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Neuropathic Pain and Quality Of Life

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Dissertação de Candidatura ao Grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Catarina Guimarães

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Porto, junho de 2026

DEDICATÓRIA

Aos meus pais, por serem o meu maior apoio em todas as etapas da vida. Obrigada por acreditarem sempre em mim, por me ensinarem a nunca desistir e por estarem presentes em cada conquista e em cada dificuldade. Tudo isto também é vosso.

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RESUMO

Enquadramento: A dor neuropática, definida pela *International Association for the Study of Pain* como a dor causada por uma lesão ou doença do sistema nervoso somatossensorial, representa uma componente relevante da dor crónica. Estudos de base populacional reportam estimativas de prevalência entre 6,9% e 10%, com substancial variabilidade geográfica e sociodemográfica. Pode surgir de um vasto leque de condições, incluindo neuropatias periféricas de origem metabólica, infeciosa ou tóxica, lesões nervosas traumáticas, radiculopatias e perturbações do sistema nervoso central, como o acidente vascular cerebral e a esclerose múltipla. A relevância clínica da dor neuropática estende-se muito para além da intensidade da dor. Os doentes experienciam frequentemente sintomas sensoriais persistentes acompanhados de limitações funcionais, distúrbios do sono e sofrimento emocional. Consequentemente, esta patologia compromete gravemente a qualidade de vida, conduzindo a dificuldades nas atividades diárias e a limitações na esfera laboral e social. Apesar do progresso considerável na compreensão dos mecanismos subjacentes, a gestão clínica permanece difícil. As opções farmacológicas de primeira linha, incluindo antidepressivos tricíclicos, inibidores da recaptação da serotonina e noradrenalina, e gabapentinoides, proporcionam apenas um alívio parcial numa proporção limitada de doentes e são frequentemente limitadas pelo seu perfil de efeitos adversos. Dada a sua heterogeneidade etiológica, complexidade diagnóstica e impacto global significativo, a dor neuropática continua a ser um importante desafio na prática clínica.

Objetivo: O objetivo desta revisão narrativa é fornecer uma síntese crítica da evidência atual sobre a dor neuropática, com foco primordial no seu impacto multidimensional na qualidade de vida. Ao avaliar as consequências físicas, psicológicas e sociais em diferentes etiologias clínicas, em conjunto com a epidemiologia, fisiopatologia subjacente, quadro diagnóstico e estratégias terapêuticas, esta revisão procura apoiar a prática clínica e orientar a investigação futura.

Métodos: Foi realizada uma pesquisa bibliográfica exclusivamente na base de dados *PubMed,* entre outubro de 2025 e abril de 2026, utilizando termos de pesquisa pré-definidos. Foram considerados estudos originais, revisões narrativas, revisões sistemáticas, meta-análises e orientações clínicas relevantes publicadas em língua inglesa. Os artigos foram selecionados de acordo com a sua relevância e contribuição para os objetivos desta revisão. A evidência recolhida foi analisada criticamente e sintetizada em secções temáticas abrangendo a epidemiologia, fisiopatologia,

desafios diagnósticos, impacto na qualidade de vida, abordagens terapêuticas e perspetivas futuras da dor neuropática.

Conclusão: A dor neuropática compromete gravemente a qualidade de vida e apresenta desafios diagnósticos e terapêuticos significativos, associados a uma fisiopatologia complexa que envolve sensibilização periférica, plasticidade neural e mecanismos neuroimunitários. O diagnóstico rigoroso assenta numa avaliação estruturada que integra a distribuição da dor, a história clínica, o exame físico e ferramentas de diagnóstico validadas, como os questionários Douleur Neuropathique 4, painDETECT e Leeds Assessment of Neuropathic Symptoms and Signs. As consequências desta patologia são multidimensionais, englobando limitações físicas, sofrimento psicológico, distúrbios do sono e impacto no desempenho profissional, apresentando perfis clínicos distintos em condições como a neuropatia diabética dolorosa, a neuropatia periférica induzida por quimioterapia, a dor neuropática crónica pós-cirúrgica e a dor neuropática central. A eficácia modesta da farmacoterapia isolada fundamenta a transição necessária para um modelo biopsicossocial centrado no doente, que integra o exercício físico estruturado, terapias cognitivo-comportamentais e estratégias nutricionais anti-inflamatórias, em complementaridade com a neuromodulação. Áreas emergentes, incluindo a medicina de precisão, a nanomedicina, a terapia com células estaminais mesenquimatosas, o plasma rico em plaquetas e as abordagens optogenéticas, oferecem vias potenciais para intervenções mais dirigidas. A gestão da dor neuropática exige uma estratégia multidisciplinar e individualizada, na qual o sucesso terapêutico deve ser avaliado não apenas pela redução da intensidade da dor, mas pela verdadeira restauração da independência funcional e da qualidade de vida do doente.

Palavras-chave: Dor neuropática, Qualidade de vida, Fatores psicológicos, Fatores psicossociais, Gestão da dor, Terapêutica, Neuralgia, Dor crónica

ABSTRACT

Background: Neuropathic pain, defined by the International Association for the Study of Pain as pain caused by a lesion or disease of the somatosensory nervous system, represents a relevant component of chronic pain. Population-based studies report prevalence estimates between 6.9% and 10%, with substantial geographical and sociodemographic variability. It can arise from a wide range of conditions, including peripheral neuropathies of metabolic, infectious, or toxic origin, traumatic nerve lesions, radiculopathies, and central nervous system disorders such as stroke and multiple sclerosis. The clinical significance of neuropathic pain extends well beyond pain intensity alone. Patients frequently experience persistent sensory symptoms accompanied by functional limitations, sleep disturbances, and emotional distress. Consequently, this condition severely compromises health-related quality of life, leading to difficulties in daily activities and reduced occupational and social participation. Despite considerable progress in understanding its underlying mechanisms, clinical management remains difficult. First-line pharmacological options, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids, provide only partial relief in a limited proportion of patients and are frequently constrained by adverse effects. Given its heterogeneous causes, diagnostic complexity, and significant overall burden, neuropathic pain continues to be a major challenge in clinical practice.

Objective: This narrative review aims to provide a critical synthesis of the current evidence on neuropathic pain, with a primary focus on its multidimensional impact on quality of life. By evaluating the physical, psychological, and social consequences across different clinical etiologies, alongside the epidemiology, underlying pathophysiology, diagnostic framework, and therapeutic strategies, this review seeks to support clinical practice and guide future research.

Methods: A literature search was conducted exclusively in the PubMed database from October 2025 to April 2026 using predefined search terms. Original studies, narrative reviews, systematic reviews, meta-analyses, and relevant clinical guidelines published in English were considered. Articles were selected according to their relevance and contribution to the aims of this review. The retrieved evidence was critically analyzed and synthesized into thematic sections covering epidemiology, pathophysiology, diagnostic challenges, impact on quality of life, therapeutic approaches, and future perspectives of neuropathic pain.

Conclusion: Neuropathic pain severely compromises quality of life and poses significant diagnostic and therapeutic challenges, driven by a complex pathophysiology involving peripheral sensitization, neural plasticity, and neuroimmune mechanisms. Accurate diagnosis relies on a graded framework that integrates pain distribution, clinical history, physical examination, and validated screening tools, such as the Douleur Neuropathique 4, painDETECT, and Leeds Assessment of Neuropathic Symptoms and Signs questionnaires. The consequences of this condition are multidimensional, encompassing physical limitations, psychological distress, sleep disturbances, and occupational impairments, with distinct profiles across conditions such as painful diabetic neuropathy, chemotherapy-induced peripheral neuropathy, chronic postsurgical neuropathic pain, and central neuropathic pain. The modest efficacy of pharmacotherapy alone supports a necessary shift toward a patient-centered biopsychosocial model that integrates structured physical exercise, cognitive-behavioral therapies, anti-inflammatory nutritional strategies, and neuromodulation. Emerging fields, including precision medicine, nanomedicine, mesenchymal stem cell therapy, platelet-rich plasma, and optogenetic approaches, provide potential pathways for targeted interventions. The management of neuropathic pain requires an individualized, multidisciplinary strategy where success is measured not solely by reductions in pain intensity, but by the genuine restoration of the patient's functional independence and quality of life.

Keywords: Neuropathic pain, Quality of life, Psychological factors, Psychosocial factors, Pain management, Therapeutics, Neuralgia, Chronic pain

ABBREVIATIONS LIST

BTX-A	Botulinum Toxin Type A
CIPN	Chemotherapy-Induced Peripheral Neuropathy
DN4	Douleur Neuropathique 4 Questionnaire
GABA	Gamma-Aminobutyric Acid
HRQoL	Health-Related Quality of Life
IASP	International Association for the Study of Pain
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
NeuPSIG	Neuropathic Pain Special Interest Group
NMDA	N-methyl-D-aspartate
NNT	Number Needed to Treat
NP	Neuropathic Pain
PDN	Painful Diabetic Neuropathy
QoL	Quality of Life
QST	Quantitative Sensory Testing
RCT	Randomized Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
SCI	Spinal Cord Injury
SNRI	Serotonin-Noradrenaline Reuptake Inhibitor
TCA	Tricyclic Antidepressant
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation

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INTRODUCTION

Neuropathic pain (NP) is formally described by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system".[1] This formulation separates NP from other major categories of pain. Nociceptive pain results from activation of peripheral receptors following actual or threatened tissue injury, such as inflammation or mechanical trauma. In contrast, nociplastic pain refers to "altered nociception despite no clear evidence of actual or threatened tissue damage, or disease or lesion of the somatosensory system".[2] Together, these distinctions themselves accentuate the importance of a mechanism-based understanding of pain conditions. NP is particularly recognized for the coexistence of sensory amplification, presenting as burning or shock-like pain, allodynia, and hyperalgesia, with areas of sensory loss. This combination is considered a defining clinical pattern and often guides the diagnostic process.[1]

A wide spectrum of medical conditions can injure or disrupt somatosensory pathways. Peripheral neuropathies of metabolic, infectious, or toxic origin, traumatic nerve lesions, radiculopathies and central disorders such as stroke or multiple sclerosis are among the most frequent causes. Although prevalence estimates differ across studies, NP consistently appears as a significant contributor to the global burden of chronic pain and disability.[3] Its clinical relevance is reinforced by demographic aging and by the growing number of people living with chronic metabolic, oncological, and neurological diseases.

The consequences of NP go beyond its sensory manifestations. Patients frequently report sleep disturbance, fatigue, limited mobility, symptoms of anxiety or depression and difficulties engaging in daily tasks. These multidimensional effects contribute to considerable reductions in health-related quality of life (HRQoL), sometimes reaching levels comparable to other debilitating chronic illnesses. Recent evidence additionally emphasizes the relationship between NP, emotional well-being and social participation, showing how pain may shape a person's functioning far more broadly than its sensory features alone.[4]

Although scientific understanding of the mechanisms underlying NP has advanced considerably, treatment continues to be challenging. First-line pharmacological options, including tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and gabapentinoids, deliver considerable benefit to only a proportion of patients, and side-effects commonly constrain long-term use.[1] Therefore, multimodal approaches combining medication, physical rehabilitation, education and psychological interventions are increasingly recommended, though implementation and effectiveness vary widely across clinical settings.[5] In recent years, growing attention has focused on the contribution of neuroimmune mechanisms to the persistence of NP. Experimental

work demonstrates that activation of microglia and astrocytes, together with the release of pro-inflammatory mediators, amplifies nociceptive signaling and supports the transition to chronic pain, making glial-neuronal interactions a likely target for upcoming therapies.[1,6]

Given its complexity, diverse etiologies and severe impact on quality of life (QoL), NP is still a major challenge in contemporary medicine. A narrative review capable of integrating current knowledge on mechanisms, diagnostic approaches, therapeutic strategies and their consequences for daily functioning is therefore essential to support clinical practice and inform future research.

METHODS

To conduct this narrative review, a comprehensive literature search was performed exclusively using the PubMed database between October 2025 and April 2026. To retrieve the relevant evidence, the following Medical Subject Headings (MeSH) terms were utilized: "Neuropathic pain", "Quality of life", "Psychological factors", "Psychosocial factors", "Pain management", "Therapeutics", "Neuralgia", and "Chronic pain".

The selection process prioritized peer-reviewed original articles, systematic reviews, meta-analyses, and consensus guidelines published in English and available in full text. Following the initial database query, the retrieved articles were screened for relevance based on their titles and abstracts. Selected full-text manuscripts were then critically evaluated to extract pertinent data concerning the epidemiological burden, underlying pathophysiology, diagnostic challenges, and therapeutic approaches. Finally, the gathered information was synthesized into a well-structured narrative to comprehensively address the management of NP and its multidimensional impact on patients' QoL.

RESULTS

Epidemiology

NP constitutes an important component of chronic pain in the general population. Population-based studies conducted in community settings report prevalence estimates ranging from approximately 6.9% to 10%, with values varying according to the populations studied and the criteria used to identify NP. These estimates indicate that NP represents a frequent clinical condition within the spectrum of chronic pain encountered at the population level.[7,8]

Within populations reporting chronic pain, NP features are observed in a relevant proportion of individuals. Surveys conducted in primary care and community samples indicate that a subset of individuals with chronic pain fulfill criteria compatible with NP, contributing to the entire distribution of chronic pain phenotypes observed in epidemiological studies.[9] Such evidence

supports the recognition of NP as a common component of chronic pain populations rather than as an isolated or rare entity.[4]

Prevalence estimates of NP vary substantially across studies and geographical regions. Population-based investigations report a wide range of prevalence values, showing differences in study design, population characteristics and diagnostic approaches used to identify NP in epidemiological surveys.[7] Data reported from different countries further demonstrate variability in prevalence estimates across populations, with values differing between cohorts studied in distinct settings. This variation is a consistent feature of the epidemiological data available for NP.[4]

Differences in the epidemiological distribution of NP are seen across populations with distinct demographic and clinical characteristics. In community-based populations, chronic pain with neuropathic characteristics has been reported more frequently among women than men. In a large population-based survey conducted in France, a higher prevalence of chronic pain with neuropathic characteristics was observed in women, causing sex-related differences in prevalence estimates at the population level.[8]

Marked geographical variability has also been documented in epidemiological estimates of NP. Data from population-based studies conducted in different countries indicate substantial differences in prevalence across areas. Prevalence values of approximately 3.2% have been reported in Japan, while estimates ranging from 6.9% to 8.2% have been described in European populations such as France and the United Kingdom. Even higher prevalence values have been reported in other regions, including 10.6% in Morocco and 10%-14.5% in Brazilian cohorts. Together, these data illustrate the wide variation in NP prevalence across geographical contexts.

Variability in prevalence estimates is additionally influenced by differences in the socioeconomic characteristics of the populations studied. Population-based analyses of chronic pain demonstrate higher prevalence among individuals with lower income levels and among those who are unemployed, encompassing pain conditions with neuropathic characteristics. These socioeconomic gradients contribute to heterogeneity in the distribution of NP within and between populations.[4]

Distinct epidemiological patterns are also evident when populations are stratified according to underlying clinical characteristics. In neurological populations, NP is frequently reported in association with central and peripheral nervous system disorders, including stroke and other neurological diseases, causing persistent NP symptoms in these cohorts.[10] In contrast, community-based populations contain a broader range of underlying conditions, including metabolic and post-infectious etiologies, resulting in more heterogeneous clinical presentations of NP.[4]

Taken together, the distribution of NP across populations defined by sex, geographical context, socioeconomic conditions and underlying clinical characteristics contributes to the heterogeneity

observed in epidemiological prevalence estimates. This heterogeneity represents a central feature of the epidemiological profile of NP.[4,8]

Pathophysiology

NP arises as a direct consequence of a lesion or disease affecting the somatosensory nervous system and is sustained by a complex, active interaction of mechanisms at peripheral, spinal, and supraspinal levels. Rather than showing a single pathological alteration, NP results from a cascade of structural, molecular, and functional changes that disrupt normal sensory signal processing and pain modulation, consequently leading to persistent pain perception and marked clinical heterogeneity.[3,8]

At the peripheral level, injury to sensory nerves induces profound alterations in primary afferent neurons. Damage to peripheral axons and dorsal root ganglion neurons is associated with abnormal impulse generation, including spontaneous and ectopic discharges arising from injured nerve endings and neuronal cell bodies. These pathological discharges cause persistent abnormal afferent input to the central nervous system and represent an important mechanism underlying spontaneous pain and dysesthetic sensations characteristic of NP syndromes.[3,11] Peripheral nerve injury is accompanied by changes in the expression, distribution, and function of ion channels, particularly voltage-gated sodium channels, which lower activation thresholds and increase neuronal firing. This state of peripheral hyperexcitability amplifies nociceptive signaling and facilitates the persistence of ongoing pain.[12]

Peripheral sensitization is additionally reinforced by inflammatory and immune-mediated processes that develop in response to nerve injury. Activation of immune cells in peripheral tissues and within the dorsal root ganglia results in the release of pro-inflammatory mediators, including cytokines and chemokines, which directly modulate nociceptor excitability. These mediators enhance responses to mechanical and thermal stimuli and contribute to the development of hyperalgesia and allodynia. Sustained peripheral inflammatory activity maintains altered sensory input to the spinal cord and plays a major role to the transition from acute nerve injury to chronic NP.[11]

Persistent abnormal peripheral input causes substancial plastic changes in the spinal dorsal horn, leading to central sensitization. Central sensitization is characterized by increased excitability of second-order neurons, enhanced synaptic transmission, and expansion of receptive fields, resulting in exaggerated responses to both noxious and innocuous stimuli. At the molecular level, increased glutamatergic transmission and activation of N-methyl-D-aspartate (NMDA) receptors amplify synaptic signaling. In parallel, a reduction in inhibitory control mediated by gamma-aminobutyric

Acid (GABA) and glycine leads to spinal disinhibition, further facilitating nociceptive transmission and sustaining pain over time.[13,14]

Non-neuronal cells are critical contributors to the maintenance of central sensitization. Following nerve injury, microglia and astrocytes become activated in the spinal cord and release pro-inflammatory mediators that enhance neuronal excitability and amplify pain signaling. The interaction among neurons, immune cells, and glial cells forms a self-sustaining neuroimmune network that promotes the development of chronic pain, even after the initial lesion stabilizes. These neuroimmune mechanisms are recognized as central components of the pathophysiology of chronic NP.[4,11]

Beyond the spinal cord, NP is associated with functional and structural alterations in supraspinal pain-processing regions. Neuroimaging studies exhibit changes in activity and connectivity within brain areas involved in sensory discrimination, affective processing, and cognitive modulation of pain, including the thalamus, primary and secondary somatosensory cortices, insula, and anterior cingulate cortex. Persistent abnormal sensory input and deafferentation drive maladaptive cortical plasticity, causing altered representation of sensory information and leading to the chronicity and complexity of NP.[15,16]

Although these mechanisms are shared across NP conditions, disease-specific processes contribute to etiological heterogeneity. In painful diabetic neuropathy (PDN), chronic hyperglycemia induces metabolic and microvascular alterations that promote oxidative stress, mitochondrial dysfunction, and progressive axonal degeneration. These changes impair nerve conduction and result in loss of sensory fibers, providing a structural substrate for NP. Peripheral nerve damage in this context frequently coexists with spinal and supraspinal sensitization mechanisms, which further sustain pain symptoms over time.[17]

In Chemotherapy-Induced Peripheral Neuropathy (CIPN), NP results from direct neurotoxic effects of antineoplastic agents on peripheral sensory neurons. Experimental and clinical evidence demonstrates damage to dorsal root ganglion neurons, axonal degeneration, and alterations in neuronal excitability following exposure to chemotherapeutic drugs, particularly platinum compounds, taxanes, and vinca alkaloids. These alterations interfere with normal sensory signal transmission and contribute to persistent sensory symptoms, including pain, paresthesias, and numbness.[18] In some patients, central sensitization mechanisms further contribute to symptom persistence, particularly when NP becomes chronic.[3]

NP also constitutes an important component of chronic postsurgical pain. Surgical procedures involving tissue trauma and potential nerve injury may induce a combination of peripheral nerve damage, inflammatory responses, and central sensitization. Experimental and clinical studies indicate that alterations in peripheral nociceptors, spinal dorsal horn neurons, and descending

modulatory pathways contribute to the development and persistence of NP after surgery.[19,20] More recent mechanistic syntheses further describe chronic postsurgical pain as the result of sustained peripheral and central plasticity driven by nerve injury, neuroinflammation, and maladaptive modulation within pain pathways.[21] Chronic postsurgical pain frequently presents with neuropathic characteristics, particularly in patients with evidence of nerve injury related to surgical procedures, showing the contribution of neuropathic mechanisms to chronic postsurgical pain syndromes.[22]

Central NP arises from lesions affecting somatosensory pathways within the central nervous system, such as those following stroke or spinal cord injury (SCI). In these conditions, disruption of normal sensory processing leads to abnormal spontaneous neuronal activity and enhanced central excitability, resulting in persistent pain in the absence of ongoing peripheral injury. These syndromes illustrate the dominant role of central mechanisms in the generation and maintenance of NP.[10]

Taken together, NP represents the dynamic interactions among peripheral sensitization, spinal and supraspinal plasticity, and neuroimmune mechanisms. The relative contribution of each process varies according to the underlying etiology, including metabolic, toxic, surgical, and central nervous system causes, accounting for the marked heterogeneity observed in clinical presentation and disease course among individuals with NP.[3,22]

Diagnosis

The diagnosis of NP remains clinically challenging and demands integrating multiple sources of evidence supporting a lesion or disease affecting the somatosensory nervous system.[3] Unlike nociceptive pain, NP cannot be identified through a single diagnostic test and instead relies on a structured clinical reasoning process that combines symptom characterization, neurological examination, and complementary investigations.[1] This complexity contributes to diagnostic variability across clinical settings and partly explains differences in reported prevalence estimates in epidemiological studies.[7]

To address these challenges, international experts have proposed standardized diagnostic frameworks that use a grading system to classify NP as possible, probable, or definite based on predefined criteria. This grading system was developed to improve diagnostic consistency in both clinical practice and research and is grounded in the identification of pain with a neuroanatomically plausible distribution, a medical history compatible with somatosensory system damage, supportive clinical findings, and, when available, confirmatory diagnostic tests. By emphasizing the convergence of multiple diagnostic elements rather than reliance on any single criterion, this approach illustrates the multifactorial nature of NP.[23]

A detailed clinical history constitutes the cornerstone of the diagnostic assessment. NP is commonly described using characteristic symptom qualities, such as burning sensations, electric-shock-like pain, stabbing pain, and tingling or painful cold, which are widely recognized by patients with somatosensory system involvement.[3] Pain distribution often follows a neuroanatomical pattern corresponding to peripheral nerve territories, dermatomes, or central nervous system pathways, thereby supporting a neuropathic mechanism when consistent with known anatomical organization.[1] NP occurs in a wide range of clinical contexts, including metabolic disorders, exposure to neurotoxic agents, surgical nerve injury, and diseases affecting the central nervous system.[3]

The diagnostic process is further complicated by the frequent coexistence of neuropathic and nociceptive mechanisms within the same individual, resulting in mixed pain states that do not conform to strict categorical definitions. This overlap is particularly relevant in chronic pain conditions, where partial neuropathic components may coexist with ongoing nociceptive input, underscoring the importance of mechanistic assessment instead of purely symptom-based classification.[2]

The Neuropathic Pain Special Interest Group (NeuPSIG) guidelines describe sensory examination as an integral component of the clinical assessment of NP and emphasize its role within a comprehensive diagnostic evaluation rather than as an isolated procedure. Within this system, sensory examination helps document sensory abnormalities in the painful area and adjacent regions, which may support somatosensory nervous system involvement when interpreted in conjunction with pain distribution and clinical history.[24]

In small fiber neuropathy, the diagnosis cannot be established solely on clinical symptoms or a routine neurological examination and requires objective confirmation of small fiber involvement. According to validated diagnostic criteria, reduced intraepidermal nerve fiber density on skin biopsy and/or abnormalities detected by quantitative sensory testing (QST) constitute the core diagnostic elements for confirming small fiber neuropathy in both clinical practice and research settings.[25]

Complementary diagnostic investigations are therefore used selectively to support the presence and anatomical localization of somatosensory system involvement when clinical evaluation raises suspicion of NP. Neurophysiological studies, including nerve conduction studies and electromyography, provide objective evidence of large-fiber dysfunction and are particularly useful in evaluating peripheral neuropathies when abnormalities are detected. However, normal neurophysiological findings do not exclude NP, particularly in disorders predominantly affecting small nerve fibers, which may not be detected by conventional electrophysiological techniques.[1]

In cases where central NP is suspected, neuroimaging plays an important diagnostic role by identifying lesions affecting the brain or spinal cord that disrupt somatosensory pathways.

Magnetic resonance imaging is commonly used to detect ischemic, traumatic, or demyelinating lesions, and imaging findings that correlate with the clinical presentation provide confirmatory evidence within the diagnostic framework.[10]

QST may provide additional functional information by assessing sensory detection and pain thresholds across modalities and by contributing to the characterization of somatosensory dysfunction profiles. Nevertheless, due to variability in methodologies, limited availability, and incomplete standardization across clinical settings, QST is currently regarded as a complementary diagnostic tool rather than a routine component of NP diagnosis.[24]

Validated screening questionnaires have been developed to support the identification of NP features in clinical and research settings. These instruments were designed to help distinguish NP from non-neuropathic pain by capturing symptom qualities and sensory phenomena associated with lesions or diseases of the somatosensory nervous system.

The Douleur Neuropathique 4 Questionnaire (DN4) was specifically developed to discriminate NP from non-neuropathic pain syndromes through a combination of patient-reported symptom descriptors and simple bedside sensory examination items. Its development was based on comparing pain syndromes associated with nervous system lesions and those related to somatic tissue injury, allowing the identification of items with high discriminative value for NP. The DN4 demonstrated good diagnostic performance in differentiating neuropathic from non-neuropathic pain and has been applied in both clinical practice and epidemiological studies.[26]

The painDETECT questionnaire was developed as a screening instrument to identify NP components in patients with chronic pain, particularly in conditions in which neuropathic and nociceptive mechanisms may coexist. It is based exclusively on patient-reported symptom characteristics and pain patterns and does not require findings from clinical sensory examination. The questionnaire demonstrated good sensitivity and specificity for detecting NP components and was designed to facilitate recognition of neuropathic features, particularly outside specialized pain clinics.[27]

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale combines patient-reported symptom descriptors with brief clinical sensory testing to estimate the likelihood that pain is neuropathic in origin. Its development focused on identifying symptom patterns and sensory signs that distinguish NP from nociceptive pain conditions. The LANSS demonstrated the ability to classify pain as predominantly neuropathic or non-neuropathic and has been used both as a clinical screening tool and as a research instrument.[28]

Although these questionnaires differ in structure and method of administration, they were developed as screening instruments to support the identification of NP features rather than to provide a definitive diagnosis. In their original validation studies, these tools were explicitly intended to aid clinical assessment by identifying patients with a higher likelihood of NP, while

emphasizing that comprehensive clinical evaluation remains necessary for diagnostic confirmation.[26-28] The official validated versions of these instruments are included in the Attachments section of this thesis (Attachments 1-5).

Overall, the diagnosis of NP is based on the application of a standardized grading system that combines information on pain distribution, clinical history, sensory findings, and confirmatory investigations when available, allowing classification of NP as possible, probable, or definite according to predefined criteria.[23]

Impact On Quality Of Life

NP has been associated with consequences that go beyond the sensory experience of pain, affecting multiple dimensions of HRQoL, including physical capabilities, emotional stability, and overall daily functioning. This considerable burden is further compounded by the frequently limited effectiveness of currently available pharmacological treatments, as a substantial proportion of patients achieve only partial symptom relief accompanied by persistent functional limitations.[31] Consequently, chronic NP is best understood through a comprehensive biopsychosocial framework, in which pain-related physical disability and concurrent emotional distress contribute equally to the overall burden of the disease.[32]

From a functional perspective, NP has been consistently linked to severe limitations in routine daily activities and a marked reduction in overall physical performance. Affected individuals frequently report significant difficulties with basic tasks, which inevitably lead to maladaptive changes in activity patterns and a consequent loss of personal independence. These physical limitations tend to exert a sustained, detrimental impact on the patient's QoL, particularly in those with chronic, refractory symptoms.[33] Furthermore, NP has been strongly associated with reduced work productivity, increased occupational absenteeism, and general impairment in usual activities, highlighting its profound socioeconomic consequences.[34] Beyond overt absenteeism, the critical phenomenon of presenteeism must also be recognized, where patients, often driven by financial necessity, continue to fulfill their professional responsibilities despite severe pain and sleep deprivation. This sustained maladaptive effort ultimately culminates in deep physical and emotional exhaustion.[4]

In addition to physical impairments, NP is intrinsically associated with a massive psychological burden, with depressive symptoms being frequently reported among affected individuals. Emotional distress has been described as an important component of the overall disease burden and may influence pain perception and clinical outcomes.[35] In addition, psychological factors such as anxiety and fear have been associated with increased pain severity and greater functional

limitations in specific conditions such as PDN.[36] Lower scores in generic health status questionnaires and poorer self-perceived health have also been reported in patients with NP, supporting the relevance of patient-reported outcomes in this population.[8] Furthermore, maladaptive cognitive responses, such as pain catastrophizing and kinesiophobia, often develop in these patients and represent robust predictors of pain-related disability and functional decline.[4]

Sleep disturbance and reduced overall well-being have also been described in individuals with NP. These factors have been reported to be associated with persistent symptoms and may further affect daily functioning.[33] Lifestyle-related factors, including reduced physical activity and increased stress, have also been investigated in relation to NP and may influence symptom severity and overall impact.[37]

Within specific etiologies, PDN has been linked to a significant impact on patients' well-being, particularly in the psychological domain. Symptoms of anxiety and depression are highly prevalent in individuals with diabetic nerve damage and have been shown to amplify pain perception and overall symptom severity. These psychological comorbidities are directly associated with increased functional disability and a substantially greater burden of disease.[36] In addition, impairments in QoL, particularly in domains related to daily functioning and emotional well-being, have also been reported in NP populations.[7] Sleep disturbances are also a common complaint in PDN, further contributing to a state of chronic exhaustion and reduced well-being.[36] PDN has also been associated with poorer mental health and lower overall QoL when compared with painless diabetic peripheral neuropathy.[38] Furthermore, specific functional impairments such as walking difficulties, reduced mobility, and fear of falling actively contribute to the persistent physical decline of these patients.[39]

In the oncological context, CIPN represents a clinically devastating complication associated with life-saving cancer treatments. Patients affected by this iatrogenic condition commonly report severe sensory symptoms, which have been directly correlated with major functional limitations and difficulties in performing previously routine activities. In some patients, persistent symptoms may continue after completion of treatment, contributing to the overall burden experienced within the broader context of cancer survivorship.[40] These persistent sensory abnormalities have been continuously associated with high levels of emotional distress and a reduced sense of well-being.[4]

Chronic postsurgical NP has been described as a complication following various surgical procedures, often persisting indefinitely over time. The presence of persistent pain following an operation has been associated with a reduced QoL.[20] Additionally, chronic postsurgical pain has been reported to interfere with daily activities, particularly when the painful sensations persist far beyond the expected physiological recovery period. The fact that persistent symptoms remain present long after the postoperative healing phase strictly reflects the chronic and maladaptive nature of this

iatrogenic condition.[41] This persistent postsurgical pain is also associated with emotional distress as part of its broader impact on well-being.[21] Consequently, NP persisting beyond the normal postoperative timeframe has been universally recognized as a relevant and debilitating long-term clinical outcome.[41]

Central NP emerges in the specific context of structural lesions or diseases directly affecting the central nervous system. In these affected individuals, centralized NP has been closely associated with reduced QoL and overall well-being.[31] Furthermore, psychological factors, predominantly including depressive symptoms, have been described in these patients and are intimately associated with the overall burden of the condition.[35] Pain may coexist with neurological deficits, further increasing disability and dependence in daily activities. The persistence and complexity of NP in neurological conditions contribute to its clinical relevance and overall burden.[33] In SCI, NP has been linked to a reduced QoL and greater psychological burden, including symptoms of anxiety and depression.[42]

Overall, NP is associated with a multidimensional impact across physical, psychological, and functional domains. This multidimensional burden has been described through different clinical contexts and patient populations.[31] Psychological factors, including depression, represent an important component of this burden and have been associated with NP.[35] Differences in the specific clinical context, symptom persistence, and associated comorbidities contribute to the vast variability in how NP affects QoL across different etiologies.[3] These differences will be further summarized in Table 1.

Therapeutic Approaches

The management of NP requires a structured, evidence-based therapeutic approach, as treatment outcomes remain modest with currently available interventions. Current recommendations support a stepwise approach in which treatments are selected according to the balance between efficacy, adverse effects, accessibility, and overall clinical applicability. Within this framework, TCAs, SNRIs, and α2δ ligands are recommended as first-line treatments for NP. Topical therapies, including capsaicin 8% patches, capsaicin cream, and lidocaine 5% plasters, are recommended as second-line options. Botulinum Toxin Type A (BTX-A), repetitive transcranial magnetic stimulation (rTMS), and opioids are considered third-line treatments in selected patients.

Because clinically meaningful pain relief is not achieved in all patients, management frequently requires treatment adjustment or sequential therapeutic trials. The choice of therapy should therefore take into account individual tolerability, contraindications, comorbidities, and treatment goals.[43] Successful management also requires attention to functional outcomes and QoL, rather

than pain intensity alone.[44] For this reason, multidisciplinary care integrating pharmacological and non-pharmacological interventions may be beneficial in chronic NP.[33]

Non-pharmacological approaches represent an important component of management, particularly when symptoms persist despite medication. Exercise programs have been described as potentially beneficial complementary strategies in patients with NP.[36] Psychological and rehabilitation interventions may also improve pain intensity and pain-related disability associated with chronic NP.[44] When conservative treatment is insufficient, minimally invasive interventional procedures may be considered to improve pain control and QoL.[41]

Overall, current evidence supports the use of pharmacotherapy and non-invasive neuromodulation as treatment options for NP.[43]

Pharmacological Management

The administration of medications remains an important strategy for alleviating symptoms and improving the quality of life of individuals with NP.[5] Modern clinical recommendations uniformly recommend adopting a sequential, tiered approach when prescribing these pharmacological agents.[10] Despite this, therapeutic results frequently remain limited, with a large proportion of individuals not experiencing satisfactory analgesia from existing drugs.[45] The effectiveness of these treatments is typically constrained because they offer symptom control rather than addressing the fundamental disease mechanisms.[33] Additionally, the extended administration of systemic medications frequently correlates with significant negative reactions and the possible onset of pharmacological tolerance.[46]

TCAs, such as amitriptyline and nortriptyline, are strongly recommended as first-line agents across international guidelines.[43] These drugs achieve analgesia mainly by blocking the reuptake of noradrenaline and serotonin, consequently amplifying the descending networks that inhibit pain.[5] Systematic reviews validate their therapeutic success, revealing an advantageous number needed to treat (NNT) of around 4.6 to obtain significant analgesic effects.[43] Common adverse events associated with these drugs include dry mouth, confusion, cognitive impairment, postural hypotension, blurred vision, urinary retention, drowsiness, and sedation.[47] Therefore, due to their sedative and anticholinergic properties, alongside an elevated susceptibility to falls, the prescription of TCAs is commonly discouraged in older adults.[43]

SNRIs, notably duloxetine and venlafaxine, are also strongly recommended as first-line treatment options.[48] Their mechanism of action similarly involves preventing serotonin and norepinephrine reuptake, thereby enhancing descending pain inhibitory pathways. While TCAs generally exhibit superior efficacy compared to SNRIs, the latter group has a more favorable safety profile.[5]

Nevertheless, patients may still experience adverse effects such as nausea, dry mouth, headache, hypaphrodisia, dizziness, drowsiness or insomnia, decreased appetite, and hypertension.[47]

Gabapentin and pregabalin are other first-line drugs widely used in the management of NP. These agents act by targeting the α2δ subunit of voltage-gated calcium channels, thereby decreasing central sensitization and neuronal excitability.[5] For these specific ligands, the combined NNT is calculated to be approximately 8.9.[43] Typical adverse effects include sedation, dizziness, weight gain, and a recognized risk of misuse and abuse.[5] Additionally, contemporary systematic assessments of randomized controlled trial (RCT) attest to the restricted clinical success of pregabalin, which presently stands as the primary medication associated with fraudulent or illicit prescriptions.[48]

Topical therapies, including capsaicin 8% patches, capsaicin cream, and lidocaine 5% plasters, are recommended as second-line options specifically for peripheral NP.[43] By inhibiting sodium channel activity, the 5% lidocaine transdermal patch delivers targeted analgesia while minimizing the incidence of systemic adverse reactions.[5] Consequently, these topical interventions can serve as suitable primary treatments for fragile populations, including elderly individuals, patients with complex comorbidities, and those subjected to polypharmacy.[43] Formulations containing high doses of capsaicin function by stimulating the transient receptor potential vanilloid 1 channel, which subsequently dampens nociceptor reactivity and induces a reversible state of nerve defunctionalization. In patients with conditions such as CIPN and PDN, nerve biopsies have demonstrated regeneration of intraepidermal and subepidermal nerve fibers after treatment, a finding associated with reduced pain intensity.[49] The predominant negative reactions linked to this topical agent remain confined to the administration area, typically presenting as papules, itching, pain, and erythema.[33]

When earlier interventions prove insufficient, opioids, rTMS, and BTX-A are classified as third-line therapeutic choices for NP management.[43] Administered via subcutaneous injection, BTX-A achieves analgesia by impeding the exocytotic release of nociceptive neurotransmitters from sensory neurons.[5] Despite its therapeutic potential, its clinical use is limited by the need for specialized training, the requirement for repeated administration, and high treatment costs.[5] Due to the severe potential for addiction and misuse, contemporary protocols dictate that potent opioids should be restricted to a third-line role, specifically for individuals experiencing escalating pain that remains unresponsive to alternative sensible therapies. Tramadol, which was previously classified as a second-line option, is now considered within the opioid class and likewise recommended as a third-line treatment, with a weak strength of recommendation.[43] Adverse effects that limit opioid clinical utility include izziness, drowsiness, nausea, vomiting, constipation, urinary retention, itch, and respiratory depression.[47]

Clinicians frequently combine medications when a single drug offers inadequate symptom relief.[45] This multimodal approach is generally preferred because it may provide complementary analgesic effects while preserving a more favorable tolerability profile.[16] For patients not responding to moderate doses of monotherapy, combining a gabapentinoid with duloxetine or a TCA is often considered a preferable alternative to merely escalating the drug dose. Conversely, recent meta-analyses have failed to demonstrate that combining opioids with either antidepressants or gabapentinoids provides consistent superiority over monotherapy.[45] Therefore, therapeutic regimens must be highly individualized, carefully weighing factors such as drug interactions, patient-specific contraindications, and potential pharmacokinetic profiles.[10]

Non-Pharmacological Management

Given that pharmacotherapy frequently fails to provide complete analgesia and is often accompanied by dose-limiting adverse events, contemporary guidelines advocate for a comprehensive, multimodal treatment paradigm. Integrating non-pharmacological and conservative strategies aims not only to mitigate pain severity but also to address the psychological and physical impairments that profoundly diminish the patient's QoL.[4]

Physical exercise is currently recognized as a fundamental neuroprotective and analgesic intervention.[6] Modalities such as aerobic conditioning, progressive resistance training, and mind-body exercises (e.g., Tai Chi and yoga) have demonstrated substantial efficacy in alleviating hyperalgesia and improving functional mobility throughout various neuropathic conditions.[50] Recent molecular evidence elucidates that routine physical activity exerts its analgesic properties by modulating glial cell dynamics within the central and peripheral nervous systems. Exercise actively promotes a phenotypic shift in microglia and macrophages from a pro-inflammatory (M1) to a beneficial, anti-inflammatory (M2) state, while simultaneously downregulating astrocytic hyperactivation. This cellular modulation diminishes the release of neuroexcitatory cytokines and upregulates the production of endogenous opioids and brain-derived neurotrophic factor (BDNF), collectively dampening central sensitization and neuroinflammation.[6]

Furthermore, chronic nerve pain is inextricably linked to severe psychosocial comorbidities, including sleep disturbances, clinical depression, and pain catastrophizing.[4,51] Consequently, psychologically based interventions constitute essential parts of interdisciplinary pain rehabilitation programs. Cognitive-behavioral therapy (CBT), acceptance and commitment therapy (ACT), and mindfulness-based stress reduction techniques are currently the most validated approaches.[32] By systematically modifying maladaptive cognitions, addressing kinesiophobia (the fear of movement), and adjusting behavioral responses to pain, psychological therapies can help improve pain-related disability and emotional distress.[4] Consistent with this therapeutic potential, current evidence

reveals that between half and two-thirds of clinical trials report tangible reductions in pain-related disability and emotional burden following these interventions. Nevertheless, given the substantial methodological diversity across the existing literature, these promising outcomes should be interpreted with appropriate clinical caution.[32]

Emerging research also highlights the considerable impact of dietary lifestyle interventions in managing the underlying mechanisms of NP.[37] Chronic pain pathophysiology is heavily influenced by systemic inflammation and oxidative stress, which exacerbate nociceptor sensitivity.[51] Adopting anti-inflammatory nutritional patterns, such as the Mediterranean, whole-food plant-based, or low-calorie diets, has been associated with significant reductions in neuropathic symptom severity.[37] These diets are inherently rich in natural antioxidants, polyphenols, and essential micronutrients, which help to restore redox homeostasis, inhibit pro-inflammatory signaling pathways, and support the gut-brain axis, consequently providing a safe, accessible, and cost-effective adjunctive therapeutic strategy.[51]

Neuromodulation and Interventional Therapies

When pharmacological treatments fail to provide sufficient analgesia, neuromodulation and interventional therapies offer critical alternative pathways, providing a range of procedural interventions to alter neural circuit function. Among non-invasive options, transcutaneous electrical nerve stimulation (TENS) delivers low-voltage currents through surface electrodes to inhibit ascending nociceptive transmission, making it a portable, inexpensive modality for localized pain. However, the clinical utility of this superficial stimulation is often restricted by a lack of robust evidence supporting its long-term analgesic efficacy.[5] rTMS has appeared as a promising central neuromodulatory approach that can mitigate NP intensity while simultaneously alleviating comorbid depressive symptoms.[35] The widespread clinical application of this magnetic technique is strictly contraindicated in patients with a history of epilepsy or those possessing implanted metallic devices such as cardiac pacemakers.[46] Transcranial direct current stimulation (tDCS) represents another non-invasive technique that applies low-intensity electrical currents to modulate cortical excitability and promote neuroplastic changes. It is associated with a highly favorable safety profile, with adverse effects usually limited to mild skin irritation.[48]

For more intractable conditions, implantable devices such as spinal cord stimulators are frequently indicated, demonstrating significant improvements in pain intensity and QoL for individuals with failed back surgery syndrome. Nevertheless, this invasive surgical procedure carries notable hardware and biological risks, including lead migration, localized infections, severe neurological injuries, and a gradual loss of therapeutic efficacy over time.[5] In highly refractory scenarios, deep brain stimulation offers an intracranial target for pain modulation, yet its application is strictly

limited by considerable surgical hazards, including intraoperative seizures, wound infections, and lead fractures.[46] Alternatively, ablative surgical procedures employing physical methods like radiofrequency are utilized to purposely destroy specific neural structures, thereby providing effective symptomatic pain relief. The primary disadvantage of these destructive interventions is the predictable functional impairment of the targeted nerve, which can occasionally result in localized sensitivity deficits.[52]

Etiology-Specific Therapeutic Considerations

The profound pathophysiological heterogeneity of NP requires the development of individualized treatment algorithms based on specific etiologies and underlying mechanisms.[1] Trigeminal neuralgia represents a distinct condition where standard NP medications are not generally recommended, and instead, sodium channel blockers like carbamazepine and oxcarbazepine serve as the absolute first-line treatments. For patients with classic trigeminal neuralgia who do not respond to pharmacotherapy, microvascular decompression is a highly effective surgical intervention that addresses the underlying neurovascular conflict and provides immediate freedom from pain in the vast majority of cases.[52]

The anatomical distribution of the pain also guides therapeutic selection, as international guidelines recommend targeted agents like 8% capsaicin patches or 5% lidocaine plasters as second-line therapies for localized peripheral neuropathies.[43] The high-concentration capsaicin patch provides long-term pain relief through the reversible defunctionalization of TRPV1-expressing nociceptors, although its application is frequently associated with transient site reactions such as erythema and burning sensations. Interestingly, evidence suggests that this initial nerve defunctionalization mediated by the capsaicin patch is subsequently followed by the functional regeneration of cutaneous nociceptors.[49] The use of localized topical treatments is explicitly proposed as an appropriate first-line option for vulnerable populations, including older adults and patients with polypharmacy. This is particularly relevant because systemic first-line drugs, namely TCAs, are generally contraindicated in geriatric patients owing to their high potential to induce sedation, anticholinergic toxicity, and subsequent fall-related injuries.[43]

Beyond specific disease etiologies, clinical phenotyping through QST offers a sophisticated approach to customize analgesia by predicting individual treatment responses. For instance, patients displaying the "irritable nociceptor" sensory phenotype have demonstrated a markedly superior analgesic response to oxcarbazepine compared to individuals without this specific profile. Finally, exploring genetic variations in pain-related genes, such as mutations in SCN9A, which encodes the Nav1.7 voltage-gated sodium channel, provides another critical avenue for developing highly personalized analgesic therapies.[1]

To provide a comprehensive overview of current clinical guidelines, Table 2 summarizes the established pharmacological and non-pharmacological therapeutic approaches for NP management, detailing their primary mechanisms of action and main clinical limitations.

Future Perspectives

The transition from basic laboratory research to clinical practice is driving the development of innovative therapeutic modalities to overcome the limitations of conventional NP management.[53] Nanomedicine represents a emerging frontier by utilizing nanoscale carriers, such as polymeric or inorganic nanoparticles, to encapsulate drugs or genetic materials for targeted cellular delivery. Recent discoveries demonstrate that these nanomaterials can successfully mitigate microglial activation and oxidative stress, thereby providing long-lasting pain relief while minimizing off-target systemic toxicity. Despite these considerable benefits, the clinical implementation of nanotherapeutics is currently hindered by unresolved concerns regarding their long-term biodistribution and potential cumulative toxicity within the human body. Furthermore, significant technological barriers remain before these treatments can reach daily hospital care, prominently including challenges in large-scale industrial manufacturing, physiological stability, and consistent batch-to-batch quality control.[47]

Within the fast evolving field of regenerative medicine, mesenchymal stem cells offer an innovative strategy that actively repairs damaged nerves rather than merely suppressing symptomatic pain. The remarkable analgesic efficacy of these cells stems from their potent ability to secrete neurotrophic factors, induce axonal remyelination, and shift the microglial profile towards an anti-inflammatory state. However, the widespread clinical use of stem cell therapy is presently obstructed by a profound lack of standardized protocols concerning optimal cellular dosing, ideal transplantation timing, and the most effective delivery routes. Additionally, clinicians must carefully consider potential biological adverse effects, particularly the possibility of genetic instability or tumor malformations occurring during the necessary in vitro expansion and purification processes.[54]

As a promising autologous regenerative therapy, platelet-rich plasma (PRP) involves injecting concentrated platelets to reduce local neuroinflammation and promote tissue healing. The primary biological advantage of this therapy is its high concentration of growth factors, which can stimulate tissue repair and effectively modulate underlying pain pathways. While PRP has already been successfully established in the management of musculoskeletal conditions, such as osteoarthritis and tendinopathies, emerging evidence highlights its expanding clinical applications for NP management by enhancing peripheral nerve regeneration. However, the widespread clinical

integration of these advanced regenerative approaches is still challenged by the need to fully translate these laboratory advances into consistent and standardized patient care protocols.[53]

As a systemic and highly accessible alternative, neuro-nutritional therapies and dietary lifestyle interventions are increasingly being explored as adjunctive strategies to manage chronic pain.[37] Recent evidence highlights that specific dietary components, such as melatonin and other antioxidant-rich natural products, can actively restore neuronal redox homeostasis and modulate neuroinflammation pathways. The incorporation of these dietary patterns offers a lower-risk perspective compared to conventional pharmacological treatments, which are frequently limited by severe side effects and suboptimal long-term efficacy.[51] Despite these promising biological mechanisms, the definitive clinical validation of dietary interventions is currently hindered by the scarcity of large, high-quality, and double-blinded RCTs. Specifically, severe methodological limitations, including small sample sizes and substantial heterogeneity in dietary protocols across studies, prevent the establishment of standardized, reliable nutritional guidelines for hospital care.[37]

Shifting towards strictly molecular interventions, novel techniques such as optogenetics and chemogenetics utilize light-sensitive proteins or engineered receptors to precisely manipulate the excitability of specific neuronal populations. Animal models have revealed that these genetic approaches, along with viral vector-mediated delivery of analgesic genes, can silence hyperactive nociceptive circuits without causing the systemic tolerance typically seen with chronic opioid use. While these approaches provide unprecedented specificity, their application in humans is currently precluded by serious safety concerns regarding the inherent toxicity and unpredictable immune responses associated with viral delivery vectors. Moreover, a critical technical barrier to clinical translation is the profound difficulty of accurately pinpointing the damaged nerve fiber, as even minor misplacement during genetic intervention can irreversibly disrupt normal neurological function.[46]

DISCUSSION

Effectively managing chronic NP remains one of the most demanding clinical challenges, largely due to the persistent gap between diagnostic complexity and the modest efficacy of available pharmacological therapies. As previously described, because objective confirmatory investigations are frequently limited in routine practice, clinicians must rely predominantly on clinical history, physical examination, and validated patient-reported screening instruments, such as the DN4, LANSS, and painDETECT questionnaires. Following clinical identification, treatment is often complicated by the fact that fewer than half of patients achieve satisfactory relief.[3] First-line agents,

primarily comprising gabapentinoids, TCAs, and SNRIs, frequently fall short of clinical expectations. These drugs often provide limited effect sizes and lead to high withdrawal rates due to dose-limiting adverse events, leaving many patients without adequate symptom control.[1]

Because current diagnostic and therapeutic pathways frequently fail to provide complete analgesia, NP imposes a devastating and prolonged burden on the patient's HRQoL, which is the central focus of this review. The persistence of unresolved pain functions as an intricate cognitive and emotional stressor, significantly increasing the risk of psychiatric comorbidities such as clinical depression and severe anxiety. As evidenced in the literature, these emotional disorders amplify the perception of pain and directly exacerbate overall symptom severity and functional disability.[4] Beyond the psychological toll, patients routinely endure profound physical limitations. Chronic fatigue, severe sleep disturbances, and reduced functional mobility, such as walking difficulties and fear of falling, are hallmarks of the condition, directly impairing occupational functioning and leading to increased absenteeism.[33] Ultimately, this multifaceted burden drastically deteriorates the patient's overall well-being, reinforcing the critical need to evaluate therapeutic success not merely by pain score reductions, but by the meaningful restoration of sleep, mobility, and psychosocial stability.

Addressing the well-documented shortcomings of exclusive pharmacotherapy requires shifting the clinical approach to NP toward an integrated biopsychosocial model.[4] Indeed, persistent nociception functions as an intricate cognitive condition that continually disrupts affective regulation and the broader mechanisms of the central nervous system.[16] As a result, targeted psychotherapeutic and rehabilitative approaches, most notably cognitive behavioral practices and mindfulness-oriented protocols, have emerged as key recommendations to diminish both the severity of the painful sensation and the associated functional impairment.[44] In tandem with these cognitive strategies, tailored physical training acts as a scientifically validated adjunct intervention that effectively reduces symptomatology across a variety of neuropathy contexts.[50] On a cellular level, regular physical activity provides crucial neuroprotection by modulating glial cell activity and dampening neuroinflammatory responses within the nociceptive pathways.[6] Moreover, tailored lifestyle adjustments, encompassing precise nutritional regimens and the use of nutraceuticals, are gaining recognition as effective strategies to counteract the biological drivers of pain persistence. The current literature demonstrates that nutritional modifications, specifically low-calorie, plant-focused diets, confer substantial anti-inflammatory and neuroprotective effects, ultimately leading to a marked decrease in neuropathic distress.[37] More precisely, boosting the consumption of dietary antioxidants and anti-inflammatory compounds, particularly melatonin, plays an active role in reestablishing the redox equilibrium of neurons and downregulating neuroinflammatory circuits.[51] In essence, the convergence of these non-pharmacological pillars fosters a highly

synergistic milieu that stimulates beneficial neuroplasticity, thereby empowering individuals to reclaim their daily functional independence and enhance their overall QoL.

Despite ongoing advances in pharmacology, effectively translating emergent analgesic paradigms into routine clinical practice remains a substantial hurdle. A prominent methodological limitation arises in contemporary clinical research, which frequently measures efficacy using isolated pain-intensity metrics rather than categorizing cohorts by underlying pathophysiological drivers and appraising broader functional restoration.[5] Moreover, generalizing preclinical findings encounters severe constraints because conventional murine models fail to emulate the intricate psychosocial variables and heterogeneous origins inherent to human neuropathic syndromes.[55] To overcome these translational obstacles, future management paradigms must inevitably shift toward precision medicine, tailoring therapeutic strategies to the individual's distinct genomic signature and phenotypic presentation.[53] In experimental settings, viral vector-based methods like optogenetics and chemogenetics have shown the ability to selectively silence nociceptive pathways. These targeted approaches offer a potential way to overcome the systemic tolerance typically caused by traditional drugs.[46] On a molecular scale, deploying nanotherapeutics offers an advanced mechanism for targeted drug transport, which extends the window of clinical efficacy while simultaneously curbing systemic toxicity.[47] Additionally, the integration of machine learning algorithms permits an intricate examination of biomarker repositories, thereby sharpening diagnostic precision and optimizing real-time clinical judgment. To bridge the gap between scientific innovations and daily practice, prospective frameworks will increasingly depend on the combined effects of tissue-regenerative interventions and selective neuromodulatory techniques.[53] Ultimately, connecting fundamental neuroscience with therapeutic success requires healthcare providers to adopt an individualized, multidisciplinary strategy aimed at fully restoring the patient's functionality and overall well-being.

CONCLUSION

NP is a highly complex condition that extends far beyond physical discomfort, consistently impairing a patient's sleep, emotional stability, and daily routine. Although the scientific understanding of its underlying mechanisms has grown considerably, achieving reliable clinical relief remains a major hurdle. Diagnosis continues to rely heavily on subjective screening instruments, and first-line pharmacological treatments often yield only partial analgesia while causing limiting adverse effects. As a result, a large number of patients are left dealing with persistent symptoms and a deteriorating QoL.

The severity of this daily burden is deeply tied to the underlying clinical context. Conditions such as PDN frequently bring about severe emotional distress and progressive mobility loss, whereas chemotherapy-induced and chronic postsurgical neuropathies impose prolonged physical limitations that severely disrupt cancer survivorship and postoperative recovery. Recognizing these distinct clinical profiles is fundamental, as it underscores that NP is not a uniform entity but a highly variable condition that requires specific assessment.

To address these clear therapeutic gaps, clinical management needs to shift from a strictly biomedical perspective toward a solid biopsychosocial approach. Given that medication alone is rarely sufficient, integrating non-pharmacological strategies like structured physical exercise, cognitive-behavioral therapies, and targeted nutritional changes has become essential. Rather than serving merely as supportive care, these interventions actively help to control neuroinflammation, improve functional mobility, and allow patients to cope with the heavy psychological toll of chronic pain.

Moving forward, the future of pain management will depend on the successful application of precision medicine. Experimental technologies such as viral vector-mediated therapies, nanomedicine, and regenerative treatments are laying the groundwork for highly specific interventions that can silence nociceptive pathways without inducing systemic toxicity. Ultimately, bridging the gap between laboratory research and daily medical practice requires highly individualized care strategies. Success in treating NP should be measured not just by a reduction in pain scores, but by the genuine restoration of the patient's independence and overall QoL.

TABLES

Table I: Impact Of Neuropathic Pain On Quality Of Life According To Etiology

Etiology	Physical And Functional Impact	Psychological Impact	Other Relevant QoL Dimensions
Painful diabetic neuropathy	Increased functional disability; walking difficulties, reduced mobility, and fear of falling; physical decline	Symptoms of anxiety and depression; amplify pain perception and overall symptom severity; psychological comorbidities	Impairment in QoL, particularly in domains related to daily functioning and emotional well-being; Sleep disturbances; state of chronic exhaustion; poorer mental health and lower overall QoL
Chemotherapy-induced peripheral neuropathy	Severe sensory symptoms; major functional limitations and difficulties in performing previously routine activities	High levels of emotional distress	Persistent symptoms may continue after completion of treatment; overall burden experienced within the broader context of cancer survivorship; reduced sense of well-being
Chronic postsurgical neuropathic pain	Interference with daily activities; painful sensations persisting far beyond the expected physiological recovery period	Emotional distress	Reduced QoL; persistent symptoms remain present long after the postoperative healing phase; broader impact on well-being; relevant and debilitating long-term clinical outcome
Central neuropathic pain	Neurological deficits; increasing disability and dependence in daily activities	Depressive symptoms; greater psychological burden, including symptoms of anxiety and depression.	Reduced QoL and overall well-being; persistence and complexity of NP in neurological conditions contribute to its clinical relevance and overall burden

Table II: Overview Of Therapeutic Approaches For Neuropathic Pain Management

Treatment Line / Category	Specific Interventions	Primary Mechanism of Action	Clinical Considerations And Limitations
First-Line Pharmacotherapy	Tricyclic Antidepressants (TCAs) (e.g., Amitriptyline, Nortriptyline)	Blocking the reuptake of noradrenaline and serotonin, consequently amplifying the descending networks that inhibit pain	High efficacy but limited by side effects (dry mouth, confusion, cognitive impairment, sedation). Generally discouraged in older adults due to sedative and anticholinergic properties, alongside an elevated susceptibility to falls
	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (e.g., Duloxetine, Venlafaxine)	Preventing serotonin and norepinephrine reuptake, thereby enhancing descending pain inhibitory pathways	Presents a more advantageous safety record compared to TCAs, though adverse effects such as nausea, dizziness, drowsiness or insomnia may occur
	Anticonvulsants (Gabapentin, Pregabalin)	Targeting the α2δ subunit of voltage-gated calcium channels, leading to a decrease in central sensitization and neuronal excitability	Effective, but frequently associated with sedation, weight gain, dizziness, and a recognized risk of misuse and abuse
Second-Line Pharmacotherapy	Topical Agents: Lidocaine 5% plasters	Inhibiting sodium channel activity, delivering targeted analgesia while minimizing the incidence of systemic adverse reactions	Recommended for localized peripheral neuropathies. Suitable primary treatment for fragile populations (e.g., elderly individuals, patients with complex comorbidities, and those subjected to polypharmacy)

	Topical Agents: Capsaicin 8% patches	Stimulating the transient receptor potential vanilloid 1 (TRPV1) channel, which dampens nociceptor reactivity and induces a reversible state of nerve defunctionalization	Recommended for localized peripheral neuropathies. Provides long-term pain relief, but negative reactions remain confined to the administration area (typically presenting as papules, itching, pain, erythema, and burning sensations)
Third-Line Pharmacotherapy	Botulinum Toxin Type A	Impeding the exocytotic release of nociceptive neurotransmitters from sensory neurons	Administered via subcutaneous injection. Limited by high treatment costs, the need for specialized training, and the requirement for repeated administrations
	Opioids (Potent opioids, Tramadol)	Not detailed in the reviewed literature	According to NeuPSIG guidelines, their use is restricted to selected cases (specifically for escalating pain unresponsive to alternative sensible therapies), due to severe risks of addiction, misuse, respiratory depression, and pharmacological tolerance
Non-Pharmacological And Biopsychosocial	Physical Exercise (Aerobic, resistance, mind-body therapies)	Modulating glial cell dynamics (shifting microglia from a pro-inflammatory M1 to an anti-inflammatory M2 state) and upregulating the production of endogenous opioids and BDNF	Fundamental neuroprotective and analgesic intervention to control neuroinflammation, improve functional mobility, and mitigate pain-related disability
	Psychological Therapies (CBT, ACT, Mindfulness)	Systematically modifying maladaptive cognitions, addressing kinesiophobia, and adjusting behavioral responses to pain	Critical components to help improve pain-related disability and address severe psychosocial comorbidities, including clinical depression, and pain catastrophizing

	Nutritional Interventions (Plant-based, low-calorie diets, melatonin)	Restoring redox homeostasis and inhibiting pro-inflammatory signaling pathways.	Safe, accessible, and cost-effective adjunctive therapeutic strategy to counteract systemic inflammation and oxidative stress
Neuromodulation And Interventional	Non-Invasive Neuromodulation (rTMS, tDCS, TENS)	Inhibiting ascending nociceptive transmission (TENS) and modulating cortical excitability (tDCS)	tDCS offers a highly favorable safety profile. rTMS mitigates both pain and comorbid depressive symptoms but is strictly contraindicated in patients with a history of epilepsy
	Invasive/Surgical (Spinal cord stimulators, deep brain stimulation, ablative procedures)	Altering neural circuit function or purposely destroying specific neural structures (ablation)	Spinal cord stimulators demonstrate improvements for failed back surgery syndrome, but carry notable hardware and biological risks

ATTACHMENTS

Attachment 1: Questionnaire Douleur Neuropathique en 4 Questions (DN4) – Portuguese version

QUESTIONÁRIO ESPECÍFICO PARA RASTREIO DE DOR NEUROPÁTICA – DN4

Por favor, responda às seguintes questões, assinalando uma única resposta para cada alínea.

QUESTIONÁRIO DO DOENTE

Questão 1: A dor apresenta uma, ou mais, das características seguintes?

	sim	não
1 – **Queimadura**		
2 – **Sensação de frio doloroso**		
3 – **Choques eléctricos**		

Questão 2:Na mesma região da dor, sente também um ou mais dos seguintes sintomas?

	sim	não
4 – **Formigueiro**		
5 – **Picadas**		
6 – **Dormência**		
7 – **Comichão**		

EXAME DO DOENTE

Questão 3: A dor está localizada numa zona onde o exame físico evidencia:

	sim	não
8 – **Hipoestesia ao tacto**		
9 – **Hipoestesia à picada**		

Questão 4: A dor é provocada ou aumentada por:

	sim	não
10 – **Fricção leve (“*brushing*”)**		

Source: Retrieved from Associação Portuguesa para o Estudo da Dor (APED). (2007). *Diversos questionários sobre dor crónica* (Vol. 15, nº 4). Revista Dor. https://www.aped-dor.org/socios/material_bibliografico/diversos_Questionarios_Dor-Rev_DOR_Volume15-n4-2007.pdf

Attachment 2: Questionnaire Douleur Neuropathique en 4 Questions (DN4) – English version

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes	no
1 - **Burning**		
2 - **Painful cold**		
3 - **Electric Shocks**		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes	no
4 - **Tingling**		
5 - **Pins and Needles**		
6 - **Numbness**		
7 - **Itching**		

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes	no
8 - **Hypoesthesia to touch**		
9 - **Hypoesthesia to prick**		

Question 4: In the painful area, can the pain be caused or increased by:

	yes	no
10 - **Brushing**		

Source: Retrieved from Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lantéri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., & Vicaut, E. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain, 114*(1-2), 29–36. https://doi.org/10.1016/j.pain.2004.12.010

Attachment 3: Questionnaire painDETECT – Portuguese version

painDETECT

QUESTIONÁRIO SOBRE DOR

Data: ..... **Paciente:** **Apelido:** **Nome:**

Como avalia a sua dor **agora**, neste momento?

0 1 2 3 4 5 6 7 8 9 10

ausente máxima

Qual a intensidade da dor **mais forte** que sentiu nas últimas 4 semanas?

0 1 2 3 4 5 6 7 8 9 10

ausente máxima

Em média, qual a intensidade da dor que sentiu nas últimas 4 semanas?

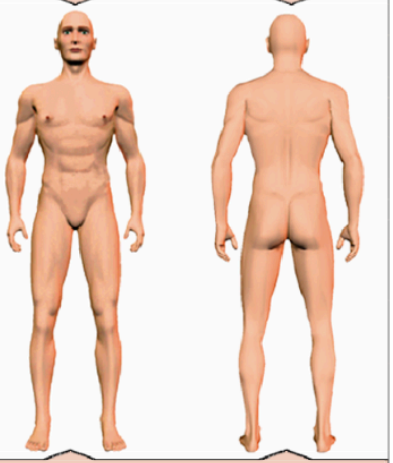
0 1 2 3 4 5 6 7 8 9 10

ausente máxima

Assinale a imagem que melhor descreve a evolução da sua dor:

- **Dor constante com ligeiras variações** ☐
- **Dor constante com crises de dor** ☐
- **Crises de dor sem dor nos intervalos** ☐
- **Crises frequentes de dor com dor nos intervalos** ☐

Por favor indique **a principal zona de dor**



A sua dor espalha-se a outras regiões do corpo? sim ☐ não ☐

Se sim, indique a direcção para onde a dor se espalha.

Sofre de sensação de queimadura ou ardor (p. ex., como se tocasse em urtigas) nas zonas indicadas?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

Sente uma sensação de picada ou formigueiro na zona da dor (como formigas a caminhar ou uma vibração eléctrica)?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

Um toque superficial (com roupa, cobertor) nesta zona provoca dor?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

Tem crises repentinas de dor na zona afectada, como choques eléctricos?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

O frio ou o calor (como a água do banho) provoca-lhe dor ocasional nesta zona?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

Sofre de sensação de dormência nas zonas que indicou?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

Uma leve pressão nessa zona, por ex., com um dedo, desperta dor?

nenhuma ☐ insignificante ☐ ligeira ☐ moderada ☐ forte ☐ muito forte ☐

(A preencher pelo médico)

nenhuma	insignificante	ligeira	moderada	forte	muito forte
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Pontuação total ☐☐ **de 35 no máximo**

Source: Retrieved from Santos AIC. *Fiabilidade e validade de constructo do PainDETECT Questionnaire*. Setúbal: Instituto Politécnico de Setúbal, Escola Superior de Saúde; 2017. http://hdl.handle.net/10400.26/19752

Attachment 4: Questionnaire painDETECT – English version

Item	Score
*Gradation of pain**	
• Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	0–5
• Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	0–5
• Is light touching (clothing, a blanket) in this area painful?	0–5
• Do you have sudden pain attacks in the area of your pain, like electric shocks?	0–5
• Is cold or heat (bath water) in this area occasionally painful?	0–5
• Do you suffer from a sensation of numbness in the areas that you marked?	0–5
• Does slight pressure in this area, e.g. with a finger, trigger pain?	0–5
Pain course pattern	
Please select the picture that best describes the course of your pain:	
 Persistent pain with slight fluctuations	0
 Persistent pain with pain attacks	–1
 Pain attacks without pain between them	+1
 Pain attacks with pain between them	+1
Radiating pain	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5
Questions used to document pain, but which were not used in the scoring, are not shown

Source: Retrieved from Freynhagen, R., Baron, R., Gockel, U., & Tölle, T. R. (2006). painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Current medical research and opinion, 22*(10), 1911–1920. https://doi.org/10.1185/030079906X132488

Attachment 5: Questionnaire Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

THE LANSS PAIN SCALE

Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____ **DATE**_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO - My pain doesn't really feel like this..... (0)

b) YES - I get these sensations quite a lot..... (5)

2) Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO - My pain doesn't affect the colour of my skin..... (0)

b) YES - I've noticed that the pain does make my skin look different from normal .... (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO - My pain doesn't make my skin abnormally sensitive in that area..... (0)

b) YES - My skin seems abnormally sensitive to touch in that area..... (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

a) NO - My pain doesn't really feel like this ..... (0)

b) YES - I get these sensations quite a lot ..... (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

a) NO - I don't really get these sensations..... (0)

b) YES - I get these sensations quite a lot ..... (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO, normal sensation in both areas ..... (0)

b) YES, allodynia in painful area only ..... (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas ..... (0)

b) YES, altered PPT in painful area ..... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) .....

If score < 12, neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12, neuropathic mechanisms are **likely** to be contributing to the patient's pain

Source: Retrieved from Bennett M. (2001). The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain, 92*(1-2), 147–157. https://doi.org/10.1016/s0304-3959(00)00482-6

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