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Review on Neuropathic Pain

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ABSTRACT

Neuropathic pain is defined as "Pain is observed as disease of the somatosensory nervous system." The cause of pain is very wide-ranging and may certainly be idiopathic**.** Two nerve damage classifications have been described and they are outlined. These are first line and second line. Neuropathic pain is generated by electrical hyperactivity of neurons along the pain pathways. The sensory pathway consists of at least three neurons, and lesions anywhere along the pathway can lead to neuropathic pain. A successful clinical management for neuropathic pain requires balancing the advantages and side effects of available drugs, lifestyle interventions, and treating the underlying cause if possible for the management of neuropathic pain requires various lines of treatment i.e first line and second line treatment which includes various types of drugs.

Keywords: Neuropathic pain, Hyperalgesia, Neuralgia, Neuronal Hyperactivity, Neurapraxia.

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INTRODUCTION

Neuropathic pain is defined as "Pain is observed as disease of the somatosensory nervous system." The cause of pain is very wide-ranging and may certainly be idiopathic. Neuropathic pain may often be doubted or identified through some of the classical descriptions of the pain that patients can give, such as: 'burning, shooting, tingling, electric shocks, sharp, nagging, walking on hot coals'[1-6] Nerve pain or neuropathic pain is originated due to damage to nerve or nerve disease. There may be sensitivity to the skin (allodynia) when light touch or clothes rubbing on the area can cause severe pain. In the area of pain there may be chances of numbness.[3] The hallmarks of neuropathic pain are chronic diseases like hyperalgesia and allodynia. Allodynia may be defined as pain resulting from a stimulus that ordinarily does not elicit a painful reaction (e.g., light touch). An increased sensitivity to normally painful stimuli is mainly called as Hyperalgesia. Within the area of injury immediately primary hyperalgesia is caused by sensitization of C-fibers. Secondary hyperalgesia, caused by sensitization of dorsal horn neurons, occurs in the undamaged area surrounding the injury[1,2] an injury to a nerve can result in a problematic with the muscle or during sensation is loss. In some people it can also cause pain. Two nerve damage classifications have been described and they are outlined. A first degree injury or neurapraxia will recuperate quickly within days after the injury or it may take up to 3 months. The recoveries are going to be complete with no lasting muscle or sensory drawback. A second degree injury or axonotmesis will also have complete recovery however the recovery will be much slower than a first degree injury[7]. Neuropathic pain is associated with increased drug prescriptions and visits to health care providers. The estimation of the incidence and prevalence of neuropathic pain has been difficult because of the lack of simple diagnostic criteria for large epidemiological surveys in the general population. Thus, the prevalence of neuropathic pain in the chronic pain population has mainly been estimated on the basis of studies conducted by specialized centers with a focus on specific conditions, such as post herpetic neuralgia, painful diabetic polyneuropathy, post-surgery neuropathic pain, multiple sclerosis, spinal cord injury, stroke and cancer.

The recent development of simple screening tools in the form of questionnaires has helped conduct several large epidemiological surveys in different countries (the United Kingdom, the United States, France and Brazil) and provided valuable new information on the general prevalence of neuropathic pain. In using screening tools, such as the Douleur Neuropathique 4 questions or the Leeds

Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, the prevalence of chronic pain with neuropathic characteristics has been estimated to be in the range of 7–10%.[8]

ANATOMY

Nerves are connected to your brain and spinal cord to the muscles and skin giving you movement and feeling. If there is an damage or injury to the nerve, then there will be an disturbance in the information being conveyed to the skin or muscles from the brain. In the arm and the legs there are larger nerves present the size of that nerves are like pencil and these nerves are made up of tens of thousands of nerve fibers and these are similar to the telephone cable and these nerve fibers are grouped togetherly in fascicles. Some nerves like the median and ulnar nerve in your arm have motor and sensory fascicles giving you movement and feeling to your hand.[8]

NEUROPATHIC PAIN MECHANISMS

Neuropathic pain is generated by electrical excitation of neurons between the pain pathways. The sensory pathway consists of at least three neurons, and lesions anywhere along the pathway can lead to neuropathic pain. Neuropathic pain (neural plasticity) caused by changes in the expression of neuronal ion channels and receptors, synaptic connectivity, and anatomy [1]

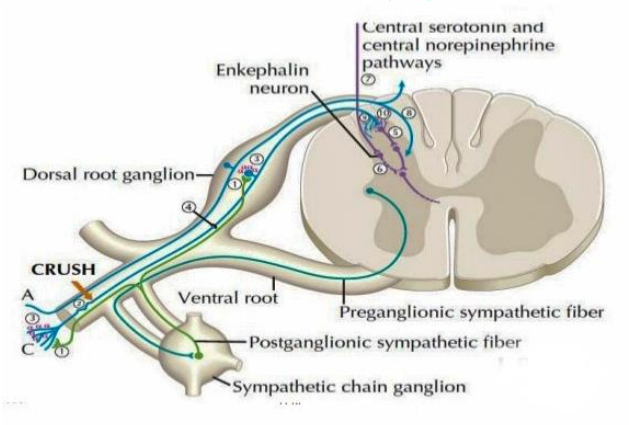


Figure 1: Mechanism of Neuropathic pain

1. Central Mechanisms in Neuropathic Pain

With repeated or sufficiently intense stimulation, spinal and supraspinalnociceptive pathways can become sensitized to subsequent stimuli. With persistent nociceptive input], like that seen in peripheral neuropathy, this central sensitization becomes maladaptive. IASP gives definition of central sensitization as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub threshold afferent input". At the synapse of second-order neurons, this increased responsiveness can involve changes in calcium permeability, receptor overexpression, and synapse location also promoting a chronic pain state are microglia, whose hyperactivation triggers the release of pain-promoting mediators . Another major contributor to ongoing pain is in supraspinal regions, the resulting misbalance between descending facilitation and inhibition. Maladaptive subcortical and cortical plasticity also contributes to painful interpretation of incoming signals, with the ultimate result promoting a chronic pain state.[6,12]

2. Peripheral Mechanisms in Neuropathic Pain

Chronic neuropathic pain through multiple routes is caused due to peripheral nerve damage. While the insult may be localized, the responses that lead to chronic pain are not. Peripheral terminals of pain-processing unmyelinated C fibers and thinly-myelinated Aδ fibers can spur the development of neuropathic pain after being affected by metabolic damage, toxins, medications, cytokines, and other inflammatory mediators resulting in fiber density changes and neuronal hyper excitability. Along the axon, injuries such as trauma, compression, hypoxia, inflammation, overstimulation, and chemical damage can induce fiber degeneration and alterations in channel expression and composition, in turn resulting in ectopic firing and faulty signal transmission. In response to axonal damage and its sequelae, satellite glia and autonomic neurons can incur pain-promoting states though alterations in their overall numbers, distribution, sprouting patterns, and channel expression. In the Dorsal root ganglia and trigeminal ganglia, primary afferent cell bodies can be exposed to chemical, mechanical, and excitotoxic damage, and in neuropathic pain states shows maladaptive changes in their membrane composition, synapse properties, and synapse location(s). The probability of peripheral nerve damage or its progression to neuropathic pain can also be increased by genetic predispositions and/or hereditary condition. The final result of the maladaptive mechanisms undergoing peripheral nerve damage is a state of improper signaling from the peripheral neuron to its second-order targets, with multi-factorial[1, 6]

MANAGEMENT AND TREATMENT OF NEUROPATHIC PAIN

The IASP (International Association of the Study of Pain) say's that neuropathic pain as "pain caused by a lesion or disease of the somatosensory system[1-5,7,10] National Institute for Health and Care Excellence (NICE) guidance1 recommends offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment, with switching between these drugs if pain relief is not obtained or the treatment not tolerated. A successful clinical management of pain requires balancing the advantages and side effects of available drugs, lifestyle interventions, and treating the underlying cause if possible. Possible comorbidities (anxiety, depression) need to be considered when choosing the best treatment for an individual patient.[10] To treat myofascial pain and neuropathic pain in clinical practice, frequency-specific microcurrent (FSM) has been used by numerous practitioners for more than 10 years in various specialties (MDs, DCs, NDs, PTs).[9]

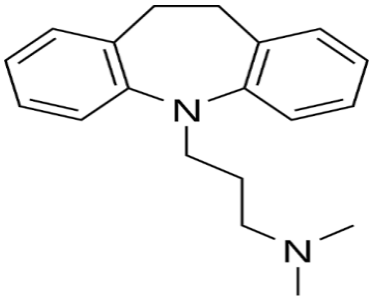
CLASSIFICATION OF DRUGS IN THE TREATMENT OF NEUROPATHIC PAIN

1. First-line drugs

- **Tricyclic Antidepressants**

The mechanism of action lies on blocking the reuptake of norepinephrine and serotonin to pre-synaptic level, limiting the hyperalgesia induced by N-methyl-D-aspartate agonists, anti-histamine action on the H1 and H2 receptors, blockage of sodium channels that allows the stabilization of neuronal peripheral level and modulation of neuronal hyperactivity at central level, blockage of alpha receptors that can eliminate pain maintained by noradrenergic stimulation and stimulation of μ-opioid receptors (despite the low affinity)]. The more relevant agents in this context are the tertiary amines such as amitriptyline and imipramine and the secondary amines such as nortriptyline (better tolerated). They may be used in the treatment of post herpetic neuralgia, painful diabetic neuropathy[1,3], The most common side effects are sedation, confusion, anxiety, anticholinergic effects such as dry mouth, increased intra ocular pressure,

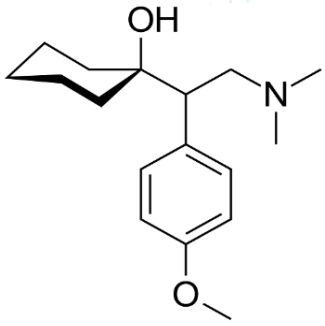
constipation, urinary retention, and orthostatic hypotension.[1,3,10,11] Treatment starts with low doses and should be titrated slowly until there is an adequate control of pain.



Imipramine

➢ **Serotonin-norepinephrine reuptake inhibitors**

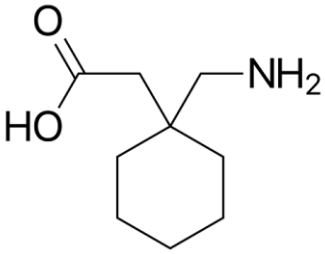
This agent are potent inhibitors of the reuptake serotonin and norepinephrine. Weak inhibitory action on dopamine reuptake is showed by both venlafaxine and duloxetine[1,5,10]. These drugs present favorable results in the treatment of neuropathic pain in multiple randomized controlled trial commonly in diabetic polyneuropathy, HIV neuropathy and oncologic neuropathic pain. The adverse effects include nausea, vomiting, constipation, somnolence, dry mouth, hyperhidrosis, loss of appetite weakness. Asthenia, fatigue, sedation, drowsiness and tremors. [1,5,10,13]



Venlafaxine

➢ **Calcium channel α2-δ ligands**

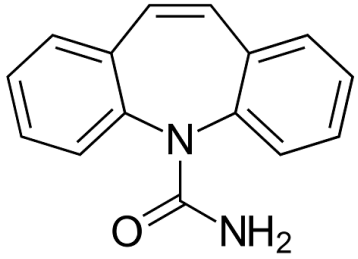
The union of the gabapentin and pregabalin to the subunit α2-δ of calcium channels voltage dependent decreases the release of glutamate, norepinephrine and substance P, decreasing the neuronal excitability. The adverse reactions that may limit their use include drowsiness, dizziness and peripheral edema, which can be reduced with gradual dose titration. Treatment starts with low doses and several weeks may be required to achieve the effective dose. Special precautions are necessary in patients with renal insufficiency. [13,14]



Gabapentin

➢ **Carbamazepine**

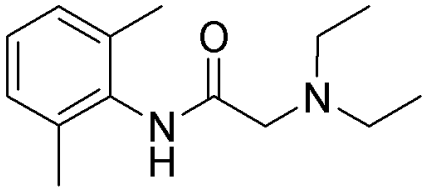
This drug is a classic antiepileptic, which blocks voltage-dependent sodium channels, inhibiting repetitive neuronal discharges and the propagation of synaptic excitatory impulses in depolarized neurons .Carbamazepine is the first-line to treat the trigeminal .Common side effects resulting from the administration of carbamazepine include drowsiness, ataxia, dizziness, nausea, fatigue and skin reactions Hematologic changes such as aplastic anemia, leukopenia and thrombocytopenia can also arise. Caution in advised in patients with impaired hepatic function. [13]



Carbamazepine

➢ **Lidocaine**

Lidocaine is a local anesthetic that causes a blockage of the movement of sodium ions to the interior of the membranes, causing a reversible blockade in the propagation of the pulse along the nerve fibers. Lidocaine 5% patches are the formulation most widely studied, constituting therapeutic option with proven effectiveness in peripheral neuropathies and allodynia, even in combination with other first-line drugs the adverse effects include skin rash, erythema, burning sensation and itching. [3]

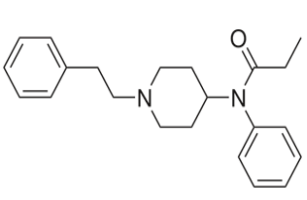


Lidocaine

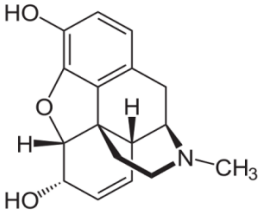
2. Second-line drugs

➢ **Opioids**

The benefit of opioids is constantly justified in the literature, in a variety of central and peripheral conditions such as post herpetic neuralgia, diabetic neuropathy and phantom limb neuropathy. The most common adverse reactions include constipation, nausea, vomiting, dizziness, drowsiness, headache and dry mouth. Provides the possibility of addiction and modification of the behavioral pattern. Opioids are regarded as second-line treatment due to their side effects, compared with tricyclic antidepressants or anticonvulsants. Furthermore, systematic study has not performed on the safety of long term treatment. Within this group, the drugs used are the fentanyl and morphine.[1,2,17,18]



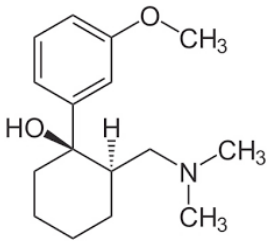
Fentanyl



Morphin

➢ **Tramadol**

Tramadol has a dual mechanism of pharmacological action which consists of agonist activity on the μ-receptors, although this affinity is much lower than the effect exerted by morphine. On the other hand, tramadol blocks synaptic reuptake of the amines, which results in similar effects to those of inhibitors of monoaminoxidase. The reuptake of norepinephrine and serotonin in central nervous system is inhibited by tramadol, preventing the transmission of the pain through the medulla. Patients with different types of neuropathy, such as diabetic polyneuropathy and post herpetic neuralgia felt less pain and improvement in quality of life following tramadol treatment. The risk of abuse of tramadol is also present with the opioids. The adverse reactions develop from tramadol administration are common to opioids. The administration of tramadol may introducing seizures in patients with history of seizures and their association with the serotoninergic drugs such as duloxetine, venlafaxine, fluoxetine, paroxetina among others, may increase the risk of serotonin syndrome. [13]

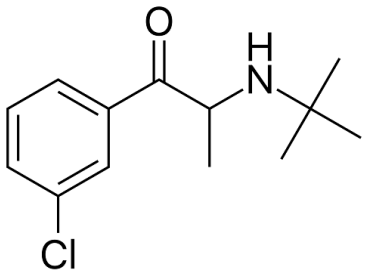


Tramadol

3. Third-line drugs

➢ **Antidepressants**

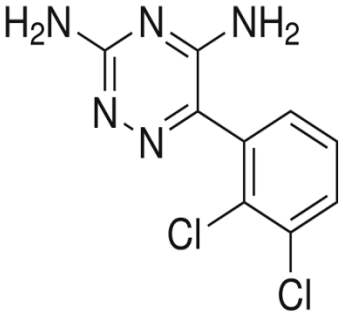
It a weak evidence that the use of serotonin reuptake inhibitors in the treatment of neuropathic pain, as released by a Cochrane review. Other antidepressants such as citalopram and paroxetine had positive effects in diabetic polyneuropathy, whereas fluoxetine did not put forward any benefit. With benefit in some neuropathic condition, Bupropion inhibits the reuptake of dopamine and norepinephrine. The adverse effects of serotonin reuptake inhibitors include nausea, vomiting, drowsiness, dizziness, agitation and tremors, with special caution in patients with risk of seizures, suicide and glaucoma. The adverse reactions given by Bupropion such as insomnia, anorexia, agitation, headaches and tinnitus. Clinical trials shows that citalopram, paroxetine and bupropion may constitute a therapeutic line when the tricyclic antidepressants and inhibitors of reuptake of serotonin and norepinephrine are not effective. [3]



Bupropion

➢ **Anticonvulsants**

To reduce the ectopic discharges in injured nerves the action of Antiepileptic drugs lies on stabilization of neuronal membrane, through various kind of mechanisms depending on the type of drug. In general, antiepileptic drugs facilitate inhibitory neurotransmission (GABA), reduce the excitatory neurotransmitter (glutamate) and modulate ionic channels existing in neuronal membrane (block sodium and calcium channels and activation of potassium channels. Lamotrigine stabilizes the neuronal membrane by acting on the voltage-gated sodium channels. In three studies it was observed that valproic acid obtained positive results for diabetic polyneuropathy and postherpetic neuralgia, however, negative results obtained from other randomized clinical study. In patients with diabetic polyneuropathy, three randomized controlled clinical trials of oxcarbazepine were published, one of which was positive and the other two negative. Carbamazepine is the first-line treatment of trigeminal neuralgia, but in other clinical conditions evidence is limited. These drugs are therapeutic options when patients do not respond to first or second-line treatment. [1,3]



Lamotrigine

CONCLUSION

The available data clearly indicates that clinical management on Neuropathic pain treatment is varying according to line of a drug treated. The available drug treatment for neuropathic pain includes first, second and third line drugs. It is shown that Neuropathic pain is generated by electrical excitation of neurons along with the pain pathways. A successful clinical management for neuropathic pain requires balancing the advantages and side effects of available drugs, lifestyle interventions, and treating the undergoing cause if possible for the management of neuropathic pain requires various line of treatment i.e first line and second line treatment which includes various types of drugs

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