



“Multimodal Approaches To Neuropathic Pain Management: A Comparative Review”

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Abstract: Neuropathic pain is a chronic painful condition that is described by hyperalgesia and allodynia resulting from injury or disease of the nervous system. Neuropathic pain is defined as chronic pain arising from damaged or altered nerves, and the pathophysiology of neuropathic pain is the activation of pain pathways. Neuropathic pain management involves pharmacological and non-pharmacological interventions at the present time. Pharmacological treatments range from first-line treatment comprising of gabapentinoids, SNRIs, and TCAs, second-line treatment involving tramadol and third-line treatment involving SSRIs and NMDA antagonists. Neuromodulation techniques, such as invasive (spinal cord stimulation, motor cortex stimulation, deep brain stimulation) and non-invasive (repetitive transcranial magnetic stimulation, transcranial focused ultrasound, transcranial direct current stimulation), provide significant non-pharmacological alternatives. Novel interventions or emerging therapies like nanomedicine, gene therapy, stem cell therapy, microneedles, and platelet-rich plasma have a great future for neuropathic pain management. This review is intended to present the current state of knowledge about neuropathic pain, pathophysiology of this disorder, and possible treatment strategies with focus on the necessity to use a complex and personalized management of neuropathic pain.

Index Terms - Neuropathic pain, Pharmacological treatment, Neuromodulation, emerging therapies, Personalized management

I. INTRODUCTION

The highly complex and distressing illness known as neuropathic pain is caused by injury or disease of any or all of the nerves responsible for touch, among other things. It is commonly compared to a burning sensation and can be produced by a light touch ^(1,2). The pain is chronic and does not respond to standard pain medications. Shingles, trigeminal neuralgia, diabetes, HIV infection, amputation, and stroke are all potential causes of neuropathic pain. The explanation for this is that nerve compression or inflammation occurs in the lumbar or cervical regions, which are known as cervical and lumbar, and result from root radiculopathies, hence the term “radiculopathy” ⁽²⁾. In comparison to other types of chronic pain, neuropathic pain is associated with sleep difficulties, anxiety, depression, and a significantly lower quality of life ⁽³⁾. About 7-10% of the general population suffers from neuropathic pain. Women (8% versus 5.7% in men) and the elderly are the most commonly afflicted demographic ^(4,5). Appropriate diagnosis of neuropathic pain frequently involves asking the patient for a full medical history, followed by a physical exam, as well as nerve tests or imaging scans to determine why it developed in the first place. In general, treatment of neuropathic pain always requires a rather multimodal approach, with concurrent usage of several medications to cope with the complexity of condition. Antidepressants, anticonvulsants, and topical medications are common treatments to start with. This can also have good outcomes with physical treatments, occupational therapy, and psychological interventions, including cognitive-behavioral therapy, in the management of neuropathic pain and its comorbidities. If conservative therapy fails, invasive techniques include spinal cord stimulation, peripheral nerve stimulation, or targeted

medication delivery devices. These neuromodulation treatments attempt to halt or modify the pain signals sent by the injured nerves ⁽⁵⁾.

EPIDEMIOLOGY AND IMPACT ON QUALITY OF LIFE:

Peripheral neuropathy (PN) is a widespread disease in India, and its etiologies may differ from one area to another with prevalence rates of 5-2400/10,000, according to community-based surveillance. Due to such an array of reasons as diabetes, some inherited neuropathies, some inflammatory ones and some toxic ones are mentioned ⁽⁶⁾. DPN or Diabetic peripheral neuropathy (DPN) is the most widespread consequence of Diabetes, with a prevalence frequency range of 18.8 to 61.9% in India. India is a multi-culture and culturally diversified country, where people of different background, based on their environment, are exposed to risk factors such as arsenic and lead which may cause some central nervous system disorders. For example, routine usage of chemotherapy particularly that has the tendency to affect autonomic peripheral nerves increases in cases of cancer, increase in incidences of connective tissue diseases, as well as the use of immunomodulating drugs with aging population are the expected factors that affect the frequency and degree of PN in Indian community ^(6,7).

PATHOPHYSIOLOGY OF NEUROPATHY:

Neuropathy is a complex and diverse disease with various etiologies which develop through different pathophysiological mechanisms. The three peripheral of nerve injury are the most common segmental demyelination, Wallerian degeneration, and the axonal degeneration

1) Segmental demyelination:

The part of the demyelination that determines the formation of myelin sheath while it leaves the nerve axon. This type of reaction is present in the mononeuropathies, sensory neuropathies, or even motor neuropathies. It makes up for about 20% of symmetric peripheral neuropathy (SPN) including the Charcot-Marie-Tooth disease.

2) Wallerian degeneration:

It follows the axon apoptosis after it has been damaged by stress or physical compression, as a result, the dying part of the nerve axon undergoes the passive degeneration process as is seen in distal axon wasting. There occurred a distinct type of impairment demonstrated by interlocating of neuropeptide Y-Y1 receptor markers ^(8,9).

3) Axonal degeneration:

The death of nerve fibers is a hallmark of many neurodegenerative diseases, which is usually associated with a slowing down of nourishing molecules to cells. It commonly shows up as symmetrical polyneuropathy, which involves weak dorsiflexion of the ankles and feet (around 80% of cases), followed by foot drop and trophic changes in the muscles. Axonal degeneration takes place, in HIV, diabetes, HCV and GBS ⁽¹⁰⁾.

CENTRAL SENSITIZATION MECHANISM

Central sensitization is a condition in which the central nervous system produces greater pain signals. This causes hyperalgesia (enhanced sensations of pain in response to painful stimuli) and allodynia (the presence of pain from normally harmless stimuli) throughout the body. It is associated with different pain conditions, ranging from neuropathic pain and migraine to irritable bowel syndrome ⁽¹¹⁾. Central sensitization takes place when neurons in both the spinal cord and the brain start to over-respond or be hyper-sensitive to pain stimuli. This might be due to constant pain messages from damaged or irritated body structures. Increased sensitivity indicates changes in the brain systems that send messages to one another. Prolonged low-level pain messages can cause spinal cord neurons to transmit higher-frequency pain signals, and touch messages can begin to trigger pain pathways (allodynia). Understanding central sensitization is critical for managing chronic pain. ⁽¹²⁾

PERIPHERAL MECHANISM

Peripheral nerve injury causes a variety of pathological events that are correlated with the initiation or perpetuation of neuropathic pain. Key peripheral mechanisms include axonal degeneration in the distal portion and axonal regrowth at the injury segment. Release of pro-nociceptive mediators by peripheral tissue, reducing the stimulation needed for activation of the sensory neurons⁽¹³⁾, Synaptic activity in axotomized peripheral nerve stump and dorsal root ganglion neurons Changes in sodium, calcium, and/or potassium channel expression in the peripheral nervous system, Morphological changes: sprouting of A β fiber terminals into

laminase II-III of the spinal dorsal horn, Increased adrenergic receptor expression and sympathetic axon terminal growth, increasing adrenergic responsiveness^(14,15). These shifts in the damaged and neighboring undamaged nociceptive neurons, in combination with central sensitization, are responsible for neuropathic pain states such as spontaneous pain, allodynia, and hyperalgesia. It is therefore imperative to understand these peripheral mechanisms to enable more targeted treatment options for both the prevention and reversal of neuropathic pain ⁽¹⁶⁾.

PHARMACOLOGICAL PAIN MANAGEMENT FOR NEUROPATHY:

A complex of symptom management strategies is employed to treat neuropathic pain since there are no specific drugs available to address its root causes. Recently, a meta-analysis of 229 studies drew attention to the drug treatment effectiveness, which led NeuPSIG to propose gabapentinoids, TCAs, and SNRIs as first-line pharmacotherapies for neuropathic pain. Lidocaine, capsaicin, and tramadol are considered second-line treatments, while botulinum toxin-A are the last options for peripheral neuropathy ⁽¹⁷⁾. When the use of a single agent is not possible, combination therapy should be introduced ^(17, 18).

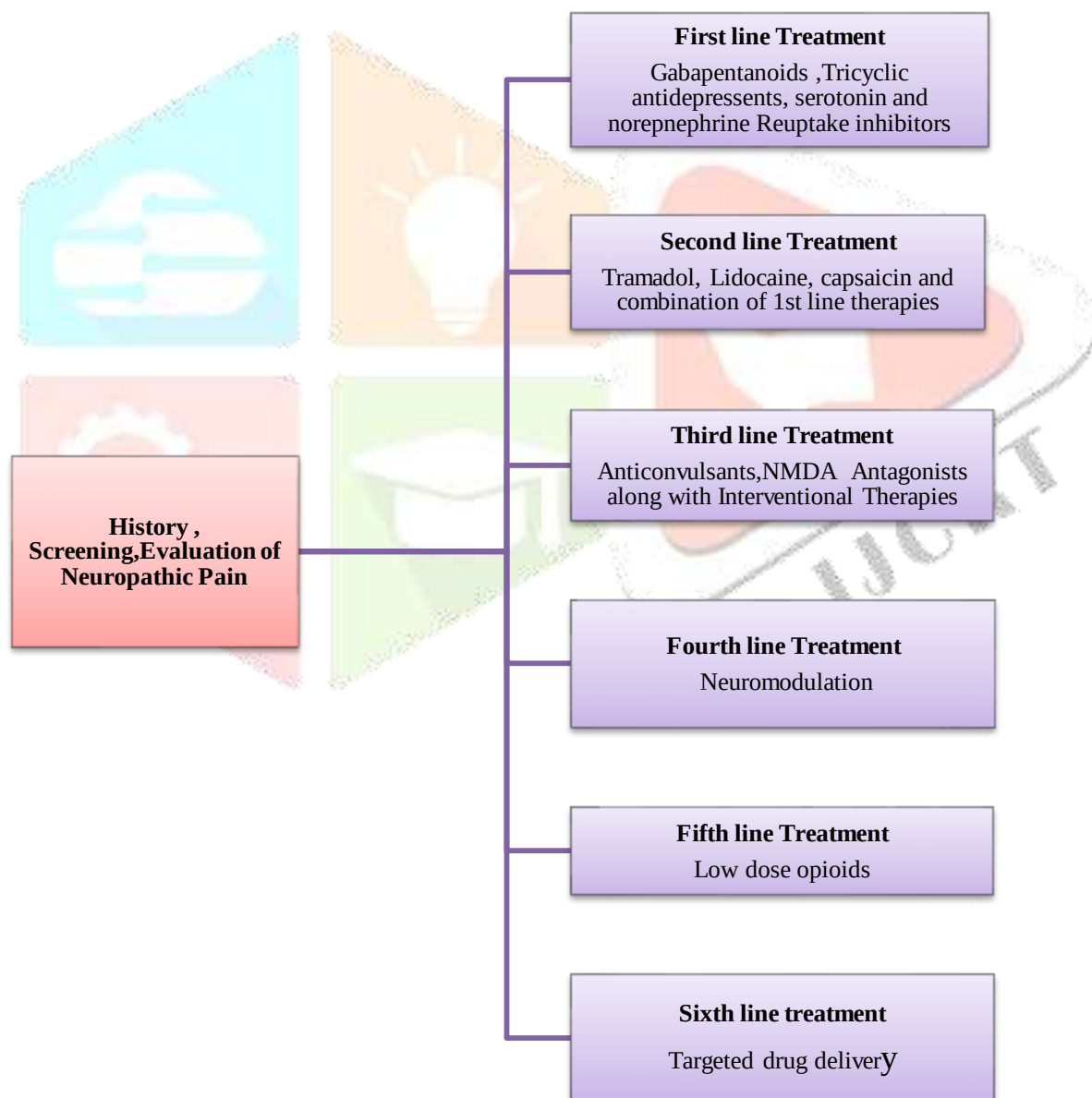


Figure 1: Comprehensive framework for managing neuropathic pain ^(18,19)

The US Food and Drug Administration has approved gabapentin for managing neuropathic pain, with gabapentin and pregabalin being the most common drugs. Gabapentinoids interact with the $\alpha 2$ - δ subunit of voltage-gated calcium channels, preventing calcium from entering presynaptic terminals and limiting the release of pro-excitatory neurotransmitters. They are effective in managing diabetic peripheral neuropathy, post-herpetic neuralgia, spinal cord injury pain, and phantom limb pain^(20,21). Tapentinoids increase synaptic availability of neurotransmitters by blocking their reuptake by serotonin and norepinephrine and also activate or modulate cholinergic, adrenergic, and histaminergic receptors to produce analgesia. Synaptic neuropathic pain relievers (SNRIs) primarily act on serotonin and norepinephrine reuptake, enhancing the inhibitory pain pathway. Tramadol, like other opioids, works by inhibiting nociception through the binding of μ -opioid receptors and affects serotonin and norepinephrine reuptake at a relatively low level, which may explain neuropathic painkillers. Tapentadol is the only opioid medication officially approved for diabetic peripheral neuropathy, acting as an agonist of the μ -opioid receptor and an inhibitor of norepinephrine reuptake^(18,22).

Lidocaine and capsaicin are classified as second-line treatment options for neuropathic pain since they inhibit the activity of voltage-gated sodium channels and decrease the number of spontaneous ectopic nerve discharges. They are useful in treating certain localized types of neuropathic pain, such as post-herpetic neuralgia, but not for others, such as diabetic neuropathy⁽²²⁾. Capsaicin, a potent TRPV1 receptor agonist, should be considered for third- or fourth-line therapy in patients who cannot tolerate oral medications⁽²³⁾. Oxycodone and morphine are considered third-line remedies because they cannot be prescribed without special scrutiny and have a high risk of abuse. BTX-A is a third-line treatment option for peripheral neuropathic pain that has failed to respond to other pain management therapies. These treatments affect various systems, such as sodium channels, TRPV1 receptors, opioid receptors, and synaptic transmission, and are placed in the neuropathic pain management guidelines⁽¹⁷⁾.

NMDA antagonists are drugs that work against NMDA receptors in the CNS and can be used for the treatment of neuropathic pain. These are ketamine, dextromethorphan, memantine, and amantadine; however, they are mostly restricted by side effects at higher doses^(17,24). Other interventional measures, including epidural injections, pulsed radiofrequency, sympathetic block, and radiofrequency ablation, have also been described as possible interventions for managing neuropathic pain. These therapies include some shots or minor surgery with the aim of reducing pain in particular limbs. But there are some disadvantages related to their use, mainly because there is not enough clinical information to establish the effectiveness of these drugs and their side effects. It has also been noted that not all patients can undergo these therapies because they come with complications like infection, bleeding, or nerve injury^(25,26).

NON-PHARMACOLOGICAL NEUROPATHIC PAIN MANAGEMENT:

Pain is a major social problem; many patients do not find adequate relief from their pain through medications. Some techniques of neuromodulation can be more effective in pain management based on pathophysiological considerations. This field employs both invasive and noninvasive methods to modify abnormal brain activity, which has more accuracy compared to drugs and more reversibility compared to surgery. Neuromodulation method is used when pharmacological treatments are not possible because of the risks and costs. The EFNS (European Federation of Neurological Societies) and the NICE (National Institute for Health and Care Excellence) approve the use of neuromodulation in the management of neuropathic pain. Other technique such as noninvasive techniques that can alter the tissue of the brain without the use of surgery^(27,28)

Table No 1: Classification of neuromodulation method

Invasive	Non invasive
Spinal cord stimulation (SCS) Motor cortex stimulation (MCS) Deep Brain stimulation (DBS)	Repetitive transcranial magnetic stimulation (rTMS) Transcutaneous electrical nerve stimulation Transcranial focused ultrasound (tFUS) Transcranial direct current stimulation (tDCS)

Spinal Cord Stimulation (SCS)

SCS is a therapy procedure that involves implantation of electrodes to create electric fields that will modulate the dorsal horn and column of the spinal cord thus masking pain signals in the spinothalamic tract⁽²⁹⁾. This is probably because the A β fibers are blocked in the dorsal horn; this hinders the input of afferent and the release of inhibitory neurotransmitters. Stimulation is directed to the dorsal root ganglion, vagus nerve and the trigeminal nerves. Tonic (40-100 Hz) stimulation decreases the pain intensity, and further decrease is observed with the help of high-frequency or burst stimulation⁽³⁰⁾.

Motor Cortex Stimulation (MCS)

MCS is applied for neuropathic patients who failed medication treatment, for instance, stroke pain, multiple sclerosis, phantom limb pain, spinal cord injury. MCS applies epidural stimulation of the motor cortex at about 50 Hz; how it works is not known, but may prevent the reorganization of somatosensory and motor cortex that causes deafferentation pain. However, achieving patient responsiveness is not easy because of the risks and the procedure's intrusiveness, with no reversal possible⁽³¹⁾.

Deep Brain Stimulation (DBS)

DBS is an implantation procedure in which electrodes are placed in the brain areas that include but not limited to sensory thalamus, internal capsule, and periaqueductal/periventricular gray matter for modulating the neural processing of pain and neuropathic pain. There are many components of a DBS system which include an electrode that is surgically placed, an electrical generator, wires and a programmer for wireless adjustment of the settings⁽³²⁾. However, research carried out on the Medtronic DBS systems indicated that the procedure was not very successful in the long run as only 14-22% of the patients got a reprieve from the pain after 24 months. These complications include, infection risk that is expected to be at 2.6 – 5% in the patients, failure of the hardware (at 5.5 %) and harm caused by stimulations⁽³³⁾. Sensor material selection is crucial, capacitive materials like titanium nitride and tantalum oxide are preferred to faradaic materials, for instance, platinum to enhance biocompatibility.

Repetitive Transcranial Magnetic Stimulation (rTMS):

Magnetic stimulation (MS) is a non-invasive technique that creates short-lasting magnetic fields to induce electromotive and hence, eddy currents in the brain. Repetitive transcranial magnetic stimulation (rTMS) is an intervention that applies magnetic fields to stimulate the neurons of the cerebral cortex and possibly alter the long-term neural connections⁽³⁴⁾. rTMS has been useful in managing chronic pain with significant relief for central neuropathic pain and fibromyalgia patients. It can be performed at a low frequency, which is continuous, or at a high frequency, pulsatile, with pulsatile rTMS at a higher frequency demonstrating a higher level of pain relief compared to sham stimulation. However, several side effects have been reported, and they include rarely seen conditions such as seizures, hypomania, headaches, and electrode scalp burns. Some of the safety concerns of using such devices are overheating and the failure of the device^(35,36).

Transcutaneous Electrical Nerve Stimulation

Transcutaneous Electrical Nerve Stimulation (TENS) is a form of neuromodulation where the electrical currents are passed through the skin to specific dermatomal regions to obtain segmental anesthesia⁽³⁷⁾. TENS modalities include conventional TENS, which employs a high-frequency low-intensity current to block the segmental pathway, as well as acupuncture-like TENS (ALTENS), which uses a low-frequency high-intensity current to stimulate the extra-segmental inhibitory pathway. It is useful in the management of hyperalgesia by interfering with the afferent stimuli in the CNS and reestablishing normal central pain regulation; it is particularly useful in disorders such as fibromyalgia. TENS is associated with certain precautions, such as those contraindicated in patients with cardiac pacemakers, implantable cardioverter-defibrillators, pregnancy, and epilepsy. It should not be applied directly to the affected area or where there is a break in the skin or loss of sensation in the area supplied by a specific nerve. TENS-induced analgesia is peripheral, spinal, and supraspinal and is exerted by μ and δ opioid receptors^(38,39).

Transcranial Focused Ultrasound (tFUS)

tFUS is an invasive method that acts on neural activity by using piezoelectric materials such as lead zirconate titanate with focal spot precision. It translates the supplied electrical signal into mechanical oscillations, and a 250 kHz, 30 msec bursting tFUS can decrease the connectivity of the brain network^(40,41). Some important advances in transcranial systems have been made by the researchers by creating an MR-compatible 128-channel random-phased ultrasound array along with enhancing the focal and electronically steering. This technique is also of value in noninvasive pain relief; other pilot trials suggest other diagnostic and therapeutic uses. Some of the characteristics that have been looked at include various frequencies of the ultrasound, ranging from 1/5 sec of intensely focused ultrasound at a fundamental frequency. Focusing on 15 MHz, it seems reasonable to differentiate neuropathic tissues from the normal ones for the Sprague-Dawley model with partial sympathetic nerve ligation. It is possible to influence tFUS in such a manner that it would produce both excitatory and inhibitory effects, depending on the stimulation parameters and paradigms. Pain is a complex phenomenon that is assessed individually and is the result of the brain's complex functional connections⁽⁴²⁾.

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation is a non-invasive procedure where the routine electrical current is passed to the scalp and the change in cortical excitability of neurons can help in reducing the pain in neuropathic pain and chronic low back pain patients^(43,44). It enhances the alpha spectrum of the cerebral cortex somatosensory area, resulting in the rewiring of the neural circuits. tDCS is applied in chronic pain management, whereby placing electrodes on the patient's head and passing a weak electrical current over a specific part of the brain disrupts neurotransmission, ion channels, and non-synaptic plasticity. It has shown efficiency in various types of pain, for instance, fibromyalgia pain, neuropathic pain, and migraine⁽⁴⁵⁾. New protocols like increased intensity and cerebellar tDCS are in the pipeline in the field as they are proven to be effective in treating the purpose of pain. Hence, the combination of tDCS with other therapeutic procedures, including mirror therapy and motor imagery, could be used in pain management for patients with chronic pain^(46,47). Transcutaneous spinal direct current stimulation (ts-DCS) is an extraneous method, probably a self-executable protocol, and has shown an analgesic effect coupled with a suppressive influence of the nociceptive processing and provided indications towards chronic pain therapy⁽⁴⁸⁾.

RECENT ADVANCES IN NEUROPATHY PAIN MANAGEMENT:

Nanomedicine

Nanomedicine has been found to be more effective in delivering the drugs for neuropathic pain (NeP) at reduced doses and with minimized side effects. Recent studies in animal models have shown that nanocarriers like liposomal and nanoparticles can enhance the CIRCULATION time of the drug and facilitate the delivery of the drug to the target tissue or organ for better therapeutic effects⁽⁴⁹⁾. In this study, the authors synthesized a nanoparticle-hydrogel delivery system (NHDS) of esketamine and observed that the NHDS increased the antinociceptive activity in comparison to the free form in mice. nZnO has also been investigated in the treatment of NeP since it discharges zinc ions, which are NMDA receptor antagonists of the non-competitive type. A study that used theranostic nanomedicine observed that pain was alleviated for 24 hours and slightly

more than 6 days, accompanied by a reduction in macrophage and mast cell infiltration ⁽⁵⁰⁾. Like other nanomedical applications in managing NeP, the technique is still under development but has the possibility of delivering drugs specifically, in low concentrations, and with sustained pain relief consistent with the immune neuropathology of the condition.

Gene Therapy:

Gene therapies also have a potential application in the treatment of neuropathic pain through the replacement of functionally impaired genes. Somatic gene therapy is aimed at the alteration of the disease in the patient without impacting their capacity to reproduce and pass on the new gene to their offspring, while germline gene therapy impacts genes in cells that are responsible for sperm and fertilized eggs, hence heritable. Some of the methods and techniques used in gene therapy include Viral vectors, non-viral vectors, and Direct gene transfer ⁽⁵¹⁾. Certain studies have shown that using gene therapy, the communication of the nociceptive signals can be stopped at the supraspinal level particularly the medulla oblongata which is associated with pain control. Due to the problems arising from the targeting of the medulla oblongata, the study has been centered on other regions, which are easier to reach, especially in reference to the diseases of chronic pain, such as: complex regional pain syndrome or fibromyalgia ⁽⁵²⁾. Gene therapy for pain include the introduction of genes that produce substances that would block the nociceptive receptor or change the nociceptive molecules in neurons. Three main gene therapy approaches have been used to deliver analgesic genes in the nervous system: Those are the cell-based therapies, plasmids and oligonucleotides, and viral based vectors. Viral vector gene therapy is by far the most widely used technique in the delivery of genes to the nervous system since it harnesses the virus' ability to transfer infection alongside expressing its genes in the host cells. However, gene therapy also has some limitations of dosing, safety, efficacy, and some ethical issues in the neuropathic pain management. Further research needs to be conducted to develop the new and efficient vectors for gene delivery that would be targeted to the specific tissues without damaging the surrounding healthy cells ⁽⁵³⁾.

Microneedles

Microneedles have been used in neuropathic pain treatment by administering anti-CGRP peptides to the target site and providing efficient and safe pain-relieving effects. These dissolvable MNs for systemic administration are prepared from materials such as sodium carboxymethyl cellulose (SCMC) wherein it avoids injections by offering a painless and localized delivery system with no side effects. The mechanism of action includes blocking of peripheral CGRP receptors by the anti-CGRP peptide and the ability to reduce hypersensitivity and provide analgesia, which indicates the efficacy of the treatment at least comparable to lidocaine or subcutaneous injection and superior to systemic gabapentin treatment. CGRP8-37 administration by using MNs was proven to be as effective as conventional treatments based on the findings of several scientific studies, which might point to the effectiveness of applying this specific strategy in neuropathic pain treatment. This targeted approach not only guarantees effective pain relief but it also reduces the side effects which are characteristic of the traditional treatments. Also, microneedles can be made to deliver medicine in a controlled and steady manner, meaning that patients with pain can be given relief that lasts for quite a while. In conclusion, microneedles have the potential to be an effective option for the management of neuropathic pain since it can enhance the treatment results and positively affects the quality of life in patients with the chronic condition ⁽⁵⁴⁾.

Stem Cell Therapy

stem cells hold the crucial role in human bodies to grow and stay healthy. They help in embryogenesis, organogenesis, and even fix up damaged tissues. Depending on their specialty stem cell are classified as adult stem cells, embryonic stem cells, pluripotent and multipotent stem cells. They all play a huge role in our development and maintenance. For chronic neuropathic pain, stem cell therapy has shown promise evidence. MSCs have the ability to produce neurotrophic factors that can help regenerate brain cells ⁽⁵⁵⁾. They've shown promise in treating lower back pain by promoting the growth and specialization of nucleus pulposus cells towards the chondrogenic lineage. The potential of these cells in the field of molecular medicine can potentially alleviate or even stop various diseases and provide protection for the nervous system in cases of injury, including neuropathic pain ⁽⁵⁶⁾. Some research indicate that stem cells may not only help to reduce neuropathic pain but also improve motor function in animal models. Gene therapy has the ability to generate stem cells that are genetically developed to release molecules for halting the pain. Mesenchymal stem cell shows promising result in neuropathic pain research as they have characteristic to expand, genetic stability, and ease of collection and transportation. Stem cell therapy influence the balance between these two types of factors that are neurotropic and neuroinflammatory factor, that contribute in relaxation for neuropathic pain caused by conditions like sciatic nerve injury, diabetes-induced neuropathy, and spinal cord injury ^(57,58). But some more studies and clinical trials are needed to fully understand the overall impact of stem cell therapy on the neuropathy pain.

Platelet-Rich Plasma Therapy (PRP)

Neuropathic pain is the class of pain which involve damaged of nerve twines, and there is evidence that PRP therapy could provide relief from pain. PRP is made from an anticoagulated blood sample that is enriched with platelets which release growth factors to stimulate the healing of injured body tissues. Some research indicated that the administration of PRP injections helps in the management of pain in patients diagnosed with peripheral neuropathy ⁽⁵⁹⁾.

PRP can promote nerve regeneration through various mechanisms:

- Neuroprotection
- Stimulation of vascular regeneration
- Promotion of axonal regeneration
- Regulation of inflammatory response
- Relief of nerve collateral muscle atrophy

Neuropathic pain can be treated through PRP as it has regenerative and anti-inflammatory effects due to the presence of platelets. PRP works by mobilizing the healing process directly at the site of the nerve injury by carrying out angiogenesis, tissue repair and nerve regeneration when it is injected into the affected site. This can help lessen pain, numbness and other neuropathic symptoms ^(59,60). According to a recent study conducted on patients diagnosed with diabetic neuropathy, the amount of pain and nerve dysfunction experienced markedly lowered in patients who had PRP injections than in a control group that did not. Therefore, PRP treatment is a viable, non-surgical technique for the management of neuropathic pain. Due to the fact that it can activate the body's regenerative systems that are inherent to the human body, PRP can help in regeneration of nerves, decrease inflammation, and thus manages neuropathies enhancing patient's quality of life (61).

FUTURE ASPECTS

Neuropathic pain management have optimistic future because there are several strategies that need to incorporate superior pharmacological treatments, newly developed neuromodulation techniques, nano therapies, gene therapy and stem cell therapies. Current research is shifting towards exploring how one can integrate the existing models for generating the best treatment strategy based on any feature of a patient. Further research opportunities include investigation of the potential synergistic effect of pharmacotherapy with neuromodulation, gene therapy with stem cell therapy and the advancement in individualized medicine, the issue of implementation from molecular to clinical, advancing techniques in neuromodulation, and the advancement of novel therapeutic interventions in neuropathic pain such as Nanomedicine, Gene therapy, Stem cell therapy, Microneedles and PRP therapy. Overcoming some of these limitations in translation and refining the animal models will prove impactful in bridging the gap between neuropathic pain research and development and clinical application to produce better and targeted treatments for neuropathic pain patients and therefore improving their quality of life.

CONCLUSION

Neuropathic pain is complex and challenging to treat, and its management involves the use of medications, neuromodulation therapy, and other forms of treatment depending on the patient's characteristics. The first-line management consists of gabapentinoids, TCAs and SNRIs, second-line management entails tramadol while third-line management is SSRIs and NMDA antagonists. Non-pharmacological interventions such as invasive and non-invasive neuromodulation methods also appear to be quite effective. Some promising therapies are nanomedicine, gene therapy, stem cell therapy, microneedle, and platelet-rich plasma. Thus, integrating these various approaches allows for better treatment of neuropathic pain and more favorable outcomes for patients. Further exploration and improvement of these treatment approaches will be the key to the development of neuropathic pain management in the future and allow for better treatment of people suffering from this type of pain.

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