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Editorial

Neuropathic Pain and its Management

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INTRODUCTION

Pain is a distressing sensory and emotional experience connected to real or potential tissue damage, or one that is portrayed as such damage, according to the International Association for the Study of Pain (IASP).[1] There are many different pathophysiologic processes and interpretations of pain, which can vary greatly in severity, quality, and duration.[2]

The process that follows an initial injury or illness of the somatosensory nerve system is known as neuropathic pain. Hyperalgesia, an abnormal heightened sensitivity to stimuli, and allodynia, a nociceptive reaction to non-noxious stimuli are characteristics of neuropathic pain. The aetiology or anatomic location of this illness, which is the outcome of numerous different pathogenic pathways, is typically used to define it.[3]

The conditions and pathophysiological states that predispose to the development of neuropathic pain include metabolic conditions like Peripheral Diabetic Neuropathy (PDN), neuropathies brought on by viral infections like post-herpetic neuralgia and HIV, leprosy, and leprosy, autoimmune conditions like multiple sclerosis and Guillain-Barre syndrome, chemotherapy-induced peripheral neuropathies, and damage to the nervous system caused by traumatic origin.[4]

Pain that is not brought on by acute injuries might be uncomfortable for the patient or it can change a person's life, lower their quality of life, and affect their family as well. The term "pain" refers to a variety of feelings that have their own anatomical and physiological systems, starting with receptors and ending in the brain cortex. For the patient, it denotes disease and suffering; for the doctor, it is a symptom.[5]

Electrophysiological techniques can demonstrate that feeling is a physical sensation, but in reality, it is merely a subjective one. A stimulus's intensity and quality depend on a variety of internal and external elements, therefore it might be perceived differently under diverse somatic and mental situations. The way each person experiences pain is quite unique and might change from time to time even within the same person.[6]

A person's perception of pain is influenced by their emotional state, the circumstances around how they first experienced the pain, and whether they believe it to be a hazardous signal. It is difficult to quantify the intensity of pain. Arousal, concentration, distraction, and expectation are some examples of the variables that affect how we perceive pain.[7] There are several physiological processes taking on in our body before we even become aware that something hurts. In (milli)seconds, painful stimuli must be processed. Acute pain signals approaching or subsequent danger, whereas persistent pain makes the affected bodily component, such as an immobilized and inactive leg, more likely to recover.

NOCICEPTIVE PATHWAY

The sensation of warning against the possibility of tissue damage or showing damage already sustained as a result of illness or injury is known as nociceptive pain. A pain receptor may originate from internal organs (the eye, ear, nasopharynx, heart, blood vessels, stomach organs, and the pelvis) or from external tissues (integuments, skin, and mucosal pain). Moreover, muscles, joints, and bones all experience pain. Outside of the neurological system, chemical and physical agents can irritate pain receptors. The physiologically unharmed nervous system converts this stimulation into electrical impulses, which are then transmitted to areas where they are recognized as pain. They travel to the reticular system, where they activate the cerebral cortex and limbic system, which control the emotional response to pain, as non-specific impulses. The brain's brain centres develop the defense reaction.[8] Inflammation of the nociceptors, or pain receptors, is what causes pain. Free nerve terminals called nociceptors react to painful stimuli. Skin, the organ of motion (periosteum, joint capsule, ligaments, muscles), the cornea of the eye, and tooth pulp all contain nociceptors. They are also widely distributed in the organ walls, peritoneum, pleura, and meninges of the body. They communicate information to the brain when they are stimulated by biological, electrical, thermal, mechanical, and chemical stimuli. Pain is felt when sensations are sent from

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the spinal cord to the brain's central nervous system.[9] Impulses travel to the substantia gelatinosa's dorsal horn of the spine, where they connect with dorsal horn neurons, before travelling to the brain. The thalamus is where pain is first felt. It continues to the cerebral cortex and limbic system, which are where pain is sensed and processed.[10]

Due to their location at the tip of the nerve fibres, nociceptors are straightforward structures. A and C types of fibres are involved in the transmission of pain. The big A fibres, which are generally activated by a cut, an electric shock, or a physical blow, create severe, well-defined pain. They are myelinated and can let an action potential to go at a speed of roughly 20 meters per second in the direction of the CNS.[11] The speed of transmission across A fibres causes the body to react before the pain stimuli does. As a result, the afflicted body part retracts before the person feels any pain. This enables a prompt reaction, such as "escape" or "fight" preparedness. Opioid receptors are almost completely absent from these fibres, whereas the pain receptors at the terminals are constantly alert. There are few options for pharmacologically altering these receptors. Using analgesic medications, chronic, "slow" pain is typically easy to block but "sharp," "fast" pain is more challenging to do so. The smaller C fibres convey dull burning or hurting sensations after the so-called first pain, which is referred to as the "second pain."[12]

C fibres are delicate and prone to tearing. Since they lack the myelin coating, the conduction of painful impulses is extremely slow—between 0.5 and 2 m/s. A "net" made up of several C fibres is created.[4,8] As a result, the area covered by branching C-fibres is typically wide, and the patient can only roughly localize the pain. Mechanical, thermal, and chemical stimulation cause C fibres to respond. They trigger both pain and pruritic stimuli (a characteristic of the histamine-sensitive fibres).[13] Patients report the pain produced by C fibre as being quick, jerky, and pulsating. The opioid receptors are the most significant receptors found at the terminals of these nerve fibres. The proteins that make up these receptors are produced in ganglion cells, where they are then delivered by the axons to the synapse in the corners of the spinal cord as well as to nerve terminals in limbs and other organs. In the cell membrane of nerve endings, inactive receptors known as "sleeping receptors" are present. By way of inflammation, they might "awaken".[14,15]

The injured perineurium can be penetrated by a variety of cytokines, which then activate the receptors. The opioid receptors are subsequently sensitized and activated in this manner, enabling them to respond to both endogenous and exogenous opioids.[16] Prostaglandin and other mediators also "sensitize" the C-fibre nerve terminals. A non-steroidal anti-inflammatory drug's reduction of prostaglandin formation and corticosteroids' inhibition of inflammation both decrease the sensitivity of the nerve fibres to pain and raise the threshold for it.[17,18] The immunological and neurological systems work together to support this fundamental defense strategy. Pain consequently manifests in two stages. Fast-conducting A fibres mediate the first phase, whereas C fibres are responsible for the second. The significance of physiological pain as a cautionary signal to safeguard human safety cannot be overstated.[19]

Different types of pain are listed in the following table.

Types of Pain	Anatomical Pain
	Physiological Pain
	Pathological Pain
	Deep Pain
	Vascular Pain
	Bone and Joint Pain
	Myalgia
	Organ Pain
	Wired Pain
	Neuralgia
	Radicalgia
	Causalgia
	Convolutional Pain
	Phantom Pain

A well-known definition of chronic pain is pain that persists for longer than the typical course of an acute accident or illness, or pain that recurs for months or years. The benefit of this definition is that it may be used to characterize any conditions that fall under the category of chronic pain, even if it does not take into account the impairment caused by the pain, the existence of particular symptoms, or the ostensible etiological basis.

This is especially true because the phrase "chronic pain" is used to describe a wide range of illnesses that all share the presence of persistent pain.[20]

Reasons of neurological pain are listed below.

Reasons of Neurological Pain	Disease
	Injury
	Infection
	Limb Loss
	Vitamin B deficiency
	Carpal tunnel syndrome
	Thyroid problem
	Facial Nerve problem
	Arthritis

NEUROPATHIC PAIN

Injury to neural tissue in the Central Nervous System (CNS) or Peripheral Nervous System (PNS) initiates or causes neuropathic pain.[21] Neuropathy is a disturbance of function or a change in one or several nerves.

Because neuropathic pain can occur in areas without feeling and encompass oddly shaped areas, it can occasionally be challenging to diagnose. Patients with neuropathic pain frequently express discomfort from stimuli that are not typically harmful, such as a breeze or light touch, in addition to spontaneous pain.[22,23]

About 30% of all neuropathic pain happens because of diabetes, but other diseases like alcoholism and shingles can cause neuropathic pain.

Types of neuropathic pain are listed below.

Types of Neuronal Pain	Causes
Trigeminal Pain	Compression of trigeminal or its branches
Postherpetic Pain	Shingles
Complex regional pain syndrome	Trauma
Diabetic neuropathy	Persistent Hyperglycemia
Central Pain	Trauma to the spinal cord
Phantom Pain	Amputation
Post incisional Pain	Surgery

The 1965 development of the Gate Theory demonstrated that the PNS and CNS are more than just a network of wires passively gathering nociceptive data. Instead, the nervous system is dynamic, and activity inside it shapes and reshapes its form and function. It continuously increases or decreases the impulses that the brain finally interprets as pain at each level.[24] The passage of "painful messages" on their journey to the brain can be affected by other nerve messages, which are potent transmitters capable of reducing or increasing the passage of "painful messages," despite the fact that all pain signals reach the spinal cord.[25] Even ordinary daily activities can cause the release of hormones in the spinal cord that increase the amount of noxious traffic reaching the brain when someone has chronic pain because the "gate" is left open, allowing for the persistence of pain messages.

Similar but more complicated mechanisms at the brain level enter a "descending modulation" pathway that leads to the spinal cord. Further "fine tuning" of the ascending route is provided by this.[26]

INFLAMMATION AND PAIN

A painful stimulus results in inflammatory changes at the stimulation site and activates immune cells as well as inflammatory mediators.[27] The nociceptors are affected by cytokines and protons that the immune cells create, depolarizing the cell membrane and causing action potentials that can travel down the nerve fibres of the pain pathway. The opening of voltage- and ligand-gated ion channels (such as Na^{+}, Ca^{+2}, P2, and transient receptor potential-TRP) causes the depolarization of the nociceptive membrane.[28] Nerve Growth Factors (NGF, BDNF), which act on tyrosine kinase receptors to change the sensitivity of the nociceptors, are also secreted by the immune cells that have become sensitised.[29] A prolonged response to stimulation results from lowering the nociceptors' threshold for activation. The degenerating nerves emit substance P and CGRP when there is nerve damage as a result of the injury, which increases the creation and release of more inflammatory mediators and causes a protracted pain response.[30] Tyrosine kinase receptors B in the secondary afferents of the spinal cord are activated by BDNF. The induction and initiation of both allodynia (i.e., increased pain sensation in response to an innocuous stimulus) and hyperalgesia (i.e., increased pain sensation in response to a mild noxious stimulus) have been linked to the NMDA receptors, which are thought to play a significant role in the transmission of chronic persistent pain.[31,32] Presynaptic inhibition of pain fibres by inhibitory interneurons, which release GABA, modulates pain transmission at the superficial layers of the dorsal horn and prevents the production of excitatory amino acids.[33,34] Due to increased excitatory amino acid release and hyperactivation of NMDA receptors, which can result in the death of inhibitory interneurons, injuries, particularly those involving neuronal damage, lessen the GABAergic impact. The prolonged refractory pain syndromes, which can occasionally be independent of peripheral painful stimulus and resistant to therapy, may be explained by this transcription-dependent central sensitization.[35] Specifically in the dorsal horn of the spinal cord, the descending pathways originating from cortical and sub-cortical areas affect the transmission of pain.[36]

The dorsal horn's alpha-2 adrenergic receptors are stimulated by the locus coeruleus's descending noradrenergic pathway. This decreases the production of substance P, hyperpolarizes the sensory afferents, and depolarizes the GABAergic neurons, which inhibits the transmission of pain signals.[37] Both inhibitory effects (by activating 5-HT1A and 5-HT7 receptors) and excitatory effects (through 5-HT2A and 5-HT3 receptors) are produced by the descending serotonergic pathway from the nucleus raphe magnus on pain transmission.[38,39] The opioid system, which contains receptors for the endogenous and exogenous peptides known as endorphins, enkephalins, and the dynorphins, is a key inhibitory mechanism of nociception in the body. The afferents in the brain, spinal cord, and peripheral nerves include receptors for these opioids.[40-42] In addition to the three main classes, it has been discovered that receptors like sigma, nociception, and toll-like receptors play a role in the analgesic effect and the adverse consequences (such as tolerance and dependency) of opioids.[43-45] The opioid peptides alter nociceptive input in two

ways: either they open potassium channels, which hyperpolarize neurons and reduce spike activity, or they block neurotransmitter release by preventing Ca^{2+} influx into the presynaptic terminal. The Periaqueductal Grey (PAG), Nucleus Raphe Magnus (NRM), and Dorsal Raphe (DR), as well as the Caudate Nucleus (CN), septal nucleus, hypothalamus, habenula, hippocampus, and the dorsal horn of the spinal cord, all contain high densities of opiate receptors. Following acupuncture and placebo-induced pain alleviation, it has been discovered that opioid production and activity are boosted.[46,47]

SYMPTOMS AND DIAGNOSIS

The symptoms of neuropathic pain include:

Spontaneous pain (pain that comes without stimulation)

Shooting, burning, stabbing, or electric shock-like pain; tingling, numbness, or a "pins and needles" feeling.

Evoked pain

Pain brought on by normally non-painful stimuli such as cold, gentle brushing against the skin, pressure, etc. This is called *Allodynia*. Evoked pain also may mean the increase of pain by normally painful stimuli such as pinpricks and heat. This type of pain is called *Hyperalgesia*.

An unpleasant, abnormal sensation whether spontaneous or evoked (*Dysesthesia*).

Trouble sleeping, and emotional problems due to disturbed sleep and pain.

Pain that may be lessened in response to a normally painful stimulus (*Hypoalgesia*).

Peripheral neuropathy symptoms and signs include:[48,49]

- Gradual beginning of tingling, prickling, or numbness in your hands or feet that may go up into your legs or arms.
- Pain that is throbbing, searing, jabbing, or sharp.
- A high threshold for touch.
- Pain that occurs during actions that shouldn't cause it, such foot pain when placing weight on it or when it's covered by a blanket.
- Falling and poor coordination.
- Muscle sluggishness.
- Feeling like you should be wearing socks or gloves but aren't.
- If the motor nerves are impacted, paralysis.

Diagnosis[50]

Physical examination

Taking a thorough medical history: The doctor will take complete medical history of the patient, including symptoms, lifestyle, toxin exposure, habits and any family histories of neurological (nervous system) problems.

A neurological exam: Examination of body posture and coordination in addition to tendon reflexes, muscle strength, and muscle tone.[51]

Blood tests: These can find signs of illnesses that can cause peripheral neuropathy, such as vitamin deficiencies, diabetes, aberrant immunological function, and others.

Imaging exams: CT or MRI scans can check for tumours, herniated discs, pinched (compressed) nerves, blood vessel abnormalities, and other conditions affecting the bones and blood vessels.[52]

Tests of nerve function: Muscles' electrical activity is captured by Electromyography (EMG), which can identify nerve damage. To record electrical activity as the muscle contracts, a tiny needle (electrode) is placed into the muscle.[53]

At the same time your doctor or an EMG technician obtains an electromyogram, he or she typically performs a nerve conduction study. Flat electrodes are placed on the skin and a low electric current stimulates the nerves. The doctor will record your nerves' responses to the electric current.[54,55]

Tests of other nerve functions: Some of them could be an autonomic reflex screen, which documents the functioning of the autonomic nerve fibres, a sweat test, which gauges your body's sweat production, and sensory tests, which document your perception of touch, vibration, cooling, and heat.[56,57]

A biopsy of a nerve: In order to check for anomalies, a tiny section of a nerve, typically a sensory nerve, may be removed.[58]

Skin biopsies: In order to check for a loss in nerve endings, your doctor may remove a little amount of skin.[59]

IS IT GENETIC?

In terms of clinical phenomenology, molecular mechanisms, and the kinds of injuries that cause it, neurological pain is diverse. Similar to the majority of chronic diseases, this variety results from a confluence of hereditary and environmental factors.[60] We won't be able to employ whole-genome screens to identify unique and shared genetic processes within these populations until we can precisely stratify neurological suffering. Such stratification will make it possible to develop new treatments and improve the targeting of already available ones for each distinct phenotype of chronic pain.[61,62] For instance, HLA-B is linked to anxiety and feeling unpleasant, HLA-DQB1 is linked to narcolepsy

and anxiety, and PKRCA is linked to neuroticism. The genetic overlap between these comorbidities and neurologic pain has to be investigated further. Genetic research have revealed that 16-50% of chronic pain is genetically influenced, leading to the discovery of various pain genes, including OPRM1, TRPV1, SCN9A, COMT, MTHFR, TNFA, GCH1, ESR1, ABCB1, P2RX7, CHRNA6, and CACNG2. However, no research has yet been done on the genetic mechanism that underlies both neurological and inflammatory pain.

PHARMACOLOGICAL TREATMENTS

The search for innovative therapeutic agents with greater efficacy and safety is necessary because traditional analgesics like Non-Steroidal Anti-Inflammatory Medications (NSAIDs) and opioid agonists (e.g., morphine) are ineffective in some pain disorders and have issues of side effects.[63,64] The secretion and metabolism of neurotransmitters like serotonin, norepinephrine, neurokinin, GABA, and glutamate, as well as their receptors like NMDA, are significant targets. Studies on pain treatment are increasingly involving ion channels, such as sodium channels, N-type calcium channels, TRP and P2 receptors.[65,66] Effective nerve pain management may also involve targeting the pain modulatory systems, which include endocannabinoids and CB receptors, central opioid receptors, nerve growth factors, and glial cells.[67]

Anticonvulsant and antidepressant drugs are considered the first line of treatment of neuropathic pain.

Tricyclic antidepressants (such amitriptyline and imipramine) are useful for treating neuropathic pain because they prevent serotonin and noradrenaline from entering the ascending analgesic pathways.[68] The widespread systemic effects involving other receptors, such as the cholinergic and histaminergic, which might result in cardiorespiratory effects, glaucoma, and urine retention, may impair the favorable effects of the aforementioned drugs, though. Modern medications with less affinity for cholinergic and histaminergic receptors, including venlafaxine and duloxetine, increase both serotonin and norepinephrine activity in the pathways that control pain. There are less adverse effects with venlafaxine and duloxetine for treating painful polyneuropathies and diabetic neuropathy.[69]

Anti-convulsants such as Pregabalin and gabapentin are recommended as the first-line treatment for neuropathic pain. It has been discovered that anti-convulsants including carbamazepine, sodium valproate, oxcarbazepine, topiramate, vigabatrin, and levetiracetam have analgesic effects because they increase GABA activity, reduce glutamate release, block NMDA receptors, and block Ca^{+2} and Na^{+} channels on neuronal membranes.[70] Trigeminal neuralgia can be effectively treated with carbamazepine and oxcarbazepine.[71] However, it has not yet been established that the use of more modern anticonvulsants is more effective than using conventional analgesics to treat neuropathic pain or any other type of pain syndrome.[72,73] Dextromethorphan, amantadine, memantine, and ketamine, as well as substances with variable degrees of NMDA antagonism, have all been shown to be effective analgesics.[74,75] The need for further research into an NMDA antagonist with high efficacy and fewer side effects arises from the fact that NMDA antagonism causes undesirable psychological side effects, which become more severe with systemic treatment. The aforementioned analgesics, which were formerly thought of as GABA analogues, are now known to more specifically bind with voltage-gated calcium channels and suppress glutamate release at presynaptic and post synaptic locations, both peripherally and centrally.[76-78]

Opioids and gabapentin together have been shown to have synergistic effects in reducing neuropathic pain. There has long been research into the endocannabinoid system as a crucial modulatory mechanism for pain alleviation. It is hypothesised that this mechanism contributes to the analgesic effects of some of the more popular analgesics, such as paracetamol.[79] THC and cannabidiol are examples of CB1 receptor agonists that have shown effectiveness in treating chronic pain problems.[80] However, the unintended psychotic side effects severely restrict their use. Recent research has demonstrated that CB2 receptor agonists can effectively reduce pain, possibly through peripherally stimulating immune cells. In animal models of acute and chronic pain, metabolising enzyme inhibitors, such as FAAH and MAGL inhibitors, have shown effectiveness in lowering pain sensitivity. Future analgesics will likely target the endocannabinoid system because it has receptor and enzyme targets in the peripheral nervous system.[81]

Anaesthesia drugs like lidocaine aberrant buildup of sodium channels is a contributing factor in the abnormal electrical activity in damaged neurons and neuromas. Consequently, a sodium channel-blocking medication may aid in neuropathic pain relief. These drugs include oral mexiletine (which works in a manner similar to that of lidocaine), intravenous lidocaine (which also inhibits C-fiber polysynaptic evoked activity and suppresses dorsal horn neurons to the C-fiber input), and oral tocainamide.[82,83] Baclofen, a GABA-B-receptor agonist, has been demonstrated to be useful for treating neuropathic pain as a result of the key role the GABAergic system in the spinal cord plays in modifying pain management.[84]

Patients with peripheral neuropathic pain are advised to use **topical medications like capsaicin** as a backup treatment option. Voltage-gated sodium channel blockade by lidocaine patches lessens spontaneous ectopic nerve firing. Transient receptor potential cation channel subfamily V member 1, sometimes referred to as vanilloid receptor 1 (TRPV1), is a powerful receptor agonist that is produced by capsaicin. Due to their complexity in follow-up and monitoring as well as their possible negative side effects from drug usage, oxycodone and morphine are two potent opioids that are advised as third-line treatments.[85,86]

Based on its capability to suppress synaptic exocytosis and, consequently, neuronal transmission, **BTX-A,** also listed as a third-line therapy, is a strong neurotoxin frequently used to treat spasticity. Patients with allodynia and focal peripheral neuropathic pain have showed positive results with BTX-A subcutaneous injection. In cases of peripheral neuropathic pain that are unresponsive to other treatments, NeuPSIG advises using BTX-A as a last resort.[87]

It has been shown that pro-inflammatory mediators are released by activated glial cells and that these mediators contribute to neuropathic pain.[88] Blocking glial cell activation, preventing the biosynthesis of cytokines, and counteracting the effects of pro-inflammatory cytokines are some potential strategies for treating neuropathic pain.[89]

Numerous clinical studies have demonstrated the potential efficacy of chemicals derived from cannabis in the management of neuropathy associated with diabetes, chemotherapy, and multiple sclerosis. *Cannabis sativa* is a complex plant with about 100 cannabinoids. The delta-9 Tetrahydrocannabinol (-9-THC), which has intoxicating effects, is the cannabinoid that has been the subject of the most research.[90]

individuals with neuropathic pain may try Sativex, which the FDA has already approved for the treatment of spasticity in individuals with multiple sclerosis.[91] Even if they occasionally fail to provide sufficient symptomatic relief or their use is constrained by their adverse effects, NMDAR antagonist medications may be taken into consideration for the treatment of neuropathic pain. Individuals with neuropathic pain may try Sativex, which the FDA has already approved for the treatment of spasticity in individuals with multiple sclerosis.[92] Even if they occasionally fail to provide sufficient symptomatic relief or their use is constrained by their adverse effects, NMDAR antagonist medications may be taken into consideration for the treatment of neuropathic pain. Nevertheless, more research is required to judge the effectiveness of these medications.

Antidepressants and antiepileptic medications, taken in proportionate quantities, are the first-line therapy that are advised. Due to its negative side effects, it is typically advised to utilise opioids in second- and third-line treatments. Particularly strong opioids, such as oxycodone and morphine, are utilized in the third-line treatment, while tramadol and the FDA-approved tapentadol are used in the second-line treatment.[93]

Drug delivery techniques based on nanotechnology offer hope for overcoming some drugs' poor solubility and bioavailability. The use of nanocarriers in the treatment of pain is a brand-new field of study with a lot of room for development and clinical advantage. It is crucial to mention the potential for repurposing medications that have already demonstrated benefit in animal models of neuropathic pain and are now licensed for other uses. By lowering neuroinflammation, metformin and simvastatin were successful in reducing pain. Undoubtedly, neuroinflammation presents prospective therapeutic targets in neuropathic pain, and among these, microglial receptors (such as P2X7R and CX3CR1) may be the focus of treatment for the chronic pain condition. There is a lot of research being done on natural substances to relieve chronic pain. A cycle of neuroinflammation and cellular activation is sparked by the regulation of pro- and anti-inflammatory mediators and is typically resistant to pharmaceutical therapy. These cells' abnormal activity triggers the onset of neuropathic pain.[94]

NON-PHARMACOLOGICAL TREATMENTS

Multimodal therapy/Alternative medicinal therapies

For alleviation, some persons with peripheral neuropathy turn to complementary therapies. The following treatments have showed some promise, even though researchers haven't looked at them as carefully as they have most medications:[95]

Acupuncture: Inserting tiny needles into various body sites may lessen the symptoms of peripheral neuropathy. It can take several sessions before you start to see progress. When carried out by a licenced professional using sterile needles, acupuncture is typically regarded as safe.[96]

Alpha-lipoic acid has long been utilised as a therapy for peripheral neuropathy. Alpha-lipoic acid consumption should be discussed with your doctor because it may impact blood sugar levels. In addition, skin rash and stomach discomfort are possible adverse effects.

Herbs: Some plants, such evening primrose oil, may assist diabetics with neuropathy experience less pain.

Amino acids: Individuals with diabetes and those who have had chemotherapy may benefit from amino acids like acetyl-L-carnitine. Symptoms like nausea and vomiting could occur.

OTHER THERAPIES

TENS stands for **Transcutaneous Electrical Nerve Stimulation.** Various frequencies of a mild electric current are delivered to the skin through electrodes. For roughly a month, TENS should be used for 30 min per day for pain reduction.[97]

Plasma exchange with intravenous immunoglobulin: People with specific inflammatory disorders may find relief from procedures like intravenous immune globulin and plasma exchange, which help to reduce immune system activation. Plasma exchange entails drawing blood from the body, purifying it of antibodies and other proteins, and then reintroducing it. Immunoglobulin treatment involves giving patients high doses of proteins (immunoglobulins) that function as antibodies.[98]

Physical therapy can help with movement improvement if muscle weakness is apparent. requiring a wheelchair, a cane, a walker, or hand or foot braces.[99]

Surgery is necessary to relieve the strain on the nerves if it is the cause of neuropathies, such as pressure from tumours.

Non-invasive Transcranial Brain Stimulation treatments: Patients with refractory neuropathic pain may benefit from non-invasive transcranial brain stimulation treatments such as repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). Through a brief magnetic field, rTMS causes electrical currents to flow through the cortex.9 According to a landmine victim study on Phantom Limb Pain (PLP), high-frequency rTMS (10Hz) can dramatically lessen the discomfort for up to 15 days after treatment.[96] Although the efficacy of rTMS and high-frequency SCS has been demonstrated in patients who have failed to respond to conventional medical care, much more research has to be done in this area.[100]

Cervical Spinal Cord Stimulation (SCS): Another alternative therapy for those who don't respond to conventional medicine is SCS. SCS, also known as dorsal column stimulation, is an invasive procedure that includes stimulating the spinal cord's dorsal columns with electrical impulses at frequencies of about 50 Hz (administered by an implanted pulse generator) in order to reduce the overexcitability of the brain's neurons. The electrodes can be implanted surgically by a laminotomy or percutaneously using an epidural needle. The use of SCS has led to successful treatments for a number of neuropathic pain syndromes.[101]

PATIENT COUNSELLING

Patients can be counselled on various aspects listed below which also will contribute for better pain management.

Taking care of the feet, especially if diabetes is prevailed: Daily inspection is required for calluses, cuts, and blisters. Wearing padded shoes and nice, loose cotton socks is recommended. To keep bedcovers off warm or delicate feet, one can use a semi-circular hoop, which is readily accessible in medical supply stores.[102]

Exercise: Regular exercise, such as three times a week of walking, can enhance muscle strength, lessen the pain associated with neuropathy, and help regulate blood sugar levels. Yoga and Tai Chi are both gentle exercises that can be beneficial.

Meditation: Meditation is particularly proven to relax the aggravated nerves.

Cessation of smoking: Smoking can reduce blood flow, which raises the risk of foot issues and other neuropathy consequences. Stopping to smoke helps in pain reduction.

Eating healthy meals: To ensure you receive vital vitamins and minerals, good nutrition is very crucial. Include lean protein, healthy grains, fruits, and veggies in your diet.

Avoiding excessive alcohol: Peripheral neuropathy may get worse after drinking.

Monitoring blood glucose levels: If one has diabetes, this will aid in controlling blood sugar levels and may help with neuropathy associated with diabetes.

It is crucial to find new potential therapeutic targets in order to create novel pharmacological agents since neuropathic pain is a problem that is challenging to treat and consequently affects the quality of life for many people.

Due to the complexity of neuropathic pain, integrated approach is now being looked at. Integrative medicine uses a combination of therapies and lifestyle changes to treat and heal pain.

Finally, individualized treatment plan is the way forward for better management of the pain.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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