Neuropathic pain typically presents as chronic and insidious deep-seated pain of varying localization associated with other neurologic symptoms (like allodynia, paraesthesia, hyperalgesia, and numbness). Response to treatment is typically poor and impact on quality of life is profound. The first contact with the patient gives the physician the best opportunity to thoroughly evaluate the pain.

Hyperalgesia is abnormal hypersensitivity to stimuli. In hyperalgesia, normal stimuli give exaggerated response. Allodynia however is a condition where mild non-painful stimuli like the body touching clothing, causes pain. These conditions seem to involve thick (Aβ) afferent fibers, which mediate tactile sensation, but not pain, under normal conditions. Damage to peripheral sensory neurons with hyper-excitability, and sustained firing are plausible explanations for these scenarios.9.

Some conditions like peripheral vascular disease presents with neuropathic as well as pain from inflammatory and other noxious stimuli. Care must be taken to ensure that other components of pain are considered in the treatment plan for these patients. In complex regional pain syndrome for instance, the pathophysiologic mechanisms are complex and poorly understood.14 Sensory neurologic

dysfunction with autonomic dysregulation and vascular hyperactivity have all been implicated. Treatment with routine pain medications is therefore sub-optimal. 15

THE PATIENT: Patient variables are important in formulating a treatment plan for neuropathic pain. Patient's age, occupational status, work, social, religious demands and treatment expectations should be core considerations in the treatment of neuropathic pain2. Certain physiologic and social considerations limit the use of certain drugs for treatment of neuropathic pain2. Response to pain treatment also differ from one patient to another depending the pain etiology, the patient's threshold for pain, the perception of pain etiology by the patient as well as the effectiveness of treatment. Compliance level to treatment will also depend on certain variables like route of drug administration, drug characteristics, patient's perception of drug complications and the general perception of the appropriateness of treatment plan. A good treatment plan takes into consideration these unique variables to ensure optimal compliance and effective treatment outcome3.

THE PLAN: The American Pain Society recommends that pain should be assessed by health care providers (HCPs) as a 'fifth vital sign.16,17 This underscores the relevance of detailed patient evaluation (clinical history and examination) and relevant or adequate investigations in ensuring the formulation of a good treatment plan. Pain should not be seen a mere associate of varying clinical conditions but a serious indicator requiring proper attention.

Hasty prescriptions for pain treatment should give way to detailed evaluation of the complains, the constraints and the deep concerns on the patient. Mathias et al have reported that the perception of patients about the unwilling of their care-providers to carefully listen to their concerns leading to medication overprescrition.18 Both McCormark et al and Epstein et al19,20 have advocated patient-centered care in the treatment of chronic pain. Patient-centered care involves openness and attentiveness to patient care preferences and needs. It also promotes communication and engagement of patients in decision-making. Medication adherence, patient satisfaction and treatment outcomes have all been noted to have improved with patient centered care.20,21 A more open and wholistic approach to evaluation will aid the care provider to navigate through the myriad of possible causes of neuropathic pain and detect the often-associated psychiatric symptoms like depression and anxiety which are potent triggers to reduction in the quality of life. The possible causes of neuropathic pain are as tabulated below:

Groups	**Specific Diseases**
Metabolic	Diabetic peripheral polyneuropathy,
Viral	Post-hepatic neuralgia, trigeminal neuralgia, HIV neuralgia
Hereditary neuropathies	Inflammatory bowel disease,
Nerve injury	Phantom limb pain, spinal cord injury, post stroke pain
Autoimmune disorders	Multiple sclerosis, rheumatoid arthritis

Chronic post-surgical neuropathic pain	Iatrogenic Peripheral nerve injuries, failed back syndrome
Degenerative disease	Spinal disc degenerative disease, parkinson's disease

Table 2 *(Some causes of neuropathic pain)*

THE PILL: Several drugs have been used in the treatment of neuropathic pain. The Special Interest Group on Neuropathic Pain (NeuPSIG) proposed agbapentinoids, tricyclic antidepressants (TCAs), and selective serotonin–norepinephrine reuptake inhibitors (SNRI) as the first-line drugs for neuropathic pain.22 Tramadol, Lidocaine and Capsaicin and have been proposed as the second-line treatment, third line treatment include the use of opioids such as Morphine and Oxycodone, and botulinum toxin-A (BTX-A).

Drug Class	Drug	Mechanism Of Action	Dosage	Complications	Clinical Uses
GABAPENTINOIDS					
	Gabapentin	Binds to the voltage-dependent calcium channel auxiliary subunit α2δ, hence suppressing the presynaptic calcium influx and inhibiting the release of excitatory neurotransmit	150–600 mg/day	Vertigo, peripheral swelling, lethargy blurred vision	Good response in the treatment of diabetic pain, herpetic neuralgia and lumber disc degenerative disease.
	Pregabalin	Same as above	75–150mg/day	Lethargy, vertigo, peripheral swelling, increased body weight	Good results in the treatment of phantom limb pain, herpetic neuralgia and pain from cord degeneration

TRICYCLIC ANTIDEPRESSANTS					
	Amitriptyline	Inhibits serotonin and noradrenaline reuptake from the presynaptic terminals. Also has inhibitory effects on cholinergic, adrenergic, and histaminergic receptors and ionic channels.	10–150 mg/day	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention	Useful in the treatment of painful neuropathy, nerve injury pain, post-herpetic neuralgia, pain, and pain following spinal cord injury. Contraindicated in patients with glaucoma, heart conduction deficits and prostatic hyper trophy.
	Nortriptyline	Same			
	Imipramine	Same			
	serotonin-norepinephrine reuptake inhibitor				
	duloxetine	Inhibits the reuptake of serotonin and norepinephrine at the synaptic level.	20–120 mg/day	Nausea, lethargy, constipation, ataxia, dry mouth	Used for most conditions of neuropathic pain. should be used with caution in patients with cardiac anomalies
	venlafaxine	Same	150-225mg/day	Nausea, vertigo, lethargy, hyperhidrosis, hypertension	
OPOIDS					
	Tramadol	A μ-opioid agonist that inhibit pain transmission through the presynaptic and post-synaptic μ-opioid receptors.	25–400 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia	Useful in the treatment of neuropathic pain. Dependence is a risk.
	Tapentadol	Same	50-600 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia	Quite effective in the treatment of diabetic pain.

	Morphine	Same	10–120 mg/day	Nausea, vomiting, constipation, dizziness, and lethargy	Treatment of diabetic neuropathy and other forms of neuropathic pain
	Oxycodone	Same	10-120 mg/day	Nausea/vomiting, constipation, lethargy, respiratory control	Treatment of diabetic neuropathy and other forms of neuropathic pain
TOPICAL AGENTS					
	Lidocaine	blocks voltage-gated sodium channels locally, reducing spontaneous ectopic nerve discharge	5% patches or gel	Local erythema, itching and rash	Useful for ambulatory care, good results in scar infiltration and local applications
	Capsaicin	Potent receptor agonist (transient receptor potential cation channel subfamily V member 1 also known as vanilloid receptor 1 (TRPV1)). Cause depletion of substance p.	8% patches or gel	Pain, erythema, itching; rare cases of high blood pressure. Needs prolonged use before a good effect can be created.	Useful for ambulatory care, good results in scar infiltration and local applications
	Ketamine		0.5%, patches or gel	Mild itching.	Good results in the treatment of allodynia
NEUROTOXINS	Botulinum toxin	A potent neurotoxin that inhibits synaptic exocytosis and therefore the neural transmission.	25–300 U BTX-A 0.9% saline	Pain at injection site	Useful in the treatment of spastic pain especially in patients with focal peripheral neuropathic pain and allodynia.
ANTIEPILEPTIC DRUGS					

	Carbamazepine	Sodium channel blocker	400-800mg per day in divided doses.	Dizziness and somnolence	Treatment of trigeminal neuralgia

Table 3 *(Drugs used in the treatment of neuropathic pain)*

INTERVENTIONAL THERAPY

Drug treatment is not always successful in neuropathic pain. The limitations of drug treatment include, its complications, dependence with chronic use (more common with opioids), patient's perception of its ineffectiveness especially with prolonged use as well as the cumulative cost. When pain is chronic and recalcitrant, treatment path becomes turbulent, and outcome become less predictable. It is therefore the duty of the pain practitioner to formulate newer treatment methods. These interventions range from percutaneous injections to more invasive transections along the pain pathway.

The use of less invasive methods has been advocated since they are generally regarded as being safer, more acceptable to the patient, more respectful of the patient's concerns and more predictable. Some of these methods have been highlighted in table 4.

TYPE	MECHANISM	CLINICAL USES	SPECIAL CONSIDERATION	SIDE EFFECT
Steroid injections	Inhibition of phospholipase A2 and other inflammatory mediators.	Perinural steroid injection provides temporal pain relief for 1-3months in chronic recalcitrant pain	Epidural infiltration for lumber radiculopathies is the commonest example. Though reduction on pain intensity has been widely documented, it has no effect in reducing the chance of surgical intervention [23,24,25]	Spine infection, hematoma, and sepsis have been reported though rare. Particulate steroid and iatrogenic injury to the cord have also reported. [26,27,28,29]
Spinal cord stimulation	A monophasic square-wave pulse (frequency ranging 30–100 Hz) is applied. Burst (40 Hz burst with five spikes at 500 Hz per burst) and high-frequency (10 kHz with sinusoidal waveforms) spinal cord stimulation,	It's a safe, reversible and cost –effective means of treating diabetic neuropathy with poor response to other forms of treatment. Useful in the treatment of failed back surgery syndrome and in irritable bowel syndrome.	The electrodes can be inserted percutaneously through an epidural needle or surgically implanted by laminotomy.	Monophasic stimulation is notorious for causing paraesthesia.[33,34]

	provide paraesthesia-free stimulation[30,31,32]			
Dorsal root ganglion, peripheral nerve and peripheral nerve field stimulation	Interruption of pain transmission to higher centers by poorly understood mechanisms. [35,36]	Effective relief for peripheral neuropathies.	The patient is able to control stimulation by turning the device on and off and adjusting stimulation parameters as needed.[37,38]	The electrode delivers rapid electrical pulses that are felt like mild tingles (so-called paresthesia) Nerve injuries can also occur.[39]
Transcranial cortical neurostimulation	Magnetic and electrical stimulation as a way of distorting pain transmission.	Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) of the pre-central motor cortex at levels below the motor threshold have been proposed as treatment options for patients with refractory chronic neuropathic pain[40,41]	More useful when psychiatric symptoms are predominant.	Repetitive transcranial magnetic stimulation (rTMS) can affect metallic implants.
Deep brain stimulation	Involves stimulation of the brain through internally placed electrodes (leads) with percutaneously placed control switches.	Spastic pain not relieved by conventional medications.	More useful when psychiatric symptoms are predominant.	Misplacement of the wires with the electrodes, known as leads. Bleeding
Intrathecal therapies	Intrathecally placed tubes for intermittent	For chronic debilitating painful conditions		Tube infection and tube dislodgement.

	delivery of medications [42,43]			
Physical therapy	Manual repetitive pressure/ stimulation of specific site to reduce pain.	Useful for neuropathic pain from several etiologies. May be combined with medications.	Repeated sessions will be required.	Minimal. Quite safe.
Psychotherapy	Central suppression of pain	More useful with predominant associated symptoms	Effect rated as low to moderate.	Minimal. Quite safe.

Table 4 *(Interventional methods in the treatment of neuropathic pain.)*

DEVELOPMENT OF ALGORITHMS FOR MANAGEMNT OF NEUROPATHIC PAIN

The various drugs available for treating neuropathic pain and the frequent need to ascend the treatment ladder calls for the formulation and practice of algorithms. Bates et al43 have stated that a good algorithm should cover assessment, multidisciplinary conservative care, pharmacological management, and interventional therapies. They recommended six strata of treatment.

- Multidisciplinary conservative care and non-opioid medications (tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, gabapentanoids, topicals, and transdermal substances) as first line therapy
- Combination therapy (first line medications) and tramadol and tapentadol as second line
- Serotonin-specific reuptake inhibitors/anticonvulsants/NMDA antagonists and interventional therapies as third line
- Neurostimulation as a fourth line treatment
- Low-dose opioids (no greater than 90 morphine equivalent units) as fifth line
- Targeted drug delivery is the last-line therapy for patients with refractory pain.

They further opined that their proposed algorithm provides a useful visual guide to primary care and family physicians.

Based on practice limitations and evidence from available literature, we propose four treatment strata following initial evaluation using the four-pronged approach.

1. **First line:** Conservative treatment (Multidisciplinary approach) with use of low dose Gabapentinoids. Conservative care involves clinical psychotherapy, physiotherapy as well as occupational and social re-education. This requires multiple disciplines, no drug treatment and detailed evaluation. It should form the basis for treatment.45,46,47 Gabapentinoids (Gabapentin, pregabalin) are commonly available and affordable in our place of practice. They have shown good efficacy in the treatment of neuropathic pain. We recommend that these medications should be started in low dose along-side non-pharmacologic care. Both methods

have been shown to have remarkable reduction in pain intensity on the Visual analogue scale. 48,48,50.

2. **Second line:** High dose Gabapentinoids with or without tricyclic antidepressants (amitriptyline, nortriptyline, imipramine). Patient with persisting pain after initial thorough evaluation and on first line treatment for 4-8weeks can be commenced on the second line treatment. Finnerup et al. in their assessment of the efficacy of pregabalin reported a dose response, with a greater response seen in those taking 600 mg daily than in those taking 300 mg.49 Gilron et al. have shown that pregabalin combined with Nortriptyline give better response than pregabalin alone. Also, pregalin combined with imipramine have been reported to show a two-point drop in the numeric pain rating scale when compared with pregabalin alone.51
3. **Third line:** Opoids with or without first line medications. Both tramadol and Tapendadol have shown good efficacy and safety in the treatment of diabetic peripheral neuropathy, trigeminal neuralgia, and cancer-related neuropathic pain.52-54
4. **Fourth line:** interventional therapies. Epidural steroid injection has found common practice in the study location for radiculopathy pain that is unresponsive to medications. Local data to support its use is however lacking. The American Pain Society (APS) reported fair evidence and provided a weak recommendation for the use of epidural steroid injection in persistent radiculopathy due to herniated lumbar disc54. The neuropathic pain group have recommended that fluoroscopic guidance increases the precision, improves the efficacy, and reduces the need for frequent injections in patient with radiculopathic pain48. Transcortical stimulation and peripheral nerve stimulation are not common practices at the study location.

CONCLUSION

Neuropathic pain may arise from several etiologies and poses treatment challenges. The myriad of drugs and other treatment available necessitate the development of treatment protocols. Gabapentinoids remain the first line drugs in the treatment of neuropathic pain. Tricyclic antidepressants and strong opioids are commonly used as second line and third line treatment.

A four-pronged approach to patient evaluation and treatment ensures optimal assessment and good treatment of patients. A good review of the extent and peculiarities of the pain with a thorough assessment of the patient will ensure that a good plan is formulated with appropriate pills centered on meeting the patient's unique social and occupational needs while minimizing complications.

Non-pharmacological treatment options are reserved for chronic recalcitrant cases with associated psychiatric and other symptoms. Percutaneously placed self-controlled leads obviates the need for frequent clinic visits and provides for prolonged and flexible pain control.

Compliance with ethical standards

Acknowledgement

None.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

Ethical approval not needed

Statement of informed consent

Informed consent not needed.

Funding Support

The study was funded by the researchers

Authors' contributions

Both authors were involved in the conceptualization, planning and implementation of the study. Data collection team was headed by TED. All authors contributed to the interpretation of the results and read and approved the final manuscript.

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