

NEUROPHYSIOLOGICAL MECHANISMS AND PHYSIOTHERAPEUTIC STRATEGIES IN THE MANAGEMENT OF CHRONIC NEUROPATHIC PAIN: EMERGING CLINICAL EVIDENCE

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ABSTRACT

Chronic neuropathic pain is a complex, disabling condition that is caused by lesions or diseases of the somatosensory nervous system. It is sustained by peripheral nerve dysfunction, ectopic activity, dysregulated ion channels, neuroimmune dysfunction, central sensitization, maladaptive brain network function and neuroplasticity. Current pharmacologic treatments may not adequately relieve symptoms, underscoring the need for comprehensive, mechanism-targeted rehabilitation strategies. This review summarizes current evidence on the neurophysiological mechanisms underlying chronic neuropathic pain and examines physiotherapeutic interventions that may modulate these mechanisms. Therapeutic exercise, pain neuroscience education, manual therapy, neuromuscular re-education, mirror therapy, graded motor imagery, electrotherapy, neuromodulation, and virtual reality-based rehabilitation are discussed in relation to pain modulation, functional recovery, and patient-centered outcomes. Emerging clinical evidence supports the use of personalized rehabilitation approaches guided by pain phenotype, functional impairment, and neurophysiological profiles. Future directions include biomarker-guided rehabilitation, artificial intelligence-based prediction models, digital health integration, and standardized outcome assessment. A mechanism-based physiotherapy framework may improve treatment precision, enhance functional outcomes, and support long-term management of chronic neuropathic pain.

KEYWORDS: Chronic neuropathic pain, Central sensitization, Physiotherapy, Neuroplasticity, Rehabilitation

INTRODUCTION

Chronic neuropathic pain (CNP) is a complex and debilitating condition due to lesions or diseases of the somatosensory nervous system. Neuropathic pain is a type of pain resulting from altered neural processing and associated with symptoms like burning pain, electric shock-like pain, paresthesias, allodynia, and hyperalgesia, which are not seen in nociceptive pain. Although there has been a great deal of research into pain and its clinical management, neuropathic pain continues to be under recognised and untreated and is a significant challenge for interdisciplinary healthcare globally [1]. The complex etiologies of neuropathic pain are linked to a complex pathogenesis that includes entanglements among peripheral nerves, spinal pathways, supraspinal structures, immune responses and psychosocial factors, all of which make it difficult to treat.

Population ageing, growing incidence of chronic diseases and the improvement of survival rates of people with diseases that cause nerve damage have significantly contributed to the global burden of chronic neuropathic pain. The evidence suggests that chemotherapy-induced peripheral neuropathy (CIPN) continues to be one of the most common causes of chronic neuropathic pain in cancer survivors, affecting a significant number of cancer survivors around the world. A systematic review and meta-analysis of 28 countries confirmed that chronic painful neuropathy is a common problem in CIPN patients and is an emerging public health concern [2]. Likewise, diabetes mellitus remains a leading cause of neuropathic complications; with an ever-increasing burden of diabetes globally, the rate of diabetic peripheral neuropathy and its associated pain syndromes is projected to further increase. This chronic condition of diabetic foot disease and other diabetic neuropathic complications is another reason for the importance of effective preventive and therapeutic interventions [3].

In addition to its clinical symptoms, chronic neuropathic pain also generates significant economic and health care costs. Chronic pain is a powerful driver of disability, loss of work productivity, increased health care costs and limited quality of life. Population-based studies have shown that chronic pain is a significant contributor to disease burden and that many people suffer from chronic pain regardless of their age, sex, or socioeconomic status [4]. In addition, the ramifications of chronic pain are emotional, social, sleep, anxiety and depression. More recent research also indicates that women tend to suffer more disability and poorer health-related quality of life from chronic pain than men [5].

Neuropathic pain is a very common pain problem among people with musculoskeletal disorders. There is growing evidence from community health care settings that the neuropathic pain dimensions are frequently present in chronic low back pain patients, thus increasing the complexity of diagnosis and management [6,7]. These results suggest that neuropathic mechanisms could be present together with nociceptive and nociplastic pain mechanisms, thus highlighting the importance of using holistic assessment strategies that allow identification of the underlying mechanism of pain.

Chronic neuropathic pain is mostly managed using medication such as antidepressants, anticonvulsants, topical agents and opioids. The efficacy and adverse effects of treatment, however, are limited and treatment resistance and long-term adherence are suboptimal for many patients [8]. Therapies targeting the transient receptor potential vanilloid 1 (TRPV1) receptors and capsaicin-mediated pathways have been found to be promising recently, especially with respect to the treatment of diabetic neuropathy; however, these therapies do not necessarily provide sufficient treatment for the complex neurophysiological changes associated with chronic neuropathic pain [9]. There is now an increased awareness of the need for rehabilitation approaches that involve multiple disciplines and focus on mechanism, especially ones that go beyond controlling symptoms.

Contemporary management of neuropathic pain has led to the appearance of physiotherapeutic interventions. RBT, Sensorimotor retraining, pain neuroscience education, neuromodulation techniques, and other physiotherapeutic interventions have shown potential to modulate pain pathways, induce neuroplasticity and enhance functional outcomes. There is current evidence that exercise training could have beneficial effects via a number of mechanisms such as exercise-induced hypoalgesia, anti-inflammatory modulation, improved endogenous pain inhibition and better psychosocial functioning [10]. The developments are consistent with the overall trend of personalized, mechanism-based pain management, merging insights from the neurophysiology of pain with clinical rehabilitation.

Considering the high prevalence and burden of chronic neuropathic pain, and the emerging evidence that physiotherapeutic treatment is effective, an up-to-date overview of the existing neurophysiological mechanisms and rehabilitation strategies is justified. This knowledge of the effect of specific interventions on peripheral and central pain mechanisms could inform the creation of more effective, personalised pain management strategies [11]. Thus, this review critically analyzes the neurophysiological mechanisms underlying chronic neuropathic pain, summarizes current physiotherapeutic treatment options, and evaluates emerging clinical evidence for rehabilitation of chronic neuropathic pain based on mechanism of disease. The aim of this study is to:

1. To study critically ways in which neurophysiological mechanisms contribute to chronic neuropathic pain, as well as their clinical relevance
2. To assess the current physiotherapeutic interventions for peripheral and central pain mechanisms.
3. To integrate the new clinical evidence of mechanism-based approaches to rehabilitation.

2. Neurobiology of Chronic Neuropathic Pain

2.1 Definition and Classification

Neuropathic pain is pain that occurs as a direct consequence of a lesion or disease of the somatosensory nervous system, which processes sensory information including touch, temperature and pain [12,13]. It can be broadly divided into peripheral neuropathic pain and central neuropathic pain depending on the site of the damaged area. Neuropathic pain can be caused by injuries to peripheral nerves, or disorders of the brain or spinal cord. In some clinical conditions both central and peripheral mechanisms are involved, and this may cause diagnostic difficulties and difficulties in the choice of treatment.

2.2 Peripheral Mechanisms

2.2.1 Mechanical Damage

Peripheral nerves are a common site of mechanical injury that is a major cause of neuropathic pain. If the nerve is damaged, the damaged axons or neurons in the DRGs could generate spontaneous ectopic discharge, resulting in abnormal electrical activity without external stimulation [14]. These abnormal messages are sent to the brain and perceived as pain. Ongoing ectopic activity leads to ongoing pain perception and facilitates the development of long-lasting pain processing changes. This makes nerve damage the trigger and continued source of chronic neuropathic pain even when the tissue damage is gone.

2.2.2 Ion Channel Dysregulation

The expression and activity of voltage-gated sodium, potassium and calcium channels in sensory neurons are markedly affected following nerve injury [15]. These ion channels control the excitability of neurons and the transfer of signals between them. Often the dysregulations result in overactivity and heightened sensitivity to sensory input. The net result of these changes is abnormal pain signaling and results from increased sodium channel activity, decreased potassium channel activity, and altered calcium channel expression. Such molecular and electrophysiological modifications improve the generation and propagation of nociceptive impulses, and are important in the initiation and maintenance of chronic, neuropathic, states of pain.

2.2.3 Neuroimmune Interactions

The development of neuropathic pain after a nerve injury is important in neuroimmune interactions. Damage to peripheral nerves leads to recruitment and activation of immune cells such as macrophages and T lymphocytes that send out pro-inflammatory cytokines and chemokines [16]. The inflammatory mediators directly act on the peripheral neurons to make them more sensitive and responsive to stimuli. This interaction between the immune and nervous systems helps to maintain nociceptor activation and sensitization. Continuous neuroimmune signalling leads to chronic inflammation and contributes to the maintenance of neuropathic pain after the injury.

2.2.4 Peripheral Sensitization

Peripheral sensitization is defined as an enhanced responsiveness of the nociceptors after exposure to inflammatory mediators that are released from injured tissues or nerves [15,16]. Prostaglandins, cytokines and growth factors lower the threshold for activation of sensory nerve endings, increasing their sensitivity to mechanical, thermal and chemical stimuli. Consequently, stimuli that are not normally painful can become painful or painful stimuli can cause exaggerated responses. This enhanced sensitivity is a key component of neuropathic pain and plays a major role in the pain chronicity and intensity.

2.3 Central Mechanisms

2.3.1 Central Sensitization

Central sensitization is one of the important mechanisms involved in neuropathic pain, and it refers to the increase in the sensitivity of neurons of the spinal cord and other brain regions as a result of the prolonged presence of nociceptive input [17]. This increased excitability increases pain signals and decreases the threshold for neuronal activation. It is thus possible for patients to have allodynia, or sensitivity to pain from normally non-painful stimuli, and hyperalgesia, or increased sensitivity to painful stimuli. Central sensitization can likewise help pain continue after the acute injury has healed, and has a significant role in the shift from acute to chronic neuropathic pain.

2.3.2 Synaptic Plasticity

Synaptic plasticity refers to changes in the strength and effectiveness of the synaptic connections in pathways involved in pain processing that are activity dependent. After nerve injury, chronic nociceptive activity leads to changes in the structure and function of neurons and synapses, such as alterations in the release of neurotransmitters and changes in receptor levels [18]. Extensive epigenetic modifications also control pain signaling gene expression. Plasticity is beneficial in most cases, but can be maladaptive and contribute to a prolonged process of abnormal pain. These changes allow these networks to remain hyperactive and enable the transition from acute to chronic, neuropathic pain.

2.3.3 Altered Descending Pain Modulation

The descending pain modulatory system is essential for a modulating effect on pain perception which involves an inhibitory or facilitatory effect of supraspinal centers. In neuropathic pain, this regulatory system is impaired, with a decreased inhibitory and increased facilitatory signal [19]. This results in increased pain transmission in the spinal cord, which increases the pain sensitivity and duration of the pain. This imbalance is caused by changes in the neurotransmitter systems such as serotonin and norepinephrine. Impaired descending modulation thus plays an important role in the chronicity and severity of neuropathic pain.

2.3.4 Cortical Reorganization

Chronic neuropathic pain leads to structural and functional reorganization of brain regions related to sensory processing, emotional control and cognition [20]. Over time, these changes in neural functioning occur in the somatosensory cortex, anterior cingulate cortex, and prefrontal cortex. These changes can affect how one feels pain, their emotions, focus and decision making. Additional factors such as neuroinflammation and gliosis may also play a role in the development of cortical remodeling. This reorganization corresponds to the brain's plastic response to chronic pain, but is frequently accompanied by abnormal reorganization of the brain, leading to chronic pain and its related psychological problems.

2.4 The role of glial cells in neuroinflammation.

Neuroinflammation plays a crucial role in neuropathic pain and is characterized by activation of microglial cells and astrocytes in the central nervous system (CNS) [21]. After nerve injury, these cells produce pro-inflammatory cytokines, chemokines, and neuromodulators that increase the excitability of the neurons and promote pain transmission. Glial cells also modulate synaptic function and play a role in central sensitization. Chronic pain is maintained by continuing cytokine-mediated signalling. Thus, neuroinflammation and glial activation have been suggested to play a critical role in the pathophysiology of neuropathic pain.

2.5 Brain Network Alterations

Neuroimaging studies have shown that chronic neuropathic pain is correlated with substantial changes of large-scale networks in the brain, such as the default mode network (DMN), the salience network (SN), and the sensorimotor network (SMN) (Figure 1) [22–24]. These networks become disconnected and thus impair the integration of sensory, emotional, cognitive and motor processes. These shifts can help reinforce maladaptive neural activity patterns that can contribute to chronic pain. Chronic neuropathic pain has also been associated with emotional disorders, attention deficits, and decreased motor function, providing a broad range of neurological changes associated with chronic neuropathic pain.

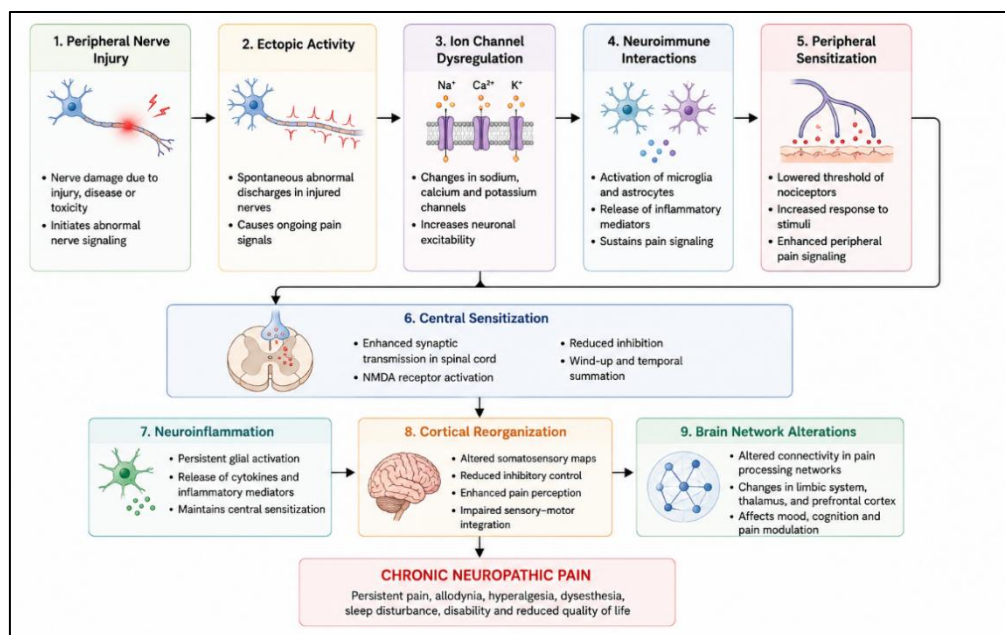


Figure 1: Neurophysiological Mechanisms Underlying Chronic Neuropathic Pain

3. Neurophysiological Assessment of Neuropathic Pain

3.1 Quantitative Sensory Testing (QST)

The quantitative sensory testing (QST) is a psychophysical test, standardised to assess sensory dysfunction in patients with neuropathic pain [25,26]. QST can be used to detect peripheral and central sensitization, to establish sensory phenotypes and to help with diagnosis, by measuring responses to thermal, mechanical and vibration stimuli. There is increasing emphasis on its role in mechanism-based pain assessment and patient stratification for targeted therapeutic interventions in recent guidelines.

3.2 Electrophysiological Measures

Electrophysiological methods allow to objectively assess integrity of the somatosensory pathway and peripheral nerve function. Electromyography (EMG) is useful for determining denervation and neuromuscular abnormalities, but nerve conduction studies are used to assess the functional state of sensory and motor nerves [27]. Laser-evoked potentials provide information on the function of small fibers and integrity of the nociceptive pathways. These measures are all used to diagnose, determine the severity, and monitor neuropathic disorders.

3.3 Neuroimaging Biomarkers

The development of neuroimaging has become an important tool that helps to understand the central mechanisms of neuropathic pain. Altered brain activity and connectivity in pain-processing networks can be examined using functional MRI (fMRI) [28]. The positron emission tomography (PET) can provide data about neuroinflammation, neurotransmitter systems and metabolic changes, as well as diffusion tensor imaging (DTI) can assess structural changes in white matter tracts related to pain transmission. These modalities help to detect objective biomarkers related to chronicity of pain and treatment response.

3.4 Emerging Biomarkers

New biomarkers have the potential to enhance the diagnosis and individualized treatment of NEP. Pathological processes can be evaluated with markers of neuronal inflammation such as cytokines and glial activation markers. Neurotrophic factors that promote neuronal survival and plasticity could be used to predict disease course and recovery[29,30]. Moreover, digital biomarkers of wearable devices, mobile apps and machine learning algorithms are becoming a key area of interest to assess the symptoms and functional outcomes continuously, in clinical practice (Table 1).

Table 1: Neurophysiological Assessment Tools in Neuropathic Pain

Method	Primary Assessment	Clinical Utility	Ref.
QST	Sensory function	Pain phenotyping	[25, 26]
EMG	Muscle activity	Detects denervation	[27]
NCS	Nerve conduction	Large-fiber assessment	[28]
LEPs	Nociceptive pathways	Small-fiber evaluation	[29]
fMRI/PET/DTI	Brain activity and connectivity	Mechanistic insights	[30]

Physiotherapeutic interventions and their mechanism

Physiotherapy is an important part of the multi-disciplinary approach to the treatment of chronic neuropathic pain, working on both the biological and the psychosocial aspects of chronic pain. As opposed to pharmacologic treatments that are mainly geared towards symptom management, physiotherapeutic treatments target dysfunctions in the nervous, musculoskeletal and sensorimotor systems. Physiotherapy helps to restore functional ability through the use of exercise therapy, sensorimotor retraining, manual therapy, education, and graded exposure strategies, while decreasing pain

intensity and disability. A variety of neurophysiological and neuropsychological mechanisms have been identified as underlying the effectiveness of these interventions, which affect pain processes in both peripheral and spinal as well as supraspinal mechanisms. Exercise-induced hypoalgesia is one of the main mechanisms that contribute to relief of pain through physiotherapy. Therapeutic exercise has been demonstrated to desensitize pain in a number of ways, such as improving neuromuscular function, inflammatory response modulation, and activation of endogenous pain inhibitory systems [31]. Exercise promotes the release of anti-inflammatory cytokines and myokines from skeletal muscles that can inhibit pro-inflammatory responses that underlie neuropathic pain. Moreover, exercise stimulates the release of endorphins, endocannabinoids, serotonin and norepinephrine, all of which help to inhibit pain and increase pain tolerance. All these physiological changes together decrease the transmission of nociceptive signals and improve general physical function. Another mechanism by which physiotherapy impacts on chronic neuropathic pain is via neuroplasticity rehabilitation. There are often maladaptive changes in the CNS that accompany persistent pain such as cortical representation, motor planning, and sensory processing changes. Interventions designed to reverse these changes focus on neuroplasticity and include repeated task-specific sensory and motor inputs to promote adaptive reorganization of the nervous system [32]. With regular practice and functional movement training, patients can establish neural pathways that become more efficient, which will allow them to better move, perceive and function. The sensorimotor retraining is particularly interesting for chronic neuropathic pain due to its capacity to improve the reorganization of the cortex and the disturbed body perception.

Chronic pain often shrinks the brain's representation of the affected body part, making the person less aware of their body, less able to control its movements, and less perceptive, which may lead to faulty sensory integration [33,34]. Tactile discrimination training, laterality recognition, movement retraining and mirror therapy are techniques used to restore normal sensory processing and motor function. These interventions could enhance the accuracy of body representation and sensorimotor integration, thus decreasing the intensity of their pain and aiding in the functional recovery. Physiotherapy also affects descending pain modulation systems that have a critical role in the regulation of the transmission of pain. Descending inhibitory pathways are frequently impaired and the endogenous pain control processes are diminished in chronic neuropathic pain disorders, which leads to increased facilitation of pain and decreased endogenous pain modulation [35–37]. Therapeutic exercise and movement-based interventions have been proven to engage these inhibitory pathways, decrease central sensitization and improve pain inhibition. Better how-to of the pathways that descend means less pain felt and better long-term pain management.

Physiotherapy has neuro-physiological effects as well as focusing on a range of important psychological and behavioural factors affecting chronic pain outcomes. Chronic neuropathic pain patients often exhibit fear of movement, pain catastrophizing, low self-efficacy, and avoidance behaviors, which can be associated with disability and chronic pain. Through educational interventions, graded activity programs, and cognitive-behavioral principles incorporated into physiotherapy, patients gain confidence in moving, decrease fear-related behaviors, and enhance coping skills. These psychophysiological changes have a positive impact on treatment compliance, functional status and quality of life. Thus, physiotherapy should be used as a holistic strategy to chronic neuropathic pain to address biological, psychological, and behavior mechanisms that play a role in maintaining chronic pain and disability (Figure 2).

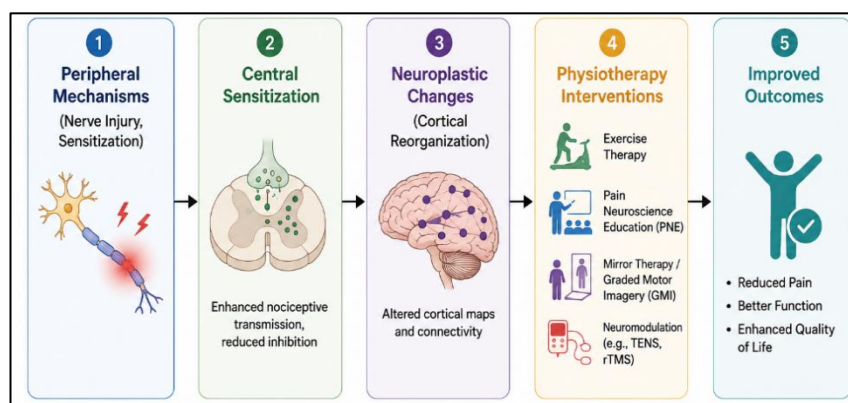


Figure 2: Mechanism-Based Physiotherapy Framework

5. Physiotherapeutic Strategies in Chronic Neuropathic Pain

5.1 Therapeutic Exercise

Therapeutic exercise is a fundamental, non-medicinal treatment approach and an essential part of chronic neuropathic pain management that helps to alleviate pain, build strength, improve mobility and enhance quality of life. Exercise programmes (aerobic, resistance, combined) [38]. This could be useful for patients with diabetic neuropathy, chemotherapy-induced peripheral neuropathy, and central neuropathic pain, and it may be able to improve function and decrease disability.

5.2 Pain Neuroscience Education (PNE)

Neuropsychic pain education teaches patients about the mechanisms of neuropathic pain, central sensitization and hyperactivity of the nervous system [39, 40]. It can be combined with active physiotherapy to help to decrease fear, adherence and to provide self-management support. Evidence is stronger, however, when PNE is coupled with exercise and rehabilitation.

5.3 Manual Therapy

Manual therapy can play a role in neuropathic pain by enhancing mobility, decreasing mechanical sensitivity and modifying peripheral and central pain [41]. Passive techniques may be indicated with care and in addition to active techniques; especially with low back pain and cancer treatment-associated neuropathic pain.

5.4 NEUROMUSCULAR RE-Education and Motor Control Training.

Re-education of the neuromuscular system and motor control training is designed to regain movement coordination, proprioception, balance and functional confidence. These strategies are particularly important in diabetic peripheral neuropathy and chemotherapy induced peripheral neuropathy [42] where loss of sensation, weakness and gait instability lead to disability and poor quality of life.

5.5 Graded Motor Imagery and Mirror Therapy

Neuroplasticity-based interventions focused on altered body representation, movement fear and maladaptive cortical processing include mirror therapy and graded motor imagery [43]. While there is some direct evidence available for these in specific pain conditions (e.g., complex regional pain syndrome, phantom limb pain, and peripheral neuropathic disorders), these may be of benefit in some neuropathic pain populations.

5.6 Electrotherapy and Neuromodulation

Neuromodulatory or electrotherapy devices such as TENS, interferential therapy, neuromuscular electrical stimulation (NMES) [44, 45]. New stimulation procedures may have a beneficial effect in neuropathic pain modulation by acting on the descending inhibitory pathway and nociceptive transmission (Table 2).

Table 2: Physiotherapeutic Interventions and Proposed Mechanisms

Intervention	Primary Mechanism	Main Outcome	Ref.
Exercise Therapy	Exercise-induced hypoalgesia	Pain reduction	[38]
PNE	Cognitive reframing	Reduced catastrophizing	[39,40]
Manual Therapy	Descending modulation	Improved mobility	[41]
Mirror Therapy/GMI	Neuroplasticity	Improved motor control	[42]
TENS	Pain pathway modulation	Analgesia	[43]
Virtual Reality	Sensorimotor integration	Functional improvement	[44]

6. Emerging Clinical Evidence

Clinical evidence in recent years has been building to support the increasing importance of rehabilitation-based interventions in the management of neuropathic pain. There are studies that show the advantages of the use of VR technology in chronic neuropathic pain after spinal cord injury (SCI) that demonstrate the advantages of technology-assisted rehabilitation approaches [46]. Likewise, yoga has been found to be effective in pain control, symptom management and improving quality of life in cancer-related pain and diabetic autonomic neuropathy, respectively, by enhancing physical functioning. Systematic reviews and meta-analyses also suggest that the use of mind-body therapies such as yoga and related interventions can lead to significant analgesic effects when used as a part of a multidisciplinary rehabilitation program [47,48]. The available comparative evidence indicates that multi-modality interventions (such as a combination of exercise, behavioral therapy and emerging digital interventions) have more positive results than single-modality interventions (Table 3). Personalised rehabilitation strategies are also a recent trend. Phenotype-based treatment strategies seek to match interventions with individual presentations and the underlying pain mechanisms while precision rehabilitation uses patient characteristics, functional impairments, and neurophysiological profiles to help guide the selection of interventions and their outcomes[49]. These advances are helping to create a new approach to the treatment of chronic neuropathic pain that is more individualized and mechanism-based.

Table 3: Emerging Clinical Evidence in Neuropathic Pain Rehabilitation

Intervention	Design	Main Finding	Ref.
Virtual Reality	RCT	Reduced neuropathic pain	[46]
Yoga Therapy	RCT	Improved quality of life	[47]
Yoga vs Exercise	Clinical Trial	Better autonomic outcomes	[48]
Mind-body therapies	Meta-analysis	Significant pain reduction	[49]

7. Integrated Mechanism-Based Rehabilitation Model

7.1 Linking Pathophysiology to Intervention Selection

Mechanisms-based rehabilitation focuses on the underlying neurophysiology of neuropathic pain, which is the focus for therapy. Exercise therapy, sensory retraining, neuromodulation and targeted pharmacologic therapies may be useful for peripheral-dominant phenotypes that involve nerve injury, ectopic activity and peripheral sensitization [50]. Central sensitization-dominant phenotypes are characterized by maladaptive central processing, increased central sensitization, and altered pain modulation and require interventions like pain neuroscience education, graded activity, cognitive-behavioral interventions and pain neuroscience training with emphasis on neuroplasticity [51]. A multimodal approach is often needed for mixed presentations (peripheral and central involvement) and involves multiple modes of treatment, such as physical, psychological, and pharmacological, to successfully treat the complexity of presentation and functional impairment.

7.2 Proposed Clinical Decision Framework

Chronic neuropathic pain clinical decision making should include a thorough evaluation of symptom characteristics, neurophysiological findings, functional limitations, and psychosocial factors. Dominant pain mechanisms help inform treatment, intervention selection and enhance treatment efficacy (Figure 3). The use of patient phenotyping, mechanism-

based rehabilitation, and continuous monitoring of outcomes can help with precision care, maximize gains in function after rehabilitation, and improve long-term management of neuropathic pain conditions [52, 53].

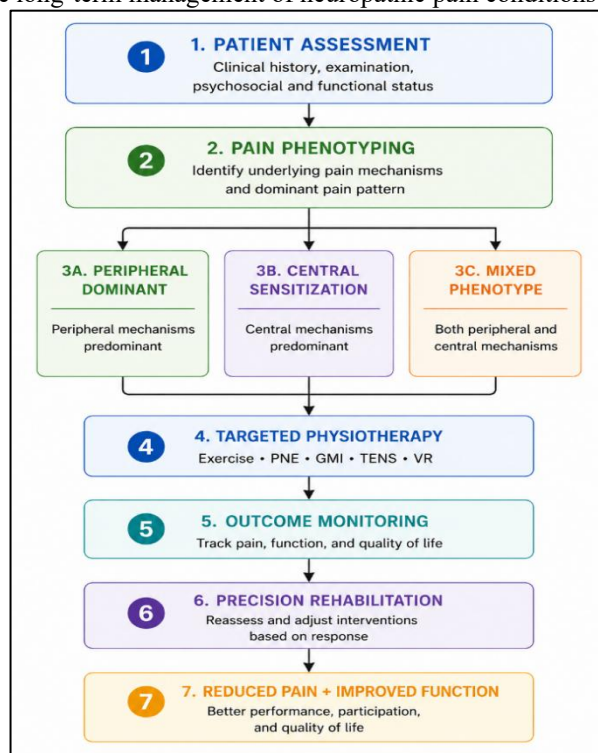


Figure 3: Integrated Mechanism-Based Rehabilitation Model

8. Knowledge gaps and future research directions

The mechanism of neuropathic pain and the strategies for rehabilitation, there are still some missing pieces in terms of knowledge. A great difficulty is the absence of validated biomarkers that provide information to guide rehabilitation and predict the result. The selection of interventions tailored to the individual, using biomarker guided rehabilitation, may be helpful in identifying the pain mechanism, improve patient stratification and inform the selection of interventions. Likewise, developments in AI and predictive analytics can provide opportunities to combine large clinical, electrophysiological and imaging datasets for the development of predictive models of prognosis and treatment response. The other field of interest is precision physiotherapy. Rehabilitation programs must be more than generic and individualized rehabilitative interventions based on patient phenotypes, neurobiological characteristics and functional impairments. Digital health technologies, like wearable sensors, telehealth, virtual reality systems, and remote monitoring, can help to increase access, adherence and long-term outcomes. This is especially beneficial for patients who cannot easily get around or who don't have access to certain rehabilitation facilities. Moreover, there is high variability in outcome assessment between neuropathic pain studies. There is great variation in measures of pain and functional assessment and quality of life measures, making the comparison of results across studies difficult and evidence synthesis challenging. Development of standardized outcome measures and a set of core assessment frameworks will be key to enhancing the quality of research, multicenter collaboration.

9. CONCLUSIONS

Chronic neuropathic pain is a complex and multifactorial process in which peripheral nerve function is impaired and central sensitization occurs, neuroinflammation is present, maladaptive neuroplasticity is triggered and brain network activity is altered. These neurophysiological mechanisms could be responsible for chronic pain, dysfunction and poor quality of life and should be addressed with holistic and individualized approaches. Some emerging evidence suggest that physiotherapeutic interventions, such as therapeutic exercise, pain neuroscience education, manual therapy, neuromuscular re-education, mirror therapy, neuromodulation, and digital rehabilitation can positively impact pain-related mechanisms and functional outcomes. The mechanism-based rehabilitation framework provides an opportunity to individualise rehabilitation interventions based on the underlying pathophysiological mechanisms, potentially leading to more effective and targeted rehabilitation interventions. The current advances in biomarker research, AI, precision rehabilitation, and digital health technologies further solidify the promise of personalized care. But there are still more well-done studies, common outcome measures and clear implementation protocols in clinical practice to be developed. In summary, a future research direction in neurorehabilitation for chronic pain lies in the combination of knowledge on the neurophysiology with knowledge of patients focused rehabilitation to best optimize and enhance recovery, improve quality of life, and advance the field of precision pain medicine.

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