



NEUROPATHIC PAIN-AN ENERVATING DISEASE

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Abstract: Neuropathic pain is a chronic pain that worsens the quality of life of the patient occurring as a result of peripheral or central nerve injury. It is characterized by spontaneous ongoing and evoked increased pain sensation upon contact with noxious or non-noxious stimuli. The management of neuropathic pain involves interdisciplinary approach and mainly focuses on pharmacological treatment. The drugs found effective in management of neuropathic pain are antiepileptics, antidepressants, opioid analgesics, NSAID'S (Non-Steroidal Anti Inflammatory Drugs), local anesthetics. Combination therapy is generally required in patients with severe neuropathic pain.

Keywords: Antidepressants, Antiepileptic, Local anesthetics, NSAID'S, Neuropathic pain, Opioid analgesics

INTRODUCTION

Neuropathic pain arises due to injury to single nerve or more than one nerve. The International Association for the Study of Pain (IASP) defines neuropathic pain as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system"^[1]. There are multiple etiologic causes of neuropathic pain which include infectious agents, trauma, metabolic diseases, neurodegenerative diseases and many others. The physiologic pain arises from the activation of peripheral nociceptors in injured tissue whereas neuropathic pain arises from abnormal physiology of central and peripheral nervous system and may be unrelated to ongoing tissue damage or inflammation^[2]. The pathophysiology of neuropathic pain is complex as it involves numerous inflammatory mediators and neurotransmitters. It has been observed that some patients may not show any signs of nerve injury but have severe neuropathic pain whereas some may experience no pain though significant signs of nerve injury are present.

Although this type of pain can occur at any age but it is more common with older people. Neuropathic pain can be a combination of many sensory symptoms such as paresthesias (numbness or tingling), dysesthesias (electric shock phenomenon), hyperesthesia (increased sensitivity to mild painful stimuli), hyperalgesia (increased sensitivity to normally painful stimuli), hyperpathia (pain produced by subthreshold stimuli), spontaneous pain and allodynia (pain produced by normally non painful stimuli). The neuropathic pain can be stimulus evoked, spontaneous, or can be a combination of both. Neuropathic pain is difficult to treat mainly because of

its resistance to medications and adverse effects associated with medication^[3].

Types of Neuropathic Pain:

1) Peripheral neuropathic pain: This is a result of damage to peripheral nerves of the body. Peripheral nerves run from brain and spinal cord to arms, hands and lower extremities, so, peripheral neuropathy can occur in any of these parts of the body. It mainly results from diabetes, HIV/antiretroviral drugs, heavy metal toxicity, nutritional deficiency, trauma etc^[4]. It is of following types:

a) Postherpetic neuralgia: It's a painful condition which occurs due to nerve damage caused by Varicella zoster virus infection. It generally occurs on chest and back but can also occur on other body parts. It may continue from months to years even after skin has healed^[4].

b) Complex regional pain syndrome (CRPS): It is a newer term for reflex sympathetic dystrophy (RSD) and causalgia. In this condition there is severe and chronic pain and generally occurs in hand, foot, face. Some of its symptoms are swelling, itching, burning, shooting pain but its exact cause is still unknown^[5].

c) Peripheral diabetic neuropathy: It is a consequence of diabetes mellitus and comprises of the disorders of peripheral nerve. Generally it is categorized as focal or diffused^[6].

d) Carpel Tunnel Syndrome: This is a common disorder involving median nerve. It generally occurs due to compression or injury to median nerve. The symptoms include numbness, tingling and pain in hand

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or wrist and symptoms may get relieved by shaking or rubbing hands ^[7].

e) Trigeminal neuralgia: Trigeminal Neuralgia is a condition that affects fifth cranial nerve, called the trigeminal nerve. It is characterized by a sudden brief, severe, electric shock-like or stabbing pain typically felt on one side of your face, provoked by light touch ^[8].

f) Phantom limb syndrome: It is commonly followed by amputation. The amputation is followed by a feeling that the amputated body part is still present. Both central and peripheral factors contribute to it and it may get triggered by psychological factors ^[9].

g) HIV sensory neuropathy: Pain associated with HIV is common and could be due to symmetrical sensory polyneuropathy or as a result of antiretroviral therapy ^[10].

2) Central neuropathic pain: This occurs as the area of the brain and spinal cord that senses the pain is injured. It may result chronic pain in several body parts. It is of following types ^[11].

a) Central post stroke pain: This type of pain occurs after stroke and also known as thalamic syndrome; because it is believed that it occurs in people who had a stroke affecting the thalamus.

b) HIV myelopathy: HIV patients may get myelopathy without any visible neuropsychological symptoms of HIV encephalopathy. It is accompanied by immunosuppression ^[12].

c) Parkinson disease pain: Although its neurophysiology is still not well understood and is generally overlooked symptom in Parkinson disease. The symptoms include burning, tingling and pricking sensations ^[13].

d) Spinal cord disease pain: It is very common with patients of spinal cord injury and can occur in all parts of body. The feelings generally observed are stabbing, tingling and burning ^[14].

e) Syringomyelia: It is the dilatation of the central canal of the spinal cord or formation of abnormal tubular cavities in spinal cord. Symptoms include pain and weakness in back, shoulders, legs, arms and loss of sensation ^[15].

3) Cancer associated neuropathic pain: Cancer and its treatment causes pain. Mainly the causes are pain from medical tests, tumor, chemotherapy and radiation therapy. It is mainly of following types. ^[16]

a) Chemotherapy induced pain- Chemotherapy-induced peripheral neuropathy is a major dose limiting side effect of many commonly used chemotherapeutic agents, including platinum drugs, taxanes, epipodophyllo toxins and vinca alkaloids.

b) Post mastectomy pain- Mastectomy is followed by a chronic neuropathic pain and is generally accompanied by burning or constricting discomfort in anterior chest wall and medial arm. ^[17]

c) Neuropathy secondary to tumor infiltration or nerve compression- This condition arises when the lymphoma cells directly compresses its nearby peripheral nerve.

Pathophysiological mechanism of neuropathic pain ^[4,18]

The pathophysiological mechanism of neuropathic pain is complex and difficult to understand. The major physiological pathways involved in neuropathic pain are

1. Peripheral /Nociceptor sensitization
2. Central sensitization
3. Sympathetic activation
4. Disinhibition

Peripheral/Nociceptor sensitization – Nociceptors are primary afferent neurons which respond to mechanical, chemical, thermal noxious stimuli. Two types of nociceptor fibers namely c- fibers and A δ fibers are involved in transmission of pain from sites to spinal cord and are modulated by various exogenous or endogenous peptides namely prostaglandins, calcitonin, bradykinin, substance P, neurotransmitters (excitatory amino acids, neurokinin, serotonin, noradrenaline, histamine) and growth factors. After axonal damage and degradation of myelin sheath and macrophages as well as other immune cells (neutrophils and T cells) infiltrate. This leads to the release of proinflammatory cytokines (interleukins, Tumor necrosis factor α), inflammatory mediators (bradykinin and prostaglandin) and growth factors (nerve growth factor) these changes cause allodynia and hyperalgesia.

2. Central sensitization-This is the abnormal hyperexcitability of centrally located nociceptor neurons. This is supposed to start in spinal cord after peripheral injury and release of neurotransmitters (glutamate, GABA and calcitonin) and tachykinins (neuropeptides substance P and neurokinins). These substances bind to neural receptors and activate N – methyl D- aspartate (NMDA) receptors which increase intracellular calcium levels through N type of calcium channels. This triggers series of biochemical reactions in neurons of dorsal horn. The threshold for activation gets decreased and the response to the stimulus gets

increased as well as larger surface area of neuron is available for reception of stimulus. These changes result in hypersensitivity and hyper excitability of spinal neurons.

3. Sympathetic activation: This process is generally related to complex regional pain syndrome (CRPS) though its principles are also shared by other types of neuropathic pain which are postherpetic neuropathy, phantom limb syndrome, traumatic neuropathy. There are direct and indirect mechanisms which contribute to it. The increase in sympathetically mediated vasomotor activity leads to altered microcirculation, impaired oxygen and nutrition this gives the protons to act as potent nociceptive stimuli.

4. Disinhibition: This occurs when the control mechanisms along inhibitory pathways disappear or are suppressed. This further triggers abnormal excitability in central neurons. It is believed that central sensitization and disinhibition together with certain peripheral changes lead to allodynia. In allodynia the pain is evoked by a non-painful stimulus such as clothes rubbing against skin.

Pharmacological treatment of neuropathic pain:^[18]

The pharmacological treatment of neuropathic pain is started according to the patient needs and preferences. The drugs mainly used in neuropathic pain include antidepressants, anticonvulsants, local anesthetics, opioid analgesics. Table.1 summarizes the prescribing information for each of the following medications including their mechanism of action, starting dose and major side effects.

Antidepressants:

Antidepressants don't aim at preventing peripheral pain but decrease TNF and PGE2 activity. The peripheral analgesic action of TCA's is shown by blockade of peripheral noradrenergic receptors and they are also considered in first line treatment. Antidepressants employed in neuropathic pain are TCA's (amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline), SNRI's (duloxetine, venlafaxine). They are effective in all kinds of neuropathic pain especially in peripheral neuropathic pain. Their analgesic action exhibited by them is mainly due to NA and serotonin reuptake inhibition.

Anticonvulsants:

The mechanism of action of anticonvulsants includes blockade of voltage-gated sodium channels, blockade of voltage-gated calcium channels, direct or indirect enhancement of inhibitory GABAergic neurotransmission, and inhibition of glutamatergic neurotransmission. The result is that they reduce the neuronal hyper excitability which helps prevent seizures in epilepsy and it is known that neuropathic

pain is also characterized by neuronal hyper excitability thus anticonvulsants bring relief in neuropathic pain. They are extensively used in treatment of neuropathic pain but they cause side effects such as ataxia, drowsiness, dizziness. They are found effective in postherpetic neuralgia, diabetic neuropathy. The anticonvulsants mainly used are (Gabapentin, pregabalin, lacosamide, lamotrigine).

Table.1: Showing different drugs their mechanism of action with starting dose and their major side effects

Drug	Mechanism Of Action	Starting Dose	Major Side-effects ^[19]
TCA(Nortriptyline, Desipramine)	Inhibits reuptake of serotonin, NE, blocks Na ⁺ channels, anticholinergic	25 mg OD 150mg OD	Sedation, anticholinergic effects
SNRI(duloxetine)	Inhibition of both serotonin and NE	30 mg OD	Nausea
Anticonvulsants (Gabapentin)	Decreases release of glutamate, norepinephrine, and substance P, with ligands on α -2- δ subunit of voltage gated calcium channel	100-300 mg once to three times daily/1200 mg three times daily	Sedation, dizziness, peripheral oedema
Local Anesthetic (Lidocaine Patch/iv)	Blockade of sodium channels	1-3 Patches,iv 1-5 mg/kg over 30 min	Local erythema, Rash
(Opioid analgesics) Morphine, oxycodone	μ -receptor agonism (oxycodone also causes κ -receptor antagonism)	Nausea/vomiting, constipation, dizziness	10-15mg morphine every 4 h or as needed (equianalgesic doses should be used for other Opioids)

Local anesthetics:

The local anesthetics mainly used in neuropathic pain are lidocaine, lignocaine in concentration 5% - 10%. They are found very effective in postherpetic neuralgia and cause no significant side effects. As they have local action so they are indicated in patients with localized peripheral neuropathy but not for patients with central neuropathy. They are mainly used to subside pain and improve the quality of life of patient.

Opioid analgesics:

It is known that Opioids act primarily as agonists at endogenous opioid receptors. The various opioid receptors include delta, kappa, and mu, and mu receptor is known to play the maximum role in analgesic action. Opioids do not act by altering pain threshold, or transduction. They change the way of perceived pain in the afferent pathway of the central nervous system. It is believed that excessive activation of NMDA receptors in the central nervous system by glutamate is largely responsible for neuropathic pain thus simple analgesics are generally found ineffective

in controlling neuropathic pain. So, opioid analgesics are used such as morphine, tramadol, fentanyl, codeine, oxycodone, methadone, buprenorphine. They are effective in both peripheral and central neuropathic pain as some of them also act by blocking the reuptake of norepinephrine.

NSAID's:

NSAID's are not effective in treatment of neuropathic pain. Paracetamol has been found effective in controlling allodynia. They are combined with opioid analgesics to gain better control on pain [17, 19]

Combination Therapy: [20]

Combination therapy is prescribed in case of failure of first line or second line treatment. Combination therapy such as an antidepressant with an anti-epileptic, or an antidepressant or anti-epileptic with an opioid analgesic, is commonly followed for neuropathic pain. While following combination therapy comparison between various combinations should be made and any marked improvement in disease, major or minor adverse effects should be closely monitored. Combination therapy is generally adopted to gain maximum relief from symptoms. Some popular and highly beneficial combinations are gabapentin with morphine or pregabalin with morphine. Combination therapy gives additive benefits and provides better control over the pain and other unpleasant symptoms associated with the disease.

Management of Neuropathic pain: [21]

Successful treatment of neuropathic pain starts with appropriate diagnosis and assessment of pain though the diagnosis of neuropathic pain is often challenging as some symptoms of neuropathic pain may also be associated to other types of pain. Attention should also be paid on other adverse effects of neuropathic pain such as depression, sleep disturbances, anxiety or any other affect on quality of life of patient. Other important parameters in management of neuropathic pain include patient education and support. The effect of the treatment is assessed by repeated evaluation of the symptoms and their intensity.

First line Treatment: The drugs which can be used for first line treatment include TCAs, SNRIs and anticonvulsants but the most preferred drugs are gabapentin and pregabalin. Pregabalin has better bioavailability than gabapentin so it has superseded gabapentin. Starting dose of pregabalin should be 150 mg and up titration can be done up to maximum tolerated dose but should not exceed 600mg per day, Amitriptyline- starting dose should be 10 mg and an up escalation can be done upto 75 mg per day.

Second line treatment: If first line drugs treatments are not effective in controlling the symptoms; then combination of first line drugs can be used such as anticonvulsants with antidepressants etc.

Third line treatment: If second line drugs treatment did not approach satisfactory results then opioid analgesics or topical lidocaine can be added to the second line drugs treatment. They have demonstrated satisfactory results and they have also been used as the first line treatment in cases where prompt relief from pain is required.

Treatment in elderly:

With advancing age there are more chances of developing neuropathic pain thus elderly patients are at higher risk. Effective assessment and treatment of neuropathic pain is difficult in elderly patients. Assessing pain in the elderly patients is often associated with significant obstacles. Older adults frequently fail to report pain because they may view that it is an expected part of old age or because they are fearful that it may lead to more diagnostic testing or added medication. Treatment of neuropathic pain in elderly patients requires lot of skills as they have altered pharmacokinetics and pharmacodynamics which affects metabolism or clearance of drugs thus the dose of drugs should be titrated cautiously. The starting dose should be low and escalation of dose should also be slow, and the dose should also be adjusted according to liver and renal function. There should be close monitoring of side effects in elderly patients.

Recent Advances in Pharmacological Treatment of Neuropathic Pain:

Botulinum toxin type A (BTX-A) given intradermally is another novel topical treatment approach that has been shown to relieve focal painful neuropathy [22], and painful diabetic polyneuropathy in two RCTs (Randomized Control Trial). After multiple intradermal injections pain relief lasted for 12 weeks. A phase 2 RCT found that the neuronal nicotinic acetylcholine receptor agonist ABT-594 significantly reduced pain intensity compared with placebo in patients with painful diabetic neuropathy [23].

CONCLUSION

As neuropathic pain is one of the most common condition that are encountered in general medical practices in today's scenario. There are multiple factors and pharmacological treatment options for neuropathic pain but counseling on stress management and pain management programs sometimes may help people with chronic neuropathic pain.

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