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Review Article

A Review Article on Neuropathic Pain

Timothy Allen, MD, Ph.D[1], Giridhar M.N.V, MD,MBA[1*], Ghazaleh Shoja E Razavi MD[2*]

[1]*Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA.*

[2]*Dir. Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, USA.*

**Corresponding author: Dr. Ghazaleh Shoja E Razavi MD, Dir. Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, Tel: 1- 416-520-8835; Email: ghazaleh.shoja@gapsos.com*

Giridhar M.N.V, MD,MBA, Dr. Lead Medical Officer, Global Allied Pharmaceutical,

Tel: 1-321-445-1969; Email: giridhar.maddirevula@gapsos.com

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Abstract

Neuropathic pain is a pathological pain, caused due to damaged nerves, as a result of an injury on the somatosensory system. Its effect is mainly on the outside of the brain and spinal cord. Therefore, it is mainly considered as " peripheral neuropathy pain", which has yearly impacted, over 20 million Americans. A nerve fiber injury, does effect the functionality of the nerve at the site of damage or around the injury. Its prevalence depends on the type of neuropathy; but in the general population; it is counted around 7-8%. The etiology of neuropathic pain is complex and varied in different cases. These include neurodegenerative disease, physical trauma, infectious agents and metabolic diseases. There is considerable variation in treatment initiation, dosage, drug selection. In general, Antidepressants (antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs],serotonin–norepinephrine reuptake inhibitors [SNRIs]), anticonvulsants (antiepileptic), topical lidocaine,tramadol and opioid analgesics are the options available for treatment. Even though treatment of Neuropathic pain is still a challenge to manage, and evidence of clinical recommendations for pharmacological management are required in the area of its management. The main obstacle for the neuropathic pain is the lack of awareness and misconception about neuropathic pain's complexities, which often leads to misdiagnosis and mistreatment. This article focuses on the various types of treatment, prognosis and management of the neuropathic pain.

Keywords: Antidepressants; Neuropathic pain; peripheral neuropathic pain, Diabetic neuropathy pain, TCA (tricyclic antidepressant), IASP (The International Association for the Study of Pain), Anticonvulsant, and Opioid.

Abbreviations

IASP= International Association for the Study of Pain
DPN = diabetic peripheral neuropathy
SSRI = selective serotonin reuptake inhibitor
SNRI = serotonin norepinephrine reuptake inhibitor

TCA =tricyclic antidepressant
PHN = Postherpetic neuralgia
RCT = randomized clinical trial
NeuPSIG = Neuropathic Pain Special Interest Group
NP= Neuropathic pain
DPN= Diabetic peripheral neuropathy
NE= norepinephrine
NMDA= N-methyl-d-aspartate

Introduction

According to IASP (International association for the study of pain), neuropathic pain arises as a result of lesion or disease, which affects the somatosensory system [1]. It is a chronic condition, which arises due to the damage or pathological changes in the peripheral nervous system [2]. Once the tissue is damaged, a set of excitability alteration occurs in the peripheral nervous system, which establishes a deep and reversible pain, along with hypersensitivity in the surrounding tissues, which helps in the healing process. In contrast, persistent pain syndromes do not stimulate biological advantage. However, both syndromes, cause suffering and distress for the patients. Such unbearable pain that has typically resulted from the damage of the peripheral and central nervous system is known as neuropathic pain. It can be present as sensory deficit, which can be partial or complete loss of sensation in addition to paresthesias, dysaethesia and hyperpathia [3].This pain is characterized as shooting, stabbing, burning or like an electric shock [4]. Neuropathic pain interferes with the process of normal pain signaling and induces spontaneous or sensitizational activity of the nervous system, due to which patients feels pain [5].

Absence of transduction may lead to the differential prognosis via neuropathic pain from the non neuropathic pain [6]. Rate of release of neurotransmitters increase on a cellular level (which helps in the signals of pain), combined with the impaired ability of the nerves for the regulation of stimulating pain signals from the affected area [7]. According to National Health Services, neuropathic pain consist of peripheral nerve damage only. It does not explain the paresthesia and dysesthesia, associated with damaged nerve of central nervous system. Peripheral nervous system consists of nerves, which are outside the brain and spinal cord. When it affects one nerve, the condition is termed as 'mononeuropathy' and if it affects more than one nerve root; the condition is called 'polyneuropathy'. The most common type of polyneuropathy affects, primarily longest nerves, starting from lower extremity. Over a period of time, it may gradually spread to other nerves as well.

According to National Health Services, there are basically three common types of nerves involved in peripheral neuropathy:

- The autonomic nerves (also called "automatic" or "involuntary" nerves because it cannot be controlled)
- Motor nerves (it controls the muscles of the body under our conscious condition)
- Sensory nerves (convey the sensations from a part to the brain) [8].

Neuropathy can be caused by various factors [9]. Various causes of neuropathic pain have been described in Table-1.

Factors	Description
Diabetes	• Most common condition associated with neuropathy, • Characteristic of diabetic neuropathy is seen when,the damage affects almost all three nerve fiber (motor neurons and the autonomic nervous system.
Deficiency of Vitamins	• B12 deficiency results in the damage to the nerves.
Autoimmune neuropathy	• Rheumatoid arthritis, systemic lupus, and Guillain-Barre syndromes like autoimmune disease can cause neuropathies.
Infection	• HIV/AIDS, Syphilis, Leprosy, Lyme disease are the examples, can damage the nerves.
Post-herpetic neuralgia	• Varicella-zoster virus infection causes neuropathy.
Alcoholic neuropathy	• Alcoholism is a one of the factors of peripheral neuropathy, but the exact reason is still little known.
Genetic or inherited disorder	• Friedreich's ataxia and Charcot-Marie-Tooth disease is genetic disorders which can also cause neuropathy pain.
Amyloidosis	• A condition in which abnormal protein fibers get deposited in the tissues or organ and can cause neuropathy.
Uremia	• Concentrated waste product in the bloods which leads to the neuropathy.
Toxins and poisons can damage nerves	• Arsenic, mercury, gold compounds, lead, nitrous oxide, and organophosphate pesticides and some industrial solvents.
Drugs or medication	• vincristine (Oncovin, Vincasar),Taxanes (Paclitaxel, Docetaxel), Platinium Compounds (Cisplatin, Caprboplatin and Oxaliplatin) .isoniazid (Nydrazid, Laniazid) and antibiotics such as metronidazole (Flagyl) causes nerve damage as its side effect.
Trauma/Injury	• Decreased level of blood flow (ischemia) to the nerves can also lead to long-term damage.
Tumors	• Benign or malignant tumors of the nerves may damage the nerves directly, by invading the nerves, or cause neuropathy due to pressure on the nerves.
Idiopathic	• Idiopathic term is used for medicine, which denote the fact that no cause is known.

Table 1. Causes of Neuropathy Pain According to Melissa Conrad Stoppler 2014. [9]

Signs and symptoms of Neuropathic Pain:

According to the type of damaged nerve or site of damaged nerve, symptoms of neuropathy can vary from person to person. Neuropathic pain can be present as numbness and tingling in hand and feet, burning pain, lack of coordination, muscle weakness, changes in Blood pressure and dizziness [10]. Sensory related abnormalities are listed below in Table-2.

Hypoaesthesia	- Reduction in touch sensation.
Hypoalgesia	- Reduction in pain sensation.
Paraesthesia	- Sensational feeling of tingling.
Hyperalgesia	- Increment of response to painful stimuli.
Allodynia	- Pain resulting from a stimulus, which generally doesnot produce pain
Hyperpathia	- an experience of abnormal pain, to a stimuli. Could be severe with continuous pain.
Dysaesthesia	Could be spontaneous or evoked, and unpleasant.

Table 2

Sensory related abnormalities in neuropathic pain [11]

Epidemiology of Neuropathic pain:

Chronic pain is a major problem for the patients and the physicians, which affects 28-65% of the patients in the U.S.A [12,13]. Depending upon its frequency, duration and intensity, it can be defined as "Chronic". Generally, this chronic condition is considered, when pain does not go off and persist for a long period of time, of at least 3 months. [12, 13].

Around 25 % of the population suffers from neuropathic pain. The main etiologies for neuropathic pain are low back pain, cancer or traumatic injury [14]. Estimated prevalence of neuropathic pain is based on specific cause, which is approximately 1-2% [15]. Data source are some sets of groups, experiencing difficulties such as, low back pain [16, 17 18], diabetes mellitus [19], nerve entrapment syndrome, multiple sclerosis[16], or patients who attended specialized healthcare center [20], but this information cannot be applied to everyone in the public. Some communities work on the prevalence of neuropathic pain, with the use of survey tool S-LANSS [Leeds Assessment of Neuropathic Symptoms and Signs] or collect data from self –report or administrative data tools, like Berger criteria [21, 22].

Pathophysiological aspects of neuropathic pain

Pathophysiology of neuropathic pain is still under preclinical and clinical stage. Primary lesion of a nerve is the main etiological condition for the neuropathic pain, which involves dysfunction of the pathway of the nerve, directly or indirectly. Responsibility of painful stimuli is associated with lightly myelinated Aδ and unmyelinated C fibers. High threshold can cause stimuli and spontaneous activity is also observed in injured neurons. Physiological change may be caused due to neuropathic condition. Central changes at spinal cord levels or in CNS can be induced by peripheral lesions. Table 3 discusses the etiology associated pathophysiology for neuropathic pain.

Categories of pain	Description
Toxic	Most common conditions, result of chemo and radiotherapy, Isoniazid and thallium are agents causing Neuropathic pain. Lead and arsenic also causing nerve damage.
Metabolic	Diabetes and Nutritional deficiencies like beri beri are the main disease which can results in neuropathic pain, Alcohol also causes neuropathy when thiamine (vitamin B1) deficiency is present.
Trauma	It can happen as a result, in phantom limb syndrome and/or complex regional pain.
Compressive	External pressure on nerve axons, and nerve entrapment can leads to the ischemic changes, prolonged injury also cause nerve damage.
Autoimmune	There is possibility to have some antibodies which interact with their pathophysiology and are responsible for immune therapy. It includes CIPD (Chronic inflammatory demyelinating polyneuropathy and vasculitic neuropathy.
Infectious	Post-herpetic neuralgia, Lyme Disease (spirochetes), Chagas' Disease , leprosy (trypanosomes), HIV, and Guillain-Barré
Congenital/Hereditary	Syndrome (post-infectious) can cause neuropathic pain. Charcot-Marie-Tooth Disease (burning pain in extremities) and Fabry's Disease are examples of peripheral neuropathic pain associated with congenital abnormalities; and also other hereditary conditions like amyloidosis produces painful conditions.

Table 3. Etiology associated pathophysiology for neuropathic pain. [23,24].

Diabetic Neuropathy

The diabetic neuropathies, affect the several parts of the nervous system, with varied clinical manifestation. Approximately, 60-70% of patients with diabetes, may develop some type of neuropathy at any time, but in most of the cases it develops with the age and persistence of disease for a longer duration. It is more common in patients with uncontrolled blood glucose, hypertension and with high levels of cholesterol and triglycerides. There are four different types of diabetic neuropathy; peripheral, autonomic, proximal or focal.

DPN (Diabetic peripheral neuropathy) is a most common type and it affects up to 50% of the patients, having type II diabetes. Diagnosis and management of DPN, require careful examination of the lower limb and maintenance of optimal glycemic control [25,26].

Diabetic Polyneuropathy

It is a condition, in which several peripheral nerves get damaged. It can be caused by infections, drugs, cancers, toxins, disorders and nutritional deficiencies. The severity of the condition can be assessed by nerve conduction studies plus electromyography, blood and urine test. It can be acute as well as chronic. Drugs such as amitriptyline, gabapentin, lidocaine and mexiletine can be effective in this condition [27].

Management of DPN

It is difficult to estimate the prevalence of neuropathic pain in the patients with diabetes, but crudely reported around 3-25% of patients, might have experience of neuropathic pain [28]. Diagnosis of DPN patients, totally depends upon the description of pain. The symptoms may be described as prickling, sharp and aching like an electric shock, hyperalgesia and allodynia. Management of DPN consists of symptomatic therapies, which improve symptoms of the DPN, without changing the effect of underlying cause or natural history [28].

Approaches on treatment of DPN, mainly focuses on modifying the disease process or with, improvement of symptoms. In this condition, primary aim involves the protection of lower limb, from the damage of the reliving pain, to improve the physical well being or reducing psychological distress [29]. The focus remains on maximizing diabetic control and medication for relieving pain. The relationship between glycemic level and neuropathy pain remains controversial in this case. Drugs like ACE inhibitors, aldose reductase inhibitors and alpha lipoic acid can play a vital role in the treatment of DPN. Opioids, antidepressant and antiepileptic, in combination with capsaicin, are effective in relieving DPN. Along with some adverse effect, Tramadol and oxycodone, with effective response for the limited duration, are the subject for the usefulness, as a first line of therapy. These medication such as, TCA or Tramadol and oxycodone have been widely used, but due to their anticholinergic and sedative properties, patients may not be able to tolerate them. Some antiepileptic drugs, such as gabapentin and pregabalin have role in treating DPN. It is hard to nominate the single drug as the first line of treatment, because combination of low drug doses, may provide better treatment option for DPN [30].

Postherpetic neuralgia (PHN)

It is a form of neuropathic pain, which mainly affects the vulnerable population, such as immunocompromised people, elderly patients as well as diabetics. It occurs due to Herpes zoster infection. Shingles is characterized by painful skin, Paulo vesicular rash, also occurs due to the infection of herpes zoster virus. PHN is a result of outbreak of shingles and causes persistent nerve pain [31]. In the USA, each year about 1 million individuals, get infected by this virus [32]. Diagnosis of postherpetic neuralgia, depends on the recognition of signs and symptoms of herpes zoster infection and the location of AHZ (acute herpes zoster) and associated neuropathic pain, in the same dermatome, which already sowed typical herpetic lesions. However, in rare cases, neuralgia might be present, without any clinical presentation of zoster infection and its typical skin rashes that is called Zoster skin eruption. Treatment of PHN can be done through analgesic pharmacotherapy and a series of drugs, developed for this type of pain. PHN or other types of NP, which do not respond against the NSAID, needs to be considered for other therapeutic options, which includes antiepileptic , antidepressant and other opioids. Neuropathic Pain Analgesic Ladder for PHN, follows the three step process. The primary or first step of treatment for PHN, includes certain antiepileptic, antidepressant, TCAs or SNRI. Some opioids and topical drug treatment also have significant result, but only in the second and third step of the ladder, due to its adverse events. In second step, the combination of tramadol, with first line of drugs has been evaluated, whereas in third step of management, first line of drugs, in combination with potent opiates such as morphine, methadone, buprenorphine transdermal and oxycodone, are evaluated. However, the treatment allocation varies and depends on various factors, including dosage, drug selection, therapeutic outcome etc [33].

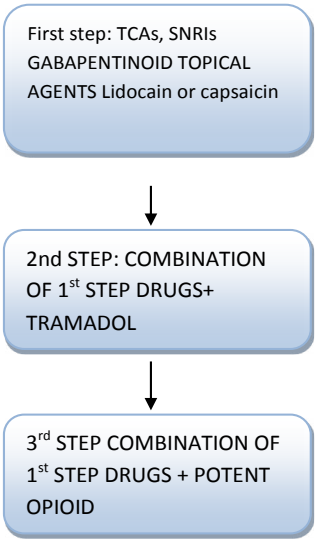

Figure 1. Analgesic ladder for the treatment of neuropathic pain [33].

Trigeminal neuralgia (TGN)

Trigeminal neuralgia, which is also known as “tic douloureux”, have characteristics of severe pain, in 5th cranial nerve. Shock like, facial pain and burning sensation are the main characters of the typical or classic form, “type 1” of TGN. It lasts only for a few seconds to two minutes per episode. But, this episode can happen in quick succession. In “type 2” of TGN, patients can feel stabbing pain, burning, aching, but with low intensity than

type 1 [34]. Existing theories are unable to explain the pathophysiology about the TGN. According to current evidence, site of generation for trigeminal nerve is CNS. This is the slowly evolving process, in which blood vessels gets the compression or can develop, because of brain tumor or alteration, that may disturb the neural function, because of the formation of MS plaque at the dorsal root entry zone, which subsequently increases the excitability in trigeminal afferent. There is contradiction in evaluating pathophysiology of TGN. Some of the group favors and have documented sensory impairment in TGN, using neurophysiological methods and sensory testing. Trigeminal ganglion shows unique pathological changes, including degenerative hypermyelination and production of microneuromata. However, the whole mechanisms involved, are not clear. Absence of neurogenic inflammation in patient with TGN, is the major evidence of being involved in peripheral nervous system. Vasodilation is involved in the TGN and normalizes, when the pain is under control [35].

Vinik et al. have analyzed the clinical trial to know the efficacy and safety of [DS-5565] mirogabalin, in the treatment of painful diabetic neuropathy. A randomized clinical trial (RCT) on 452 adult diabetic patients, were administered with multiple dose range of 5, 10, 15, 20 and 30 mg per day or Pregablin for five weeks with 300 mg/day. All safety and clinical analysis like electrocardiogram and adverse events were observed. As per results, Mirogabalin had significant reduction in average daily pain score and is considered as promising treatment option for painful diabetic neuropathy [36].

In 2014, S Maarbjerg et al, described the clinical behavior of TN, and analyzed 158 adult patients. It was more prevalent in women, rather than men and was mainly located in the right side of the face. 31% of the patients were showing autonomic symptoms, and 29 % of them did not opt for surgery. The first series of study showed persistent high pain in the patients [37].

In 2014, Gaul et al, studied treatment of TN and NP due to traumatic dental or surgical lesions. Anticonvulsant medicine, TCA antidepressant, and surgery are the main option of treatment, for trigeminal neuralgia. In the latter article, about 4 patients were treated by capsaicin 8%, in the affected area and showed significant positive results, in control of the associated pain, in the head and facial region. It might be an additional treatment with anticonvulsants or antidepressants, in first line treatment with limited side effect [38].

Medication for the Neuropathic pain

Tricyclic Antidepressants: First line of therapy for the neuropathic peripheral pain

TCA is the first line of treatment, but still its mechanism is little known. Nortriptyline HCl and Amitriptyline are the primary TCA, used by physicians to treat Neuropathic pain [39]. TCA may reduce the feeling of neuropathic pain, by inhibiting the presynaptic reuptake of serotonin and noradrenaline. Along with these mechanisms, ion channel blockade and N-methyl-D-aspartate receptor, play a key role in the pain reliving mechanism. Sindrup and his associates performed a clinical trial and reported that TCA may relieve the pain, in every 4-5 patients, while treating with serotonin nor-adrenaline reuptake inhibitors and in 7 patients of serotonin inhibitor case [40].

TCAs are affordable and effective in the treatment of DPN,but the pateints are asked to take appropriate precautionary measures, while using them. TCAs are contraindicated in patients, with a history of cardiac disease because it also has anticholinergic effects [41]. In 2014, L. Hearn et al, analysed the activity of desipramine (TCA) for neuropathic pain in adults, and noticed the adverse events related to this disease. 177 patients were analyzed, out of which painful diabetic neuropathy (104) and postherpetic neuralgia (73) cases were reported. 145 patients were administrated with 12.5 mg to 250 mg daily. Comparative studies in placebo were done, using 3 drugs- fluoxetine, clomipramine and amitriptyline. These drugs were given for two to six weeks. The result of this clinical trial shows to support desipramine for the treatment of neuropathic pain [42].

Anticonvulsants

Carbamazepine is the first anticonvulsant that has been studied for the treatment of neuropathic pain in diabetic, PHA and trigeminal neuralgial condition. It decreases the conduction of Na+ channel and inhibits ectopic discharges. Results of the trials, using carbamazepine have been found positive in the treatment of painful diabetic neuropathy, trigeminal neuralgia and postherpetic neuralgia. Gabapentin is a type of anticonvulsant, which also acts as an analgesic and is used for the treatment of pain and trigeminal neuralgia. Based on the favorable results of both drugs, Gabapentin should be used as first choice of therapy. Gabapentin and carbamazepine are functionally, completely active in the role of anticonvulsant drugs, as well [43]. Phenytoin, Carbamazepine, and valproate are some long-established anticonvulsants, since 1960s [44]. Phenytoin is also an anticovulsant and its efficacy is best as an antinociceptive agent. Lamotrigine, Phenobarbital, valproic acid, clonazepam, tiagabine are the agents, used for neuropathic pain, but the efficacy of these drugs is still under consideration. Mechanism of action of these anticonvulsants drugs. includes either disturbance in the glutamatergic neurotransmission or possibly, altering the pathway of voltage-gated ion channels. Main aim of anticonvulsants is membrane stabilization. Carbamazepine and phenytoin reduce the action of descending excitatory pathways and at the same time, it also stimulates the inhibitor mechanism [45].

Selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitor (SNRI)

It is a class of antidrepressent, used for the management of diabetic neuropathy. Paroxetine is most common example of SSRI in patients with diabetic neuropathy, but it was measured less effective than imipramine (TCA), when observed in clinical trials. Sometimes imipramine is discontinued and replaced with paroxetine, due to intolerable side effects, whereas paroxetine does not show any side effect. So, 40mg paroxetine/day dose is safe to use for the peripheral diabetic patients [46]. SSRI and SNRI are currently among the medications, used as the first choice for the treatment of neuropathy, but their efficacy is still under further evaluation, through different clinical trials. If there is a condition, when TCA and anticonvulsant doesnot work, or are contraindicated, then SSRI and SNRI might be safely prescribed for the patients [47]. Serotonin-norepinephrine reuptake inhibitors have the characteristic activity of muscarine, histaminic and alpha 1 post synaptic receptor. Serotonin and noradrenaline are released from the nerve terminal to the location of synaptic cleft and after that, it binds with the post-synaptic receptors. SNRI helps in the blocking of proteins at the pre-synaptic neuron and works as reuptakers, due to which, increment of the concentration of neurotransmitters occurs at the synaptic cleft [48]. Duloxetine (SNRI), can also used for the painful peripheral neuropathy [49, 50].

Opioids

Opioids are generally prescribed, while the patient experiences moderate to severe pain, despite receiving adequate dose of previously mentioned treatments. It is a psychoactive chemical, used for pain control [51]. Clinical trials have shown the efficiency and efficacy of opioids (such as methadone, oxydone, morphine and levorphanol), and results are significant in the treatment of DPN, phantom limb pain and painful polyneuropathy [52]. Tramadol is also a weak opioid that has widely been studied in patients with moderate to severe neuropathic pain. The main mechanism of Tramadol involves activation of μ opioid receptor, which helps in the inhibition of reuptake of noradernaline and serotonin in the central nervous system. It is a weak opioid agonist and possess the same properties that of TCA.

Drug name	Mechanism of action in neuropathic pain	Common Adverse reactions	Special Consideration
Morphine	μ-opioid agonist		Constipation requires, concomitant bowel regimen Tramadol also blocks reuptake of 5 –HT; Note that the opioid receptor binding affinity is low, 6000x<that of morphine
Oxycodone	μ-opioid agonist		
Oxymorphone	μ-opioid agonist		
Tapentadol	μ-opioid agonist, inhibits reuptake of norepinephrine		
Tramadol	μ-opioid agonist, inhibits reuptake of norepinephrine	Drowsiness, sedation, constipation, dizziness, nausea/vomiting	
Fentyle (Abstral, Actiq, Duragesic, fentora, onsolis, Sublimaze, generic)	μ-opioid agonist		
Hydrocodone	μ-opioid agonist		
Levorphanol	μ- and k -opioid agonist, NMDA receptor antagonist, inhibits reuptake of NE		
Methadone	μ -opioid agonist, NMDA receptor antagonist, inhibits reuptake of NE		

Table 4. List of opioids drugs used for neuropathy pain: [53]

NMDA (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate) antagonists

A new class of drug, which are used for painful diabetic neuropathy, such as memantine and dextromethorphan. Study of NMDA antagonists are in exploratory phase [53]. These agents have psychotomimetic properties [54].

Topical Lidocaine

It is a sodium channel blocker, used for the treatment of neuropathic pain and post herpetic neuralgia [55]. In randomized clinical trial, total 5 % of the lidocaine patches have shown positive clinical outcome, in patients with PHN and allodynia. [56,57]. Lidocaine with 50% gel showed significant relief in the pain in PHN, upto 8 hours.

Lidocaine gel (5%) has demonstrated significant pain relief for up to 8 hours in postherpetic neuralgia.

Capsaicin

Patches of highly concentrated Capsaicin were studied in a randomized clinical trial, in patients with PHN and HIV neuropathy in 3 trials.PHN patients, in a phase 2 study, reported the effectiveness of high concentration and low concentration of patches, in reducing the pain with capsaicin, for the period of 8 weeks [58,59].

An overall summary of the evidence-based treatments, recommended for the management of neuropathic pain are outlined in Table-5.

Drug Therapy	Diabetic peripheral neuropathy	Post herpetic neuralgia	Trigeminal neuralgia
First Line	Duloxetine, Gabapentin, Pregabalin, Tri-cyclic Antidepressants Venlafaxine	TCAs Gabapentin, Pregabalin, 5% lignocaine patch Capsaicin	Carbamazepine Oxycarbazepine
Second or Third Line	Tramadol Opioids	Opioids Tramadol	Baclofen Lamotrigine

Table 5

Evidence-based treatments recommended for the management of neuropathic pain [60-65].

Conclusion

Lesions and other ailments have effects on the somatosensory system, which are considered as primary cause of neuropathic pain and represent important neurological challenges. Multiple mechanisms, such as peripheral sensitization ectopic activity are responsible for the neuropathic pain. Management of the neuropathic pain is a big challenge for the researchers. There are many drugs of choice; including but not limited to, tricyclic antidepressants, anti-convulsants and local anesthetics. TCA, SSNRIs, and topical lidocaine are examples, which are recommended as the first line of therapy. Additionally, second and third line of treatment would positively impate the patients' therapies. Management of neuropathic pain should be considered as an integral component for an overall comprehensive approach.

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