Abstract
Neuropathic pain is a type of chronic pain caused by a lesion or disease of the somatosensory nervous system. The pathophysiology of neuropathic pain is very complex, not fully understood and different from that somatic pain. It has a deleterious effect on health related quality of life, and leads to increased health-care costs and its management is extremely difficult. The response to currently available treatments is less promising, so newer agents with better efficacy and safety are needed. Currently tricyclic antidepressants and anticonvulsants like gabapentin and pregabalin are considered as the 1st line drugs but these are not able to produce complete relief. Various recent drugs are: high dose capsaicin patch, topical lidocaine, botulinum toxin A, lacosamide, Selective Serotonin Reuptake inhibitors, NMDA antagonists. Certain new targets like endocannabinoid system and various neurotrophic factors like BDNF, NT3, NT4, and GDNF are undergoing preclinical and clinical trials and their role in the treatment of neuropathic pain is still emerging.

Key words: Neuropathic pain, nociception, post herpetic neuralgia, painful diabetic neuropathy, recent drugs

Introduction
Neuropathic pain (NP), a disorder in the structure and function of peripheral, motor, sensory, and / or autonomic neurons either partially or completely often goes under-diagnosed and under-treated. According to the new definition by IASP, NP is a type of chronic pain caused by a lesion or disease of the somatosensory nervous system. Lesion means the directly damage to somatosensory system, while disease refers to indirectly injury by metabolic stress, autoimmune conditions or inflammatory and so on. It has a deleterious effect on health related quality of life, and leads to increased health-care costs. The management of patients with chronic NP is extremely difficult, and the response to currently available treatments is less promising. Therapy includes both pharmacological and various non-pharmacological measures.

It is a common symptom in many diseases or injuries of the peripheral or central nervous system. Lesions of the nervous system may lead to potentially irreversible changes and imbalance between excitatory and inhibitory systems, leading to neuropathic pain syndromes.

The pathophysiology of NP is very complex, not fully understood and different from that somatic pain where the initial stimulus of the peripheral nociceptor is produced by a chemical change as a result
of tissue damage. Knowledge of the basic difference between somatic and NP is critical for the effective pain management in NP and to know that why conventional analgesics usually fail to produce any benefit. [3] Local and central changes induced by peripheral nerve injury triggers a series of changes that ultimately results in neurologic dysfunction, both sensory and motor functions are completely lost as there is total disruption of neural transmission. [4] Most NP states have been considered to arise from peripheral nervous system (PNS) rather than central nervous system (CNS) injuries. Most commonly associated PNS causes include; post diabetic neuralgia (PDN), post herpetic neuralgia (PHN), post traumatic neuralgia (PTN), and iatrogenic injuries. Most commonly associated CNS injuries include; stroke, multiple sclerosis (MS), and Parkinson’s disease (PD). It is now established that chronic low back pain, fibromyalgia and some other conditions may also present with secondary CNS neurodegeneration. [5]

As the treatment of NP is challenging because of its multiple aetiologies, symptoms and underlying mechanism and also because of the limited usefulness of the available therapies, there is great need of newer potential therapies for the treatment of this devastating condition. This review is mainly highlighting the recent therapies that are becoming increasingly available for the management of NP and also the drugs under development for the same condition.

Recent drugs for the treatment of NP
Among the currently available drugs, antidepressants (Nortriptyline, Desipramine, Duloxetine, Venlafaxine) [6, 7, 8, 9] and anticonvulsants (Gabapentin and Pregabalin) [10, 11, 12, 13] are considered to be the 1st line agent for the treatment of NP. Apart from these agents, drugs like opioids (Morphine, Oxycodone, Methadone, Levorphanol, Tramadol etc.) [14, 15, 16] also have an established role in its treatment. The above drugs have been used for the management of various conditions like diabetic neuropathy, post herpetic neuralgia and other neuropathic pain syndromes. Over the past few years’ considerable number of drugs has been evaluated for the treatment of NP as the available drugs have lesser therapeutic gain and greater number of adverse effects. It is seen that only 40-60% of the patients achieve clinical benefit with existing drug therapy and some kinds of neuropathic pain conditions may not respond to currently available drugs. [17] Following are the recent drugs for the treatment of neuropathic pain:

High-Concentration Capsaicin Patch
A high-concentration capsaicin 8% patch was recently approved by EU and US- FDA for post-herpetic neuralgia and painful HIV associated neuropathy. Capsaicin is an agonist of the transient receptor potential vanilloid receptor (TRPV1) and activates TRPV1 ligand-gated channels on pain fibers, causes depolarization, the initiation of an action potential, and the transmission of pain signals to the spinal cord. After several days of treatment TRPV1-containing sensory axons are desensitized and inhibit the transmission of pain. Low-concentration capsaicin is currently recommended as third-line therapy of NP, but its main
disadvantage is several times application per day, thus reducing the patient compliance.\cite{18, 19} To avoid this problem and to improve the effectiveness, high-concentration capsaicin patch was developed. In various clinical trials, it has shown rapid and sustained effects, produced significant analgesic effect in patients with painful HIV-associated neuropathy and applications for a period of around 48 weeks is generally considered efficacious and safe with minimal toxicity.\cite{20, 21} Adverse reactions are generally seen at the application site due to local reactions and include pain, erythema, edema and itching but initial pain often required opioids. It is seen that there is a potential risk of high blood pressure during application that occurs probably due to severe pain (careful BP monitoring is required).\cite{22}

**Botulinum Toxin A (BTX-A)**

Botulinum toxin (BTX) is a neurotoxin produced by the bacterium Clostridium botulinum having seven different serotypes (A-G).\cite{23} It has been widely used in many clinical conditions including migraine, cervical dystonia and for cosmetic corrections etc. The use of BTX-A in neuropathic pain, however, is uncommon, and the application of the analgesic effect is still emerging. It is recently discovered as topical treatment for focal painful neuropathy and painful diabetic neuropathy. It has shown to possess analgesic effects which are independent of its action on muscle tone, possibly by modulating neurogenic inflammation. Multiple intradermal injections are given in affected area and analgesia lasts for around 12 weeks. In two recent RCTs, its long-term efficacy was reported. Series of injections of BTX-A, from 100 to 200 units, were given to patients with traumatic origin associated neuropathy and also to patients with painful diabetic neuropathy. Recent studies have shown its beneficial effects in painful diabetic neuropathy where there as a significant pain reduction during 12 week therapy as compared to placebo.\cite{24} The findings are consistent with a positive effect of BTX-A on peripheral sensitization, but the role of a central effect has not been determined so far. One session of multiple intradermal injection of BTX-A produces long-lasting analgesia in patients with focal painful neuropathies and diabetic neuropathic pain, and is particularly well tolerated.\cite{23, 25} It has also shown significant anti nociceptive effects in post herpetic neuralgia and trigeminal neuralgia and improved the quality of life of the patients without causing any deleterious adverse effect.\cite{26, 27} It has an excellent safety profile with no systemic side effects, though pain at injection site is common. Although it has shown promising results for various types of NP, long term trials involving large number of patients using different study designs are required to further explore this effect.

**Topical lidocaine**

Topical lidocaine has shown efficacious analgesic effects in patients with post herpetic neuralgia and allodynia.\cite{17, 22} The lidocaine patch is currently FDA approved for the treatment of post-herpetic neuralgia. It may be used off label for treatment of other pain conditions. Its analgesic mechanism is still unclear but it is
assumed to block sodium channels so that it can reduce ectopic nociceptive pain signal transmission. [28] Topical application offers a good benefit to risk ratio with mild local adverse reactions (e.g. erythema or rash). It is particularly useful for patients with localized peripheral neuropathic pain. [17, 22] Currently, topical lidocaine has not shown any efficacy in central NP. It is a safe treatment with no or limited systemic side effects. New evidence from an open-label study suggests that lidocaine patches are useful, not only in post herpetic neuralgia or much localized NP but also in painful diabetic neuropathy. [29] In a trial long-term treatment of ≥12 months with the 5% lidocaine medicated plaster was effective and well tolerated in PHN patients, the findings supported the recommendations to use the 5% lidocaine medicated plaster as baseline therapy for localized NP after herpes zoster infection. [30] In another study done in patients with PHN and painful DPN, combination therapy with 5% lidocaine medicated plaster and pregabalin provided a clinically significant pain relief and it was safe and well-tolerated. [31] In various studies, Quality of life markedly improved in patients of NP and long-term treatment provided sustained relief in patients with neuropathic pain. The risk of systemic adverse events and interactions with concomitant medication remains minimal due to low systemic exposure, mild to moderate application site reactions are the most common adverse effects. [32]

**NMDA receptor antagonists**

The N-methyl-D-Aspartate (NMDA) receptor has been proposed as a primary target for the treatment of NP. It has been suggested that the NMDA glutamate receptors in the dorsal horn plays an important role in both inflammation and nerve injury-induced central sensitization. High intensity pain stimulus for a prolonged duration induces a series of events which leads to the activation of NMDA receptor. Activation of the NMDA receptor is associated with abnormalities in the sensory (peripheral and central) system, resulting in neuronal excitation and various pain manifestations like spontaneous pain, allodynia, hyperalgesia. [33, 34, 35, 36] Blocking of these receptors by NMDA antagonists may be helpful in reversing the pain pathology and reducing the pain.

Recently, NMDA antagonists like ketamine, dextromethorphan, memantine, amantadine and methadone have been studied for their analgesic effect in NP. Ketamine is probably the most investigated NMDA receptor antagonists for the treatment of neuropathic pain. It has strong affinity for the receptors and binds equally to the NMDA subtypes 2A to 2D. Because of this property, it may have a more beneficial effect in such a complex disease as, compared with more selective NMDA receptor antagonists. It leads to long-term blockade of the receptor and strong inhibition of the neuronal hyperexcitability occurring in NP. The main disadvantage of this nonselective strong binding property is the higher number of adverse effects due to its binding to neuronal structures not involved in pain. The S (+) enantiomer of ketamine has favorable side effect profile and is twice as potent analgesic compared
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Therefore, lower doses of S (+) ketamine may reduce side effects, while providing pain reduction comparable to racemic ketamine. Therefore, ketamine especially S (+) ketamine may be a promising intervention for pain relief in NP. [36]

Amantadine is NMDA blocking drug that has shown mixed results in various clinical trials. In A double-blind, randomized, placebo-controlled multicentric trial cancer patients who had surgical NP. [37] In a randomized order, patients received a 200-mg infusion of amantadine or placebo 1 week apart from each other. Spontaneous and evoked pains were measured 48 hours before, during, and after treatment. On average, there was an 85% pain reduction with amantadine versus 45% with placebo (P = 0.009) at the end of the infusion. When comparing mean pain intensity 48 hours prior to and following treatment, amantadine had a 31% reduction in pain (P = 0.006), whereas the placebo showed an insignificant pain reduction of 6% (P = 0.40).

In another study of amantadine in 19 patients who failed to respond to the conventional treatments for NP. The patients were given oral amantadine 100 mg/day for 1 week and titrated to 200 mg/day. The results showed pain reduction in only 2 (10.5%) of the 19 patients but adverse effects were experienced in 52.6% of the patients, including dry mouth, drowsiness, hallucinations, excitation, irritation, dizziness, dyskinesia, and alopecia. [37, 39]

Methadone is another NMDA antagonist used in NP. It has been shown to be a promising option to use as a replacement opioid in patients having poorly controlled analgesia or experiencing adverse effects while on other opioids. Lesser number of adverse effects and more reduction in pain were reported when morphine was replaced with methadone. [40] In a double-blind, randomized, controlled, crossover trial, Methadone also demonstrated effectiveness in patients with refractory NP. [41]

Unfortunately, use of methadone is really challenging because of: [37]

- Long and variable half-life of approximately 8 to 59 hours,
- Many drug interactions (with QTc prolonging agents and CYP3A4 and CYP2D6 inhibitors).
- E.C.G monitoring is required.
- Opioid conversion is difficult as methadone increases in potency with increasing doses of morphine

Memantine has a rapid onset of action and safe side-effect profile. In a randomized, double-blind, crossover study, memantine was administered to a group of 19 patients with chronic pain due to post operative nerve injury, no significant difference in pain reduction was found with memantine versus placebo. [42] In another study with memantine in patients with HIV-associated sensory neuropathy, it failed to produce any beneficial effects. [43]

In two crossover trials, the authors studied the effect of two NMDA blockers, dextromethorphan and memantine in patients with painful diabetic neuropathy (DN) and postherpetic neuralgia (PHN). Dextromethorphan was effective in a dose-related manner in selected patients with DN.
and shown no effect on PHN, suggesting a difference in pain mechanisms.\textsuperscript{44}

In a qualitative systematic review the effect of N-methyl-D-aspartate (NMDA) receptor antagonists on reducing postoperative pain, the evidence in favor of preventive analgesic action was strongest in the case of dextromethorphan and ketamine, with 67% and 58%, respectively, of studies suggesting a reduction in pain beyond the clinical duration of action of the given drug.\textsuperscript{45}

NMDA receptor antagonists seem to be a promising therapy for NP but additional studies are required to explore the therapeutic potential of NMDA receptor antagonists in neuropathic pain and till now they have shown mixed results, although ketamine seems to be the most promising.

\textbf{ABT-594}

ABT-594 is a neuronal nicotinic acetylcholine receptor agonist. It has shown potent analgesic activity in various animal models of NP. In a randomized, multicenteric, double-blind, placebo-controlled phase 2 study, it significantly reduced the pain intensity compared with placebo in patients with painful diabetic neuropathy. Unfortunately the treatment was associated with many dose-related adverse effects, but the study suggests that further development of this drug class may present new therapeutic options. The most frequently reported adverse effects were nausea, dizziness, vomiting, abnormal dreams, and asthenia. This study established proof of concept for neuronal nicotinic acetylcholine receptor (NNR) agonists as a new class of drugs for treating NP.\textsuperscript{46}

\textbf{Selective Serotonin Reuptake Inhibitors}

Currently, SSRIs are considered as third line drugs for NP because of their inconsistent efficacy.\textsuperscript{47} Although in some trials significant results were obtained, yet the benefits were clinically relevant only in a small number of patients. In crossover trials of paroxetine and citalopram in patients with painful DPN, the significant results were obtained.\textsuperscript{48, 49} Their use in NP may also be associated with greater flexibility in dose titration and a better safety profile than TCAs. Thus, more studies are needed to establish the role of SSRIs in NP.

\textbf{Lacosamide}

Lacosamide is a new antiepileptic drug that is FDA approved for the adjunctive treatment for partial epilepsy. It modulates collapsin-response mediator protein 2 (CRMP-2) that inhibits a key modulator of pain transmission N-methyl-D-aspartate receptor subunit NR2B and can control neuronal hyperexcitability. Because to the above effect, it has been studied in patients with painful diabetic neuropathy and the results showed modest benefit.\textsuperscript{50, 51} Recent studies do not support the use of lacosamide for the treatment of NP due to its low efficacy even at higher doses. At higher doses, the adverse effects are more and it leads to more number of withdrawals.\textsuperscript{52} Currently, it is not an approved therapy for this indication.

\textbf{Mexiletine}

Mexiletine is an oral sodium channel blocker that has been found to be effective in many NP conditions. The analgesic effect of mexiletine has been confirmed in
diabetic mice, as well as in patients with painful diabetic neuropathy. However, recent reports question the efficacy of oral mexiletine in neuropathic pain. Adverse effects were found to be more common at therapeutic doses and it seems to be a narrow therapeutic window drug. In a RCT on patients with neuropathic pain with prominent allodynia, at doses of up to 900 mg/d, mexiletine showed no significant effects on pain and alldynia of NP.

**Combination therapy**

Neuropathic pain is a complex syndrome and most of the monotherapies often fail to provide sufficient analgesia even at the highest recommended dose because a single drug is unable to effectively modify the complex cellular and molecular changes seen in chronic NP conditions. Therefore, it is logical to target different pain mechanisms using combination therapy. It helps hereby avoiding adverse effects caused by using a single medication at its maximum tolerable doses. Till date, only a small number of studies on combination therapy are available, making it difficult to draw any definitive conclusions. Studies have suggested that combination of gabapentin and pregabalin have shown better results than monotherapy for pain related to diabetic neuropathy or post herpetic neuralgia. High-concentration (8%) topical capsaicin and a 5% lidocaine were not shown to be effective add-on therapies and studies of combination therapy for cancer-related NP have yielded only limited success. Although combining opioid analgesic as a part of combination therapy provided better pain control in the majority studies but more clinical studies are needed for long time follow up of patients to fully evaluate the risk and long-term adverse effects. Both short and long-term safety studies are required to evaluate possible adverse effects resulting from the combinations therapies used for NP.

**Emerging therapies**

**Cannabinoids**

The endocannabinoid system and its role in the therapy of NP, has been recently studied. It has been demonstrated that mammalian tissues express two types of CB receptors. CB1 receptors are mainly present in CNS and CB2 are located in the periphery, particularly in immune cells. CB1 receptor-dependent retrograde mechanism in the CNS has been found to cause the release of neurotransmitters controlling pain inputs and inflammation. Recent studies suggest the role oromucosal extracts of cannabis analogs (nabilone, dronabinol and tetrahydrocannabinol) analogue in NP. They showed significant analgesic effects as compared to placebo. It is evident that cannabinoids are safe and modestly effective in NP. Their regulatory approval and clinical utility are currently limited because of their abuse potential and limitations of the formulation. Peripherally acting (at dorsal root ganglia and spinal cord) CB2 agonists are under development for the treatment of NP disorders as CB1 receptor activation produces many CNS adverse effects.

Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/ 2.5 mg cannabidiol) have been found effective in pain associated with multiple sclerosis and
in refractory peripheral NP associated with allodynia. It has been found that around 90% of the patients experienced adverse effects and one-third of the patients withdrew due to lack of efficacy or due to adverse drug reactions.\[63\] So, currently they are not the very good option for the treatment of NP.

Neurotrophins and nerve growth factors
The neurotrophins (NTs) nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) belong to a family of structurally and functionally related proteins. They play important role in peripheral and central nervous system development and regulation of survival of various subpopulations of neurons.\[64, 65\]

In recent studies, their emerging role in NP was found and explored further. NGF is a recently studied mediator in NP states. Its levels increase in many painful conditions and its administration in study animals resulted in pronounced mechanical and thermal pain.\[66, 67\] The mechanism of this effect is not known completely, but it was seen that increase in the levels of NGF by afferent neurons after a nerve injury leads an altered expression of several types of sodium channels, particularly voltage-gated sodium channels.\[68\] It has been found that NGF is able to upregulate the voltage gated sodium channels expression in NP conditions and can lead to sensitization of peripheral pain receptors.

Other facts that establish its role in NP are:\[69, 70, 71\]

- In the chronic constriction injury (CCI) model of peripheral neuropathy in rat, the levels of NGF were found to be increased in the ipsilateral dorsal root ganglia (DRG), in the spinal cord and in the periaqueductal grey matter (PAG).
- Treatment with the antihyperalgesic and neuroregenerative compounds (e.g. acetyl-l-carnitine) normalized the elevated NGF levels.
- NGF expression was also found to be increased in the red nucleus of the brain of neuropathic rats and in DRG of rat pups during postnatal life after complete Freund’s adjuvant (CFA)-induced peripheral inflammation.

BDNF is involved in the central sensitization and synaptic plasticity in the spinal cord. It contributes to both development and maintenance of neuropathic pain by activation of the dorsal horn NMDA-2B receptors.\[72\]

It has been found that BDNF levels were significantly increased in the spinal dorsal horn in the spinal nerve ligation (SNL) rat model of NP. The maximal increase in BDNF expression was found in an early stage (24-48 hours) after SNL. It indicates the possible involvement of BDNF/TrkB-mediated signalling pathway (TrkB is a member of tyrosine kinases family and it has the highest affinity for the BDNF) in the development of NP, particularly in early stage after nerve injury. BDNF expression is also significantly up-regulated in DRG sensory neurons in animal models of NP.\[73\]

It was seen that by blocking phosphorylation of TrkB (by protein kinase inhibitor, protein phosphatase 1 in the spinal cord), the development of tissue or nerve injury-induced heat and the mechanical hypersensitivity in mice can be prevented. It indicates that TrkB signalling is not only an important not only in the
induction, but also in the development and persistence of NP.\(^7\)

The role of **NT-3** and **NT-4** in the development of NP is still not clear. NT-3 has been shown to possess antagonistic effects to NGF in the nociception process, through negative modulation of NGF receptor expression.\(^75\)

**NT-4** is synthesized by DRG and expressed in the rat spinal cord.\(^76\) It is a ligand of the TrkB tyrosine kinase receptor, but it mediates to diverse effects in relation to BDNF.\(^74\) It has also been demonstrated that repeated injections of a specific antibody to NT-4 failed to reverse the thermal hyperalgesia caused by sciatic nerve ligation in mice.\(^76\)

**Glial cell line-derived neurotrophic factor (GDNF)** has been shown to prevent and reverse sensory abnormalities that developed in various NP models, without affecting pain-related behavior. GDNF reduces ectopic discharges within sensory neurons after nerve injury and this effect may involve modulation of sodium channels. This finding provides a rational basis for the use of GDNF as a therapeutic treatment for various NP conditions.\(^77\)

In view of above discussion, it is clear that lot of research is going on to find out the most effective therapies for the treatment of NP. Current therapies are not able to provide the satisfactory relief. There are many drugs in the pipeline but to prove their efficacy, studies involving proper designs, sample size and control groups are required.

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