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Review Article

Pharmacology Section

Unveiling the Hidden Agony: Exploring Neuropathic Pain in the Younger Generation: A Narrative Review

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ABSTRACT

Pain is described as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage." Neuropathic Pain (NP), a common condition, is characterised by subjective negative and positive sensations that range from numbness to debilitating agony. The prevalence of chronic pain and nerve pain in young individuals is estimated to be around 30%-50% and 6%-11%, respectively. The exact cause of NP is unknown, but research suggests that factors such as allodynia, external sensitisation, neuronal swelling, free radical damage, activation of microglia, and physiological state play a significant role in its development and progression. While there have been recent suggestions for medications, neurostimulation techniques, and interventional management, comprehensive guidelines covering all these treatments are yet to be released. Both peripheral and Central Nervous System (CNS) mechanisms contribute to the persistence of most NP types. The initial approach to treating NP in young individuals often involves pharmacotherapy. The types of drugs prescribed for general and specific types of NP in young individuals, including antidepressants and anticonvulsants, align with guidelines and consensus statements from various organisations worldwide. However, many individuals may not experience complete relief from their pain despite using these first-line treatments. Neuralgia, affecting 7 to 10% of the general population, is caused by dysfunction in the sensory organs of the body, which comprise A, A, and C fibers, as well as the brainstem and spinal cord.

Keywords: Antidepressants, Anticonvulsants, Interventional management, Psychotherapy

INTRODUCTION

The present study reviews the most recent developments in the authors' knowledge of NP. It discusses NP's clinical manifestation, physiological causes, and rational pain management. Additionally, a brief list of medications prescribed for NP is provided in the present study. The authors focused on studies that were conducted during the last six years. Pain is described as "a distressing sensory and emotional experience related to or comparable to that related to actual or potential tissue damage" in the definitions [1]. Most pain disappears after the body has healed and the noxious stimulus has been removed, but it can sometimes persist long after the stimulus has been removed and the body appears to be improving [2]. Pain is the primary reason for doctor visits in the majority of industrialised countries [3,4]. It impacts a person's overall functionality and Quality of Life (QoL) and is a key indicator of many medical disorders [5]. Additionally, individuals are more prone to becoming irritable, unhappy, and anxious. Between 20% and 70% of cases can benefit from simple painkillers [6]. Psychological factors such as diversion, motivation, cognitive-behavioral therapy, and social support can influence the intensity or unpleasantness of pain [7,8].

The International Association recommends using the following characteristics to define a patient's pain:

- Affected body parts (such as the lower limbs or abdomen)
- Potential source of pain (such as the neurological or gastrointestinal systems).
- Occurrence trends
- Cause and frequency [9].

Pain is the primary reason for emergency room visits in over 50% of cases, and people contact their family doctor due to pain 30% of the time [10,11]. The prevalence rates for chronic pain vary between 12% and 80% according to epidemiological studies, with higher rates observed in older individuals [12]. In a study of 4,703 patients, it was found that 46% had experienced discomfort in the previous month, an increase from 26% just two years earlier [13]. Girls between the ages of 12 and 14 more frequently and intensely reported chronic pain compared to boys [14].

The Neuropathic pain significantly impacts satisfaction and carries a substantial financial burden for both individuals and society [15-18]. Epidemiological surveys indicate that many individuals with NP in the younger population do not receive appropriate care [16-23]. Non-pharmacological treatments, such as psychotherapy, complementary therapy, non-invasive neurostimulation techniques, and invasive techniques, are increasingly being offered to young patients with nerve pain, typically involving a combination of therapeutic modalities in routine clinical practice [24,25].

Pharmacological treatments for NP in young individuals include the prescription of Tricyclic Antidepressants (TCA), anticonvulsants, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and anti-epileptics as the first line of treatment, followed by mild opioids and strong opioids [26,27]. However, pharmaceutical treatment is not always effective for all forms of chronic NP, and in some cases, surgical procedures may be necessary [28]. It is clinically important to recognise and differentiate (potential) NP from other pain categories, such as nociceptive pain, as it often does not respond to traditional analgesics like non-Steroidal anti-inflammatories, requiring a new analgesic approach [29].

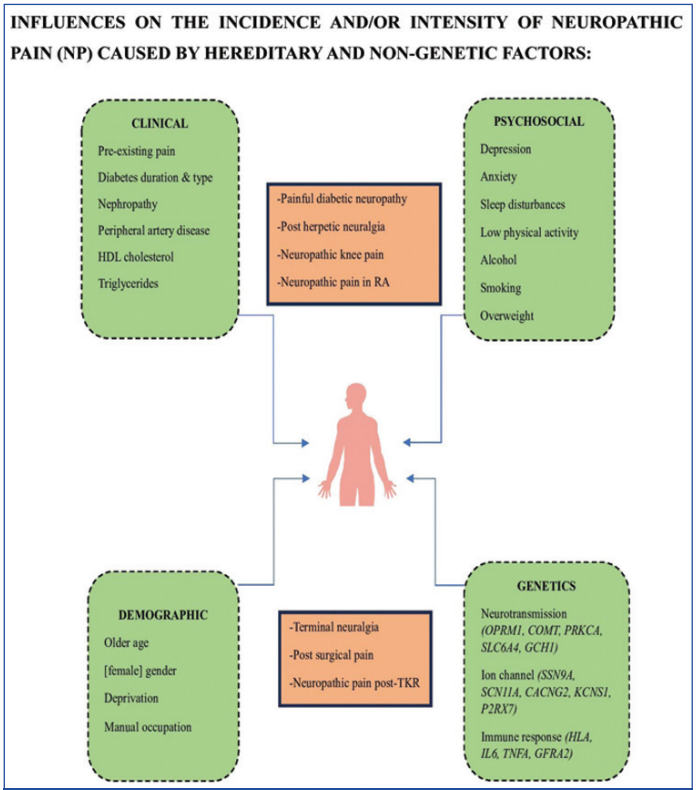
Epidemiology

Due to the lack of clinically proven diagnostic techniques for this condition, quantifying the frequency and pervasiveness of neuropathy has been challenging. One study suggests that the estimated prevalence of NP in young individuals falls between 7% and 10% [29]. Epidemiological data from various regions of India indicate a wide range of total NP prevalence in young individuals, ranging from 5 to 2400 per 10,000 people [30]. Furthermore, individuals over the age of 50 years and women are more susceptible to nerve pain, with the peak age range being between 50 and 64 years [31]. Patients with radiculopathy and persistent back pain are particularly affected [32]. The estimated frequency of persistent pain and nerve pain in

young individuals is around 30%-50% and 6%-11%, respectively [33]. The prevalence of chronic recurrent pains in children tends to increase, especially in girls, throughout adolescence [34,35].

Impact

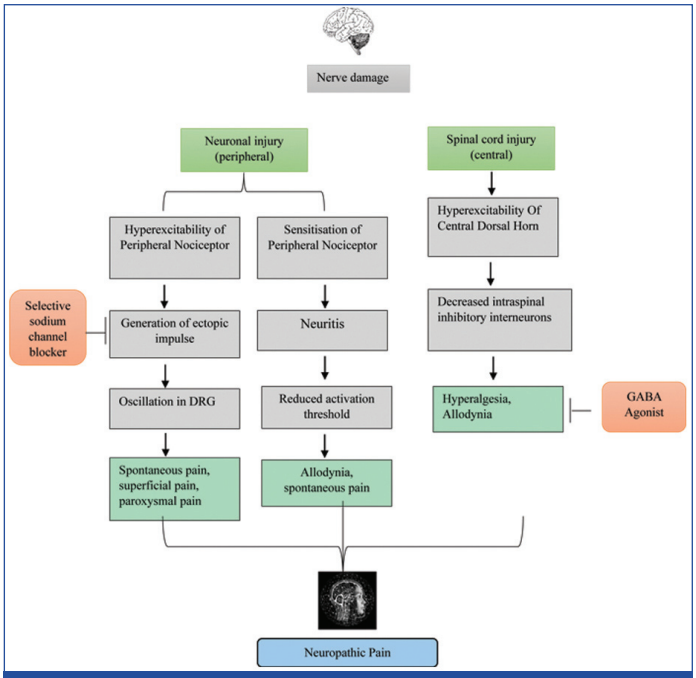
The occurrence of nerve pain and its effects on young individuals are both significant. Intensity ratings for NP in young individuals are likely to be higher compared to non neuralgic pain [36]. When considering the intensity of pain, all assessed areas of health and QoL still rank neuralgia lower than non NP [35-40]. In a population survey using the EuroQoL (EQ5D) questionnaire to assess individuals' quality of life, it was found that 17% of people with nerve pain reported a rating below 0, indicating that their QoL was "worse than death" [41,42]. Several factors contribute to this high impact, including the difficulty, intensity, and distress of the condition, as well as the cost and adverse effects of treatment (which often yield unfavorable results) [43]. There are certain factors that can induce neuropathic pain, as shown in [Table/Fig-1] [42-44]. The Mechanism of Neuropathic Pain is detailed in [Table/Fig-2] while the classification according to disease is outlined in [Table/Fig-3] [45].



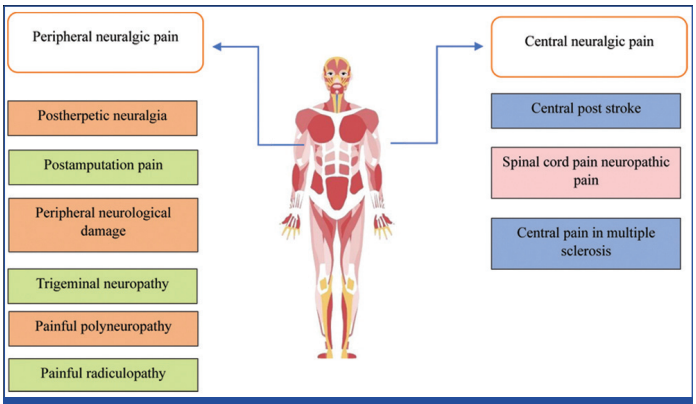
[Table/Fig-1]: Factors that induce neuropathic pain [42-44].

Trigeminal Neuropathy

Trigeminal neuropathy is a specific type of orofacial discomfort where one or more divisions of the trigeminal nerve are affected. The diagnosis is based on the patient's description of typical pain attacks that resemble electric shocks, occurring spontaneously or triggered by harmless stimuli in trigger zones. These attacks begin suddenly, stop quickly, and last from a few seconds to less than two minutes [45]. The prevailing theory suggests that impulsive pain attacks are primarily caused by cross-excitation of neighbouring neurons that are overactive, as well as spontaneous discharges in injured neurons with decreased thresholds due to recurrent discharge [46]. Inflammation, immunological response, and recurrent biochemical abnormalities may be present in the trigeminal ganglia [47,48]. Neuroimaging studies have shown minimal loss of cortex and white matter in brain regions associated with pain exacerbation, although it is unclear whether this loss is directly linked to pain or if it is a result of ongoing activity following focal nerve damage [49]. The fact that this type of neuropathic pain responds well to radiofrequency ablation, microvascular decompression, and other nerve-specific



[Table/Fig-2]: Pathophysiology of Neuropathic pain. [44]



[Table/Fig-3]: Different types of neuropathic pain [45].

therapies supports this claim, suggesting that the generator of the pain is located in the affected area [50].

Trigeminal neuralgia that occurs secondary to multiple sclerosis is the most common cause of trigeminal nerve pain, affecting 1%-5% of patients [51,52]. Secondary trigeminal neuralgia in multiple sclerosis is known to have an even greater impact on QoL. It tends to occur at an earlier age, is more commonly bilateral, and is more severe and persistent compared to primary trigeminal neuralgia [53].

Peripheral Neurological Damage

There is a clear association between the occurrence of nerve damage, such as during surgical procedures, and the likelihood of experiencing persistent nerve pain. However, there is no correlation between the severity of the injury or the type of nerve damage (transection, stretching, or crushing) and the development of neuropathic pain [54,55]. In individuals with diabetes and poor glucose control, a specific acute form of polyneuropathy may manifest, and these individuals may experience a significant improvement in their neuropathic pain symptoms when their glucose control improves [56].

Painful Polyneuropathy (PPN)

Leprosy, chemotherapy, diabetes, and Human Immunodeficiency Virus (HIV) are the most prevalent and well-known causes of PPN [57,58]. Other causes include alpha-galactosidase-A deficiency [59], channelopathies [60], vasculitis, amyloidosis, chronic inflammatory demyelinating polyneuropathy [61,62], alcohol, paraneoplastic syndrome, and autoimmune diseases such as non-

freezing cold injuries [63-65]. Vitamin deficiencies and malnutrition are also contributing factors. Intense or subacute forms of PPN can be considered a consequence of nutrient deficits resulting from weight loss, eating disorders, or weight-loss surgery [66]. Referred sensations, the spread of pain hypersensitivity and hyperesthesia to neighbouring sensory roots of the spinal nerve, and other symptoms are believed to be caused by Allodynia involving the backbone and medulla oblongata [67,68]. Following amputation, cortical reorganisation and supraspinal neuroplastic changes are also observed, although it is unclear if these changes are directly related to ongoing discomfort [69,70].

Postherpetic Neuralgia (PHN)

After the subsiding of the Herpes Zoster (HZ) rash, the persistent pain that lasts for months to years is known as PHN, which is a nerve pain disorder [71]. Following the initial varicella (chickenpox) infection, which may have occurred decades ago, the Varicella-Zoster Virus (VZV) remains latent in the body and can reactivate to cause HZ, commonly known as shingles [72]. Reactivated VZV can cause not only the characteristic rash but also a less persistent form of neuropathic pain called zoster sine herpete, which can be more challenging to diagnose and may require cerebrospinal fluid testing [73].

A survey conducted in the US between 1988 and 1994 found that over 99% of individuals under the age of 40 years had serologic evidence of previous VZV infection, putting them at risk of developing HZ [10]. It is estimated that one in three individuals may experience HZ in their lifetime, with approximately one million cases occurring each year in the US [15]. Estimates suggest that 5% to 20% of individuals with HZ will go on to develop PHN. Age significantly influences both the occurrence and severity of PHN, with over 30% of individuals over the age of 80 years experiencing PHN and 20% of individuals aged 60 to 65 years who have had acute HZ developing PHN [20].

Painful Radiculopathy

Acute sciatica is a complex medical condition that affects multiple important nerve roots. Depending on the degree of nerve compression, it can cause pain, loss of sensation, and motor dysfunction [25]. Most cases of lumbosacral radiculopathy resolve on their own. Paresthesia, a tingling or prickling sensation, is a characteristic symptom of radiculopathy [1]. Nerve root compression is typically the cause of lumbar radiculopathy. Autonomous zones refer to specific areas of the body that are connected to a single nerve root. Examples of these autonomous zones in lumbosacral radiculopathy include the medial calf for L2 and L3, the dorsum of the foot for L4, and the S1 region. Compression of the L5 nerve root can occur due to a central disc protrusion at L2-L3 or L3-L4, a lateral disc protrusion at L4-L5, a far-lateral protrusion at the L5-S1 foramen, or a lateral disc protrusion at L4-L5. The cauda equina, a bundle of nerve roots, can be affected when compression occurs at one level, increasing the likelihood of multiple nerve roots being affected, potentially bilaterally [2]. The L4-L5 and L5-S1 regions are particularly prone to damage as they are where most of the lumbar spine's mobility occurs. About 90% of compressive lumbosacral radiculopathies develop at these levels [3].

Symptoms of lumbar radiculopathy can include paresthesia, radiation of pain in the lower extremity, and numbness, affecting between 63% and 72% of patients [4-6]. A small percentage of individuals with sudden lumbago (lower back pain) have disc herniation as the underlying cause of their symptoms [7].

Central Neuralgic Pain

The condition known as central neuropathic pain can be caused by disorders that damage or impair the primary sensorimotor nervous system [8]. Common underlying disorders include multiple sclerosis, quadriplegia, and stroke, which are associated with central pain in 8-10% and 50% of patients, respectively [11-14].

Central neuropathic pain can manifest as persistent pain, sudden and unpredictable episodes (paroxysmal), pain triggered by mechanical touch or temperature stimuli, or a combination of these elements, regardless of the location of the lesion in the central nervous system or the underlying cause of CNS dysfunction. The pain can range from mild to severe or present as a combination of both [9].

Central Poststroke Pain (CPSP)

In a Danish population-based study that included all types and sites of stroke patients during a one-year period, it was found that only 7.3% of them developed CPSP, despite 40% of stroke patients experiencing chronic pain indicators four years after their stroke [15]. A diagnosis of CPSP affects 18% of patients with strokes that result in somatosensory impairments [16].

Spinal Cord Injury (SCI) Pain

According to the International Quadriplegia Pain Classification, individuals with CNS injuries and significant functional limitations may experience various types of pain. Classifying pain by type is helpful in addressing pain in patients with SCI [74]. At-level pain can be attributed to dorsal horn or root SCI, resulting in either peripheral neuropathic pain (originating in the root) or central neuropathic pain (originating in the dorsal horn) [17].

RECEPTORS INVOLVED IN NEUROPATHIC PAIN (NP)

The Neuropathic Pain and TLRs: Neuropathic Pain and T-Lymphocyte Receptors within the vertebrae, they are capable of producing proinflammatory cytokines and activating microglia or astrocytes, thereby initiating and sustaining NP and inflammatory pain. Primary sensory neurons express TLRs specifically to detect endogenous damage-associated molecular patterns and exogenous pathogen-associated molecular patterns that are generated in response to tissue injury and cellular stress [18].

T-Lymphocyte Receptor Two (TLR2): TLR2 and NP TLR2 is present in various species and it initiates the production of allergic molecules, activates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and ultimately leads to discomfort. It is predominantly expressed in microglia and other macrophages within the local and regional nervous systems. There is also limited expression of TLR2 in Schwannoma, oligodendroglia, skeletal muscle cells, vascular cells, and neurons [19].

T-Lymphocyte Receptor Three (TLR3) and NP : TLR3 and NP Based on recent studies investigating the mechanisms underlying the involvement of TLR3 in pain, preliminary findings indicate that T Lymphocyte Receptor Three (TLR3) regulates pain through both common and distinct molecular processes [21].

T Lymphocyte Receptor Four (TLR4) and NP: The growing body of research suggests that T Lymphocyte Receptor Four (TLR4) is a significant mediator associated with chronic pain. In a model of sustained contraction injury, the involvement of the spinal nerve in neuropathic pain was demonstrated through the administration of drugs. TLR4 activation may play a role in coordinating certain aspects of the healing process following nerve injury, but the use of TLR4 antagonists could potentially help prevent poorly regulated pain [22].

CLINICAL MANIFESTATION

The neuropathic pain is commonly characterised by various clinical symptoms and indicators. The presence of both positive and negative somatosensory indicators, or the coexistence of multiple sensory complaints, is a crucial diagnostic indicator for NP [23]. Positive somatosensory indicators encompass both painful and painless

sensations, while sensitivity deficits to hot and unpleasant stimuli are hallmark features of negative symptoms [24]. Paresthesias, which are characterised as tingling or crawling sensations, are uncomfortable but not painful. Spontaneous pain (not triggered by a stimulus) and evoked pain (triggered by a stimulus) are both types of painful positive indicators. Many patients with peripheral NP also experience evoked pain types (hypersensitivity), which are characterised by various sensory anomalies that may occur alongside or in combination with areas of sensory processing disorder in the skin [26]. Heat and cold hypersensitivity are less common, whereas sensitivity to mechanical stimulation is frequently observed in patients. Allodynia and hyperalgesia are subtypes of hypersensitivity. Allodynia refers to the experience of pain in response to normally non-painful stimuli [27]. Mechanical allodynia (static or dynamic) is often seen in individuals with PHN and even slight mechanical stimulation, such as brushing cotton wool over the skin, can cause excruciating pain. On the other hand, hyperalgesia is characterised by an unusually heightened sensitivity to pain in response to painful stimuli [28]. Summation, another evoked characteristic, manifests as a progressive increase in pain over time and is induced by the slow, repetitive activation of the brain with noxious stimuli (such as a pinprick) [29]. The type of sensation experienced, commonly described as searing, shooting, needle-like, or electrical, can also serve as a diagnostic indicator for NP [30].

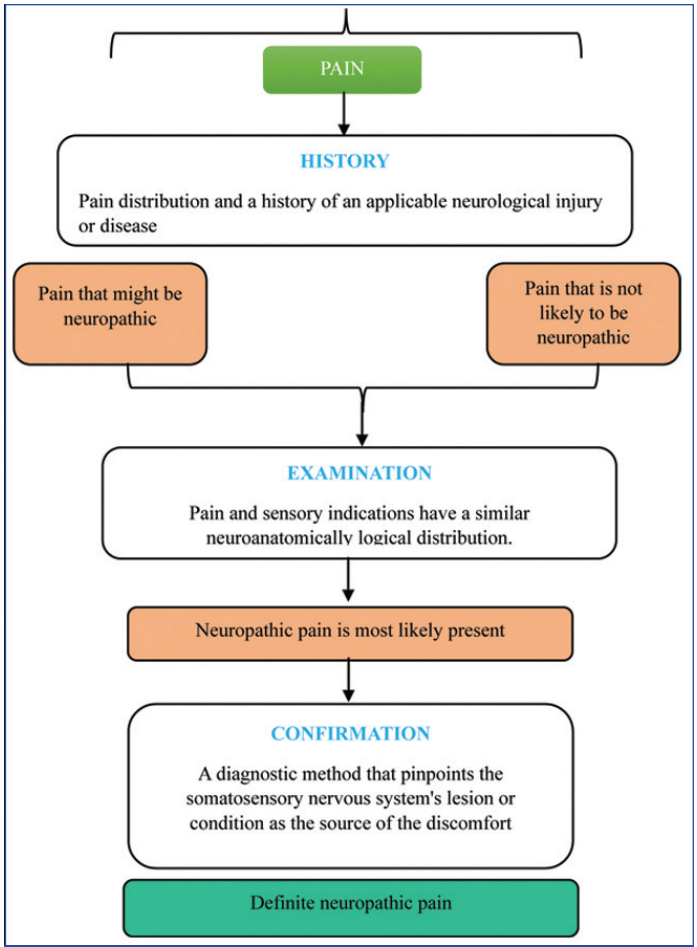
DIAGNOSIS, SCREENING, AND PREVENTION

However, establishing a "definite" NP diagnosis is infrequent, especially in the absence of specialists. According to the Worldwide Association for the Study of Pain, the following criteria must be met: 1) a diagnostic test confirming a lesion or disease in the somatosensory system, 2) a relevant neurological lesion or disease history, along with pain in a neuroanatomically plausible distribution, and 3) sensory signs in the same distribution [31]. The degree to which a pain situation is neurogenic, as opposed to nociceptive pain, can be determined [40]. To gather evidence for a "probable" NP diagnosis, clinical assessments of sensory markers, such as bedside testing and quantitative sensory testing, must be conducted. Treatment should begin as soon as NP is suspected. Numerous screening techniques have been developed to detect nerve pain issues or neuropathy-related elements of persistent pain syndromes in young individuals, based on the hypothesis that sensory perception exhibits typical characteristics suggestive of NP [38].

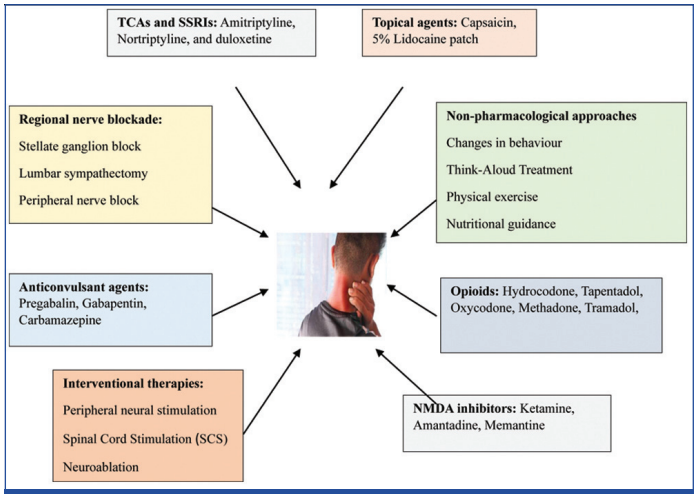
When used in patients with persistent pain, simple patient-reported questionnaires, such as the Douleur Neuropathique en 4 Questions (DN4) or pain DETECT [32,33], assess typical nerve pain symptoms, including burning, tingling, sensitivity to touch, pain caused by light pressure, electric shock-like pain, pain in response to cold or heat, and numbness. These questionnaires are highly sensitive and specific in differentiating between neuralgic and non-neuralgic pain. Another instrument, such as the Neuropathic Pain Symptom Inventory (NPSI) [34], has been enhanced to better define patient profiles, particularly for treatment trials, with a greater focus on quantifying neuropathic symptoms and dimensions [35]. [Table/Fig-4] shows a diagnostic procedure for establishing a somatosensory nervous system lesion or disease as the source of discomfort [41-47]. Various treatment approaches in neuropathic pain has been presented in [Table/Fig-5].

PHARMACOLOGICAL MANAGEMENT

Analgesics such as paracetamol, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), or mild opioids like codeine typically do not have an effect on young patients with NP. The conventional approach to treating NP in young patients involves initially using complementary and conservative pharmaceutical therapy before considering interventional techniques like nerve blocks and neuromodulation.



[Table/Fig-4]: A diagnostic procedure establishing a somatosensory nervous system lesion or disease as the source of the discomfort [41-47].



[Table/Fig-5]: Treatment approaches in Neuropathic pain [36,37].
TCAs: Tricyclic Antidepressants; SSRIs: Selective Serotonin Reuptake Inhibitors.

However, due to the insufficient efficacy of medications, an aging patient population, polypharmacy in older patients, and opioid-related side effects, there has been an increase in the use of interventional therapy. Limited availability of clinical trials makes it challenging for doctors to determine the optimal treatment approach [48-52].

The underlying causes of NP can only be treated in a limited subset of pathological conditions to alleviate suffering. The Neuropathic Pain Special Interest Group (NeuPSIG) recommends first-line therapy for NP in young patients to be Tri Cyclic antidepressants (TCAs), gabapentinoids, and Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). Potent opioids such as morphine and oxycodone, as well as Botulinum toxin-A, are recommended as third-line treatments for peripheral nerve pain, while capsaicin, lidocaine, and tramadol are recommended as second-line

treatments [39,39]. Treatment options for NP in young patients are shown in [Table/Fig-6]. Adverse reactions associated with these treatments are shown in [Table/Fig-7].

Therapy	Drug class	Drugs	Dose	Mechanism of action
First-line therapy	Serotonin-norepinephrine reuptake inhibitor	Duloxetine	20-120 mg/day	Reduces the release of many neurotransmitters at the synaptic level; calcium channel alpha-2-delta ligand; channel modulator
		Venlafaxine	150-225 mg/day	
	Gabapentinoids	Gabapentin	150-600 mg/day	
		Venlafaxine	150-225 mg/day	
	Tricyclic Antidepressants (TCA)	Amitriptyline	10-150 mg/day	Norepinephrine and serotonin reuptake inhibitor, voltage-gated sodium channel blockade, and anticholinergic action
Second-line therapy	Opioids	Tramadol	25-400 mg/day	Norepinephrine, μ-receptor agonist, and Serotonin reuptake inhibitor.
		Tapentadol	50-600 mg/day	Norepinephrine reuptake inhibitor, μ-receptor antagonist
	Topical treatment	Lidocaine	5% patches or gel	Sodium channel blocker
		Capsaicin	8% patches	De-functionalisation of nociceptor fibres caused by a TRPV1 agonist is reversible.
Third-line therapy	Strong opioids	Oxycodone	10-120 mg/day	μ-receptor agonist
		Morphine	10-120 mg/day	κ-receptor antagonist μ-receptor agonist
	Neurotoxin	Botulinum toxin	25-300 U	Blocking neuromuscular transmission, inhibiting acetylcholine release, and maybe also have central effects on neurotransmission [53,54]

[Table/Fig-6]: Treatment options for NP in young patients.

	Drug class	Drugs	Adverse reactions
First-line drugs	Serotonin-norepinephrine reuptake inhibitor	Duloxetine	Nausea, constipation, lethargy
		Venlafaxine	Nausea, hypertension, vertigo
	Tricyclic Antidepressants (TCAs)	Amitriptyline	urinary retention, anticholinergic effects, suicide risk QT prolongation (arrhythmia)
	Gabapentinoids	Gabapentin	Peripheral swelling, vertigo, blurred vision
		Pregabalin	vertigo, peripheral swelling, increased body weight
Second-line drug	Opioids	Tramadol	Seizures, Constipation, Vomiting
		Tapentadol	Seizure, Ataxia, Nausea/ vomiting
	Topical treatment	Lidocaine	Itching, Rash, abnormal redness of the skin
		Capsaicin	Itching, ache, redness of the skin, high blood pressure
Third-line drug	Strong opioids	Morphine	Nauseousness, regurgitation, Dizziness, Lethargy, Convulsion
		Oxycodone	fatigue, Nausea/Vomiting, Constipation
	Neurotoxin	Botulinum toxin	Swelling at the injection site [55]

[Table/Fig-7]: Undesirable effects of the drugs used in NP.

NON PHARMACOLOGICAL TREATMENT

Transcutaneous Electrical and Electromagnetic Stimulation

Transcutaneous Electrical Nerve Stimulation (TENS), is topically applied (over the skin) to treat several severe and persistent pain conditions [56]. TENS units typically deliver pulsed electrical stimulation to the skin using adhesive electrodes that can be adjusted for frequency (stimulation rate), intensity, and duration. The frequency modes in which TENS operates are commonly referred to as high-frequency or low-frequency modes. Low-frequency TENS is typically defined as 10 Hz or below, while high-frequency TENS is often described as up to 50 Hz or 100 Hz and higher [57].

Electroacupuncture

Electroacupuncture (EA) has proven to be an effective treatment for various pain conditions, as demonstrated by several clinical studies. Classical perspectives suggest that endorphins play a role in the analgesic effects of acupuncture, while contemporary research suggests the involvement of central opioids, monoamines, and neuropeptides. More recently, it has been discovered that the endocannabinoid receptor 1 (CB1R) pathway specifically contributes to the central analgesic effects of EA [57]. All of these neuromodulators may influence the neuronal plasticity of the ascending pathway in the spinal cord and brain, leading to a reduction in pain hypersensitivity. Various subcortical nuclei, including the habenular nucleus, preoptic area, and Periaqueductal Grey (PAG), can contribute to EA-induced analgesia in specific brain regions [40].

Photon Stimulation

Three different assessments of pain quality demonstrated a significant reduction in patients who received photon stimulation. Individuals who underwent photon stimulation showed notable improvements in their sensory perception. In contrast to the placebo group, which had sensations at only six sites, patients in the treatment group experienced sensations at almost all of the ten sites by the end of the therapy course, compared to an average of just five out of ten previously [15,16].

Dorsal Column Stimulation

One method of neuromodulating pain is Dorsal Column Stimulation (DCS). A fully implanted DCS system consists of two parts: the Implantable Pulse Generator (IPG) and the electrodes (or leads). Through the use of these implanted electrodes, DCS modifies the regional neurochemistry in the dorsal horns, reducing hyperexcitability of neurons [58]. In recent times, various neuromodulation treatments have been employed. One of these techniques, Spinal Cord Stimulation (SCS) or DCS, is an advanced neuromodulation approach that can alleviate neuropathic pain (NP) in several syndromes including Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS) types I and II, PHN, and radiculopathy [59]. DCS has been utilised in an increasing number of cases involving persistent nerve pain syndromes in young individuals, including PHN, central spinal cord pain, nerve plexus injuries, and peripheral neuropathy [58].

Repetitive Transcranial Magnetic Stimulation (rTMS): Patients with SCI experiencing refractory NP experienced analgesic effects from both real and sham rTMS. The actual rTMS group showed a reduction in pain following the therapy sessions that lasted for over a month. The sham rTMS group exhibited immediate pain relief after the therapy sessions. However, there was no significant difference observed between the two groups at any of the evaluation points. Neither the real nor the sham rTMS provided any pain relief at the 6-month follow-up [24].

The motor cortex area is believed to possess an analgesic mechanism that varies with activity. This region of the brain projects

to areas involved in pain processing, such as the thalamic nuclei, anterior cingulate cortex, and brainstem Periaqueductal Grey (PAG) matter [50].

Acupuncture

In many societies, acupuncture is employed as a pain management strategy. The practice of acupuncture involves the insertion of needles into specific tissues and stimulating them. Acupuncture points, also known as acupoints, are described based on anatomical locations, but they lack an anatomical or physiological substrate that would characterise them [60].

DISCUSSION

To reduce the overall burden of NP in young individuals, which continues to have a high prevalence and global impact, community-based approaches for prevention and management are needed. Epidemiological studies can also be utilised to predict the occurrence of nerve pain in young individuals, including the likelihood and characteristics associated with long-term outcomes. Patients are concerned about this, and it may influence treatment choices, but conducting such studies requires long-term cohort studies, which have been limited in the case of NP [61].

Since nerve pain is a challenging issue to treat and significantly impacts the quality of life for many individuals, it is necessary to explore new potential therapeutic targets in order to develop novel pharmacological treatments. Antidepressants and antiepileptic medications are the recommended first-line therapies. Opioids are typically reserved for second and third-line treatments due to their potential for adverse drug reactions. Tapentadol and tramadol, two Food and Drug Administration (FDA) approved opioids, are used as second-line treatments, while oxycodone and morphine, which are potent opioids, are used as third-line treatments [45].

CONCLUSION(S)

The term “NP” encompasses a group of disorders with diverse etiologies and patterns of pain. However, all of these disorders are characterised by a lesion or illness that affects the central or peripheral somatosensory nerve system. NP in young individuals is highly debilitating, challenging to diagnose, and often does not respond completely to treatment. Given the increasing prevalence of persistent NP and its detrimental impact on well-being, early diagnosis and treatment are crucial. It is necessary to develop new pharmacological treatments for NP in young patients. Through in-depth research into the causes of NP, numerous potential therapeutic targets have been identified, and promising novel molecules are currently being developed. The adverse effect profile of certain medications and the cost associated with making them widely accessible have been the main factors limiting recent advancements in various pharmacological modalities. Exploring nonpharmacological treatments may help develop affordable remedies with minimal adverse effects. Therefore, a combination approach that incorporates symptomatic therapy during acute episodes and a multidisciplinary strategy for long-term pain management is necessary.

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