WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 785-800. Review Article ISSN 2277– 7105

PHARMACOLOGICAL REVIEW ON NEUROPATHIC PAIN MANAGEMENT

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Article Received on
02 March 2015,

Revised on 25 March 2015,
Accepted on 15 April 2015

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ABSTRACT

Neuropathic pain is mainly generated by disorders of the peripheral and central nervous system, which can be particularly severe and disabling. Prevalence estimates indicate that majority of the population in the developed world suffer from Neuropathic pain. Clinically, Neuropathic pain is characterized by spontaneous ongoing or shooting pain responses after noxious or non-noxious stimuli and the type of pain evoke is hyperalgesia and allodynia. Identification of various pathophysiological mechanisms, such as central and peripheral sensitization and clinical assessment of signs and symptoms can help to determine the better targets in management of specific neuropathic pain disorders. Neuropathic pain responds poorly to conventional analgesics, thus management of neuropathic pain conditions based on the best scientific evidence in the literature should be followed. Treatment must be individualized for each patient which should be mechanism based, efficacy of drug, side-effect profile and drug accessibility, including cost. The aim of this review is to give a brief knowledge on target based pathophysiological mechanisms and treatment strategies of Neuropathic pain.

KEYWORDS: Neuropathic Pain, Hyperalgesia, Allodynia, Central and Peripheral sensitization.

INTRODUCTION

Pain is an unpleasant feeling often caused by intense aur damaging stimuli .Pain can be classified broadly as two types i.e. Nociceptive and Neuropathic pain. Nociceptive pain is protective and is a normal response to tissue injury, serving to warn of the presence of injury.

There is also sensitization of peripheral nociceptors and central nervous system changes, which protect the damaged area by avoiding contact.[1, 2]

Neuropathic pain is a pathologic or maladaptive pain, which results from damage to the nervous system, producing pain in the absence of stimulation of nociceptors or inappropriate response to stimulation of nociceptors.[3] Nociceptive and neuropathic pain are not synonymous with acute and chronic pain. For instance, rheumatoid arthritis is a chronic pain, which is nociceptive pain. A herniated disc can cause acute sciatic pain, which is neuropathic. Neuropathic pain is a complex, chronic pain state that usually is accompanied by tissue injury.[4] With neuropathic pain, the nerve fibers themselves may be damaged, dysfunctional or injured. This damaged nerve fibers send incorrect signals to other pain centers. The impact of nerve fiber injury includes a change in nerves function both at the site of injury and areas around the injury. Chronic pain are heterogeneous conditions that cannot be explained by a single etiology or specific lesion. Chronic neuropathic pain is common in clinical practice, and it greatly impairs the quality of life of patients. Neuropathic pain is a consequence of nerve injury characterized by the presence of exaggerated responses to painful stimuli (hyperalgesia), pain response to normally innocuous stimuli (allodynia) and spontaneous pain.These abnormal pain sensations have been associated with various complex physiological changes in the peripheral and central nervous system.[4,5]

SIGNS AND SYMPTOMS: Neuropathic pain can manifest itself as either without a stimulus (stimulus-independent pain) and/ or as pain hypersensitivity elicited after a stimulus (stimulus-evoked pain). Stimulus-independent pain includes symptoms described by the patient such as (a) continuous, burning pain (b) intermittent shooting, lancinating pain (c) some dysaesthesias. Conversely, stimulus-evoked pain describes signs the physician induces after mechanical, thermal or chemical stimulation, and usually involves hyperalgesia or allodynia. Normally, non-noxious stimuli such as brushing against clothing, or a puff of air might now elicit pain (tactile allodynia), however stimuli with sharp features, such as a stiff bristle, or the rough surface of sandpaper, will elicit considerable pain that outlasts the stimulus (mechanical hyperalgesia).[6,7]

CAUSES OF NEUROPATHIC PAIN: Neuropathic pain often seems to have no obvious cause; but some common cause of neuropathic pain include:- Excessive Alcoholism, Amputation, Back-leg and hip problems, Diabetes, Facial nerve problems, HIV infection or

AIDS, Multiple sclerosis Shingles, Spine surgery.[5,6,7] For the majority of Neuropathic Pain sufferers, the pain will persist lifelong. Co-morbidities (depression,impaired quality of life, employment, domestic issues etc) are very common.

TABLE.1: TYYPES OF NEUROPATHIC PAIN

Peripheral Neuropathic Pain:
Painful Polyneuropathy/Diabetic Peripheral Neuropathy
Radiculopathy
Trigeminal Neuropathy
Post-Herpetic Neuralgia
Post-Surgical/Phantom Limb
Chemotherapy-induced polyneuropathy
HIV sensory neuropathy
Iatrogenic neuralgias (e.g., postmastectomy pain or post-thoracotomy pain)
Complex Regional Pain Syndrome
Central Neuropathic Pain:
Post-stroke Pain
Multiple Sclerosis-related pain
Compressive myelopathy from spinal stenosis
HIV myelopathy

MECHANISMS INVOLVED IN PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Most of the current ideas regarding the pathophysiology of neuropathic pain originated from experimental work in animal models. These studies delineated a series of partially independent pathophysiological mechanisms. Recent research studies indicate that both peripheral and central mechanisms have been involved in pathogenesis of neuropathic pain.[8]

Peripheral Sensitization: Peripheral nerve injury is associated with a local inflammatory reaction of the nerve trunk and the released inflammatory mediators sensitize the axotomized nerve fibres. Following a peripheral nerve injury (eg. crush, stretch, or axotomy) sensitization occurs which is characterized by spontaneous activity by the neuron, a lowered threshold for activation and increased response to a given stimulus.[8,9] It is well reported that peripheral or perineural inflammation is measured by plasma extravasation or increased capillary permeability which causes inflammatory cell infiltrate leading to the release of various pronociceptive and pro-inflammatory mediators .Most importantly, neurogenic inflammation has also been reported in experimental models of nerve injury that implicates increased capillary permeability, leading to plasma leakage of proinflammatory and pronociceptive mediators at the local as well as adjacent sites to tissue injury . This is accompanied by enhanced release of substance P(SP) and calcitonin gene-related peptide (CGRP) in the

control of vascular tone following nerve injury. Thus, the pro-inflammatory mediators might be involved in the development and maintenance of neuropathic hyperalgesia. The Prostaglandins (PGs) including PGE2 and PGI2 (also known as prostacyclin) are also rapidly produced following tissue injury and are major contributors to peripheral sensitization. It has been reported that COX inhibitors, which inhibit the production of PGs, attenuate the thermal and mechanical hyperalgesia in animal model of neuropathic pain.[10,11]

Central Sensitization: Following a peripheral nerve injury, anatomical and neuro-chemical changes can occur within the central nervous system (CNS) that can persist long after the injury has healed. This "CNS plasticity" may play an important role in the evolution of chronic, neuropathic pain. As is the case in the periphery, sensitization of neurons can occur within the dorsal horn following peripheral tissue damage and this is characterized by an increased spontaneous activity of the dorsal horn neurons, a decreased threshold and an increased responsivity to afferent input, and cell death in the spinal dorsal horn.[10,11,12] Evidence suggests that excessive nociceptive input to the dorsal horn can have excitotoxic consequences resulting in the death of inhibitory interneurons. This inhibition may contribute to spinal hyper-excitability .This hyperexcitability is manifested by increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields and spread of spinal hyperexcitability to other segments. This so-called central sensitization is initiated and maintained by activity in pathologically sensitized C-fibers. These fibers sensitize spinal cord dorsal horn neurons by releasing glutamate, which acts on post synaptic N-methyl- D-aspartate (NMDA) receptors, and the neuropeptide substance P.

On cellular level, the central nervous system plastic changes appear to be associated with enhanced neurotransmission via the NMDA receptor. Under the appropriate conditions, C-fiber stimulation can activate dorsal horn inter-neurons, causing them to release excitatory amino acids (e.g. aspartate and glutamate), which will excite wide dynamic range (WDR) neurons via the NMDA receptor.[13, 14]

Inflammation In Neuropathic Pain: Inflammation is a body defensive mechanism against injury to body tissues. After nerve lesion, activated macrophages infiltrate from endoneural blood vessels into the nerve and DRG, releasing proinflammatory CYTOKINES, in particular TNF-α.These mediators induce ectopic activity in both injured and adjacent uninjured primary afferent nociceptors at the lesion site. In patients with inflammatory neuropathies—

such as vasculitic neuropathies or HIV neuropathy—deep proximal aching and paroxysmal pain are characteristic phenomena. COX2 and proinflammatory cytokines were found to be up regulated in nerve biopsy specimens of these patients.[14, 15]

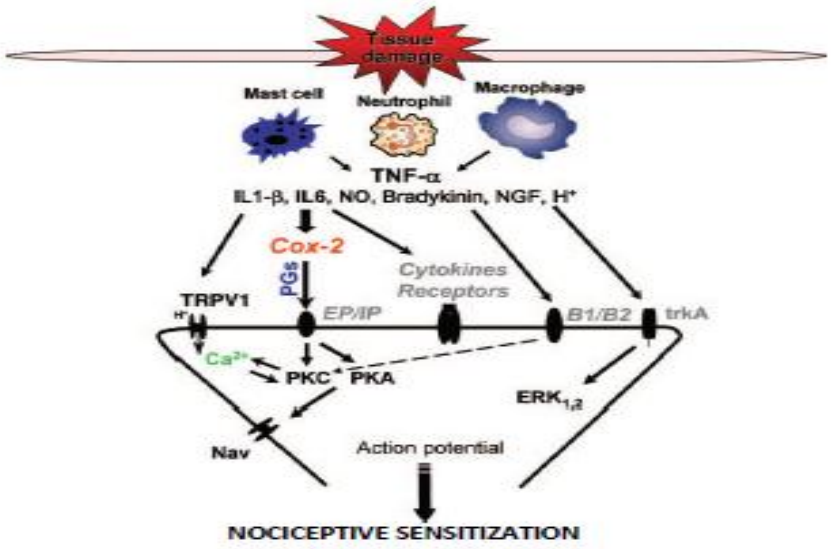

Fig.1. VARIOUS MEDIATORS IN NEUROPATHIC PAIN

Target Based Mechanisms Of Neuropathic Pain

Neuropathic pain is often associated with different mechanisms whose symptoms vary from patient to patient. Thus by knowing the various molecular targets for these mechanisms, current drug therapy for neuropathic pain can be well established. These targets include, modulation of glial cells including purinergic receptor, NMDA and GABA Receptors, Vanilloid receptors, Voltage gated calcium channels (VGCC) etc.

a) **Modulation Of Miccroglia**

Microglia play a crucial role in the maintenance of neuronal homeostasis in the central nervous system, and microglia production of immune factors is believed to play an important role in nociceptive transmission. Glial cells represent 70% of the cells in the central nervous system (CNS) under normal conditions, and microglia represent 5–10% of glia.[16;17] Microglial cells have a small soma bearing thin and branched processes under normal conditions. The most characteristic feature of microglia is their rapid activation in the CNS in response to pathological events, including trauma, ischemia, inflammation, hypoxia, neurodegeneration and viral or bacterial infection.[17,18] There is an increasing evidence that uncontrolled activation of microglial cells under neuropathic pain conditions induces the release of proinflammatory cytokines (interleukin – IL-1_,IL-6, tumor necrosis factor – TNF), complement components (C1q, C3, C4, C5, C5a) and other substances that facilitate

pain transmission. Thus, inhibiting activation of glial cells and neuroimmune cells represents a novel approach for controlling neuropathic pain.[19, 20]

Regulation of P2X4 Receptor expression in microglia: P2X4 receptors (P2X4Rs) are purinergic receptors which are upregulated after activation of spinal microglial cells. The important role of P2X4Rs in neuropathic pain is establishment of tactile allodynia after peripheral nerve injury. Importantly, inhibiting the function of over expression of P2X4Rs and P2X4R-regulating molecules suppresses the aberrant excitability of dorsal horn neurons and neuropathic pain.[21]

b) **NMDA and GABA receptors**

Excitatory glutamatergic receptors are implicated in synaptic plasticity and excitotoxicity involved in the development of NP syndromes. N-methyl-d-aspartate (NMDA) receptors are permeable to monovalent ions and calcium and blocked by extracellular magnesium. Glycine also functions as a coagonist with glutamate in activating this channel. Direct protein kinase A (PKA) mediated phosphorylation of NMDA receptors is implicated in hyperalgesia and allodynia in central but not peripheral NP syndromes.[22] Unfortunately, attempts at developing an NMDA antagonist that performs an analgesic function in alleviating NP in human subjects has been slow. One possible reason for this is the presence of NMDA receptors throughout the CNS, the non-specific activation of which can produces psychotropic effects.

The GABAergic system is a vital component of nociceptive sensory processing and modulation of its function commonly leads to the development of NP states. GABA receptors are found in both pre and post synaptic sites and function as ligand-gated chloride channels. Normal GABA receptor function is critically dependent on the activity of intracellular Cl- concentration. Both channel types, A and B, have been implicated in NP syndromes and hyperexcitability. Loss of GABA inhibition also can produce NP. The evidence that hypofunction of GABAergic tone contributes to central NP. Pharmacological treatments that enhance GABAergic function attenuates central neuropathic pain behavior and neuronal hyperexcitability.[23]

c) **Vanilloid Receptors**

The Transient receptor potential vanilloid 1 (TRPV1) is a calcium- permeable channel expressed mainly on nociceptive neurons. The TRPV1 can be activated by a number of

stimuli, including heat and protons as well as numerous chemical agents, including capsaicin.[24] The TRPV1 appears to play an important role in the development of several painful conditions including inflammatory and neuropathic pain. Moreover it has been documented that during chronic alcoholism TRPV1 receptor mediated action get sensitized and contribute in neuropathic pain.[25]

Endogenous TRPV1 agonists i.e capsaicin and modulators such as protons, anandamide and products of the arachidonic acid metabolism can be released or up-regulated by inflammation and tissue damage. Preclinically, disruption of the TRPV1 gene suggests that TRPV1 receptors are essential for inflammatory hyperalgesia. These and other published studies have suggested a potential therapeutic utility of TRPV1 antagonists in pain. Hence TRPV1 is an important target for developing novel analgesic.[26, 27]

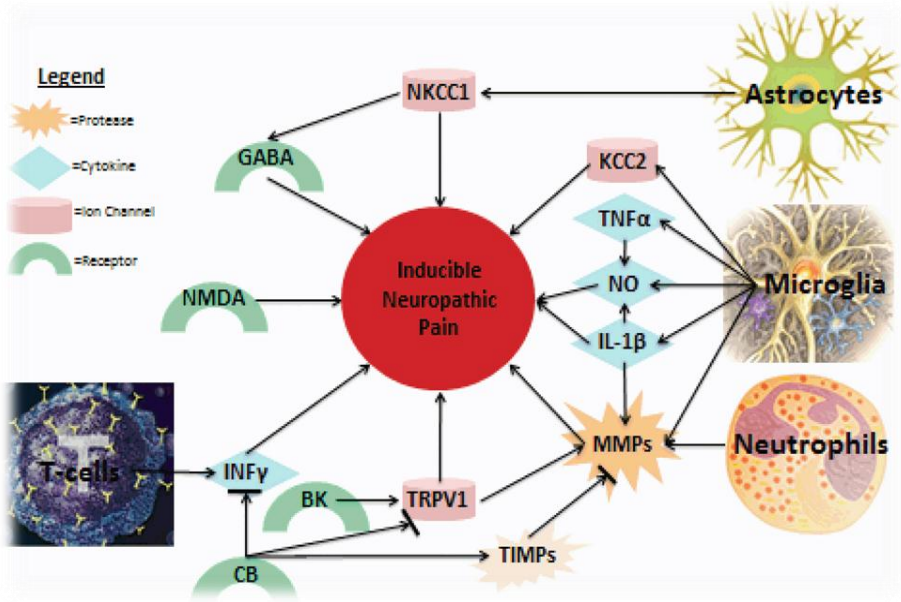

Fig.2. SUMMARY OF VARIOUS TARGETS AND PROBABLE MECHANISM FOR NEUROPATHIC PAIN.

Matrix Metalloproteases (MMPs), Matrix Metalloproteases Tissue Inhibitors (TIMPs), Na+-K+-Cl- cotransporter isoform 1 (NKCC1), K+-Cl- contransporter isoform 2 (KCC2), Cannabinoid receptors (CB), Transient Receptor Potential Vanilloid 1 (TRPV1) etc.

d) Voltage Gated Calcium Channels

Calcium entry into cells through the excitation of VGCCs is involved in electrical excitability, repetitive firing patterns, excitation–contraction coupling and gene expression.

VGCC-mediated calcium entry is the initial trigger for the release of neurotransmitters at presynaptic nerve terminals. Due to their essential role in calcium signaling, VGCCs are important targets for the treatment of pain, stroke, epilepsy, migraine and hypertension.[28]

e) **Other Targets Involves**

Matrix metalloproteases: (MMPs) are a family of zinc-dependent extracellular proteases that are involved in the digestion of extracellular matrix components as well as some cell surface proteins like adhesion molecules, receptors, growth factors and cytokines. In injured tissue, MMP-2 and MMP-9 play a key role in the inflammatory response by modulating the development of neuropathic pain. Matrix Metalloprotease Tissue Inhibitor (TIMPs) inhibits the activity of MMPs which involves binding of the N-terminal amino acid of the TIMP protein and the zinc ion coordinated to the MMP. This interaction leads to the conformational changes that prevent MMP proteolytic activity which suggest TIMPs induction may have neuroprotective activity of CNS insult. Interestingly, elevated levels of TIMP expression, induced through activation of cannabinoid receptors was shown to reduce cancer cell invasiveness. This suggests that cannabinoids may provide a therapeutic approach to the attenuation of Neuropathic pain development.[27,29, 30]

Nitric Oxide (NO) and Reactive Oxygen Species (ROS)

Reactive oxygen species such as NO and superoxide play important roles in inflammatory and immune responses, including defense mechanisms against invading microbes. They are released by a number of cell types, including neutrophils and macrophages as well as astrocytes and microglia . NO is a diffusible free radical that is synthesized by three distinct NO synthases (NOS), neuronal and endothelial forms (nNOS and eNOS) are constitutive, while the inducible form (iNOS) is upregulated in immune cells. Once released, NO can react with superoxide radicals to form peroxynitrite, which is toxic and may cause tissue damage.

NO play important role in nociception . It causes pain when injected into the skin of human subjects and contributes to peripheral hyperalgesia in the skin and joints, probably by contributing to PGE2-induced sensitization of primary afferents . Treatment with a non-specific NOS inhibitor (L-NAME) alleviates hyperalgesia and blockes ectopic mechanosensitivity of injured A-fibers.[31]

TREATMENT OF NEUROPATHIC PAIN

Current drug treatments are focused on dampening the neuronal input to consciousness by suppressing axonal function (for example sodium channel blockade) or interfering with neurotransmission (blockade of excitatory and inhibitory neurotransmitters and modulators). There are significant weaknesses in the trials that underpin current treatments for neuropathic pain. Large studies have been undertaken predominantly in patients with pain from diabetic neuropathy and post-herpetic neuralgia. The results of these studies are then extrapolated to other neuropathic pain states.[32]

Unfortunately, the cost of trials is high, and they are generally only undertaken by drug companies. This limits the likelihood of 'head to head' trials and trials of drug combinations. This means comparisons between drugs and drug classes must depend on analysis of numbers needed to treat (NNT) and numbers needed to harm, despite criticisms of this methodology. These comparisons generally favor tricyclic antidepressants over anticonvulsants and opioids.[32,33]

Neuropathic pain is likely to be an ongoing complaint. A trial of treatment in an individual patient can therefore be planned .The drugs used to treat neuropathic pain can be conveniently divided into two types: medications used to treat other conditions but found to be useful in reducing pain from nervous system damage, and analgesics. Combination therapy is commonly prescribed for neuropathic pain. It may also be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs. However, there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations.[34]

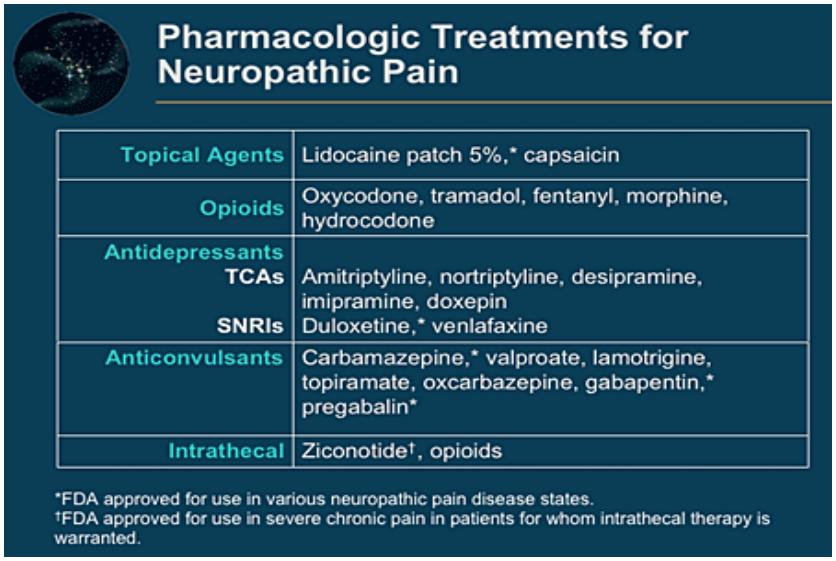

TABLE.2: Treatment Of Neuropathic Pain Is Often Considerd As Follows:

FIRST-LINE AGENTS

Two classes of medications are recommended for first-line treatment in the management of neuropathic pain, namely antidepressants and anticonvulsants.

Tricyclic antidepressants: The tricyclic antidepressants (TCAs) provide the best evidence of efficacy in the management of NP. Although the definitive mechanism of action of tricyclic analgesia is unknown, these drugs block the reuptake of noradrenaline and serotonin, block hyperplasia induced by N-methyl-D-aspartate agonists and also has sodium channel blocking properties independent of their antidepressant effects.[35, 36]

Anticonvulsants: Gabapentin and Pregabalin bind to presynaptic voltage-gated calcium channels in the dorsal horn, resulting in a decrease in the release of excitatotry neurotransmitors such as glutamate and substance P. In two studies of diabetic neuropathy and postherpetic neuralgia, gabapentin produced significant pain relief relative to placebo, and significant improvement in measures of quality of life and mood.[37,38] Pregabalin is an analogue of gabapentin with the same mechanism of action, but manifests linear pharmacokinetics and higher affinity for the presynaptic calcium channel. Pregabalin has also been studied in chronic central NP following spinal cord injury, with resulting evidence of significant pain relief.[36, 37]

SECOND LINE AGENTS

Serotonin noradrenalin reuptake inhibitors: The newer mixed serotonin reuptake inhibitors (SNRIs), venlafaxine and duloxetin are used which gives more efficacy and

improves quality of life. Duloxetin has demonstrated significant pain relief relative to placebo in patients with painful diabetic Neuropathy and mixed painful polyneuropathy at dose of 150mg to 225mg per day. However, the latter trial also compared venlafaxine with imipramine, and imipramine showed a higher proportion of responders.[37,38,39]

Topical lidocaine: It is a sodium channel blocker in the management of NP. Systemic side effects are extremely rare with this as a result of minimal blood levels. Topical lidocaine is most practical for patients with localized peripheral NP such as postherpethic neuralgia. However all of these trials were of short duration (up to three weeks) and had other limitations. Lidocane gel (5%) has demonstrated significant pain relief up to 8 h in postherpetic neuralgia. The topical application of local anesthetics such as lidocane or anti-inflammatory agents such as gallium maltolate can provide relief. A transdermal patch containing lidocaine is available commercially in some countries.[40]

THIRD LINE AGENTS

Tramadol: Tramadol is a unique analgesic agent that demonstrates low-affinity for the mu opioid receptor, and inhibits reuptake of noradrenaline and serotonin .Tramadol is a weak opioid agonists and mimics some of the properties of the TCAs. Tramadol has shown significant benefit in painful diabetic neuropathy and mixed NP syndromes. Tramadol produces less constipation and nausea than other weak opioid analgesics such as codeine , but is much more expensive.[40,41]

Opioid Analgesics: Opioids also known as narcotics are increasingly recognized as important treatment for chronic pain. They are not considered as first line treatments in neuropathic pain but remain the most consistently effective class of drugs for this condition. Due to the risk of addiction or diversion, opioids must be only used in appropriate individuals and under close medical supervision.[42,43]

Combination therapy

In cases of partial but insufficient pain relief by a single drug, combinations are often used. Due to a lack of controlled studies, the rationale for such combination therapy has mainly been based on theory, but is now supported by recent RCTs(Randomized controlled trials). The best evidence is for the combination of a TCA or an opioid with gabapentin . Such combinations are suggested to improve treatment compared with treatment with each drug alone in maximum tolerated doses.[40,41,42,44]

TABLE.3: Pharmacological Agent and summary of their mechanism of action

Medication	Mechanism of Action
TCA	Increases serotonin and norepinephrine at axon terminal via inhibiting their reuptake, blocks cholinergic, adrenergic and histamine receptors
SNRI	Increases serotonin and norepinephrine at axon terminal via inhibiting their reuptake
Lamotrigine	Sodium channel antagonist leading to inhibition of glutamate release
Gabapentine/Pregabalin	G-protein coupled receptor antagonist leading to inhibition of glutamate release
Topiramate	Stabilizes sodium channels and blocks calcium ion transmissions
Valproate	Potentiates function of GABA neurotransmitter
Mexiletine	Sodium channel antagonist in peripheral nerves
Cannabinoids	Inhibits synaptic transmission in pain pathways
Tramadol	Agonist at mu-opioid receptors and weekly increases serotonin and norepinephrine via reuptake inhibition.

Abbreviations: TCA, tricyclic antidepressants; SNRI, serotonin and norepinephrine reuptake inhibitors; GABA, gamma aminobutyric acid.

FUTURE PROSPECTIVES OF NEUROPATHIC PAIN

Existing therapies for neuropathic pain are far from effectiveness for the majority of patients. For the newer drugs with specific labels for neuropathic pain, for example, pregabalin and duloxetine, only one in four patients finds relief, and that relief is generally only a 50% reduction in pain.[45] Whereas the earliest treatments for neuropathic pain were discovered by serendipity and borrowed from other nervous system disorders like epilepsy and depression, the way in which currently developed novel therapies for neuropathic pain relies on a linear model of drug development.

A target must be selected to have, high-throughput screening should be used to identify lead compounds, leads are optimized to minimize toxicity and maximize bioavailability, and compounds are then tested pre clinically for efficacy. Existing and emerging therapeutic modalities may best be considered as part of an overall strategy for attacking the mechanisms of neuropathic pain at multiple levels of the nervous system. They range from molecular agents that affect sensory transduction to interventions at the behavioral level.[46] Thus in order to achieve a better approach to identify pain mechanism at the same time advancing treatment options, we need better transitional models, there must be better ways to capture the complexity and dynamic nature of pain in order to design more effective tests.[47]

CONCLUSION

Neuropathic pain occurring due to lesions or disease of central nervous system has become an important target for neurological treatment conditions. The diversity in pathological process

and varying etiology of neuropathic pain requires selection of treatment strategies which focus on functional and meaningful pain relief. Treatment of a patient with neuropathic pain is a long term process, thus in the beginning, the diagnostic procedures are most important. History and clinical findings should be documented clearly in the medical charts to facilitate the assessment of treatment effects. Because comorbidities such as depression, disturbed sleep, and functional impairment are common in patients with chronic neuropathic pain, these problems should also be assessed in addition to pain relief. People with chronic pain considers functioning and well-being must be appropriate target of treatment. Assessment of overall satisfaction and quality of life concludes the therapeutic effects of treatment and any side effects.

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