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Management of Neuropathic Pain in Patients With Spinal Cord Injuries: A Narrative Review

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Abstract

Spinal cord injury (SCI) is a major public health problem and a significant cause of disability, associated with serious social and financial consequences. Functional disorders observed after SCI are multiple and multidimensional, including loss of sensation and mobility, spasticity, paralysis, pressure ulcers, respiratory, urinary, and digestive complications, infections, development of cardiovascular disease, as well as chronic pain. The review was based on a literature search in PubMed, Scopus, and Google Scholar databases, with keywords such as “neuropathic pain,” “management,” “treatment,” “therapy,” “spinal cord degenerative injuries,” “spinal cord traumatic injuries,” “spinal cord neoplastic injuries,” “complications,” “quality of life,” and “functional status in daily life.” Long-term care for these patients is demanding and requires coordinated collaboration among various healthcare professionals and caregivers. In addition, the reduced ability and/or complete inability to work, as a consequence of SCI, imposes an enormous financial burden on both patients’ families and society.

Neuropathic pain (NP) is a common complication in patients with SCI, significantly affecting their quality of life (QoL) and functional status. Apart from the physical burden, NP is closely linked to emotional distress, including anxiety and depression. The difficulty in relieving NP is attributed either to the complexity of the underlying pathophysiological mechanisms or to differences among SCI patients regarding their responsiveness to treatment. The management of NP after SCI requires a comprehensive and individualized approach. Although multimodal strategies combining pharmaceutical, non-pharmaceutical, and interventional techniques appear to offer the most effective outcomes, a therapeutic approach based on the medical history of each individual patient could also have very good results, highlighting the uniqueness of each patient in the treatment that best suits them. Additional research is needed to effectively treat and relieve these specific patients.

Categories: Orthopedics, Internal Medicine, Anesthesiology
Keywords: complications, functionality in the daily life of the patient, management, neuropathic pain, quality of life, spinal cord degenerative injuries, spinal cord neoplastic injuries, spinal cord traumatic injuries, therapy, treatment

Introduction And Background

The annual incidence of spinal cord injury (SCI) in the worldwide population is estimated at 15-40 cases per million [1,2]. The main cause of SCI is considered to be blunt trauma, mainly associated with traffic accidents, while falls are the predominant cause of SCIs in the elderly. A significant percentage of this type of injury is attributed to sports and recreational activities, physical violence, work-related accidents, and iatrogenic complications; moreover, according to the relevant literature, the lifetime cost per patient in Canada exceeds $3 million, as therapeutic options remain limited for this lifelong disability [2-5]. Also, non-traumatic SCIs are caused by degenerative and neoplastic diseases [3]. Spinal cord injuries are more frequently observed in young men, although more recent epidemiological data indicate a significant increase in older age groups, something which is attributed to population aging [3].

Pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [6]. Pain is not a single phenomenon and it is classified into the following three different types: (i) nociceptive pain, which functions as a defense mechanism aiming to detect and/or avoid potentially harmful stimuli through reflexive withdrawal from the primary cause of its occurrence [7,8], (ii) inflammatory pain, which is due to tissue damage or infection, thus leading to increased sensitivity in order to prevent further mechanical stress, while at the same time inducing recovery [8], and (iii) pathological pain, including neuropathic pain (NP), which has no protective function and emerges as a disorder of the nervous system by itself [8,9]. Furthermore, concerning the explanation of the position of NP within the classification used in the article, either the International Association for the Study of Pain (IASP) or the study by Finnerup et al. defines NP as a condition resulting directly from a lesion or disease located in the somatosensory system [10,11]. According to this classification, NP is considered an abnormal neural pathology detached from normal protective tissue damage mechanisms, something which is also

supported by Pain Management Education at the University of California, San Francisco (UCSF) [12]. Additionally, according to pain management education at UCSF, the occurrence of neuropathic pain involves damage to central or peripheral nerves, and often NP becomes chronic [12]. Characteristic examples of NP, as per pain management education at UCSF, are presented as follows: (i) peripheral neuropathy, frequently attributed to diabetes, HIV, chemotherapy, and radiation treatment; (ii) neuralgia, frequently attributed to trigeminal neuralgia; (iii) spinal cord compression; and (iv) plexopathy [12].

The incidence of NP in the overall population is estimated at 6.9-10% [13]. Also, according to other studies, typical examples of NP include trigeminal neuralgia, painful polyneuropathy, postherpetic neuralgia, and central post-stroke pain [13-15]. Regarding the clinical presentation of NP, most patients describe a type of continuous or intermittent pain in the form of a burning or unpleasant sharp piercing sensation or pressure, often associated with the primary cause of pain, particularly in response to light touch or cold exposure [14].

The administration of oral analgesic, antidepressant, and anticonvulsant medications constitutes the first-line of treatment for NP, due either to the rapid action that these specific medications exhibit, or to the relative lack of complications [15,16]. However, according to other studies, oral antidepressants such as tricyclics and serotonin-norepinephrine reuptake inhibitors (SNRIs), and anticonvulsant medications (including gabapentinoids) are considered to be the first-line of pharmaceutical treatment both for NP in general and for NP due to SCIs [17,18]. Traditional oral analgesics (including paracetamol/acetaminophen, ibuprofen, naproxen, and diclofenac) are not considered first-line treatment for neuropathic pain, regardless of whether it is more general NP or NP arising from SCIs [19,20]. Moreover, the literature indicates that traditional oral analgesics are mainly used to manage nociceptive pain resulting from damage to bone tissue, muscle tissue, and joints [21]. Also, the surgical treatment of NP is preferred when conservative approaches fail or when definitive therapy is required. The latter includes the following three main interventional approaches, namely: (a) corrective/decompressive procedures [22], (b) implantation of neuromodulation or intrathecal analgesic delivery devices [23], and (c) neurosurgical ablative techniques [24].

The purpose of this narrative review is to synthesize and critically evaluate the available pharmaceutical, non-pharmaceutical, and interventional therapeutic options to treat NP after SCI by examining their efficacy, safety, and clinical applicability while identifying the most evidence-based interventions, in order to improve the quality of life (QoL) for these patients. Also, this work was not previously presented at any national or international conference, nor has it been published in any national or international scientific journal, in whole or in part.

Review

Materials and methods

To write this narrative review, articles published between January 01, 1999, and December 12, 2025, were selected. The search was performed on December 31, 2025. The literature search was conducted in the Hellenic National Documentation Centre by an information specialist, under the supervision of the principal investigator. The PubMed, Scopus, and Google Scholar databases were used, although there is a risk of selection bias. The keywords were “neuropathic pain,” “spinal cord degenerative injuries,” “spinal cord traumatic injuries,” “spinal cord neoplastic injuries,” “management,” “treatment,” “therapy,” “complications,” “quality of life,” and “functional status in daily life.” The Boolean operators AND & OR were used.

In an attempt to describe and synthesize existing research on the topic under investigation, the main issues studied in this study are presented as follows: pathogenetic mechanisms, prevention of secondary damage, the role of neuroprotective and/or neuro-regenerative agents, the assessment of SCIs (particularly under urgent conditions) by using modern imaging diagnostic methods, the classification of pain and the understanding of its mechanisms which is necessary knowledge to develop and implement effective treatment options, pharmaceutical approaches (including gabapentinoids, antidepressants, opioids, and topical agents), interventional and surgical therapeutic management (including neuromodulation and ablative neurosurgery), and non-pharmaceutical approaches (such as physical modalities, psychological and cognitive interventions, visual illusion and virtual reality). The selection of the articles was based on their title, abstract, and full-text content of the article. The literature search procedure for the selection of the articles is described below. A total of 6,196 records were initially identified, particularly (a) 2,208 records from the PubMed database, (b) 1,323 records from the Scopus database, and (c) 2,665 records from the Google Scholar database. Of these 6,196 records, we removed 3,324 duplicates, leaving 2,872 potentially eligible records. Then, 2,827 records were also excluded because they did not meet the eligibility criteria. Eligible for inclusion in this narrative review were English-language studies focusing on the following criteria: (i) NP emerged due to SCIs and (ii) the eligibility of the methods to treat NP depending on the type of SCI (pharmaceutical, intrathecal therapy, invasive and non-invasive neuromodulation techniques, rehabilitation interventions, psychological approaches, acupuncture, physical exercise, special diet, virtual reality techniques, multimodal treatment strategies). Conversely, we excluded editorial letters, study protocols, and studies that did not relate NP to SCIs or did not provide treatment-related outcome data.

Consequently, 45 full-text articles were assessed for eligibility. Of these, five articles were excluded because they did not present relevant outcome data. As a result, a number of 40 studies met the inclusion criteria and were included in the final synthesis. All the aforementioned articles are available in both PubMed and Google Scholar databases, while 38 articles out of the 40 are also indexed in the Scopus database. Following the initial literature search, we identified 163 additional studies (PubMed, Scopus, Google Scholar, and other databases) through manual reference screening and citation tracking, and included them as fully compatible with the investigated issue.

The diagram below summarizes the literature search procedure and is labeled “literature search via databases” (Figure *1*). Titles, abstracts, and full texts were screened by two co-authors independently throughout the literature search. Upon completion of the screening, an inter-reviewer consensus was carried out. Data on the identity of the studies (study design, sample size, levels of evidence, main findings, and characteristics) inserted in the writing of the article are shown in Tables *1*-*3*.

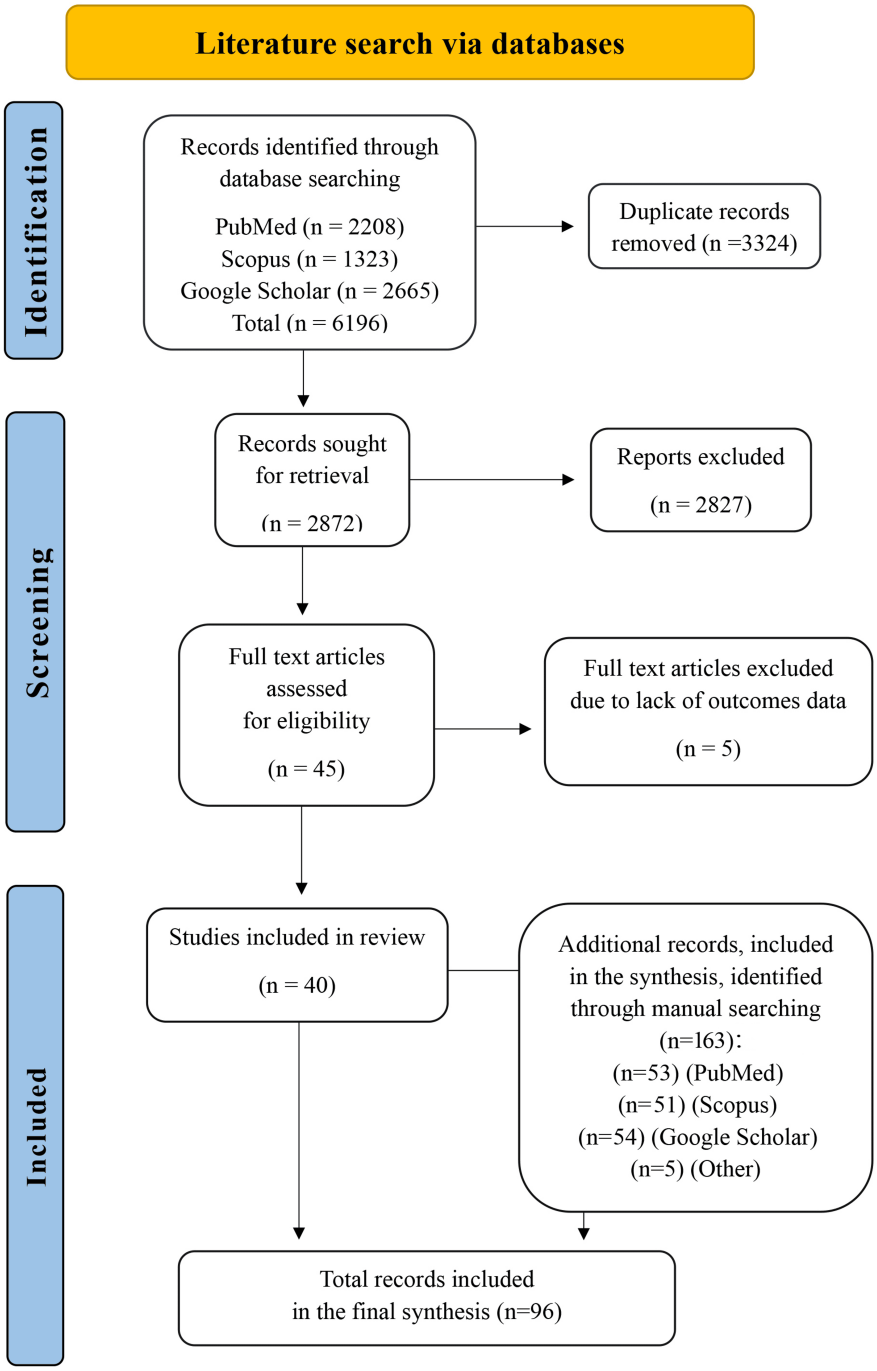


FIGURE 1: Literature search summary for the articles included in the final synthesis.

Studies	Study design	Sample size (participants)	Level of evidence	Main findings and characteristics
Pathogenetic mechanisms				
Ziu et al. [1]	Narrative review	n/a	5	Spinal shock is associated with various systemic complications, and prognosis is poor depending on the level and type of injury. Due to the high morbidity and mortality, a multidisciplinary approach including pain management, physiotherapy, occupational therapy, and nutrition is required in order to prevent devastating complications and improve QoL.

Sekhon and Fehlings [2]	Narrative review	n/a	5	Alcohol consumption and motor vehicles, as well as falls, constitute the main etiology for acute SCI occurrence in young men and in the elderly, respectively. Stabilization techniques are important to prevent complications, while pharmaceutical and surgical interventions are under examination.
Margetis et al. [3]	Narrative review	n/a	5	Etiology (vehicle collisions, falls, malignancies), epidemiology, pathophysiological mechanisms and syndromes, evaluation of motor and sensory function using the ASIA Impairment Scale, and classification of the injury after imaging are examined. In SCIs, treatment aims at stabilization in order to prevent secondary damage, while the long-term care of these patients demands the collaboration of an interprofessional healthcare team to optimize functional outcomes, mobility and independence through individualized rehabilitation programs.
Anjum et al. [4]	Narrative review	n/a	5	The existing treatments for SCIs can be improved by using new neuroprotective and/or neuro-regenerative agents. The understanding of multicellular and multi-molecular interaction mechanisms, being involved in either neuro-regeneration or neuroprotection procedures, is highlighted in order to promote and enhance repair mechanisms.
van den Hauwe et al. [5]	Narrative review	n/a	5	Spinal injuries and complications are evaluated. Safety measures adopted in sports and motor vehicles have reduced the incidence of SCIs in young and middle-aged adults. Nevertheless, in recent decades a significant increase has been observed in the elderly. Nowadays, patients survive learning to live with their disability, something which is due to the improvement of rehabilitation methods along with the improvement regarding chronic care.
Types of pain				
Loeser and Melzack [6]	Narrative review	n/a	5	The types of pain are considered to be as follows: transient pain, acute pain, and chronic pain. Acute pain is typically associated with tissue damage. Function of central and peripheral nervous system can be modulated by both tissue injury and changes emerged within the central nervous system, as well as by stress-regulation mechanisms occurring in response to such damage. Some of these modulations may persist and contribute to the development of chronic pain.
Basbaum et al. [7]	Narrative review	n/a	5	An anatomical overview of acute and persistent pain, along with an explanation of activation of nociceptors through heat, cold, mechanical, and chemical stimuli, is presented. Peripheral and central mechanisms, channels, as well as interactions are involved in the occurrence of persistent pain. Evidence suggests the pain pathway may operate via labeled lines, as heat and cold are sensed by different types of primary afferent fibers. The pain system exhibits remarkable adaptability, especially during the onset of the injury, and understanding how acute pain develops into maladaptive changes leading to chronic pain, something which, eventually, could help scientists to prevent or reverse pain's evolution.
Woolf [8]	Narrative review	n/a	5	Classification of pain (nociceptive, inflammatory, pathological) and characteristics of each type of pain are reported. Molecular sensation and pain visualization are also discussed. The nociceptive system undergoes tremendous change or plasticity when exposed to inflammatory mediators and growth factors in response to activity and injury. It appears that susceptibility to pain hypersensitivity, as well as the transition from acute to chronic pain, are affected by heritable factors.
Karcz et al. [9]	Narrative review	n/a	5	Basic mechanisms of pain, types of pain (nociceptive, neuropathic, inflammatory), mechanisms of hyperalgesia and allodynia, as well as sensitization (peripheral and central) are reported. Pain receptors, transmission, and pathways are also examined. Gate control theory of pain processes leading to chronicity of pain, as well as management of acute and chronic pain, are also investigated. Chronic pain is a highly heterogeneous condition, and most treatments are associated with adverse effects. Thus, management strategies should prioritize prevention, as the consequent sensitization of pain pathways can establish a positive feedback loop leading to pathological alterations at peripheral, spinal, and supraspinal levels.
Scholz et al.	Consensus report and	n/a	5	The classification of chronic neuropathic pain (peripheral and central) and its manifestation constitutes the first systematic and most comprehensive

[13]	expert review			attempt to categorize common painful neurological disorders.
Finnerup et al. [14]	Comprehensive narrative and mechanistic review	n/a	5	Neuropathic pain significantly affects QoL. It is characterized by ongoing or intermittent spontaneous pain, which can be accompanied by evoked pain, specifically through mediation of a light touch and/or cold. It is of major importance that the evoked pain can be disseminated to surrounding areas through peripheral and central sensitization. Therapeutic management includes the administration of medications acting on $\alpha_2\delta$ subunits of calcium channels, on sodium channels, as well as on descending modulatory inhibitory pathways.
Cohen et al. [15]	Narrative review	n/a	5	Pain might be divided as follows: (i) nociceptive pain arising from tissue damage, (ii) neuropathic pain related to nerve injury, and (iii) nociplastic pain, which has to do with sensitization of the nervous system. It should also be reported that, in practice, there is a significant overlap regarding the different types of pain mechanisms. Biological, psychological, and social factors should also be taken into account in order to evaluate the biopsychosocial model of pain. It appears that an individualized, multimodal approach including pharmaceutical therapy, psychotherapy, and invasive procedures could ameliorate the QoL in these patients.
Pain management				
Hylands-White et al. [16]	Narrative review	n/a	5	The pharmaceutical management of chronic pain (including analgesics, non-steroidal anti-inflammatory drugs, weak and strong opioids, topical analgesics and adjuvant analgesics) is examined. Interventional pain management methods such as spinal cord stimulation, DBS, rTMS, tDCS, TENS, and biopsychosocial treatments (physiotherapy, occupational therapy, clinical psychology, CBT) are also investigated. The contribution of a biopsychosocial approach along with a multidisciplinary modality to manage these patients is also reported in the study.
Hagen and Rekand [17]	Narrative review	n/a	5	Comparison of the efficacy of amitriptyline, PGB, GBP, opioids, capsaicin, lidocaine, and BTX-A was performed concerning the treatment of post-SCI NP. The first three drugs seem to be the most effective, while opioids were associated with more side effects.
Gugliotta et al. [22]	Prospective cohort study	370 participants	2	Comparison of surgical versus conservative treatment concerning lumbar disc herniation is attempted. It has been found that surgical treatment resulted in faster relief of back pain symptoms compared to conservative therapy; however, superiority in mid- and long-term outcomes was not demonstrated.
Luecke et al. [23]	Narrative review	n/a	5	Efficacy of 10 kHz spinal cord stimulation to treat chronic back and leg pain is recommended. Available evidence indicates that this approach enhances QoL and decreases the use of opioid analgesics.
Allam et al. [24]	Narrative and technology review	n/a	5	Ablation procedures (cordotomy, myelotomy, cingulotomy) to manage chronic non-cancer and cancer-related pain are examined. It seems that ablative surgery remains a key therapeutic option in cancer-related pain, while its role in non-cancer-related pain is limited, except for trigeminal neuralgia.

TABLE 1: Main findings and characteristics of the studies based on pathogenetic mechanisms, types of pain, and pain management for patients with spinal cord injuries.

QoL: quality of life; SCI: spinal cord injury; ASIA: American Spinal Injury Association; DBS: deep brain stimulation; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; TENS: transcutaneous electrical nerve stimulation; PGB: pregabalin; GBP: gabapentin; BTX-A: botulinum toxin type A; NP: neuropathic pain

Studies	Study design	Sample size (participants)	Level of evidence	Main findings and characteristics
Pharmaceutical treatment of neuropathic pain				
				It seems that PGB and GBP both appear to be effective in treating NP due

Tzellos et al. [25]	Systematic review	360 participants	1	to SCI; nevertheless, according to literature search, PGB appears to be more efficacious compared to GBP, although PGB is accompanied by more adverse effects than GBP.
Tong et al. [26]	Systematic review and network meta-analysis	628 participants	1	Examination and comparison of the safety and efficacy of PGB, GBP, amitriptyline and carbamazepine in treating NP after SCI are reported. The most effective medication appears to be pregabalin, with gabapentin to follow, although the latter is considered to be the safest option in terms of side effects.
Baastrup and Finnerup [27]	Narrative review	n/a	5	Comparison of the efficacy of antidepressants, anticonvulsants, cannabinoids, and opioids to manage NP related to SCI is presented. PGB, GBP, and amitriptyline were found to be the most effective for treating NP due to SCI.
Attal et al. [28]	Systematic review	166 physicians participated in order to provide expert feedback integrated into the SOFMER recommendations	n/a	PGB is recommended to treat NP related to SCI, as well as GBP, the latter particularly in peripheral NP. TCAs are also considered as first-line treatment when depressive symptoms coexist. Strong opioids can be administered as second-line or third-line treatment, although taking into account the probability of the occurrence of adverse effects.
Davari et al. [29]	Systematic review and meta-analysis	n/a	1	PGB was effective in reducing NP, anxiety, depression, and sleep disorders in patients with SCI, while GBP was also proved to be effective in NP reduction. Significant differences between the two medications, focusing on NP reduction and the emergence of side effects, were not recorded.
Ling et al. [30]	Systematic review and Bayesian network meta-analysis	1198 participants	1	The efficacy and safety of PGB, GBP, BTX-A, tramadol, amitriptyline, lamotrigine, ketamine, duloxetine, levetiracetam, carbamazepine, and cannabinoids regarding the treatment of NP emerging after SCI were examined. BTX-A demonstrated the best results regarding NP relief, four weeks after injury. Also, mental and sleep disorders were best managed with the administration of gabapentin, BTX-A, and pregabalin.
Lee et al. [31]	Pre-clinical experimental in vivo study	n/a	5	The administration of 17β-estradiol in order to manage NP related to SCI was found to be associated with a reduction in mechanical allodynia and thermal hyperalgesia.
Crul et al. [32]	Narrative review	8 participants	4	Local analgesic treatment including baclofen, ketamine, lidocaine, capsaicin, and phenytoin to manage NP due to SCI revealed a gradual pain's reduction. However, more placebo-controlled studies are needed to examine the influence of topical analgesics in NP related to SCI.
Mei et al. [33]	Systematic review and network meta-analysis	n/a	1	The efficacy and safety of anticonvulsants, antidepressants, BTX-A, opioids, and anesthetics to treat NP related to SCI were investigated. Pain reduction ≥50% was observed in descending order and in the specific sequence for the following drugs: anticonvulsants, anesthetics, antidepressants, BTX-A, opioids, placebo. Regarding the occurrence of recorded adverse reactions in relation to the drugs used, the order, from highest to lowest, was as follows: placebo, antidepressants, BTX-A, anticonvulsants, opioids, anesthetics. As a result, it seems that anticonvulsants, antidepressants, and botulinum toxin A have good efficacy and safety.

TABLE 2: Main findings and characteristics of the studies based on pharmaceutical treatment of neuropathic pain for patients with spinal cord injuries.

SOFMER: French Society of Physical and Rehabilitation Medicine; TCAs: tricyclic antidepressants; SCI: spinal cord injury; PGB: pregabalin; GBP: gabapentin; BTX-A: botulinum toxin type A; NP: neuropathic pain

Studies	Study design	Sample size (participants)	Level of evidence	Main findings and characteristics
Neuromodulation techniques				

Nardone et al. [34]	Narrative review	n/a	5	DBS and epidural MCS showed positive results in managing NP related to SCI, with MCS presenting fewer complications compared to DBS. Regarding the non-invasive neurostimulation techniques, tDCS was proven to reduce NP while increasing pain threshold in healthy subjects. Moreover, CES was found to be effective in treating NP due to SCI.
Shen et al. [35]	Systematic review and meta-analysis	n/a	1	Investigation of the duration of the analgesic effect of rTMS and tDCS techniques for NP management following SCI was performed. The rTMS technique showed an analgesic effect 2-6 weeks after the technique's application, while tDCS produced only a short-term reduction in pain intensity.
Saleh et al. [36]	Systematic review	127 participants	1	To evaluate the efficacy of rTMS applied to the primary motor cortex and the left dorsolateral prefrontal cortex to manage NP following SCI. A significant reduction in NP intensity was recorded.
Yu et al. [37]	Systematic review and meta-analysis	n/a	1	The efficacy of NIBS techniques in managing depression, anxiety, and NP intensity after SCI is examined. The rTMS, tDCS, and CES primary interventions did not reduce pain intensity or show any significant efficacy in depression. However, CES alone recorded a significant reduction in anxiety.
Bonomo et al. [38]	Narrative review	n/a	5	Although the evidence cited by this study appears to concern lumbar rather than specifically SCI-related neuropathic pain, nevertheless, the examination of neuromodulation techniques such as high-frequency (HF/10000 Hz) and burst stimulation in the spinal cord in order to manage NP showed that the above techniques are effective, focusing on therapeutic benefits and decreased potential side effects.
Yang et al. [39]	Randomized clinical trial (RCT)	37 participants	2	Three TMS techniques (iTBS, rTMS, and their combination) were evaluated in terms of efficacy in managing NP related to SCI. All three techniques showed some efficacy, although at different degrees. As for iTBS, significant differences were observed after its administration as a priming stimulus and as a standalone procedure.
Alternative therapeutic approaches				
He et al. [40]	Systematic review and meta-analysis	286 participants	1	It seems that acupuncture yields a significant positive effect to decrease pain severity and present pain intensity in patients experiencing neuropathic pain related to SCI.
Li et al. [41]	Narrative review	n/a	5	The effectiveness of the available methods to treat NP after SCI, such as medication, electroacupuncture, and neurostimulation techniques, was investigated. All of the aforementioned methods exhibited some degree of improvement in NP intensity. The need to combine the existing methods for better results is also highlighted.
Ge et al. [42]	Systematic review and network meta-analysis	1820 participants	1	The comparison of the efficacy and safety of therapeutic methods to manage NP related to SCI showed that iTBS presents superiority, with acupuncture and rTMS techniques to follow.
Chi et al. [43]	Systematic review	150 participants	n/a	VR approaches to manage NP after SCI had some degree of immediate and short-term analgesic effect, while long-term duration was not recorded. It seems that the combination of virtual walking and tDCS improves both pain intensity and patients' mood.
Combined therapeutic approaches				
Koukoulithras et al. [44]	Systematic review	2234 participants	n/a	Anticonvulsants showed superior efficacy in managing chronic NP due to SCI, with pregabalin further decreasing anxiety and sleep disorders. Amitriptyline, BTX-A, lidocaine, ketamine, and intrathecal administration of baclofen also showed positive clinical results in reducing NP intensity. Furthermore, non-pharmaceutical interventions like OMT, CBT, VR, as well as TENS were also associated with a reduction in pain intensity, with the latter exhibiting the greatest efficacy.
Allison et al. [45]	Systematic review	n/a	1	The effect of interventions for NP on pain interference in the daily life of patients with SCI was investigated. PGB and GBP, as well as the intrathecal administration of baclofen, along with the tDCS and TENS techniques, had

				positive effects in regulating NP.
Eller et al. [46]	Narrative review	n/a	5	The examination of pharmacological and non-pharmacological alternative approaches (exercise, thermotherapy, acupuncture, meditation, nutrition) to treat NP after SCI was investigated. A reduction in parameters such as pain, anxiety, and depression has been observed, along with improvement in the QoL in some patients.
Soler et al. [47]	Clinical trial	130 participants	2b	The combination of transcranial direct current stimulation (tDCS) along with visual illusion (VI) reduces NP following SCI as well as pain-related sleep disorders. A patient's specific sensory phenotype does not predict the treatment response; thus, the therapy is generally applicable across different sensory profiles.

TABLE 3: Main findings and characteristics of the studies based on neuromodulation techniques, alternative therapeutic approaches, and combined therapeutic approaches of neuropathic pain for patients with spinal cord injuries.

DBS: deep brain stimulation; MCS: motor cortex stimulation; NP: neuropathic pain; SCI: spinal cord injury; tDCS: transcranial direct current stimulation; CES: cranial electro-stimulation; rTMS: repetitive transcranial magnetic stimulation; iTBS: intermittent theta burst stimulation; BTX-A: botulinum toxin type A; OMT: osteopathic manipulative treatment; CBT: cognitive behavioral therapy; VR: virtual reality; TENS: transcutaneous electrical nerve stimulation; QoL: quality of life

Moreover, the Oxford Centre for Evidence-Based Medicine (OCEBM) and the study of Vatkar et al. were used to classify the levels of evidence, while the aforementioned classification is shown as follows: (1) level 1 for systematic reviews and meta-analyses, (2) level 2 for randomized controlled trials (RCTs), (3) level 3 for cohort and case-control studies, (4) level 4 for case series and reports, (5) level 5 for expert opinion and anecdotal evidence, relying on personal experience or isolated observations, and narrative reviews [48]. It is further stated that, as this work is a narrative review, no quantitative meta-analysis was performed. Effect sizes reported are those from the original studies cited.

Results

The evidence presented in this article was divided into three distinct thematic groups: pathogenetic mechanisms, types of pain, and pain management for patients with spinal cord injuries (SCIs); pharmaceutical treatment of neuropathic pain attributed to SCIs; and neuromodulation techniques, alternative therapeutic approaches, and combined therapeutic approaches for neuropathic pain due to SCIs. These issues are developed independently of each other.

We begin with an exploration of pathogenetic mechanisms, types of pain, and pain management. Within this domain, Ziu et al. examine spinal shock as a transient loss of neurological function below the level of an acute SCI, investigating its pathophysiology, the urgency of surgical decompression to prevent secondary damage, prognosis, and overall treatment [1]. The pathophysiology involved in spinal shock arising from acute SCIs is characterized by structural and chemical changes located in neural synapses below the injury level, such as high glycine concentration [49] and the inhibition of presynaptic neuron function [50], while hyperpolarization concurrently occurs in spinal motor neurons [51,52]. Furthermore, it seems that in spinal shock, functional disorders in descending pathways cause a disruption concerning both synaptic transmission and inter-neuronal conduction [53]. According to Weaver et al., when spinal shock occurs, the loss of tone associated with depression of the reflexes seems to affect the fusiform gamma-efferent system, thus dysregulating the sensitivity of the muscle stretch receptors [54]. In spinal shock, the role of inhibition of spinal cord interneurons and motoneurons from the corticospinal, rubrospinal, vestibulospinal, and reticulospinal pathways is also supported by the relevant literature [55]. Spinal shock resulting from traumatic injury to the spinal cord is considered to be a transient condition that usually improves within a period of a few days to weeks [1]. This reinforces the view that the therapeutic approach that will be applied should aim both at mitigating the consequences of the spinal cord injury and at preventing the occurrence of secondary complications as a result of the primary injury [1]. Hemodynamic and respiratory stability are considered necessary post-traumatic conditions in patients with SCI, in order to prevent further extension of the primary neurological damage [1]. This seems to be in agreement with another study, according to which the main causes of death in patients with SCI are respiratory and cardiovascular disorders [56]. Hypotension and bradycardia mainly occur in cervical and thoracic SCIs, particularly those above T6 level, due to loss of sympathetic tone [1]. In this case, it is important to maintain blood perfusion of the spinal cord with mean arterial pressure values greater than 80-90 mmHg for a period of five to seven days after an acute SCI, to avoid the occurrence of secondary ischemic damage [1], although the administered medication may be discontinued if there is no neurological improvement within 72 hours of starting administration [57,58]. As for the respiratory disturbances that frequently occur in acute SCIs, these include acute respiratory distress syndrome (ARDS) and pneumonia due to the reduction of the cough reflex [1]. Concerning the

urgent surgical decompression focusing on the prevention of secondary damage in acute SCIs, specifically when SCI is located in the cervical area, this may be crucial by diminishing spinal cord pressure, thus leading to improvement in the patient's neurological condition [1]. However, in acute SCIs, prior to proceeding with emergent surgical decompression, all the imminent risks and especially the risk of further vascular damage should be seriously considered [59]. Additionally, it is important to emphasize that the exact time indicated for surgical decompression in patients with acute SCIs has not yet been determined [1]. Nevertheless, according to the STASCIS study, surgical decompression within the first 24 hours after the acute SCI seems to be safe and is associated with improved neurological outcome (at least 2 grade AIS) six months after surgery, although further research is needed [60]. Regarding the usefulness of urgent surgical intervention in patients with acute SCIs, it has also been shown that in patients manifesting acute limb weakness due to acute blunt cervical SCI, surgical intervention was found to be significantly better (p=0.035) to improve the outcome versus those managed conservatively without surgery [61]. Furthermore, the prognosis of patients with acute SCIs, except for irregular cardiovascular and respiratory function, might be further adversely affected because of prolonged hospitalization, multiorgan failure, and sepsis [3,62]. These complications are compounding factors in a clinical landscape in which a defined overall treatment, in general, to manage pain of non-malignant etiology, including SCIs, does not appear to exist [1]. However, care should be taken when administering corticosteroids. Although the NASCIS II and III trials recorded modest neurological benefit of high-dose methylprednisolone sodium succinate (MPSS) when administered within eight hours after injury, limited efficacy and complications such as infections and bleeding from the gastrointestinal tract (GI tract) were recorded [63]. Another study reports gastrointestinal discomfort and insomnia, as well as gastrointestinal discomfort and peripheral edema, as side effects due to the administration of SNRIs and gabapentinoids, respectively, in order to pharmacologically manage NP [64]. However, in the same study, the use of SNRIs, TCAs, and gabapentinoids is recommended as first-line treatment while BTX-A and strong opioids are recommended as third-line treatment for the management of NP [64]. Moreover, it has been previously reported that in acute SCIs, the intravenous administration of methylprednisolone improves neurological dysfunction emerging at or below the level of neurologic injury [2]. In the same study, calcium influx and production of free radicals are considered central mediators of secondary injury, deteriorating neurological impairment in acute SCIs [2]. Also, due to the wide range of clinical symptoms arising from SCIs, the importance of individualized management according to medical history and existing comorbidities of each patient is underlined [3]. In acute SCIs, motor and sensory functions are mainly affected, resulting in the need for proper treatment that requires in-depth knowledge of both the anatomy and function of the spinal column and spinal cord, including neural pathways [3]. Oxidative stress, inflammation, ischemia, apoptosis, and locomotor dysfunction result as consequences of an acute SCI, leading to secondary neuronal damage [4]. Neuroprotective, immunomodulatory, and neuro-regenerative therapies seem to be of importance to treat SCIs [4]. According to this study, the use of glucocorticoids such as methylprednisolone and dexamethasone is characterized by limitations for SCI treatment [4]. The need to combine the use of neuroprotective drugs along with cellular transplantation or biomaterials, in order to combat multiple overlapping pathological pathways occurring in this type of traumatic injuries, is also reported [4]. Focusing on modern imaging methods like MDCT and MRI to diagnose and classify SCIs, it seems that MDCT is the preferred imaging modality for bone damage, while MRI is preferred for soft tissue damage [5]. The early identification of spinal cord edema or transection is also vital to predict long-term neurological prognosis in these patients [5].

Types of pain

Concerning the perception of pain, this is a complex, multidimensional experience produced by widely distributed neural networks in the brain, rather than just a direct response to tissue damage [6]. It seems that past experiences of pain and stress interact to shape how pain is perceived, leading to persistent changes in the central nervous system that can outlast initial injuries and lead to chronic pain [6].

Additionally, it appears that pain’s perception is driven by dynamic, plastic interactions between peripheral nociceptors and central nervous system pathways [7]. These molecular changes convert acute injury signals into manifestations of chronic pain, thus underlining that the understanding of these maladaptive changes would eventually lead to the prevention or reversal of pain chronicity [7]. The types of pain are also presented as follows: (i) nociceptive pain, which functions as an early warning system when something happens outside the normal limits of the human body's functioning; (ii) inflammatory pain, which is involved in healing processes; (iii) neuropathic pain, which comes from structural damage located in the nervous system; and (iv) dysfunctional pain, for the manifestation of which direct injury or damage to the tissue is not required [8]. Also, with regard to the sensitization for the perception of pain, this is distinguished into peripheral type (involving the peripheral nerves) and central type (involving the brain and spinal cord) [8].

Furthermore, the issue of neuromodulation is also important in NP, where various modern techniques can replace the alternative use of opioids, especially when it comes to chronic NP [9]. Spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS), along with deep brain stimulation, are considered to be the primary methods for modifying neurological function [9]. The chronic pain pathways are interrupted through the activation of large, myelinated A-beta sensory fibers, in order to close the spinal dorsal horn gate by enhancing synaptic inhibition and weakening central sensitization [9]. Neuropathic pain is considered to result from a disease or functional disorder located in the somatosensory nervous system and is classified

into peripheral and central neuropathic pain, thus facilitating either diagnosis or treatment approaches [13]. Causes of peripheral NP are postherpetic neuralgia, painful polyneuropathy, peripheral nerve injury, and painful radiculopathy, while causes of central NP include spinal cord or brain injury, post-stroke pain, and multiple sclerosis [13]. Peripheral and central sensitization seems to be crucial for the development of NP [14]. The sensitization of nociceptive pathways has an important role in the emergence of NP [14]. The latter indicate changes in ion channels, activation of immune cells, glial-derived mediators, as well as epigenetic regulation [14]. Therapeutic approaches include medication acting on α2δ subunits of calcium channels, sodium channels, and descending modulatory inhibitory pathways [14]. In the relevant literature, it is also reported that the physical symptoms of pain arise from the interaction between biological, psychological, and social parameters, underlining the necessity of a personalized multimodal therapeutic approach [15]. Pharmaceutical therapy, psychotherapy, integrative treatment, and invasive approaches can be included in an individualized multimodal procedure, the latter being tailored individually for each patient depending on their medical history and the comorbidities they have [15]. It appears that emotional support and a state of good health in general influence the pain-induced neuroplastic changes by promoting healing processes and reducing the intensity of chronic pain [15].

Pain management

The biopsychosocial approach, associated with a multidisciplinary curative approach to manage chronic pain of non-malignant etiology, is further supported by another study [16]. Despite the existence of pain, it also appears to be important for the quality of life of such a patient to manage his pain by undertaking activities in his life [16]. Focusing on lumbar NP attributed to lumbar disc herniation, despite the fact that this type of pain is not directly related to SCI, it has been found that in these patients, although surgical treatment six weeks postoperatively was accompanied by relief of clinical symptoms compared to conservative therapy, surgery was not shown to be better either at one or two years postoperatively [22].

The management of chronic back and leg pain has also been investigated in the relevant literature [23]. It has been found that 10 kHz spinal cord stimulation (10 kHz SCS) provides long-term relief for chronic back and leg pain, significantly reducing opioid use and improving QoL without causing paresthesia [23]. The study showed high response rates (60%-80%), making it an effective treatment option, even for patients unsuitable for surgery [23]. Also, as for the use of neurosurgical ablative procedures to manage pain, it seems that their role is narrow for chronic pain of non-malignant etiology [24]. The outcomes from the spinothalamic tract, dorsal column's visceral pathway, and the anterior cingulate cortex were examined, showing that these techniques are more useful for persistent cancer-related pain than for chronic pain of other etiology [24].

Pharmaceutical treatment of neuropathic pain attributed to spinal cord injuries

Gabapentin (GP) and pregabalin (PB) were studied to examine their efficacy for the management of NP in SCI [25]. Pregabalin was found to be more effective than gabapentin, although pregabalin was associated with more side effects compared to gabapentin [25]. Also, while for pregabalin visual analog scale (VAS) scores were significantly reduced, for gabapentin this was achieved at a maximum dose of 3600 mg/day [25]. A more recent study examined parameters such as the average pain intensity after treatment and the proportion of patients who discontinued treatment because of adverse effects, concerning the management of NP related to SCI [26]. The medications administered were pregabalin, gabapentin, carbamazepine, amitriptyline, and placebo [26]. The efficacy order, based on the average NP intensity following treatment, was, in decreasing order, pregabalin, gabapentin, amitriptyline, carbamazepine, and placebo; while, concerning the adverse effects, the order in decreasing order was pregabalin, amitriptyline, carbamazepine, gabapentin, and placebo [26]. In the same study, it was also shown that pregabalin was the most efficacious and gabapentin the safest medication to treat NP related to SCI [26]. Moreover, antidepressants (such as amitriptyline and trazodone), anticonvulsants (including gabapentin, pregabalin, lamotrigine, valproic acid), and mexiletine were studied for their efficacy in managing NP that emerged after SCI [27]. Gabapentin, pregabalin, and amitriptyline significantly reduce NP after SCI [27]. Cannabinoids are recommended to treat NP of central etiology, while opioids and SNRIs appear to be effective in managing peripheral NP related to SCI [27].

The efficacy of pharmaceutical treatment to manage chronic NP related to SCI has been further examined in the relevant literature by another study, focusing on the administration of pregabalin, gabapentin, TCAs, and cannabinoids [28]. Pharmaceutical treatment was distinguished between direct clinical evidence (Grade A) for populations in which the occurrence of chronic NP was related to SCI, and indirect clinical evidence related to other neuropathic conditions [28]. Pregabalin's direct clinical evidence (Grade A) comes from randomized controlled trials (RCTs) conducted exclusively in patients with SCI, confirming its efficacy in treating central NP [28]. Gabapentin's direct clinical evidence, although more limited (Grade B), results from cohorts also strictly performed in patients with SCI [28]. However, gabapentin presents direct clinical evidence (grade A) because of its efficacy in managing peripheral NP [28]. The same study highlights the use of TCAs as direct clinical evidence (grade B) for chronic NP related to SCI being associated with depression, as well as direct clinical evidence (grade A) for other NP conditions, particularly in patients presenting depressive symptoms [28]. Cannabinoids can be administered in central NP conditions other than SCI [28].

Also, clinical assessment of the type of pain in patients with SCI seems to be of great importance in order to strictly select the appropriate treatment [17]. Amitriptyline, gabapentin, and pregabalin were identified as first-choice options to manage NP related to SCI [17]. In the same study, the use of opioids was controversial because of either side effects or the route of their administration [17]. As for the topical use of capsaicin, lidocaine, and intradermal administration of BTX-A, the evidence appears limited and needs further investigation [17].

Except for neuropathic pain, parameters also related to SCI, such as anxiety, depression, and sleep disorders, were examined [29]. The effectiveness of pregabalin and gabapentin was studied [29]. Pregabalin was found to be explicitly effective regarding all the aforementioned variables in SCI [29]. Conversely, although gabapentin was also found to be significantly effective in reducing NP in SCI, statistical significance was not established concerning its action on anxiety, depression, and sleep disturbances [29]. Furthermore, despite the fact that no statistically significant difference in side effects was recorded between the two drugs used, drowsiness, somnolence, and dizziness were reported for both medications [29].

The management of NP as well as mental disorders, including sleep disturbances, caused by traumatic SCI, was also examined in the relevant literature by another study investigating the efficacy of 11 administered medications such as BTX-A, pregabalin, gabapentin, ketamine, lamotrigine, amitriptyline, duloxetine, tramadol, carbamazepine, levetiracetam, and cannabinoids, alongside a placebo [30]. Botulinum toxin type A (BTX-A) has been shown to be the most effective treatment for NP four weeks after SCI, followed by gabapentin, pregabalin, and amitriptyline [30]. Regarding mental and sleep disturbances, which might be attributed to NP of a central etiology, gabapentin, BTX-A, and pregabalin were proven to be the most effective in regulating these specific disorders [30]. Also, gabapentin and lamotrigine showed the fewest adverse effects compared to tramadol, the latter being associated with serious side effects [30]. The effect of estrogen administration on the alleviation of NP following SCI has also been studied in an international, relevant experimental study with rats [31]. According to this study, the administration of 17β-estradiol suppresses neuroinflammation along with glial cell activation in the spinal cord [31]. As a result, both mechanical allodynia and thermal hyperalgesia were found to be significantly reduced, while both microglia and astrocyte activation in the lamina I and II of the L4-L5 dorsal horn were also inhibited [31]. Furthermore, the study reports that the analgesic effect due to the administration of 17β-estradiol was attributed to the activation of estrogen receptors, which are expressed in dorsal horn neurons [31]. The role of the applied topical analgesics to treat NP related to SCI in patients aged 49-72 years was also studied [32]. According to this study, baclofen, ketamine, lidocaine, capsaicin, and isosorbide dinitrate were considered topical analgesics, showing an over time decrease in NP after SCI [32]. Also, in the same study, the use of phenytoin, amitriptyline, baclofen, ketamine, or loperamide, as topical agents, recorded a decrease in pain of at least 3 points on the 11-point numeric rating scale being used in this treatment [32].

In another study, the efficacy of anticonvulsants, antidepressants, anesthetics, BTX-A, and opioids was examined concerning the management of NP after SCI [33]. In proportion to the percentage of patients who experienced a reduction in the intensity of neuropathic pain of 50% or more from the initial intensity, the efficacy of the drugs used, as recorded in descending order, is as follows: anticonvulsants, anesthetics, antidepressants, BTX-A, opioids, placebo [33]. Also, focusing on the prevalence of side effects, the descending order of safety was presented as follows: antidepressants, BTX-A, anticonvulsants, opioids, and anesthetics [33]. Moreover, of all the drugs used, it seems that anticonvulsants, antidepressants, and BTX-A had good efficacy and safety [33].

Neuromodulation techniques, alternative therapeutic approaches, and combined therapeutic approaches for neuropathic pain due to spinal cord injuries

Neuromodulation Techniques

Moreover, of all the drugs used, it seems that the literature highlights the potential of both invasive and non-invasive neurostimulation interventions for managing neuropathic and phantom limb pain following spinal cord injury (SCI) [34]. Within invasive modalities, deep brain stimulation (DBS) and motor cortex stimulation (MCS) have demonstrated clinical efficiency; however, DBS lacks recorded long-term efficacy, whereas MCS presents a relatively better therapeutic profile accompanied by fewer complications. Among non-invasive approaches, transcranial direct current stimulation (tDCS) applied over the sensory-motor cortex has proven to be a highly safe technique that reduces pain sensation while simultaneously increasing pain thresholds in healthy individuals. Other non-invasive methods evaluated in the same study, such as repetitive transcranial magnetic stimulation (rTMS) and cranial electrotherapy stimulation (CES), yielded mixed outcomes, showing that the analgesic effects of rTMS are typically partial and transient, while CES produces positive results in both SCI-related neuropathic pain and centrally mediated pain syndromes.

Non-invasive brain stimulation techniques (NIBS) were further examined, focusing on the efficacy of parameters such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), when applied to the motor cortex of the brain, in order to manage NP following SCI [35]. No significant difference was found regarding the analgesic effect between rTMS and sham rTMS seven days

after treatment [35]. For a period of two to six weeks after the end of the application of rTMS, a significantly better analgesic result was found for rTMS compared to sham rTMS [35]. Regarding the tDCS technique, recorded results were considered insufficient [35]. In addition, another study found that high-frequency rTMS applied to the primary motor cortex and the left dorsolateral prefrontal cortex significantly decreased NP intensity in SCI, suggesting a promising approach for managing these patients [36].

The efficacy of non-invasive brain stimulation techniques such as rTMS, tDCS, and CES on depression, anxiety levels, and the intensity of the NP related to SCI was further studied [37]. No statistically significant difference was found between active and sham stimulation concerning the reduction of NP after SCI [37]. It should also be reported that for all the applied techniques (rTMS, tDCS, CES), except for the lack of significant analgesic efficacy, no significant improvement in depression was found as well [37]. In the same study, a statistically significant decrease in anxiety was recorded immediately following treatment only for the CES technique [37].

The efficacy of spinal cord stimulation is further supported by indirect evidence from general NP management. Specifically, the narrative review by Bonomo et al. highlighted high-frequency stimulation (10,000 Hz) as an effective, paresthesia-free therapeutic option for NP [38]. Although the authors' findings primarily concern lumbar NP, they note that burst stimulation offers the following two distinct advantages: including the capacity to target a larger number of nerve fibers in the posterior columns of the spinal cord and the complete elimination of stimulation-induced paresthesia [38].

The effects of TMS techniques regarding their benefits in managing NP following SCI were also examined by another study, although their effectiveness varied [39]. Intermittent theta burst stimulation (iTBS), rTMS, and a combination of iTBS and rTMS were randomly allocated to three groups of patients with NP after SCI [39]. It has been shown that all three applied TMS techniques significantly reduced neuropathic pain, depression, and sleep disturbances after four weeks of treatment [39]. In the same study, focusing on pain relief, it should be reported that although all three techniques manifested a significant reduction in NP intensity four weeks after the application, the combination of iTBS + rTMS was significantly better at reducing NP after SCI compared to iTBS alone [39].

Alternative Therapeutic Approaches

The role of acupuncture has also been reported in the relevant literature in treating NP after SCI [40]. Pain severity, present pain intensity, and the pain region index were found to be significantly decreased after the application of acupuncture in these patients [40]. Furthermore, electroacupuncture was recorded to be more efficient than standard manual acupuncture to manage NP related to SCI [40].

Electroacupuncture, non-invasive brain stimulation techniques (rTMS, tDCS), and pharmaceutical approaches were further examined in managing NP after SCI [41]. The message of the study is that the management of this type of patient constitutes a multimodal and targeted molecular therapeutic approach [41]. Due to the lack of invasiveness and minimal adverse effects, it seems that electroacupuncture can be a very effective method for treating NP due to SCI [41]. Moreover, pharmaceutical management for NP related to SCI includes analgesic, anticonvulsant, antidepressant, and antiepileptic medication, although either suboptimal therapeutic responses or side effects have been recorded [41]. When medication fails or causes unwanted side effects that cannot be controlled, then the application of non-invasive brain stimulation techniques like rTMS and tDCS is indicated [41]. Repetitive Transcranial Magnetic Stimulation (rTMS) and tDCS stimulate the cerebral cortex by also modifying synaptic activity, with rTMS being typically applied over the primary motor cortex at high frequencies and tDCS being utilized in multimodal approaches for optimal pain reduction [41]. This study proposes the simultaneous application of pharmaceutical and non-pharmacological therapeutic methods to enhance treatment of NP related to SCI [41].

Based on the study by Ge et al., the three most effective interventions among 17 for reducing SCI-related NP were rTMS, acupuncture, and intermittent theta burst stimulation (iTBS), with iTBS showing higher efficacy [42]. In the same study, according to Surface Under the Cumulative Ranking Curve (SUCRA), acupuncture offers significant relief from NP, with its therapeutic potential being recorded as slightly lower than that of iTBS, while the rTMS technique follows (iTBS (88.8%) > acupuncture (88.6%) > rTMS (84.9%) [42].

The role of virtual reality (VR) in managing NP attributed to SCI was also examined in the relevant literature [43]. According to this study, the use of VR to treat NP in these patients was divided into the following four different approaches: (i) virtual walking, (ii) VR-augmented training, (iii) virtual illusion, and (iv) VR hypnosis [43]. Although all the aforementioned VR approaches showed some analgesic effect, their clinical significance remained unclear; combined treatment including virtual walking and tDCS was found to be most effective [43].

Combined Therapeutic Approaches

The contribution of pharmaceutical, minimally invasive, neurostimulation, and physiotherapeutic-alternative interventions to treat NP after SCI was also investigated in another study [44]. An overall

approach of this study showed that specific medications, electrical stimulation, and physical therapies significantly reduced pain intensity [44]. Gabapentin and pregabalin were proven to be effective in managing chronic NP after SCI, while pregabalin appears to further decrease both anxiety and sleep disorders [44]. In the same study, mirogabalin, a new drug in the treatment of chronic NP following SCI, appears to show good results, although further research is required [44]. Additionally, BTX-A, lidocaine, ketamine, and intrathecal baclofen significantly reduced NP intensity, while rTMS and tDCS techniques also reduced NP [44]. Physiotherapy and alternative treatments also seem to relieve pain, with TENS manifesting the greatest reduction of NP intensity in these patients [44].

Another study examined pregabalin, gabapentin, intrathecal baclofen, tDCS, and TENS, showing positive results in managing NP related to SCI, although further research is needed [45]. In addition, approaches like antidepressants, tramadol, hypnosis-biofeedback, and meditation-mental imagery did not show a clear benefit [45].

Moreover, regarding the pharmacological treatment of NP after SCI, medications like opioids, anticonvulsants, and antidepressants manifested limited efficacy, accompanied by adverse events and safety issues, thus possibly deteriorating existing functional deficits, mainly affecting gastrointestinal motility and respiration [46]. Furthermore, the same study identified non-pharmaceutical approaches to manage NP following SCI, including physical exercise, acupuncture, hyper- or hypothermia treatment, psychological treatment (such as meditation and cognitive behavioral therapy), and dietary interventions focused on ketogenic and anti-inflammatory diets [46]. It appears that the therapeutic approach for NP after SCI should be multidisciplinary and individualized based on the medical history of each patient [46].

The combination of transcranial direct current stimulation (tDCS) with visual illusion therapy in NP related to SCI was also examined in the relevant literature [47]. This study showed significant analgesic effects, as well as improvements in sleep, mood, and QoL, in these patients [47]. Although the study recorded a reduction in NP intensity, the analysis of sensory phenotype pain profiles in the same study had no prognostic value for the analgesic results attributed to combined tDCS and visual illusion treatment [47].

Discussion

As the aim of this article was to synthesize and critically evaluate the existing evidence regarding the treatment of NP associated with traumatic SCI, pathological entities that present with similar clinical symptoms but are not associated with SCI should be differentiated. Differential diagnosis of pathological entities other than SCI, with similar clinical symptoms including the occurrence of NP, is presented as follows: spinal stenosis, cardiogenic shock, hypovolemic shock, septic shock, malignancy, disk herniation, epidural hematoma, spinal infection [1].

It is also important for clinicians, regarding the holistic approach to patients experiencing NP due to SCI, to note that in patients with spinal shock resulting from traumatic SCI, treatment aimed at both preventing deep vein thrombosis and avoiding the development of pressure ulcers should be initiated immediately - even as a precautionary measure - while bowel and bladder function must simultaneously be managed [1]. Moreover, traumatic SCI can result in complete immobility and consequent venous stasis, leading to blood coagulation disorders. This gives rise to a state of hypercoagulability, which significantly increases the risk of deep vein thrombosis and potential pulmonary embolism [65,66]. Regarding the pharmacological treatment to be administered for the prevention of deep vein thrombosis (DVT) and potential pulmonary embolism (PE) in patients with acute traumatic spinal cord injury, the administration of low-molecular-weight heparin (LMWH) within 72 hours of the injury is recommended. Based on the relevant international literature, the duration of prophylactic low-molecular-weight heparin administration for deep vein thrombosis management in these patients is approximately eight weeks for one-third of the cohort and 12 weeks for another third, while for the remaining third, the continuation of treatment depends on each patient's individual condition [67]. Also, it should be reported that in SCI patients, according to the type of neurological dysfunction (presence or absence of motor impairment and walking ability), the administration of a low dose of low molecular weight heparins (LMWH) can be recommended for approximately six months following injury, while mechanical methods (compression stockings, intermittent pneumatic compression) are also indicated [68]. Regarding the management of ulcers developing in patients with traumatic SCI due to pressure exerted on their bodies from prolonged bed rest, it is recommended to turn and reposition with the appropriate log-roll technique every 2 hours [1].

Focusing on bowel function in patients with acute SCI, the usefulness of parameters like rectal stimulation, stool softeners, suppositories, bulk formers, and enemas has been discussed in the relevant literature, in an attempt to promote about 1 (one) bowel movement every other day [58]. Bladder catheterization is also necessary because urinary retention frequently occurs in patients with acute SCI, with intermittent catheterization at scheduled intervals preferred due to reduced risk of catheter-associated urinary tract infections [1]. Provided that normal bladder function is restored, the frequency of scheduled catheterizations can be diminished, while, at the same time, the use of gastroprotection with proton-pump inhibitors for four weeks is indicated for these specific patients [58,69].

Subsequently, regarding the pharmacological management of NP associated with traumatic SCI, the

effectiveness of pregabalin and gabapentin, focusing on the satisfactory relief of NP related to SCI, has been discussed in several studies in the relevant literature [17,25,27,28]. Additional medications such as amitriptyline, cannabinoids, opioids, and SNRIs can be further proposed in order to manage this type of pain [17,27]. As for the effectiveness of gabapentinoids, concerning the issue under investigation, it should be clarified that pregabalin, except for the reduction of NP intensity, also induces improvement in sleep disorders, anxiety, and depression, with gabapentin being particularly effective in terms of analgesia [29]. Furthermore, pregabalin and gabapentin have not shown significant differences concerning the occurrence of side effects [17,29]. Nevertheless, Tong et al. reported that between pregabalin and gabapentin, pregabalin was proved to be more effective in relieving NP, while gabapentin was accompanied by fewer adverse effects [26]. A more recent study found gabapentinoids, TCAs, and SNRIs to be the most effective medications for treating NP, although for trigeminal neuralgia, carbamazepine was considered the most appropriate [70]. Opioids and cannabinoids are also recommended to treat NP due to SCI, although both are accompanied by side effects and contraindications, thus limiting their everyday clinical use [28]. Based on the study by Fornasari, opioids are recommended as second- and third-line medications to manage NP due to their adverse side effect profile, including addiction, diversion, as well as abuse potential [71]. Regarding cannabinoids, nausea, headache, dizziness, sedation, mild neurocognitive impairment, and a "drug high," are registered as common side effects, given that severe adverse events appear to be rare [70]. Overall, according to the study by Ling et al., in addition to pregabalin and gabapentin, BTX-A exhibits better short-term analgesic activity, while all the above medications showed particular benefit in both sleep disorders and psychopathological manifestations [30]. However, in the same study, tramadol was found to be associated with more serious side effects, while carbamazepine, levetiracetam, and cannabinoids were not recommended to treat NP after SCI [30]. Pregabalin and gabapentin are guideline-supported first-line pharmacological options for neuropathic pain after SCI. The CanPain SCI guidelines assign both treatments a high quality-of-evidence rating and a strong recommendation [72]. Nevertheless, their supporting evidence bases differ. Pregabalin has the strongest evidence among first-line treatments for below-level SCI-related neuropathic pain, whereas the gabapentin evidence includes smaller trials with less consistent findings. These guideline ratings do not establish equal comparative effectiveness or guarantee benefit in every patient.

An updated meta-analysis of five randomized controlled trials involving 682 participants found that gabapentinoids, evaluated collectively, reduced average daily pain compared with placebo (mean difference -1.75 on a 0-10 scale; 95% CI: -3.23 to -0.28; p=0.02) [73]. However, this analysis included gabapentin, pregabalin, and mirogabalin, and its pooled findings should not be interpreted as identical efficacy for each medication. Gabapentinoids were also associated with increased risks of somnolence, dizziness, peripheral edema, and blurred vision compared with placebo [73]. Accordingly, treatment should be individualized, with monitoring of pain relief, functional benefit, and tolerability. These medications should not be described as universally effective in patients with SCI-related neuropathic pain.

The administration of 17β-estradiol, which has significantly reduced mechanical allodynia and thermal hyperalgesia in patients with SCI-induced NP, has also been discussed in the relevant literature [31]. It seems that the latter is attributed to the inhibition of the activation of neuroinflammatory microglia and astrocytes located in the spinal cord dorsal horn [31]. The therapeutic effect of 17-β estradiol administration is due to suppression of key neuroinflammatory pathways, including reduced MAPK signaling in microglia and inhibition of JNK phosphorylation in astrocytes [31]. Specifically, the levels of p-p38MAPK and p-ERK triggered in microglia, and p-JNK triggered in astrocytes, were found to be significantly decreased by 17β-estradiol [31]. Additionally, in another study, the use of local analgesics (baclofen, ketamine, lidocaine, capsaicin, and isosorbide dinitrate) may be beneficial in the treatment of SCI-induced NP, as a pain reduction of ⩾3 points on the NRS was observed [32]. It seems that topical analgesics, when applied locally to the skin and superficial nerve endings, target peripheral nociceptive mechanisms, with the aim of suppressing abnormal neuronal signaling and ion channels associated with chronic pain [32]. Specifically, local analgesics like lidocaine act directly at the application site to block voltage-gated sodium channels and prevent abnormal discharges, while other compounds reduce peripheral sensitization and minimize systemic side effects [32]. Furthermore, Mei et al. identify anticonvulsants, specifically gabapentinoids like pregabalin and gabapentin, as the optimal therapeutic choice for NP related to SCI because they offer a superior balance of efficacy and tolerability [33]. In the same study, although anesthetics showed high short-term efficacy, they present significant safety and discontinuation risks, whereas alternatives such as antidepressants and BTX-A offer promising localized or dual-action benefits [33].

Moreover, among invasive and non-invasive brain stimulation techniques presented in the relevant literature as potentially beneficial for treating post-SCI NP, DBS demonstrates low long-term efficacy, although it reduces phantom limb pain; epidural MCS is considered more promising with fewer complications compared to DBS [34]. Regarding rTMS, tDCS, and CES techniques, early and transient analgesic effects are mainly reported [34]. Specifically, rTMS partially and transiently decreases chronic pain; tDCS, when applied over the sensorimotor cortex, reduces pain sensation by simultaneously raising the neuropathic pain threshold; and CES has also been shown to effectively manage NP due to SCI [34]. Although non-invasive neuromodulation appears to be safe alternative to manage NP after SCI, nevertheless, further research is need on this issue, in order to achieve better and more targeted results for the specific patients. Another study examined rTMS and found significant analgesic benefit in medium-term follow-up (two to six weeks), rather than immediately after intervention; while for tDCS, reported data were

insufficient [35]. A possible explanation for the finding for the rTMS technique in the study of Shen et al. could be based on physiological concepts of neuroplasticity, maladaptive cortical reorganization, and cumulative neuromodulation, driving the delayed, medium-term (two to six weeks) analgesic efficacy of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) for NP due to SCI [35]. Specifically, focusing on the physiological concepts of neuroplasticity, it has been found that multisession rTMS applied daily for two weeks significantly mitigated NP after SCI by suppressing hyperexcitability in the primary motor cortex (M1) and premotor cortex (PMC), thus providing direct evidence for the accumulation of the analgesic benefits over a multi-week timeline [74]. The role of maladaptive cortical reorganization influencing the occurrence of NP resulting from SCI is also important. It seems that, due to trauma, sensory signaling from the spinal cord is disrupted, with the brain's somatosensory and motor cortices simultaneously undergoing abnormal restructuring, which is characterized by local hyperactivity, loss of intracortical GABAergic inhibition, as well as imbalanced functional connectivity between the cortex and subcortical structures like the thalamus. Concerning the aforementioned local hyperactivity, it has been shown that the degree of maladaptive cortical reorganization is directly related to pain intensity, suggesting that deafferented areas exhibit aberrant, hyperactive processing if triggered [75]. Focusing on the same issue of maladaptive cortical reorganization and local hyperactivity, structural degeneration along with altered resting-state activity simultaneously occur over a broader pain network, including the primary motor cortex as well as the primary somatosensory cortex, thus producing a baseline state of central hyperexcitability [76]. Also, the loss of intracortical GABAergic inhibition attributed to SCI is supported in the relevant literature by three studies [77-79]. It appears that, for these patients, in order to create the most favorable therapeutic design, the degree of the alteration regarding the balance between excitatory and inhibitory networks is required to be assessed individually for each patient and at different times following injury, while a very good knowledge is simultaneously demanded for both the standardization of assessment methods and molecular pathways being responsible for the occurrence of the altered cortical dysfunctions in patients after SCI [77]. In addition, the impact of glutamate excitotoxicity regarding the pathophysiology of the secondary injury cascade as a result of traumatic brain injury (TBI) and SCI has been discussed in the relevant literature [78]. As glutamate-mediated excitotoxicity is considered a major driver of secondary tissue damage in patients with traumatic SCI [78], this demonstrates that excitotoxicity causes significant loss of GABAergic cells, accompanied by a reduction in the expression of the enzyme glutamate decarboxylase (GAD), which is responsible for the synthesis of gamma-aminobutyric acid (GABA), thereby evidencing the consequent physical decline in functional inhibition [79]. Regarding the imbalanced thalamocortical functional connectivity, it should be reported that NP related to SCI is strongly associated with structural, functional, and neurochemical alterations within the thalamus [80]. These alterations include a localized reduction of GABA, as well as significant reductions in thalamic N-acetylaspartate, gamma-aminobutyric acid content, and altered blood flow in the region of the thalamic reticular nucleus [80]. These specific abnormalities are driven by the presence of NP by itself, rather than being a direct baseline consequence of SCI [80]. The above biochemical and structural deficits disrupt central processing by contributing to thalamocortical dysrhythmia and imbalanced connectivity, mainly observed in patients experiencing central NP [80]. Positive results have also been recorded for the rTMS technique when applied to the primary motor cortex and the left dorsolateral prefrontal cortex, presenting a significant reduction in the intensity of NP [36]. Contrary to the studies of Shen et al. [35] and Saleh et al. [36], the study by Yu et al. concludes that NIBS techniques overall do not significantly reduce NP and depression due to SCI, except for the CES technique appearing to provide a direct benefit in anxiety management [37]. Furthermore, although the evidence is indirect due to lumbar neuropathic pain rather than specifically SCI-related NP, the study by Bonomo et al. focuses on spinal stimulation, as two innovative techniques (high-frequency stimulation and burst stimulation in the spinal cord) are examined, with positive results in the management of the emerging NP [38]. It is suggested that burst stimulation and high-frequency (HF) stimulation utilize sub-perception therapy to eliminate the uncomfortable tingling sensation, or paresthesia, induced by conventional tonic stimulation [38]. Also, while conventional stimulation continuously activates large-diameter fibers to mask pain, HF and burst modalities regulate neural transmission below the conscious sensory threshold through localized conduction blocks and multi-pathway modulation [38]. Another study compared the efficacy of TMS techniques such as iTBS, rTMS, and their combination, concluding that they effectively relieved NP, though to different degrees, and also showing positive results for depression and pain-related sleep disorders [39]. Overall, there is a consensus in some studies that neuromodulation is promising, but disagreement is noted regarding the extent of the analgesic benefits, while the need for further larger and high-quality comparative studies is underlined [34-39].

It should also be reported that, regarding the non-pharmacological interventions, the effect of acupuncture to treat NP related to SCI, which is accompanied by positive results, has been discussed in the relevant literature [40,41], particularly for patients who cannot undergo conventional medical treatment [41]. Additionally, the literature discusses new pharmaceutical preparations, such as natural compounds and antisense oligonucleotides, with positive results and few side effects [41]. Acupuncture is mainly indicated to manage back pain, either chronic or acute, knee pain as a result of osteoarthritis, headaches, myofascial pain, chemotherapy-induced peripheral neuropathy, inflammatory bowel disease, and hypertension [81-87]. Moreover, acupuncture is not indicated for patients with an automated implantable cardioverter defibrillator (AICD), as well as for patients suffering from or being predisposed to manifest psychosis or delusions [88]. Pregnancy, anticoagulant therapy, or a medical history of bleeding disorders are not considered contraindications to acupuncture [88,89]. Furthermore, Ge et al. reported in their study that non-pharmacological rehabilitation interventions, such as iTBS, rTMS, and acupuncture, generally showed

no significant differences regarding the incidence of adverse events compared either to control or sham groups [42]. In the same study, minor localized side effects were limited to mild, transient headaches, scalp discomfort, or localized tingling with neuromodulation, as well as minor bruising or soreness at needle sites with acupuncture [42]. The role of virtual reality in decreasing NP related to SCI, especially when combined with the tDCS technique, has also been discussed in the relevant literature [43]. A possible explanation for the latter is that VR combined with tDCS reduces NP attributed to SCI due to a synergistic two-pronged attack against maladaptive neuroplasticity [90,91]. Overall, the studies agree that NP after SCI is difficult to manage, while also highlighting the importance of a combined therapeutic approach; however, they differ regarding the choice of the most appropriate one [40-43].

Additionally, according to the study by Koukoulithras et al., focusing on both pharmaceutical and non-pharmaceutical therapeutic approaches to manage chronic pain following SCI, particular emphasis has been given to the administration of gabapentin and pregabalin, while benefits are also reported for the application of tDCS, rTMS, TENS, and VR techniques [44]. It has been concluded that multimodal pain management should be tailored by physicians based on individual patient characteristics, while the need for larger-scale clinical trials is highlighted [44]. Focusing on the same study, gabapentin, pregabalin, and transcutaneous electrical nerve stimulation (TENS) provide notable pain reduction, whereas several traditional anticonvulsants and standard antidepressants show limited overall analgesic efficacy [44]. In particular, although both gabapentin and pregabalin serve as effective first-line treatments for managing neuropathic pain after SCI, the review establishes no statistically significant difference in analgesic efficacy between the two drugs [44].

Also, both pregabalin and gabapentin have demonstrated analgesic benefit in patients with SCI-related neuropathic pain. However, evidence of benefit for each drug does not establish the superiority of one over the other. In their systematic review and meta-analysis, Davari et al. reported no statistically significant difference in analgesic efficacy between pregabalin and gabapentin (mean difference -0.37; 95% confidence interval -1.67 to 0.93) [29]. The confidence interval includes zero, and its width indicates uncertainty regarding the comparative effect. This finding does not demonstrate equivalence or establish clinically meaningful superiority of either drug. Koukoulithras et al. provide a broader overview of pharmacological and non-pharmacological interventions after SCI, but their review is not used here as statistical evidence of comparative superiority between these two medications [44].

Moreover, the relevant literature by Allison et al. focuses not on the severity of NP after SCI, but on its impact on the patient's daily functioning [45]. The most promising findings from this study concern the administration of pregabalin, gabapentin, and intrathecal baclofen, as well as the application of tDCS, which showed the most reliable efficacy in reducing daily functional disruption [45]. Also, with reference to the same study, the administration of antidepressants, the application of rTMS, and certain psychological techniques such as hypnosis-biofeedback and meditation-mental imagery did not indicate a consistent benefit in these patients [45]. Furthermore, Eller et al. report that there is no single treatment universally effective to treat NP related to SCI, while at the same time non-pharmacological and individualized multidisciplinary approaches such as exercise, CBT, nutritional interventions, and meditation are also underlined [46]. The role of nutrition, as an anti-inflammatory and neuroprotective dietary approach, is also significant in the holistic management of neuropathic pain associated with traumatic SCI, and has been discussed in the relevant international literature. The importance of the contribution of proper nutrition is demonstrated by studies highlighting its role in both the prevention and management of skin lesions and abnormalities in patients with SCI [92]. For patients with traumatic SCI, daily energy intake should be adjusted to match their daily energy expenditure, which is reduced in this population [92]. It is also important that these patients consume proteins that are easily digestible yet rich in necessary amino acids and omega-3 fatty acids, while ensuring adequate hydration [92]. Dietary choices should focus on anti-inflammatory, high-fiber foods; fish and fermented foods are also recommended, as they help regulate gut microbiota and reduce the formation of advanced glycation end-products (AGEs) through appropriate food selection and cooking methods [92].

The usefulness of omega-3 fatty acids has also been indicated regarding the treatment of patients with SCI [93]. Dietary intake of omega-3 fatty acids can improve SCI recuperation due to their anti-inflammatory, anti-oxidative, neurotrophic, and membrane-integrity-preserving properties [93]. The above functions of omega-3 fatty acids are mainly mediated via the activation of G protein-coupled receptor 120 (GPR120), commonly known as the fish oil-specific receptor [93].

The impact of vitamin D deficiency as an independent predictor of neuropathic pain has also been reported in the literature. Specifically, vitamin D presents both neuroprotective and immunomodulatory effects that may influence pain perception [94]. Regarding the functional link between vitamin D and neuropathic pain, this link appears to be attributed to potential mechanisms such as modulation of neuroinflammation, regulation of neuronal excitability, and influence on neurotransmitter pathways [94]. Moreover, the role of vitamin D deficiency as a highly prevalent and strong independent predictor of neuropathic pain, particularly in individuals with chronic SCI, has been reported in the literature, suggesting its potential therapeutic administration to manage NP related to SCI [95]. Additionally, the importance and necessity for nutritional care in adults presenting with SCI and disorders with pressure injuries is further supported [96]. It seems that nutritional care in patients with SCI should be tailored separately for each patient, in an

attempt to prevent pressure injury by simultaneously managing adults with SCI and disorders [96]. It appears that according to this study, nutritional care in this type of patients should be based in parameters such as: (i) scarcity of tailored guidance (taking into account metabolic shifts and body composition changes post-injury, for each patient separately), (ii) paradoxical malnutrition risks (overlapping risks of undernutrition {deficiencies impairing wound healing}, and overnutrition/neurogenic obesity {promoting systemic inflammation by elevating pressure injury risk}), (iii) need for standardization focusing on nutritional assessment tools, monitoring protocols, as well as precision of macro- or micronutrient thresholds for wound care, (iv) call for action based on consensus-driven, evidence-based, and standardized clinical frameworks [96].

Also, Soler et al. support that combining transcranial direct current stimulation with visual illusion yields positive results in neuropathic pain relief in patients with SCI, regardless of each patient's pain profile [47]. It seems that the latter is based on both synergistic neuromodulation and universal central maladaptive plasticity [91]. Overall, the four articles suggest a combined therapeutic approach but differ on which method is most appropriate [44-47].

Conclusions

Neuropathic pain is characterized by chronicity and resistance to treatment. There is no single therapeutic intervention sufficient for its management, which necessitates an individualized and combined approach depending on the patient. Pharmacological treatment for neuropathic pain related to spinal cord injury is mainly based on the administration of anticonvulsant medications like pregabalin and gabapentin, as well as tricyclic antidepressants such as amitriptyline. However, although the aforementioned drugs are frequently listed together regarding generic neuropathic pain guidelines, it should be reported that their specific evidence base, along with their recorded effectiveness for neuropathic pain attributed to spinal cord injury, differs significantly. Specifically, pregabalin, considered the first-line treatment according to randomized controlled trials (RCTs), has higher bioavailability and a more predictable dose-response than gabapentin. Also, gabapentin, as a second-line treatment, is characterized by moderate to strong evidence, being effective although often ranks slightly below pregabalin concerning both speed and depth of neuropathic pain due to spinal cord injury. In addition, gabapentin scores appear to be better in terms of patients' safety profiles or lower treatment discontinuation rates. Amitriptyline, presenting low to moderate evidence, is suggested as a strong alternative when gabapentinoids fail, or if sleep disorders and depression are concomitant factors. At the same time, non-pharmacological interventions such as physiotherapy, psychological support, neurostimulation, and nutrition also appear to contribute positively to the overall management of NP. Further research is necessary to develop more targeted and effective therapeutic interventions.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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References

1. Ziu E, Weisbrod LJ, Mesfin FB: Spinal shock. StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL; 2024.
2. Sekhon LH, Fehlings MG: Epidemiology, demographics, and pathophysiology of acute spinal cord injury . Spine (Phila Pa 1976). 2001, 26:2-12. 10.1097/00007632-200112151-00002
3. Margetis K, Das JM, Emmady PD: Spinal cord injuries . StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL; 2025.
4. Anjum A, Yazid MD, Daud MF, et al.: Spinal cord injury: pathophysiology, multimolecular interactions, and underlying recovery mechanisms. Int J Mol Sci. 2020, 21: 10.3390/ijms21207533
5. van Den Hauwe L, Sundgren PC, Flanders AE: Spinal trauma and spinal cord injury (SCI) . Diseases of the Brain, Head and Neck, Spine 2020-2023: Diagnostic Imaging. Hodler J, Kubik-Huch RA, von Schulthess GK (ed): Springer, Cham, Switzerland; 2020. 231-40. 10.1007/978-3-030-38490-6_19
6. Loeser JD, Melzack R: Pain: an overview . Lancet. 1999, 353:1607-9. 10.1016/S0140-6736(99)01311-2
7. Basbaum AI, Bautista DM, Scherrer G, Julius D: Cellular and molecular mechanisms of pain . Cell. 2009, 139:267-84. 10.1016/j.cell.2009.09.028
8. Woolf CJ: What is this thing called pain? . J Clin Invest. 2010, 120:3742-4.
9. Karcz M, Abd-Elsayed A, Chakravarthy K, et al.: Pathophysiology of pain and mechanisms of neuromodulation: a narrative review (a neuron project). J Pain Res. 2024, 17:3757-90. 10.2147/JPR.S475351
10. An overview of neuropathic pain and its impact . (2026). Accessed: October 9, 2026: https://www.iasp-pain.org/resources/fact-sheets/an-overview-of-neuropathic-pain-and-its-impact/.
11. Finnerup NB, Haroutounian S, Kamerman P, et al.: Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016, 157:1599-606.
12. Pain management education at UCSF . Accessed: October 9, 2026: https://pain.ucsf.edu/.
13. Scholz J, Finnerup NB, Attal N, et al.: The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019, 160:53-9.
14. Finnerup NB, Kuner R, Jensen TS: Neuropathic pain: from mechanisms to treatment . Physiol Rev. 2020, 101:259-301. 10.1152/physrev.00045.2019
15. Cohen SP, Vase L, Hooten WM: Chronic pain: an update on burden, best practices, and new advances . Lancet. 2021, 397:2082-97. 10.1016/S0140-6736(21)00393-7
16. Hylands-White N, Duarte RV, Raphael JH: An overview of treatment approaches for chronic pain management. Rheumatol Int. 2017, 37:29-42. 10.1007/s00296-016-3481-8
17. Hagen EM, Rekand T: Management of neuropathic pain associated with spinal cord injury . Pain Ther. 2015, 4:51-65. 10.1007/s40122-015-0033-y
18. Bielewicz J, Kamieniak M, Szymoniuk M, Litak J, Czyżewski W, Kamieniak P: Diagnosis and management of neuropathic pain in spine diseases. J Clin Med. 2023, 12: 10.3390/jcm12041380
19. Neuropathic pain. (2015). Accessed: October 9, 2026: https://painconcern.org.uk/wp-content/uploads/2019/11/Neuropathic-Pain-v.2-WEB-REFS.pdf.
20. Schug SA, Stannard KJ: Treatment of neuropathic pain . Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists. Fitridge R, Thompson M (ed): University of Adelaide Press, Adelaide, Australia; 2011. 401-22.
21. Marcianò G, Vocca C, Evangelista M, et al.: The pharmacological treatment of chronic pain: from guidelines to daily clinical practice. Pharmaceutics. 2023, 15: 10.3390/pharmaceutics15041165
22. Gugliotta M, da Costa BR, Dabis E, et al.: Surgical versus conservative treatment for lumbar disc herniation: a prospective cohort study. BMJ Open. 2016, 6: 10.1136/bmjopen-2016-012938
23. Luecke T, Edgar D, Huse D: 10 kHz spinal cord stimulation for the treatment of chronic back and/or leg pain: summary of clinical studies. SAGE Open Med. 2020, 8: 10.1177/2050312120951369
24. Allam AK, Michael MB, Shofty B, Viswanathan A: Ablation procedures. Neurosurg Clin N Am. 2022, 33:339-44. 10.1016/j.nec.2022.02.014
25. Tzellos TG, Papazisis G, Amaniti E, Kouvelas D: Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. Eur J Clin Pharmacol. 2008, 64:851-8. 10.1007/s00228-008-0523-5
26. Tong C, Zhengyao Z, Mei L, Dongpo S, Qian H, Fengqun M: Pregabalin and gabapentin in patients with spinal cord injury-related neuropathic pain: a network meta-analysis. Pain Ther. 2021, 10:1497-509. 10.1007/s40122-021-00302-8
27. Baastrup C, Finnerup NB: Pharmacological management of neuropathic pain following spinal cord injury . CNS Drugs. 2008, 22:455-75. 10.2165/00023210-200822060-00002
28. Attal N, Mazaltarine G, Perrouin-Verbe B, Albert T: Chronic neuropathic pain management in spinal cord injury patients. what is the efficacy of pharmacological treatments with a general mode of administration? (Oral, transdermal, intravenous). Ann Phys Rehabil Med. 2009, 52:124-41. 10.1016/j.rehab.2008.12.011
29. Davari M, Amani B, Amani B, Khanijahani A, Akbarzadeh A, Shabestan R: Pregabalin and gabapentin in neuropathic pain management after spinal cord injury: a systematic review and meta-analysis. Korean J Pain. 2020, 33:3-12. 10.3344/kjp.2020.33.1.3
30. Ling HQ, Chen ZH, He L, et al.: Comparative efficacy and safety of 11 drugs as therapies for adults with neuropathic pain after spinal cord injury: a Bayesian network analysis based on 20 randomized controlled trials. Front Neurol. 2022, 13: 10.3389/fneur.2022.818522
31. Lee JY, Choi HY, Ju BG, Yune TY: Estrogen alleviates neuropathic pain induced after spinal cord injury by inhibiting microglia and astrocyte activation. Biochim Biophys Acta Mol Basis Dis. 2018, 1864:2472-80. 10.1016/j.bbadis.2018.04.006
32. Crul TC, Stolwijk-Swüste JM, Kopsky DJ, Visser-Meily JM, Post MW: Neuropathic pain in spinal cord injury:

topical analgesics as a possible treatment. Spinal Cord Ser Cases. 2020, 6: 10.1038/s41394-020-00321-1
33. Mei L, Fengqun M, Zhengyao Z, et al.: Efficacy and safety of different drug treatments in patients with spinal-cord injury-related neuropathic pain: a network meta-analysis. Spinal Cord. 2022, 60:943-53. 10.1038/s41393-022-00804-y
34. Nardone R, Höller Y, Leis S, et al.: Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: a review. J Spinal Cord Med. 2014, 37:19-31. 10.1179/2045772313Y.0000000140
35. Shen Z, Li Z, Ke J, et al.: Effect of non-invasive brain stimulation on neuropathic pain following spinal cord injury: a systematic review and meta-analysis. Medicine (Baltimore). 2020, 99:10.1097/MD.0000000000021507
36. Saleh C, Ilia TS, Jaszczuk P, Hund-Georgiadis M, Walter A: Is transcranial magnetic stimulation as treatment for neuropathic pain in patients with spinal cord injury efficient? A systematic review. Neurol Sci. 2022, 43:3007-18. 10.1007/s10072-022-05978-0
37. Yu B, Qiu H, Li J, Zhong C, Li J: Noninvasive brain stimulation does not improve neuropathic pain in individuals with spinal cord injury: evidence from a meta-analysis of 11 randomized controlled trials. Am J Phys Med Rehabil. 2020, 99:811-20. 10.1097/PHM.0000000000001421
38. Bonomo R, Bonomo G, Rubiu E, et al.: Integrative approaches in spinal cord stimulation: neuropathic pain management and motor recovery in spinal cord injury. A narrative review. Brain Spine. 2024, 4:10.1016/j.bas.2024.102781
39. Yang C, Bi Y, Hu L, et al.: Effects of different transcranial magnetic stimulations on neuropathic pain after spinal cord injury. Front Neurol. 2023, 14: 10.3389/fneur.2023.1141973
40. He K, Hu R, Huang Y, Qiu B, Chen Q, Ma R: Effects of acupuncture on neuropathic pain induced by spinal cord injury: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2022, 2022:10.1155/2022/6297484
41. Li J, Kang W, Wang X, Pan F: Progress in treatment of pathological neuropathic pain after spinal cord injury . Front Neurol. 2024, 15:10.3389/fneur.2024.1430288
42. Ge SY, Hu MM, Li KP, Wu CQ, Xu GH, Dong L: Comparative efficacy of common rehabilitation treatments for patients with neuropathic pain after spinal cord injury: a systematic review and network meta-analysis. Neurol Sci. 2025, 46:3547-57. 10.1007/s10072-025-08120-y
43. Chi B, Chau B, Yeo E, Ta P: Virtual reality for spinal cord injury-associated neuropathic pain: systematic review. Ann Phys Rehabil Med. 2019, 62:49-57. 10.1016/j.rehab.2018.09.006
44. Koukoulithras I, Alkhazi A, Gkampenis A, et al.: A systematic review of the interventions for management of pain in patients after spinal cord injury. Cureus. 2023, 15:10.7759/cureus.42657
45. Allison DJ, Ahrens J, Mirkowski M, Mehta S, Loh E: The effect of neuropathic pain treatments on pain interference following spinal cord injury: a systematic review. J Spinal Cord Med. 2024, 47:465-76. 10.1080/10790268.2023.2218186
46. Eller OC, Willits AB, Young EE, Baumbauer KM: Pharmacological and non-pharmacological therapeutic interventions for the treatment of spinal cord injury-induced pain. Front Pain Res (Lausanne). 2022, 3:10.3389/fpain.2022.991736
47. Soler D, Moriña D, Kumru H, Vidal J, Navarro X: Transcranial direct current stimulation and visual illusion effect according to sensory phenotypes in patients with spinal cord injury and neuropathic pain. J Pain. 2021, 22:86-96. 10.1016/j.jpain.2020.06.004
48. Vatkar A, Kale S, Shyam A, Srivastava S: Understanding the levels of evidence in medical research . J Orthop Case Rep. 2025, 15:6-9. 10.13107/jocr.2025.v15.i05.5534
49. Simpson Jr RK, Robertson CS, Goodman JC: The role of glycine in spinal shock . J Spinal Cord Med. 1996, 19:215-24. 10.1080/10790268.1996.11719437
50. Calancie B, Broton JG, Klose KJ, Traad M, Difini J, Ayyar DR: Evidence that alterations in presynaptic inhibition contribute to segmental hypo- and hyperexcitability after spinal cord injury in man. Electroencephalogr Clin Neurophysiol. 1993, 89:177-86. 10.1016/0168-5597(93)90131-8
51. Leis AA, Kronenberg MF, Stětkárová I, Paske WC, Stokić DS: Spinal motoneuron excitability after acute spinal cord injury in humans. Neurology. 1996, 47:231-7. 10.1212/wnl.47.1.231
52. Nacimiento W, Noth J: What, if anything, is spinal shock? . Arch Neurol. 1999, 56:1033-5. 10.1001/archneur.56.8.1033
53. Sherrington CS: The Integrative Action of the Nervous System . Yale University Press, New Haven, CT; 1920.
54. Weaver RA, Landau WM, Higgins JF: Fusimotor function. Part II. Evidence of fusimotor depression in human spinal shock. Arch Neurol. 1963, 9:127-32. 10.1001/archneur.1963.00460080037004
55. Barnes CD, Schadt JC: Release of function in the spinal cord . Prog Neurobiol. 1979, 12:1-13. 10.1016/0301-0082(79)90008-x
56. Stephan K, Huber S, Häberle S, et al.: Spinal cord injury - incidence, prognosis, and outcome: an analysis of the traumaregister DGU. Spine J. 2015, 15:1994-2001. 10.1016/j.spinee.2015.04.041
57. Yue JK, Tsolinas RE, Burke JF, et al.: Vasopressor support in managing acute spinal cord injury: current knowledge. J Neurosurg Sci. 2019, 63:308-17. 10.23736/S0390-5616.17.04003-6
58. Wang TY, Park C, Zhang H, et al.: Management of acute traumatic spinal cord injury: a review of the literature. Front Surg. 2021, 8: 10.3389/fsurg.2021.698736
59. Stokes S, Drozda M, Lee C: The past, present, and future of traumatic spinal cord injury therapies: a review . Bone Jt Open. 2022, 3:348-58. 10.1302/2633-1462.35.BJO-2021-0177.R1
60. Fehlings MG, Vaccaro A, Wilson JR, et al.: Early versus delayed decompression for traumatic cervical spinal cord injury: results of the surgical timing in acute spinal cord injury study (STASCIS). PLoS One. 2012, 7:10.1371/journal.pone.0032037
61. Huang YH, Yang TM, Lin WC, et al.: The prognosis of acute blunt cervical spinal cord injury . J Trauma. 2009, 66:1441-5. 10.1097/TA.0b013e318184ba88
62. Sun X, Jones ZB, Chen XM, Zhou L, So KF, Ren Y: Multiple organ dysfunction and systemic inflammation after spinal cord injury: a complex relationship. J Neuroinflammation. 2016, 13:10.1186/s12974-016-0736-y
63. An KD, Noh CY, Jang J, Yuh WT, Choi I: Potential pharmacologic treatments in spinal cord injury: a

narrative review. Korean J Neurotrauma. 2025, 21:237-54. 10.13004/kjnt.2025.21.e35
64. Wang J, Doan LV: Clinical pain management: current practice and recent innovations in research . Cell Rep Med. 2024, 5:10.1016/j.xcrm.2024.101786
65. Prevention of venous thromboembolism in individuals with spinal cord injury: clinical practice guidelines for health care providers, 3rd ed. Top Spinal Cord Inj Rehabil. 2016, 22:209-40.
66. Moreno-González E, Ibarra A: The critical management of spinal cord injury: a narrative review . Clin Pract. 2024, 15:10.3390/clinpract15010002
67. Cook A, Snider B, Draganich C, Berliner J, Kirshblum S: Venous thromboembolism management in acute traumatic spinal cord injury: understanding practice patterns within SCI model systems. J Spinal Cord Med. 2025, 1-9. 10.1080/10790268.2025.2580124
68. Weidner N, Müller OJ, Hach-Wunderle V, et al.: Prevention of thromboembolism in spinal cord injury - S1 guideline. Neurol Res Pract. 2020, 2:10.1186/s42466-020-00089-7
69. Jia X, Kowalski RG, Sciubba DM, Geocadin RG: Critical care of traumatic spinal cord injury . J Intensive Care Med. 2013, 28:12-23. 10.1177/0885066611403270
70. Mian MU, Afzal M, Butt AA, et al.: Neuropharmacology of neuropathic pain: a systematic review . Cureus. 2024, 16:10.7759/cureus.69028
71. Fornasari D: Pharmacotherapy for neuropathic pain: a review . Pain Ther. 2017, 6:25-33. 10.1007/s40122-017-0091-4
72. Loh E, Mirkowski M, Agudelo AR, et al.: The CanPain SCI clinical practice guidelines for rehabilitation management of neuropathic pain after spinal cord injury: 2021 update. Spinal Cord. 2022, 60:548-66. 10.1038/s41393-021-00744-z
73. João RB, Chan JO, Huang ES, Rosas GP, Vasquez AV, Thota S, Dantas JM: Gabapentinoids for neuropathic pain after spinal cord injury: an updated meta-analysis of randomized controlled trials. Pain Pract. 2025, 25:10.1111/papr.70060
74. Sun X, Long H, Zhao C, et al.: Analgesia-enhancing effects of repetitive transcranial magnetic stimulation on neuropathic pain after spinal cord injury: an fNIRS study. Restor Neurol Neurosci. 2019, 37:497-507. 10.3233/RNN-190934
75. Wrigley PJ, Press SR, Gustin SM, et al.: Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain. 2009, 141:52-9.
76. Gustin SM, Wrigley PJ, Siddall PJ, Henderson LA: Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. Cereb Cortex. 2010, 20:1409-19. 10.1093/cercor/bhp205
77. Benedetti B, Weidenhammer A, Reisinger M, Couillard-Despres S: Spinal cord injury and loss of cortical inhibition. Int J Mol Sci. 2022, 23: 10.3390/ijms23105622
78. Hou J, Klippel K, Bose P: Glutamate excitotoxicity: a key secondary injury mechanism of traumatic brain injury and spinal cord injury. Front Biosci (Landmark Ed). 2025, 30: 10.31083/FBL38904
79. Bhagwani A, Chopra M, Kumar H: Spinal cord injury provoked neuropathic pain and spasticity, and their GABAergic connection. Neurospine. 2022, 19:646-68. 10.14245/ns.2244368.184
80. Gustin SM, Wrigley PJ, Youssef AM, et al.: Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. Pain. 2014, 155:1027-36.
81. Manheimer E, White A, Berman B, Forys K, Ernst E: Meta-analysis: acupuncture for low back pain. Ann Intern Med. 2005, 142:651-63. 10.7326/0003-4819-142-8-200504190-00014
82. Scharf HP, Mansmann U, Streitberger K, et al.: Acupuncture and knee osteoarthritis: a three-armed randomized trial. Ann Intern Med. 2006, 145:12-20. 10.7326/0003-4819-145-1-200607040-00005
83. Linde K, Streng A, Jürgens S, et al.: Acupuncture for patients with migraine: a randomized controlled trial . JAMA. 2005, 293:2118-25. 10.1001/jama.293.17.2118
84. Mayhew E, Ernst E: Acupuncture for fibromyalgia - a systematic review of randomized clinical trials . Rheumatology (Oxford). 2007, 46:801-4. 10.1093/rheumatology/kel406
85. Hou S, Huh B, Kim HK, Kim KH, Abdi S: Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. Pain Physician. 2018, 21:571-92. 10.36076/ppj.2018.6.571
86. Song G, Fiocchi C, Achkar JP: Acupuncture in inflammatory bowel disease . Inflamm Bowel Dis. 2019, 25:1129-39. 10.1093/ibd/izy371
87. Yang J, Chen J, Yang M, et al.: Acupuncture for hypertension. Cochrane Database Syst Rev. 2018, 11:10.1002/14651858.CD008821.pub2
88. Hal MV, Dydyk AM, Green MS: Acupuncture. StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL; 2023.
89. Kwon S, Jung WS, Yang S, et al.: Safety of acupuncture in patients taking newer oral anticoagulants: a retrospective chart review study. Evid Based Complement Alternat Med. 2018, 2018: 10.1155/2018/8042198
90. Noble T, Boone L, El Helou A: The role of virtual reality as adjunctive therapy to spinal cord stimulation in chronic pain: a feasible concept?. Front Pain Res (Lausanne). 2023, 4: 10.3389/fpain.2023.1094125
91. Leemhuis E, Giuffrida V, Giannini AM, Pazzaglia M: A therapeutic matrix: virtual reality as a clinical tool for spinal cord injury-induced neuropathic pain. Brain Sci. 2021, 11: 10.3390/brainsci11091201
92. Areni A, Capeci W, Corsi A, Del Popolo G, De Palma L, Pelizzari L, Vercilli P: The correct nutritional intake in the prevention and treatment of skin lesions in patients with spinal cord injury. J Clin Med Res. 2026, 18:142-56. 10.14740/jocmr6399
93. Yuan Z, Shi L, Tao XN, et al.: Progress on omega-3 fatty acids for the comprehensive and targeted treatment of spinal cord injury. Bone Res. 2026, 14: 10.1038/s41413-025-00461-w
94. García-Domínguez M: The role of vitamin D in neuropathic pain: biological mechanisms and clinical relevance. Int J Mol Sci. 2026, 27: 10.3390/ijms27114671
95. Shi T, He Y, Yu Z, Li J: Vitamin D deficiency and neuropathic pain in chronic spinal cord injury: a cross-sectional study. Front Nutr. 2025, 12: 10.3389/fnut.2025.1706735
96. Wang Y, Lo MC, Fisher M, Desneves K, Nevin A, Iyer P: Nutrition care in adults with spinal cord injuries and disorders with pressure injuries: a systematic review of clinical practice guidelines. Clin Nutr. 2026, 58:10.1016/j.clnu.2026.106580