IJPSR (2023), Volume 14, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 May 2022; received in revised form, 12 July 2022; accepted, 02 August 2022; published 01 February 2023

AN INSIGHT INTO NEUROPATHIC PAIN: A SYSTEMIC AND UP-TO-DATE REVIEW

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Keywords:

Neuropathic Pain, Models, Classification, Treatment

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ABSTRACT: Neuropathic pain is a chronic illness that originates when abnormal functioning in the nervous system is observed or if the nervous system, including peripheral nerves, spinal cords, and brain, is damaged or not working properly, and originating pain. Therefore, it can be said that neuropathic pain is a chronic illness that directly impacts a large number of patients, society, and healthcare systems all over the world. The prevalence of neuropathic pain is believed to be 7-8% in the general population, and it is supposed to rise in the future. The impact of neuropathic pain on older persons is significant. The medical practitioner faces a problem in reducing neuropathic pain symptoms and improving the patient's quality of life. Older people are easily and badly affected by neuropathic pain and are more susceptible to specific adverse effects. Neuropathic pain is different from nociceptive pain, and there is a requirement for a different treatment strategy for neuropathic pain management. The present review article is based on a detailed literature survey on etiology, symptoms, disease progression, modern approaches to treating neuropathic pain, and the information about marketed drugs used for effective treatment. The recommendations of clinical practices for neuropathic pain are presented in this review and their utility in clinical practice. The outcome-based clinical data research is employed for managing neuropathic pain and mitigating the associated conditions.

INTRODUCTION: Neuropathic Pain (NP) is a chronic and complicated pain syndrome that frequently results from tissue damage. Neuropathic Pain is associated with the condition when the nervous system is damaged or not working in a good way. Sometimes, nerve filaments themselves may be damaged and malfunction, resulting in neuropathic pain. Neuropathic pain is caused by a disease or injury to the peripheral or central nervous systems and can strike at any time.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(2).607-21

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(2).607-21

These damaged nerve fibers send erroneous signals to other pain regions. A nerve function change occurs due to a nerve fiber injury at the lesion site and surrounding tissues. Positive sensory events, such as spontaneous pain, paresthesias and hyperalgesia are common clinical indicators of neuropathic pain. Neuropathic pain has been described as "the most horrifying of all the torments that a nerve wound may inflict [1].

Sensory abnormalities such as unpleasant aberrant sensations (Dysesthesia), an increased response to painful stimuli (Hyperalgesia), and pain in response to a stimulus that does not normally induce pain (Allodynia) characterized neuropathic pain [2]. Peripheral neuropathic pain is caused by a variety of conditions, including cancer, Acquired Immune

Deficiency Syndrome (AIDS), long-term diabetes, lumbar disc syndrome, herpes infection, traumatic spinal cord injury (SCI), multiple sclerosis and stroke [3, 4] post-thoracotomy, post-herniorrhaphy, post-mastectomy and post-sternotomy are all prevalent illnesses associated with peripheral neuropathy pain [5].

Pharmacotherapy for neuropathic pain has had mixed outcomes, with regularly recommended pain medications such as Non-steroidal Anti-inflammatory Drugs (NSAIDs) and opioids showing little or no effect. As a result, new therapy options must be investigated urgently. It's difficult to assess neuropathic pain in people since most stimuli induce it to cause irreversible damage. As a result, only humans are permitted to be exposed to stimuli that do not cause permanent harm. Furthermore, obtaining a large number of human subjects for such testing is difficult. As a result, validated and easily repeatable animal models of neuropathic pain are needed to advance our understanding of the mechanisms underlying neuropathic pain and to assess the analgesic potential of novel pharmacotherapies for neuropathic pain treatment. Ideal models should elicit sensory deficits such as allodynia, hyperalgesia, and spontaneous pain that are repeatable over time. Using sensory abnormalities in animals, several human physiopathological illnesses can be replicated, allowing for the investigation of pharmacotherapies. For example, peripheral nerve injury and Spinal Cord Injury (SCI) induced peripheral and central pain models of neuropathy have been established to accommodate the many etiologies and, as a result, the various manifestations of neuropathy. Chemotherapeutic drug-induced pain, cancer and Human Immunodeficiency Virus (HIV) induced pain, Post Herpetic Neuralgia (PHN), diabetic and chronic ethanol-induced pain, trigeminal neuralgia, and or facial pain models have all been built. The classification of neuropathic pain, epidemiology, and pathophysiology of numerous animal models of neuropathic pain are covered in depth in this review.

Classification of Pain: Based on the classifications established by Siddall, Taylor, and Cousins for spinal cord injury, the forms of pain are classified by symptom/sign combinations.

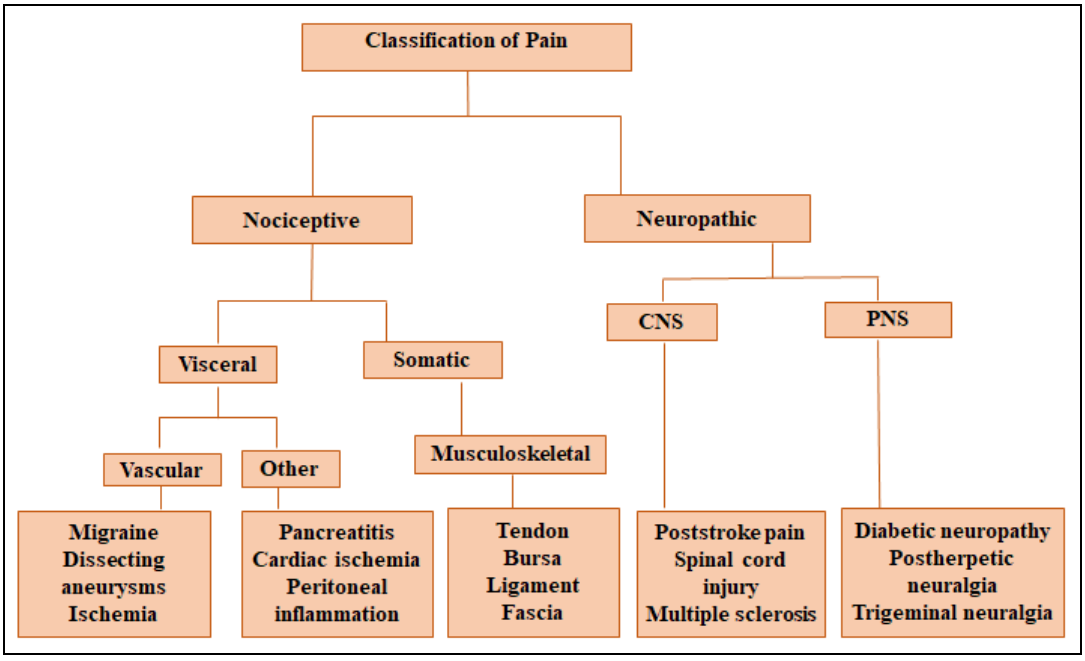

FIG. 1: CLASSIFICATION OF PAIN

Epidemiology: The lack of clear diagnostic criteria for large epidemiological surveys in the general population has made estimating the incidence and prevalence of neuropathic pain problematic. Studies undertaken by the specialized center focusing on specific illnesses, such as postherpetic neuralgia unpleasant diabetic polyneuropathy post-surgery neuropathic pain, are thus necessary. The prevalence of neuropathic pain in the chronic pain population has mostly been estimated using

multiple sclerosis, spinal cord injury, stroke, and cancer [6, 7]. Simple screening methods in the form of questions have recently been developed to facilitate the conduct of several large epidemiological surveys in nations such as the United Kingdom, the United States, France, and Brazil. They were given fresh information on the prevalence of neuropathic pain, in general, using screening tools such as the Douleur Neuropathique, the prevalence of chronic pain with neuropathic characteristics has been estimated to be in the range of 7-10% [8, 9]. Chronic neuropathic pain is more common in women (8% against 5.7% in men) and patients over 50 years old (8.9% versus 5.6% in those under 49 years old), with the most typically affected areas being the lower back and lower limbs, neck and upper limbs [10]. The most common cause of chronic neuropathic pain is lumbar and cervical painful radiculopathies. According to these findings, 40% of all patients with chronic pain, both nociceptive and neuropathic, who were referred to pain specialists in Germany have at least some neuropathic pain symptoms (such as burning sensations, numbness and tingling), with patients with chronic back pain and radiculopathy being particularly affected [11, 25].

Pathophysiology: Somatic pain (originating in the skin, bone, joint, muscle, or connective tissue) and visceral pain (originating in the internal organs) are two different types of pain (arising from internal organs such as the large intestine or pancreas). Stimulating free nerve endings, also known as nociceptors, is the initial step in producing pain. Mechanical, thermal, and chemical variables activate these receptors, which are located in both somatic and visceral regions. Bradykinins, potassium, prostaglandins, histamine, leukotrienes, serotonin, and substance-P are all known to sensitize or activate nociceptors. Action potentials are generated when receptors are activated and communicated to the spinal cord *via* afferent nerve fibers. Action potentials go from the noxious stimulus location to the dorsal horn of the spinal cord before ascending to higher areas.

The thalamus serves as a relay station, relaying pain signals to central structures for further processing. Several mechanisms in the body control pain. Neurotransmitters (e.g., enkephalins, dynorphins, and β-endorphins) and receptors (*e.g.*, μ, δ, κ) located throughout the Central Nervous System (CNS) make up the endogenous opiate system. Endogenous opioids attach to opioid receptors and alter pain impulse transmission. A descending mechanism for pain transmission control is also found in the central nervous system. This system is based in the brain and can block synaptic pain transmission in the dorsal horn. Endogenous opioids, serotonin, norepinephrine, γ-aminobutyric acid and neurotensin are all important neurotransmitters in this area.

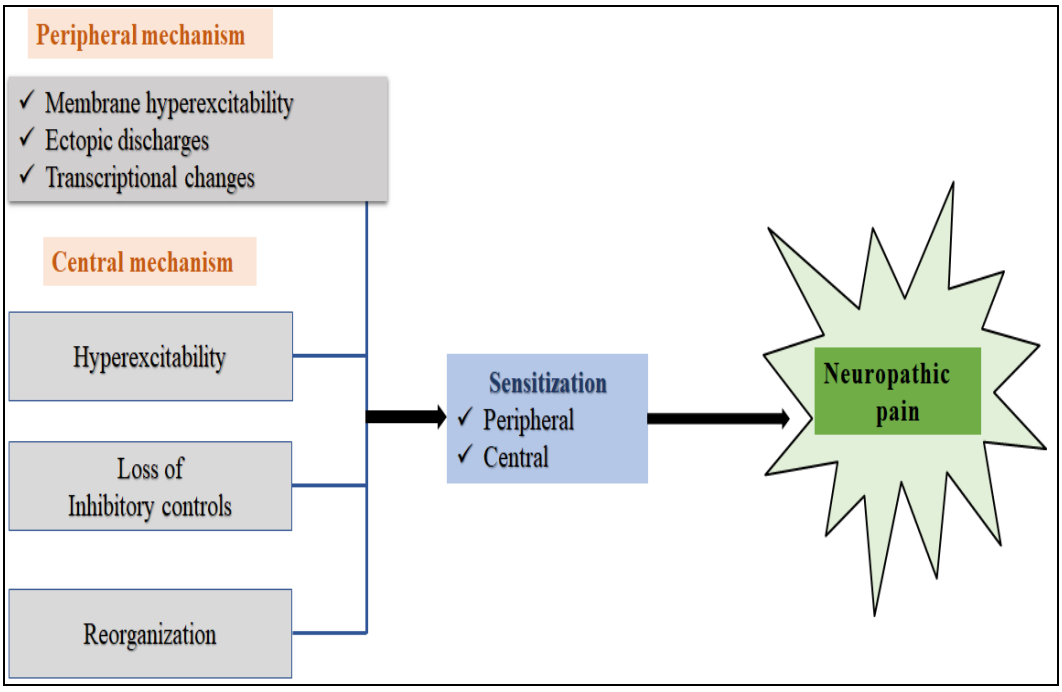

FIG. 2: PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Signs & Symptoms: Hypertension, tachycardia, diaphoresis, mydriasis and pallor are all acute pain symptoms, although they are not diagnostic. These symptoms are uncommon in chronic pain sufferers. Comorbid disorders are rarely prevalent in acute pain, and treatment effects are usually predictable. Comorbid diseases are common in chronic pain, and treatment outcomes are frequently uncertain. Because pain is always subjective, the best approach to identify it is through a patient's description, history, and physical examination. Assessing Palliative / Provoking, Quality Radiation Severity Timing (PQRST) features can provide a baseline description of discomfort (palliative and provocative factors, quality, radiation, severity, and temporal factors). Mental variables that may lower the pain threshold should be considered (anxiety, depression, fatigue, anger, and fear).

Pain can be influenced by behavioural, cognitive, social, and cultural variables. Neuropathic pain is frequently chronic, poorly understood, and difficult to treat with traditional analgesics. Exaggerated painful reactions to typically noxious stimuli (Hyperalgesia) or painful responses to usually noxious stimuli (Hyperalgesia) are both possible (Allodynia).

Sharp or dull pain, scorching, shock-like, tingling, shooting, radiating, variable in intensity, varying in location, and happening in a temporal relationship with identifiable noxious stimuli are all acute pain. Chronic pain can show in various ways, and it frequently happens without a clear link to a noxious stimulus. The appearance of chronic pain may change with time (e.g., sharp to dull, obvious to vague).

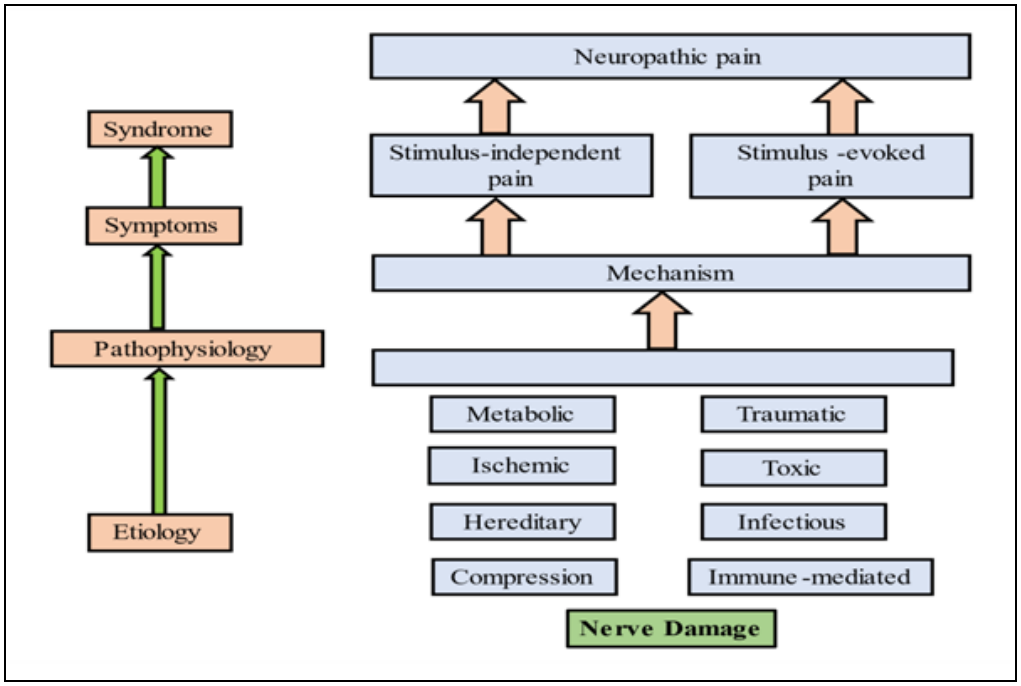

FIG. 3: ETIOLOGY, SYMPTOM AND MECHANISM

Causes and Distributions: A lesion or disease of the spinal cord/brain causes central neuropathic pain. Cerebrovascular disease impacting the central somatosensory pathways and neurodegenerative diseases are common causes of central neuropathic pain [26]. Spinal cord lesions or diseases that cause neuropathic pain include spinal cord injury, syringomyelia, and demyelinating disorders such as multiple sclerosis, transverse myelitis, and neuromyelitis optica [27]. Short unmyelinated C fibres and myelinated A-fibers, referred to as Aβ and Aδ fibers are involved in the pathophysiology of peripheral disorders that cause neuropathic pain. Peripheral neuropathic pain is expected to grow more common as the world's population ages, diabetes mellitus becomes more common and cancer and chemotherapy side effects affect all sensory fibers (Aβ, Aδ and C fibers) become more common. Peripheral neuropathic pain disorders are divided into two categories: those with a generalized (usually symmetrical) distribution and those with a localized distribution. The most clinically important painful Peripheral neuropathic pain disorders are divided into two categories:

those with a generalized (usually symmetrical) distribution and those with a localized distribution. Among the most clinically important painful generalized peripheral neuropathies are diabetes mellituspre-diabetes and other metabolic dysfunctions, infectious diseases and inflammatory disorders, inherited neuropathies, and channelopathies (such as inherited erythromelalgia, a disorder in which blood vessels are episodically blocked) and inherited neuropathies and channelopathies (such as inherited erythromelalgia, a disorder in which blood vessels) generalized peripheral neuropathies are diabetes mellitus, pre-diabetes, and other metabolic dysfunctions, infectious diseases and inflammatory disorders, inherited neuropathies and channelopathies (such as inherited erythromelalgia, a disorder in which blood vessels are episodically blocked) and inherited neuropathies and channelopathies (such as inherited erythromelalgia, a disorder in which blood vessels).

Because the feet, calves, hands, and forearms are most visibly afflicted, the topography of pain in these illnesses often involves the distal extremities, which is known as a "glove and stocking" distribution. This pattern is common in distal peripheral neuropathies, which are characterized by distal-proximal increasing sensory loss, pain, and distal weakness [28, 29]. When the disorder includes the sensory ganglia, the pain has a proximal distribution that affects the trunk, thighs, and upper arms. Pathological processes involving one or more peripheral nerves or nerve roots are responsible for painful localized peripheral diseases. Postherpetic neuralgia, post-traumatic neuropathy, postsurgical neuropathy, cervical and lumbar poly-radiculopathies, pain associated with HIV infection, leprosy and diabetes mellitus, complex regional pain syndrome type 2 and trigeminal neuralgia are all examples of this illnesses [30]. Pain distributions and triggering events can be distinctive in rare hereditary channelopathies. Inherited erythromelalgia, for example, is caused by mutations in sodium voltage-gated channel alpha subunit 9 (SCN9A), which encodes the voltage-gated sodium channel Na_v 1.7 (involved in the generation and conduction of action potentials) and is characterized by pain and erythemain the extremities, which is aggravated by heat [31]. Mechanical stimuli can produce pain in persons with severe paroxysmal pain disorder, characterized by a group of SCN9A mutations that cause pain and erythema in the sacrum and mandible [32].

Changes in Pain Signaling: Peripheral neuropathy alters the electrical properties of sensory nerves, causing an imbalance in central excitatory and inhibitory signalling and affecting inhibitory interneurons and the descending control system [33]. Sensory signal transmission and disinhibition or facilitation processes in the spinal cord's dorsal horn neurons are affected as a result. Indeed, preclinical studies have revealed numerous anatomical, molecular and electrical alterations that result in a transfer of function from the peripheral nervous system to the central nervous system, shedding insight into neuropathic pain and its treatment. In the periphery, spinal cord, and brain, there is an increase in excitation and facilitation, as well as a lack of inhibition.

Sensory pathways become hyperexcitable due to these changes, and a cascade of changes from the periphery to the brain over time may contribute to the development of chronic neuropathic pain. Ectopic activity in primary afferent fibers could contribute to the development of neuropathic pain after peripheral nerve damage. After receiving a peripheral nerve block (with painful diabetic polyneuropathy and traumatic peripheral nerve injury demonstrated a full reduction in ipsilateral spontaneous and evoked pain [34]. In people with phantom limb pain, a lidocaine intraformational epidural injection blocked the dorsal root ganglion, reducing both painful and non-painful feelings [35]. Pain-related spontaneous activity has also been detected in microneurography investigations, particularly in C fibers, implying a peripheral basis for neuropathic pain [36, 37]. Changes in ion channel function and expression, as well as in second-order nociceptive neuronal function and interneuronal inhibitory activity, all contribute to the underlying hyperexcitability in neuropathic pain.

Ion Channel Alterations: Neuropathy affects sensory signalling in the spine and brain by altering ion channels (sodium, calcium, and potassium) in the afflicted nerves, which can comprise all afferent fibres. Increased expression and activity of sodium channels at the spinal cord terminus of sensory

nerves (mirrored by enhanced expression of the $\alpha 2^{\delta}$ subunit of calcium channels) result in increased excitability signal transduction and neurotransmitter release. The importance of sodium channels can be seen in the loss or increase of pain in people with genetic channelopathies. At the same time, a shortage of potassium channels, which generally regulate brain activity, can be seen. Sensory loss occurs if an afferent fibre is disconnected from the periphery due to an injury or a lesion. On the other hand, Ectopic activity might be generated by the remnants of the fibres at the lesion site (for example, neuroma C fibre afferents), resulting in discomfort from a 'numb' area [38]. Irrigatable nociceptorsare intact hyperexcitable fibres [39]. As a result, the patient may have chronic pain, numbness, or evoked pains. Changed spinal cord inputs paired with increased calcium channel activity result in increased neurotransmitter release and enhanced excitatory synaptic transmission in the nociceptive circuit due to greater expression in the nerve terminal.

Alterations in Second-Order Nociceptive Neurons: Increased excitability of spinal neurons enhances responses to various sensory modalities and enables low-threshold mechanosensitive Aβ and Aδ afferent fibers to activate second-order nociceptive neurons (which transmit sensory information to the brain) and expands their receptive fields and results in central sensitization [40,41]. Continuous discharge of peripheral afferent fibers with the concurrent release of excitatory amino acids and neuropeptides causes postsynaptic changes in second-order nociceptive neurons, such as an excess of signalling due to phosphorylation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [42, 43].

These second-order changes, matched by increased sensory thalamic neuronal activity, can plausibly explain physical allodynia, as evidenced by animal and human research. The loss of gamma-aminobutyric acid (GABA) releasing inhibitory interneurons, which allows them to flip to excitatory activity at the spinal level, can cause hyper excitability [44]. Microglia and astrocytes, which are non-neuronal cells in the spinal cord, have less well-understood functional alterations that contribute to hypersensitivity development [45].

Mechanisms of Pain Neuropathic Variation: Minor symptoms are experienced by some people with neuropathic pain, whereas others experience severe symptoms. Patients' reactions to various pharmacological and non-pharmacological treatments (in terms of type and dose) are extremely varied. A crucial component in this variance could be how the pain message is transformed in the CNS [46, 47]. As it ascends from its entry port (the dorsal horn), travels through the CNS, and reaches the cerebral cortex, the pain signal can be amplified or diminished (the area crucial for consciousness). As a result of the numerous channels and interference, the stated relationship between the level of peripheral pathology and the extent of the pain syndrome can be altered. Most neuropathic pain sufferers have a pro-nociceptive pain modulation profile, indicating that pain signals in the CNS are amplified [48].

Thus, diminished descending endogenous inhibition (indicated by less-effective Chlorpheniramine (BOX-1), aided by sensitization of ascending pain pathways (represented by the greater temporal summation of painful stimulations), or both might disinhibit pain perception. Temporal summation is improved in both neuropathic and nonneuropathic pain, but the increased slope is higher in neuropathic pain sufferers. CPM is less helpful in individuals with a variety of pain conditions than in healthy controls [49]. The concept of using pain modulation for a more individualized approach to pain management seems appealing. According to the study, the pain modulation profile can predict the onset and severity of persistent postoperative pain [50, 54].

Patients with a facilitatory pro-nociceptive profile may be treated with a drug that reduces facilitation (such as gabapentinoids), while patients with an inhibitory pro-nociceptive profile may be treated with a drug that increases inhibitory capacity; if these findings are confirmed in larger studies (for example, serotonin-noradrenaline reuptake inhibitors). Patients with both a low CPM and a high temporal summation may need a combination of treatments Duloxetine (a selective serotonin-noradrenaline reuptake inhibitor) and tapentadol (a noradrenaline reuptake inhibitor) both restore CPM in patients [55]. Furthermore, when pain is treated, a patient's altered pain modulation profile can be

restored to normal, as shown by arthroplasty surgery in osteoarthritis patients; when the diseased joint is replaced, most patients will be pain-free and the central and peripheral processes will return to normal. Expectancy-induced analgesia, in which patients' opinions and desires influence changes in responsiveness to treatment for neuropathic pain, has a major impact on pain modulation. In laboratory settings, expectation-induced analgesia affects clinical pain in irritable bowel syndrome idiopathic and neuropathic pain [56, 61] investigated expectation-induced analgesia in people who had neuropathic pain after a thoracotomy. Patients were given lidocaine in the open (that is, patients were told: "The agent you have just been given is known to reduce pain in some patients powerfully") or hidden (that is, this is a control condition for the active medication) manner according to a previously described protocol; the results showed a large reduction in ongoing pain, maximum wind-up-like pain and an area of hyperalgesia in the open group, confirming previous reports. These findings point to an endogenous pain inhibitory mechanism that could be useful in clinical trial designs and practices for phenotyping neuropathic pain patients. Such effects should be minimized in clinical trials and purposefully augmented in daily clinical operations as a strategy to maximize pain management.

Animal Models of Neuropathic Pain: There are various types of neuropathic pain models in **Table 1.**

TABLE 1: DIFFERENT TYPES OF ANIMAL MODELS FOR NEUROPATHIC PAIN [62]

S. no.	Name of models	Principle of injury	Species	References
1	Axotomy (complete sciatic nerve transection)	Axotomy (complete sciatic nerve transection)	Rats	63
2	Chronic constriction injury	Four loose ligatures around sciatic nerve	Rats & mice	64
3	Partial sciatic nerve ligation (Seltzer Model)	Tight ligation of one-third to half of sciatic nerve	Rats & mice	65
4	Spinal nerve ligation	Tight ligation of L5 and L6 spinal nerves tight ligation of L7 spinal nerve	Rats Rats	66 67
5	Spared nerve injury	Axotomy of tibial and common peroneal nerves	Rats & mice	68
6	Tibial and sural nerve transection	Axotomy of tibial and sural nerves	Rats	69
7	Ligation of common peroneal nerve	Ligation of common peroneal nerve	Mice	70
8	Sciatic cryoneurolysis	Freezing of the sciatic nerve	Rats	71
9	Caudal trunk resection	Resection of caudal trunk	Rats & mice	72
10	Sciatic inflammatory neuritis	Injection of zymosan, HMGand TNF-alpha aroundthe sciatic nerve	Rats & mice	73
11	Cuffing-induced sciatic nerve injury	Implantation of polyethylene cuff around the sciatic nerve	Rats & mice	74,75
12	Photochemical-induced sciatic nerve injury	Thrombosis in small vessels supplying sciatic nerve by photosensitizing dye and laser	Rats & mice	76
13	Laser-induced sciatic nerve injury	Radiation mediated reduction in blood supply to the sciatic nerve	Rats	77
14	Weight-drop or contusive spinal cord injury	Dropping a weight over the exposed spinal cord	Rats & mice	78,79
15	Excitotoxic spinal cord injury	Intraspinal injections of excitatory amino acids	Rats & mice	80
16	Photochemical spinal cord injury	Thrombosis in blood vessels supplying the spinal cord by photosensitizing dye and laser	Rats	81
17	Spinal hemisection	Laminectomy of T11-T12 segments.	Rats	82
18	Drugs-induced Anti-cancer agents (vincristine, cisplatin, oxaliplatin, paclitaxel) Anti-HIV agents (2,3 dideoxycytidine, didanosine)	Anti-HIV agents (2,3-dideoxycytidine,didanosine)	Rats & mice Guinea pigs Rabbits& rats	83 84,85
19	Diabetes-induced neuropathy Streptozotocin-induced Genetic models	Persistent hyperglycemia-induced changes in the nerves	Rats & mice	86,87
20	Bone cancer pain models Femur, calcaneus, tibial, humerus bone	Inoculation of cancerous cells into respective bones Growing a tumor in the vicinity of the	Rats & mice	88,89

	cancer pain (a) Neuropathic cancer pain (b) Skin cancer pain	sciatic nerve Injection of melanoma cells in the plantar region of the hind paw	Mice Mice	90,91 92
21	HIV-induced neuropathy	Delivery of HIV-1 protein gp 120 to the sciatic nerve	Rats	93
22	Post-herpetic neuralgia Varicella Zoster virus Herpes simplex virus (a) Non-viral model	Injection of virally infected cells in the footpad Depletion of capsaicin-sensitive Afferents with resiniferotoxin	Rats & mice Rats	94,95 96,97
23	Chronic ethanol consumption/withdrawal	Administration of ethanol over an extended period (around 70 days)	Rats	98
24	Pyridoxine-induced	Administration of high-dose pyridoxine for a long period	Dogs & rats	99
25	Trigeminal Neuralgia	Compression of trigeminal ganglion chronic constriction injury to the infraorbital nerve	Rats Rats	100 101
26	Orofacial pain	Injection of formalin, carrageenan into temporomandibular joints and maxilla	Rats & mice	102
27	Acrylamide-induced	Administration of acrylamide for a prolonged period	Rats	103,104

Pharmacological Treatment for Neuropathic Pain: Because of misunderstandings regarding the pathophysiology of their pain, the elderly and the young are at a higher risk of undertreatment. The process of pain management is shown in **Fig. 4**. The agents used for pain management are non-opioid and opioid agents respectively.

Nonopioid Agents: Analgesia should be initiated with the most effective analgesic with the fewest side effects. Adult dosage, half-life, and selected pharmacodynamics of FDA-approved non-opioid analgesics are shown in **Table 2**.

Non-opioids are preferred over opioids for mild to moderate pain. Salicylates and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) diminish the number of pain signals received by the CNS by reducing prostaglandins produced by the arachidonic acid cascade. NSAIDs may be especially beneficial in the treatment of cancer-related bone pain.

NSAIDs are more prone to induce gastrointestinal problems. Salicylate salts have fewer Gastrointestinal (GI) adverse effects than aspirin and don't stop platelets from clumping together. Reye's syndrome can occur if aspirin-like chemicals are administered to children or teenagers with influenza or chickenpox. Acetaminophen possesses analgesic and antipyretic properties but not much in the way of anti-inflammatory properties. When taken in excess, it is extremely hepatotoxic.

Opioid Agents: The beginning of action for oral opioids takes about 45m and the maximal effect takes about 1 to 2 h. Demonstration of equianalgesic dosages, dosing guidelines histamine-releasing properties, significant side effects and opioid pharmacokinetics are present in **Table 2** and **3**.

The equianalgesic doses are simply a suggestion; doses must be tailored to the patient's needs. Partially agonists and antagonists compete for opioid receptor sites with agonists, resulting in mixed agonist-antagonist action.

They may target analgesic receptor sites with greater selectivity, resulting in fewer adverse effects. Analgesics should be given around the clock in the early stages of acute pain therapy. Schedules can be employed on an as-needed basis as the unpleasant state subsidies. Chronic pain management can also benefit from round-the-clock administration. Patients with acute pain may be given extremely high doses of opioids with no negative side effects, but once the pain lessens, even low dosages may be too much for them.

Most itching and rash caused by opioids is due to histamine release and mast cell degranulation rather than an allergic reaction. When an opioid causes an allergic reaction, medication from a different structural class of opioids should be tried with caution. A mixture of agonist/antagonist classes performs like morphine-like agonists for these uses [105].

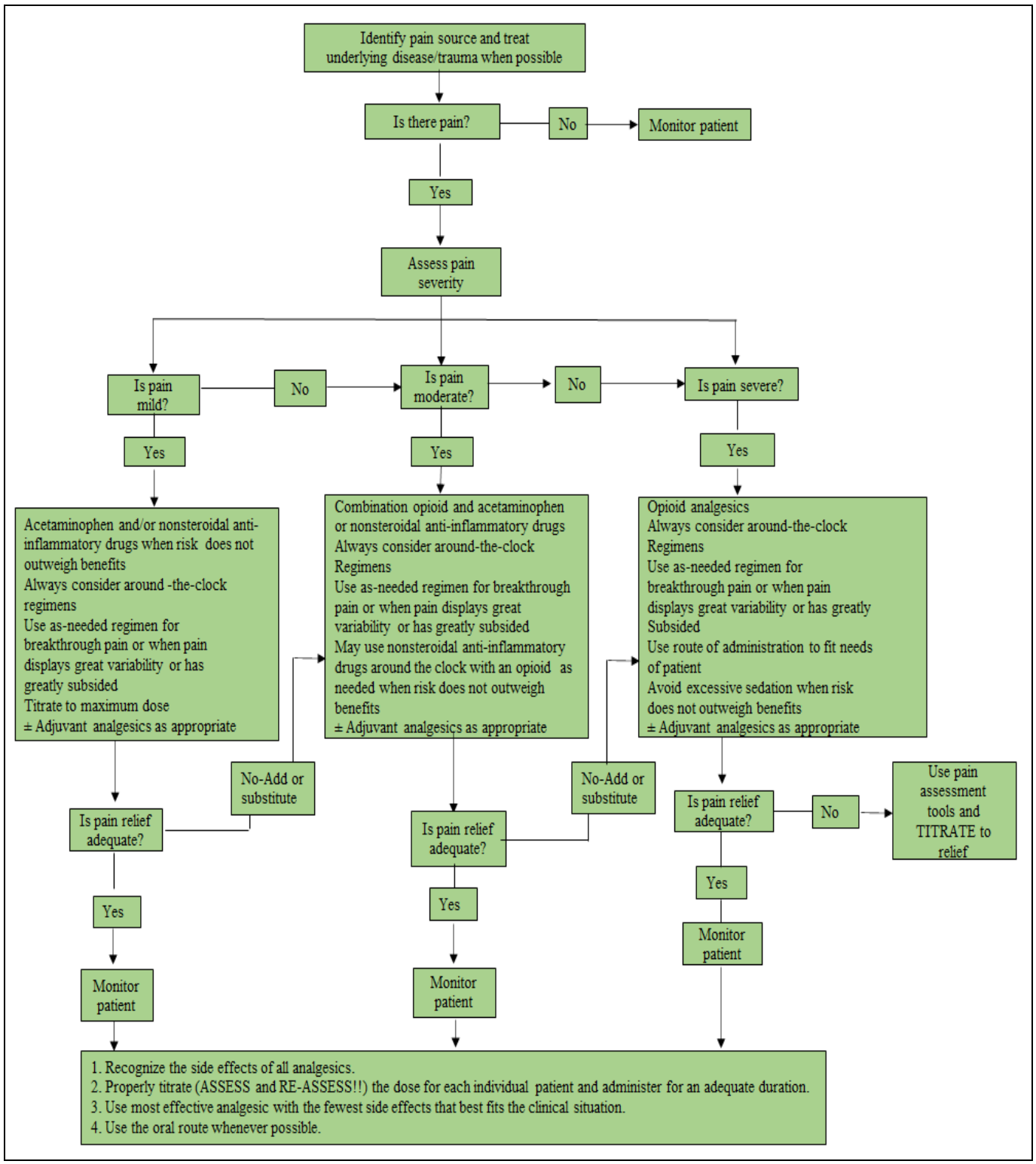

FIG. 4: THE PROCESS OF NEUROPATHIC PAIN MANAGEMENT

TABLE 2: FDA-APPROVED NON-OPIOID DRUGS

Class and generic name	Half-life	Dosage (mg)	Maximal dose (mg)
Salicylates: Acetylsalicylic acid-aspirin	0.25	325-1,000 q 4-6 h	4,000
Magnesium-anhydrous (Doan's,	Nd/Nd	304-607 q 4 h	3,738
combinations of choline and magnesium	8-12	607-934 q 6 h	1,500
are available) Diflunisal (Dolobid,)		500-1,000 initial	
		250-500 q 8-12 h	
Para-Aminophenol: Acetaminophen[a]	2-3	325-1,000 q 4-6 h	4,000[b]

(Tylenol)			
Fenamates: Meclofenamate Mefenamic	0.8-2.1	50-100 q 4-6 h	400
acid (Ponstel)	2	Initial 500 250 q 6 h (maximum 7 days)	1,000[c]
Pyranocarboxylic acid: Etodolac	7.3	200-400 q 6-8 h	1,000
(immediate release)			
Acetic acid: Diclofenac potassium		In some patients, an initial 100, 50 three	150[d]
(Cataflam)	1.9	times per day	
Propionic acids: Ibuprofen[a] (Motrin)	2-2.5	200-400 q 4-6 h	3,200[e]
Fenoprofen (Nalfon) Ketoprofen Naproxen	3	200 q 4-6 h	2,400[e]
(Naprosyn, Anaprox) Naproxen sodium[a]	2	25-50 q 6-8 h	1,200[f]
(Aleve, various)	12-17	500initial	3,200
	12-13	500 q 12 h or	300
		250 q 6-8 h	1000[c]
		In some patients, 440 initial f	660[f]
		660f 220 q 8-12 hf	
Pyrrolizine carboxylic acid: Ketorolac-	5-6	30-60 (single) IM dose only)	30-60
parenteral Ketorolac-oral indicated for	5-6	15-30 (single) IV dose only)	15-30
continuation	11	10 q 4-6 h (maximum of 5 days,	60-120
with parenteral only		which includes parenteral	40
Cyclooxygenase-2 inhibitors: Celecoxib		doses) In some patients, initial oral	400
(Celebrex)		dose of 20 Initial 400 followed by	
		another 200 on the first day, then 200	
		twice daily	

a: available both as a non-prescriptionover-the-counter preparation and as a prescription drug. b: Some experts believe 4,000mg/high c: Up to 1,250 mg on the first-day d: Up to 200 mg on the first-day e: Some individuals may respond better to 3,200 mg as opposed to 2,400mg, although well-controlled trials show no better response; f: Nonprescription dose.

TABLE 3: OPIOID ANALGESIC

Class and name of drugs	Chemical source	Route	Equianalgesic dose in adults (mg)	Onset (minutes) /Half-life (hours)
Phenanthrenes (morphine-like	Naturally,	i.m, p.o, i.m	10, 30, 1.5, 7.5	10-20/2, 10-20/2-3
agonists): Morphine,	occurring	p.o, i.m	1, 5[a], 10, 2 (acute), 4	10-20/2-3, 10-
Hydromorphone, (Dilaudid)	Semisynthetic	R, p.o, i.m	(acute), 1 (chronic), 1	20/12-16, 10-30/3,
Oxymorphone (Numorphan, Opana)	Semisynthetic	p.o, i.m	(chronic), 15-30[b]	30-60/4, 30-60/2-3
Levorphanol Codeine Hydrocodone	Semisynthetic	p.o, i.m, p.o	15-30[b], 5-10[b], 20-30[c],	10-20/3-4, 7-15/3-4
(availableas a combination)	Naturally	p.o, p.o, i.m, p.o	75, 50-150[b]	
Oxycodone	occurring	i.m,	0.1, 25 mcg/hour [d]	
Phenylpiperidines (meperidine-like	Semisynthetic	Transdermal	Variable[e] Variable[f]	
agonists): Meperidine (Demerol)	Semisynthetic	Buccal,,	(acute)	
Fentanyl (Sublimaze, Duragesic)	Synthetic	transmucosal,		
Diphenylheptanes (methadone-like	Synthetic	i.m		
agonist): Methadone	Synthetic			
(Dolophine) Propoxyphene	Synthetic,	p.o, i.m	Variable[f] (acute)	30-60/12-190, 30-
(Darvon) Agonist-antagonist	Synthetic	p.o, p.o, i.m, p.o	Variable[f,] (chronic)	60/6-12, 15-30/2-3,
derivatives: Pentazocine (Talwin)	Synthetic,	i.m, Intranasal	Variable[f](chronic)	10-20/3-4 <15/5,
Butorphanol (Stadol) Nalbuphine	Semisynthetic,	i.m, i.m, i.v, p.o	65[b], Not	10-20/2-3, 1-2 (IV),
(Nubain) Buprenorphine (Buprenex)	Semisynthetic		recommended, 50[b], 2,	2-5(IM)/0.5-1.3,
Antagonists: Naloxone (Narcan)	Synthetic		1[b](one spray), 10,	<60/5-7
Central analgesic: Tramadol (Ultram)	Synthetic		0.4, 0.4-2[g], 50-100[b]	

a: The American pain society considers 5mg rectal morphine = 5mg rectal oxymorphone. b: Starting dose only (equianalgesic not shown). c: Starting doses lower (oxycodone 5-10mg, meperidine 50-150mg). d: Equivalent po morphine dose= 45-134 mg/day. e: For breakthrough pain only. f:The equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose has been. g: Starting doses to be used in cases of opioid overdose.

Morphine and Congeners (Phenanthrenes): Many clinicians regard morphine to be the first-line treatment for moderate to severe pain. In ambulatory patients and with the initial dose, nausea and vomiting are more likely. As the dose is raised, respiratory depression becomes more pronounced. It usually presents as a decrease in respiratory rate, as well as a weakened cough reflex. Patients with underlying pulmonary dysfunction are more likely to have respiratory

problems. Naloxone can be used to treat respiratory depression. When opioid analgesics are used with alcohol or other CNS depressants, CNS depression is increased, which is hazardous and even lethal. Morphine causes venous and arteriolar dilatation, leading to orthostatic hypotension (low blood pressure). Dehydrated patients are more vulnerable to morphine-induced hypotension. Because it lowers myocardial oxygen demand, morphine is frequently used to relieve pain associated with myocardial infarction. Constipation, spasms of the sphincter of Oddi, urine retention, and itching (due to histamine release) are all side effects of morphine. In head trauma patients who are not ventilated, morphine-induced respiratory depression may raise intracranial pressure and confound neurologic test results.

Meperidine and Congeners (Phenylpiperidines): Meperidine is less effective and has a shorter duration of action than morphine; the metabolite normeperidine accumulates in high dosages or in people who have kidney failure, causing tremors, muscle twitching, and possibly seizures. It is no better than morphine in most circumstances and should not be used long-term. Meperidine should not be combined with monoamine oxidase inhibitors in the elderly or those with renal impairment since it might produce severe respiratory depression, excitation, delirium, hyperpyrexia, and convulsions. Fentanyl is a synthetic opioid with a meperidine-like structure. It's frequently used as a supplement to general Anesthesia in anesthesiology. It has a higher potency and a shorter duration of action than meperidine. Chronic pain that requires opioid analgesics can be treated with transdermal fentanyl. It takes 12 to 24 h after applying a patch to achieve the best analgesic effect and analgesia can continue up to 72 h. After increasing a dose, it can take up to 6 days to attain new steady-state levels. As a result, the fentanyl patch should not be used in cases of acute pain. A fentanyl lozenge and a buccal dosage form are available to treat breakthrough cancer pain.

Methadone and Congeners (Diphenyl Heptanes): Methadone has oral effectiveness, a longer duration of action and the ability to reduce withdrawal symptoms in heroin users. With repeated doses of methadone, the analgesic's duration of action is lengthened, although significant drowsiness is also possible. Despite its usefulness for acute pain, it is most typically used for persistent cancer pain.

Opioid agonist-antagonist Derivatives: This class induces analgesia and has a lower misuse potential than morphine due to its ceiling effect on respiratory depression. However, psychotomimetic reactions (*e.g.,* hallucinations and dysphoria with pentazocine), a ceiling analgesic effect, and the potential to induce withdrawal in opioid-dependent individuals have limited their use.

Opioid Antagonists: Naloxone is an opioid antagonist that binds to opioid receptors competitively but does not have an analgesic effect. It's utilized to counteract the negative effects of opioid agonists and agonist-antagonists.

Central Analgesic: Tramadol is a centrally acting analgesic that binds to opiate receptors and inhibits the reuptake of norepinephrine and serotonin by a small amount. It's used to alleviate the pain that's moderate to severe. Tramadol's side-effect profile is similar to that of other opioid analgesics. It may also make you more likely to have a seizure. Although it has no advantage over other opioid analgesics in treating acute pain, it may be effective in treating chronic pain, particularly neuropathic pain.

Combination Therapy: Analgesia is often superior to monotherapy when an opioid and non-opioid oral analgesic are used together, and lesser doses of each medication may be used. An NSAID with a timed opioid dose is generally beneficial for painful bone metastases.

Evaluation of Therapeutic Outcomes: Regular monitoring of pain severity, relief, and medicine side effects is critical. The type of pain and the medications used dictate the frequency and timing of assessments. Chronic nonmalignant pain may only necessitate daily (or less frequent) monitoring, whereas postoperative pain and acute cancer pain may necessitate hourly evaluation. All the quality of a patient’s life must be examined regularly. The best way to deal with opioid-induced constipation is to avoid it. With prolonged opioid usage, patients should be advised on proper fluid and fiber consumption and a laxative should be administered.

If acute pain does not go away within the expected time frame (typically 1 to 2 weeks), the cause should be investigated further.

CONCLUSION: Neuropathic pain is a common ailment that has a detrimental impact on those who suffer from it. Several professional organizations have developed clinical practice guidelines for diagnosing and treating neuropathic pain. Still, methodological and conceptual issues limit their applicability in routine clinical practice and the reliability of the evidence on which these guidelines are based. Innovative pharmacological therapies are required to address the present challenges surrounding the treatment of neuropathic pain, such as limited pain relief efficacy and poor quality of life in people affected.

Because neuropathic pain has numerous etiologies, various animal models of neuropathic pain have been developed. Models based on ligation-mediated peripheral nerve injury have grown increasingly popular. On the other hand, peripheral nerve branch-based models have distinct advantages and are now being employed more frequently.

Spinal hemisection and excitotoxin-induced SCI are the models of choice for studying central pain pathways. Furthermore, several research organizations have used pain models generated by chemotherapeutic medications, diabetes, HIV, alcoholism, and other etiologies to better understand the pathophysiology and manage pain in clinical settings.

ACKNOWLEDGEMENTS: The author is grateful to the IFTM University, Moradabad, for providing the necessary facilities for this review work.

CONFLICTS OF INTEREST: The authors declare no conflict of interest regarding the publication of this paper.

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How to cite this article:
Sharma H, Rani T and Khan S: An insight in to neuropathic pain: a systemic and up-to-date review. Int J Pharm Sci & Res 2023; 14(2): 607-21. doi: 10.13040/IJPSR.0975-8232.14(2).607-21.