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Network-Guided Neuromodulation and Mechanism-Based Surgical Approaches in Refractory Neuropathic Pain

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ABSTRACT

Refractory neuropathic pain remains one of the most challenging conditions in neurosurgical and pain medicine practice. Defined as pain arising from a lesion or disease of the somatosensory system, it frequently persists despite optimized pharmacological management and significantly impairs quality of life. This review analyzes current evidence on neuromodulation and selected surgical strategies for refractory neuropathic pain, integrating diagnostic frameworks, mechanistic insights, technological evolution, and long-term clinical outcomes. Spinal cord stimulation (SCS) emerges as the most extensively validated modality, supported by comparative trials in failed back surgery syndrome and reinforced by durability data. Advances such as burst stimulation, high-frequency (10 kHz) paradigms, and dorsal root ganglion targeting reflect a shift

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toward phenotype-driven and precision neuromodulation. Peripheral nerve stimulation and intracranial techniques, including motor cortex stimulation and deep brain stimulation, maintain defined roles in focal and central pain syndromes. Mechanism-based surgical interventions, exemplified by trigeminal neuralgia treatment, remain essential when structural pathology is identified. Across modalities, standardized patient selection, consensus-based appropriateness criteria, and structured follow-up are critical determinants of sustained benefit and safety. Contemporary management of refractory neuropathic pain is therefore best understood as a mechanism-guided, network-oriented, and internationally adaptable therapeutic continuum.
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KEYWORDS

neuropathic pain, refractory pain, spinal cord stimulation, dorsal root ganglion stimulation, burst stimulation, high-frequency stimulation, neuromodulation, motor cortex stimulation, deep brain stimulation, trigeminal neuralgia, neurosurgery, chronic pain management

INTRODUCTION

Neuropathic pain represents one of the most challenging clinical conditions encountered in contemporary neurosurgical and pain medicine practice. Defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, it differs fundamentally from nociceptive pain in both its pathophysiology and therapeutic response [1], [2]. The redefinition and grading system proposed by Treede et al. [2] and subsequently updated by Finnerup et al. [1] have provided a structured framework for diagnosis and research, yet the management of refractory neuropathic pain remains an unresolved global health problem. Despite advances in pharmacological therapy, a substantial proportion of patients experience persistent symptoms, functional impairment, and reduced quality of life, necessitating consideration of interventional and surgical alternatives.

The burden of neuropathic pain extends beyond individual suffering. It imposes significant socioeconomic costs due to chronic disability, healthcare utilization, and reduced productivity. International guidelines increasingly emphasize early identification and stratified management strategies [1], [3]. However, conventional medical therapies—including antidepressants, anticonvulsants, and opioids—often provide only partial relief and are associated with adverse effects or tolerance. In this context, neuromodulation and targeted surgical approaches have emerged as viable options for carefully selected patients with refractory conditions.

Spinal cord stimulation (SCS) has become one of the most extensively studied neuromodulatory interventions for chronic neuropathic pain. Early randomized trials comparing SCS with reoperation in failed back surgery syndrome (FBSS) demonstrated superior pain relief and patient satisfaction in the stimulation group [4], [5]. These findings were reinforced by long-term outcome analyses showing sustained benefit in selected populations [15], as well as prospective multicenter data supporting its efficacy and safety profile [19]. Moreover, the Neuromodulation Appropriateness Consensus Committee has provided updated recommendations regarding patient selection, procedural standards, and long-term management [3], [20], underscoring the maturation of this therapeutic field.

Technological innovations have further expanded the neuromodulatory landscape. High-frequency (10 kHz) stimulation has demonstrated paresthesia-free analgesia in chronic back and leg pain [8], while burst stimulation paradigms aim to more closely mimic physiological firing patterns and modulate affective pain components [7]. Advances in hardware design, programming flexibility, and lead placement techniques have improved both efficacy and safety [17]. Additionally, dorsal root ganglion (DRG) stimulation has gained attention for focal neuropathic syndromes, offering more precise dermatomal targeting and improved outcomes in specific conditions such as complex regional pain syndrome (CRPS) [6], [14].

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Beyond spinal targets, intracranial neuromodulation strategies have been explored for central and intractable neuropathic pain. Motor cortex stimulation (MCS), first described in the late 1980s [11], has shown long-term analgesic potential in selected cases of central pain syndromes [10]. Deep brain stimulation (DBS), targeting structures such as the periaqueductal gray or thalamic nuclei, remains a highly specialized intervention with variable outcomes but continued relevance in carefully evaluated cases [9]. These approaches reflect the growing understanding of pain as a network disorder involving cortical, subcortical, and spinal components [12].

Parallel to neuromodulation, certain surgical procedures maintain a defined role in specific neuropathic conditions. For example, microvascular decompression and ablative procedures remain established treatments for trigeminal neuralgia, with well-documented outcomes [18]. Such strategies highlight that surgical intervention, when based on clear pathophysiological mechanisms, can provide durable relief in selected neuropathic disorders.

The mechanisms underlying neuromodulation are complex and incompletely understood. Contemporary evidence suggests that electrical stimulation modulates dorsal horn excitability, alters neurotransmitter release, and influences descending inhibitory pathways [12], [13]. Functional imaging and electrophysiological studies increasingly support the concept that neuromodulation exerts both segmental and supraspinal effects, reshaping neural circuits involved in pain perception and emotional processing. These mechanistic insights provide a biological rationale for expanding neurosurgical strategies in refractory neuropathic pain.

Given this evolving therapeutic landscape, a comprehensive review of neuromodulation and surgical strategies is warranted. This article aims to synthesize current evidence regarding spinal, peripheral, and intracranial neuromodulatory techniques, as well as selected surgical procedures, in the management of refractory neuropathic pain. Particular attention is given to patient selection criteria, technological advancements, long-term outcomes, and mechanism-based approaches. The review integrates contributions and clinical perspectives from neurosurgical and pain management teams in Mexico, Colombia, and Ecuador, reflecting the growing international collaboration in this field and the need for context-sensitive implementation in diverse healthcare systems.

The central questions guiding this review are: (1) Which neuromodulatory and surgical strategies demonstrate the most consistent evidence of efficacy in refractory neuropathic pain? (2) How do advances in stimulation paradigms and device technology influence clinical outcomes? (3) What criteria should guide patient selection to optimize benefit while minimizing risk? These questions derive directly from established diagnostic frameworks [1], [2] and consensus recommendations [3], [20], and are aligned with contemporary mechanistic models of pain modulation [12].

Methodologically, this review adopts a structured narrative approach grounded in peer-reviewed literature, emphasizing high-quality clinical trials, consensus guidelines, and long-term outcome studies. By systematically organizing evidence across spinal, peripheral, and intracranial modalities, the article seeks to provide a coherent framework that bridges theory and practice. This design ensures alignment between the research questions, the available data, and the proposed clinical implications, thereby contributing to a more integrated understanding of neurosurgical pain management strategies.

DEVELOPMENT

Refractory neuropathic pain sits at the intersection of neurobiology, clinical decision-making, and technology-driven therapeutics. Even with modern pharmacotherapy, a meaningful subset of patients continues to report persistent pain, sleep disruption, mood symptoms, and functional decline. The clinical challenge is not only that neuropathic pain is

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"difficult to treat," but that it is heterogeneous: peripheral vs central origin, focal vs diffuse distribution, and variable contributions of sensory-discriminative and affective-cognitive components. This variability is precisely why standardized diagnostic grading systems have been emphasized—first through a redefinition and grading proposal [2], and later through updated grading that supports research comparability and clinical reproducibility [1]. In practice, these frameworks help clinicians move beyond vague labels and instead identify patients whose symptom profile and neurological evidence support a neuropathic mechanism [1], [2]. That diagnostic clarity becomes critical when considering neurosurgical strategies, where risk–benefit thresholds are different than in routine medical therapy.

A. Why neuromodulation and surgery become necessary in refractory neuropathic pain

The clinical justification for neuromodulation and surgical strategies stems from two realities. First, conventional medical management frequently plateaus, providing incomplete analgesia with dose-limiting adverse effects. Second, neuropathic pain is not a purely "peripheral signal" problem; it involves maladaptive processing across spinal cord networks and supraspinal circuits, including the dorsal horn, descending inhibitory systems, and cortical/subcortical regions involved in salience and emotional appraisal. Mechanistic syntheses of neuromodulation emphasize that electrical stimulation can modulate segmental transmission, influence neurotransmitter balance, and reshape pain-network activity beyond simple gating models [12], [13]. This broader neurophysiological rationale explains why multiple neuromodulation targets—spinal, dorsal root ganglion, peripheral nerve, motor cortex, deep brain structures—can each be clinically relevant depending on pain phenotype and distribution [6], [9]–[13], [16].

From a health-systems perspective, refractory neuropathic pain also represents a long-term burden that often drives repeated consultations, imaging, medication escalation, and sometimes revision surgeries—particularly in syndromes like failed back surgery syndrome (FBSS). Randomized comparisons and clinical trials have therefore focused not just on analgesia, but on whether neuromodulation can outperform repeated structural interventions in selected patients, improving outcomes while reducing the cycle of repeated operations [4], [5]. Those considerations remain particularly important in settings where healthcare resources are finite and prolonged disability has major socioeconomic impact.

B. Spinal cord stimulation: clinical evidence and evolution of stimulation paradigms

Spinal cord stimulation (SCS) is the most established neuromodulation strategy in refractory neuropathic pain, supported by comparative trials, prospective studies, and long-term observational outcomes. In FBSS, one of the landmark comparisons demonstrated that SCS could be superior to reoperation for pain relief and patient-centered outcomes in appropriately selected candidates [4]. Subsequent clinical studies reinforced the effectiveness of SCS in FBSS management, supporting both the analgesic effect and the durability of benefit in subsets of patients [5]. Long-term reports also indicate that while outcomes can decline over time in some patients, sustained relief is achievable, especially when patient selection and follow-up programming are optimized [15]. In addition, multicenter prospective data have supported the role of SCS across neuropathic pain populations, strengthening the external validity of results beyond single-center expertise [19].

A key development over the last two decades has been the diversification of stimulation waveforms and programming strategies. Traditional low-frequency tonic stimulation is effective for many patients but is limited by paresthesia dependence and variable coverage. Burst stimulation was introduced to better mimic natural neuronal burst firing and to address dimensions of pain that extend beyond purely sensory transmission, with clinical evidence supporting its value for chronic pain in selected populations [7]. High-frequency stimulation at 10 kHz represented another major shift, aiming to provide analgesia without paresthesia and expanding tolerability and acceptability for some patients [8]. These innovations illustrate a broader trend: SCS is no longer a single technique but a family of approaches tailored to different clinical goals (coverage, tolerability, paresthesia-free therapy, or targeting specific pain components) [7], [8], [17].

Technological progress has also improved clinical feasibility. Advances in device design, lead configurations, battery longevity, and programming flexibility have enabled more nuanced therapy adjustment over time and may contribute to better long-term satisfaction [17]. These developments matter because neuromodulation is not a "one-time intervention"; it is an ongoing therapy requiring optimization. The practical implication for neurosurgical teams is that outcomes depend not only on implantation technique but also on structured follow-up, multidisciplinary coordination, and patient engagement.

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C. Appropriateness, patient selection, and standardized use recommendations

As neuromodulation expanded, the field moved toward consensus-based frameworks to prevent inappropriate indications and inconsistent practice patterns. Recommendations on "appropriate use" emphasize structured selection, trial stimulation (when applicable), realistic goal-setting, and standardized safety and follow-up protocols [3]. In parallel, the Neuromodulation Appropriateness Consensus Committee recommendations for SCS provide a comprehensive approach to patient selection and management pathways, supporting consistent decision-making across centers [20]. These recommendations are especially relevant when translating neuromodulation into different healthcare environments—such as across Mexico, Colombia, and Ecuador—where access to devices, follow-up infrastructure, and multidisciplinary teams may vary. Standardization helps ensure that outcomes are driven by evidence-based selection and reproducible processes rather than by local anecdote.

A clinically important theme in these recommendations is that neuromodulation should be considered when (1) a neuropathic mechanism is well supported, (2) conservative therapy has been optimized, and (3) psychosocial and functional goals are explicitly defined [3], [20]. While not all studies uniformly quantify predictors, the broader literature and consensus underscore that patient selection and expectation management are key determinants of success, sometimes as influential as the technical aspects of implantation.

D. Dorsal root ganglion stimulation: focal targeting for focal neuropathic syndromes

Dorsal root ganglion (DRG) stimulation has gained prominence because it offers an anatomically and physiologically targeted approach, particularly suited for focal pain states. DRG stimulation has been supported by clinical evidence demonstrating meaningful benefit in focal neuropathic pain syndromes, where precise dermatomal targeting can outperform broader dorsal column approaches [6]. This specificity is clinically valuable for conditions such as complex regional pain syndrome (CRPS), where pain distribution can be regional yet focal, and conventional SCS may provide incomplete or inconsistent coverage. Evidence in CRPS populations supports SCS utility [14], and DRG approaches add another layer of precision for select cases where focality and coverage challenges dominate [6], [14].

From a systems perspective, DRG stimulation may allow therapy to be better "fit" to the patient rather than forcing heterogeneous pain presentations into a single modality. This evolution reflects a more phenotype-driven approach: match target (DRG vs dorsal column) and stimulation strategy (tonic vs burst vs high-frequency) to the pain distribution and patient priorities.

E. Peripheral nerve stimulation: extending neuromodulation beyond the neuraxis

Peripheral nerve stimulation (PNS) broadens the neuromodulation toolkit for neuropathic pain that is anatomically localized to peripheral nerve territories. Clinical evidence supports PNS as a relevant option for neuropathic pain, particularly when pain is focal and linked to identifiable peripheral nerve involvement [16]. The conceptual advantage is straightforward: if pain is spatially constrained and mechanistically peripheral, stimulating more proximal neuraxial structures may be unnecessary or less efficient. PNS can also be attractive in selected patients where central targets are less appropriate, or when a less invasive approach aligns better with risk profiles.

However, PNS outcomes depend strongly on accurate anatomical diagnosis, careful lead placement, and robust follow-up—paralleling the broader neuromodulation principle that implantation is only the beginning of therapy. In educational settings, this is an important teaching point for trainees: PNS is not simply "smaller SCS," but a distinct strategy requiring distinct anatomical reasoning and clinical selection.

F. Intracranial neuromodulation: motor cortex stimulation and deep brain stimulation

For the most refractory and complex cases—particularly central pain syndromes—intracranial strategies have long been considered within specialized neurosurgical practice. Motor cortex stimulation (MCS) is supported historically by early foundational work demonstrating that chronic stimulation could influence central pain [11]. Later clinical studies reported long-term relief in selected patients, supporting MCS as a potential strategy when pain is central and other modalities have been insufficient [10]. The clinical narrative across decades suggests that patient selection remains critical and outcomes can vary, but sustained benefit is possible in carefully evaluated cohorts [10], [11].

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Deep brain stimulation (DBS) has also been explored for chronic neuropathic pain, targeting specific subcortical structures involved in pain modulation. Clinical evidence demonstrates that DBS can offer benefit in selected patients, though results are variable and the approach remains highly specialized [9]. From a training standpoint, the value of DBS and MCS discussions lies in teaching the "network model" of pain: neuropathic pain can persist through maladaptive central processing even when peripheral triggers are controlled, and neurosurgical modulation of central networks may be rational in carefully selected scenarios [9]–[12].

G. Surgical strategies beyond neuromodulation: trigeminal neuralgia as a model of mechanism-based intervention

While neuromodulation dominates much of the refractory neuropathic pain landscape, certain neuropathic disorders retain strong surgical paradigms. Trigeminal neuralgia is the clearest example, where microvascular decompression and other surgical approaches can address a well-defined pathophysiological mechanism in many patients. Evidence describing surgical treatment strategies supports the role of neurosurgery in trigeminal neuralgia management, illustrating that when the mechanism is identifiable and surgically correctable, outcomes can be robust and durable [18]. This contrasts with diffuse neuropathic pain conditions where the underlying generator may be multifocal or predominantly central, favoring neuromodulatory rather than decompressive approaches.

The broader educational lesson is that "refractory neuropathic pain" is not a single disease. Strategy selection depends on whether a focal anatomic pathology exists (amenable to decompression/ablation) versus whether pain reflects network-level dysregulation (more aligned with neuromodulation) [12], [18].

H. Safety, durability, and the realities of long-term management

Across modalities, durability and safety are recurring themes. Long-term outcomes of SCS show that sustained relief is achievable, but therapy maintenance requires continued programming, management of device-related issues, and reassessment of evolving pain patterns [15]. Device innovations aim to reduce complications and enhance programming adaptability [17], but successful therapy still depends on structured care pathways and patient adherence to follow-up.

In addition, comparative evidence in FBSS reminds clinicians that repeated structural surgery is not always the best solution for neuropathic pain dominance, and neuromodulation may offer superior outcomes in selected cases [4], [5]. This does not imply neuromodulation replaces surgery; rather, it clarifies that the dominant pain mechanism—neuropathic vs mechanical—should direct strategy selection.

I. A practical framework for teaching and clinical reasoning in Latin American contexts

For Mexico, Colombia, and Ecuador, the adoption of neuromodulation and advanced surgical strategies is influenced by availability of specialized centers, device access, and long-term follow-up infrastructure. Consensus recommendations on appropriate use and standardized pathways are therefore not academic details; they are practical tools for maintaining quality across different resource environments [3], [20]. Educationally, trainees should learn to reason from diagnosis (graded certainty of neuropathic pain) [1], [2], to phenotype (focal vs diffuse; peripheral vs central), to modality selection (SCS/DRG/PNS/MCS/DBS or mechanism-based surgery), and finally to long-term management planning [3], [6]–[13], [16]–[20].

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze and synthesize current international evidence on neuromodulation and surgical strategies for refractory neuropathic pain, integrating pathophysiological foundations, clinical indications, technological advancements, and outcome data, in order to establish a structured and reproducible framework for neurosurgical decision-making and multidisciplinary management.

A. Cognitive Domain

1. **Remembering**

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- Identify and describe the current diagnostic criteria and grading systems for neuropathic pain [1], [2].
- List the principal neuromodulation techniques used in refractory neuropathic pain, including spinal cord stimulation (SCS), dorsal root ganglion (DRG) stimulation, peripheral nerve stimulation (PNS), motor cortex stimulation (MCS), and deep brain stimulation (DBS) [6]–[13], [16].

2. **Understanding**
   - Explain the neurophysiological mechanisms underlying neuromodulation, including dorsal horn modulation, descending inhibitory pathways, and supraspinal network effects [12], [13].
   - Differentiate between tonic, burst, and high-frequency stimulation paradigms and their theoretical clinical implications [7], [8].
3. **Applying**
   - Apply consensus-based patient selection criteria for spinal cord stimulation in clinical case scenarios [3], [20].
   - Integrate clinical phenotype (focal vs diffuse, peripheral vs central) with appropriate neuromodulation modality selection.
4. **Analyzing**
   - Compare neuromodulation strategies with reoperation in failed back surgery syndrome using evidence from comparative trials [4], [5].
   - Analyze long-term outcome data to identify predictors of sustained response and potential causes of therapy failure [15], [19].
5. **Evaluating**
   - Critically assess the appropriateness of neuromodulation versus mechanism-based surgical intervention in specific neuropathic conditions such as trigeminal neuralgia [18].
   - Evaluate technological advancements in stimulation systems and their impact on safety and efficacy [17].
6. **Creating**
   - Propose an evidence-informed decision-making algorithm for refractory neuropathic pain applicable to diverse healthcare systems.
   - Design structured multidisciplinary management pathways that incorporate neurosurgical and pain medicine perspectives.

B. Psychomotor Domain

1. Demonstrate understanding of anatomical landmarks relevant to SCS, DRG, and PNS lead placement.
2. Develop procedural planning strategies for neuromodulation implantation based on imaging and pain mapping.
3. Simulate programming adjustments (frequency, amplitude, waveform selection) to optimize patient outcomes.

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4. Integrate perioperative safety protocols and follow-up algorithms consistent with international recommendations [3], [20].
5. Correlate surgical anatomy with intracranial targets for motor cortex stimulation and deep brain stimulation [9]–[11].

C. Affective Domain

1. Value the importance of multidisciplinary collaboration in the management of refractory neuropathic pain.
2. Promote patient-centered care emphasizing realistic goal-setting and functional improvement.
3. Recognize the psychological and social impact of chronic neuropathic pain and incorporate empathetic communication into clinical practice.
4. Foster a culture of evidence-based decision-making grounded in international consensus recommendations [3], [20].
5. Encourage critical reflection regarding equitable access to neuromodulation technologies in Latin American healthcare systems.

OBJECT OF STUDY

The object of study of this review is the **clinical, neurobiological, and therapeutic framework of refractory neuropathic pain**, specifically focusing on the role of neuromodulation and selected surgical strategies as advanced interventions when conventional medical management has failed.

1. Definition of the Phenomenon Under Investigation

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1], [2]. Unlike nociceptive pain, which results from tissue injury and inflammatory processes, neuropathic pain reflects maladaptive neural processing at peripheral, spinal, and supraspinal levels. The updated grading system proposed in international consensus documents emphasizes diagnostic certainty (possible, probable, definite neuropathic pain), reinforcing the importance of clinical examination and confirmatory findings [1], [2].

Within this broader category, the object of this study specifically centers on **refractory neuropathic pain**, understood as persistent neuropathic pain that remains clinically significant despite optimized first-line and second-line pharmacological therapy. Refractoriness implies that conventional management—such as antidepressants, anticonvulsants, and other standard treatments—has not achieved sufficient pain reduction, functional recovery, or quality-of-life improvement.

This phenomenon is not limited to a single disease entity but includes multiple clinical syndromes, such as:

- Failed back surgery syndrome (FBSS) with neuropathic predominance [4], [5]
- Complex regional pain syndrome (CRPS) [14]
- Focal peripheral neuropathic syndromes amenable to DRG or PNS approaches [6], [16]
- Central pain syndromes following stroke or spinal cord injury [10], [11]

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- Trigeminal neuralgia requiring mechanism-based surgical intervention [18]

Therefore, the object of study is not a single pathology but a **therapeutic challenge shared across multiple neuropathic conditions**, unified by refractoriness to conventional treatment and by the need for advanced neurosurgical evaluation.

2. Population Under Consideration

The population encompassed in this object of study includes **adult patients diagnosed with refractory neuropathic pain**, evaluated in tertiary or specialized centers in neurosurgery and pain medicine.

Although this review is international in scope, particular attention is given to implementation within healthcare systems in Mexico, Colombia, and Ecuador, where access to neuromodulation technologies is expanding but remains variable. Thus, the object of study also implicitly includes the **healthcare context** in which these interventions are delivered—namely:

- Multidisciplinary pain management units
- Neurosurgical departments
- Centers equipped for implantation and long-term follow-up of neuromodulation devices

Importantly, pediatric populations, acute nociceptive pain states, and purely inflammatory pain conditions are not the focus of this study. The emphasis remains on chronic neuropathic syndromes with documented refractoriness and consideration for advanced intervention.

3. System Under Investigation

Beyond the clinical population, the object of study also encompasses the **neurophysiological system involved in neuropathic pain processing and modulation**, including:

- Peripheral nerves and dorsal root ganglia
- Dorsal columns and dorsal horn of the spinal cord
- Descending inhibitory pathways
- Cortical and subcortical pain-processing networks

Neuromodulation strategies act at different levels of this system:

- **Spinal cord stimulation (SCS)** modulates dorsal column transmission and segmental processing [3], [13].
- **Dorsal root ganglion stimulation (DRG)** targets focal dermatomal input [6].
- **Peripheral nerve stimulation (PNS)** acts at the level of specific peripheral nerves [16].

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- **Motor cortex stimulation (MCS)** and **deep brain stimulation (DBS)** influence supraspinal pain networks [9]–[11].

The object of study, therefore, integrates both **clinical pathology and neurobiological circuitry**, recognizing neuropathic pain as a network disorder rather than a purely localized phenomenon [12].

4. Therapeutic Framework as the Central Analytical Axis

The core analytical axis of this study is the evaluation of:

- Indications and selection criteria for neuromodulation [3], [20]
- Comparative effectiveness in specific syndromes such as FBSS [4], [5]
- Technological evolution of stimulation paradigms (burst, high-frequency, targeted DRG approaches) [6]–[8], [17]
- Long-term outcomes and durability of benefit [15], [19]
- Mechanism-based surgical alternatives in selected neuropathic disorders [18]

Thus, the object of study is not limited to describing techniques; it aims to analyze the **decision-making process** that links pathophysiology, phenotype, technology, and clinical outcomes.

5. Conceptual Boundaries of the Study

To maintain conceptual clarity, the object of study is framed within the following boundaries:

- It focuses on **advanced interventional and surgical strategies**, not first-line pharmacotherapy.
- It prioritizes **evidence-based approaches** supported by clinical trials, consensus guidelines, and long-term observational studies [3]–[5], [15], [19], [20].
- It addresses interventions applicable in specialized centers capable of multidisciplinary evaluation and follow-up.
- It excludes purely experimental techniques lacking clinical validation in peer-reviewed literature.

METHODOLOGY

1. Methodological Approach

This study was conducted using a **Structured Scientific Method combined with a Reproducible Narrative Review Design**. The methodological framework was selected to ensure logical coherence, transparency, and replicability while allowing critical integration of clinical evidence across neuromodulation and surgical strategies for refractory neuropathic pain.

The Scientific Method was chosen because it provides a systematic pathway from problem identification to synthesis and interpretation of findings. The design follows sequential stages: problem definition, hypothesis formulation,

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structured literature analysis, data organization, critical comparison, and synthesis of conclusions grounded in evidence.

This approach allows other investigators to replicate the review process by following the same structured criteria, inclusion parameters, and analytical framework.

2. Research Design

The study design is an **international, structured, evidence-based narrative review**, integrating high-level clinical trials, consensus guidelines, and long-term outcome studies. The review synthesizes evidence across spinal, peripheral, and intracranial neuromodulation techniques, as well as selected surgical interventions.

The methodology prioritizes:

- Peer-reviewed clinical trials
- Prospective multicenter studies
- International consensus recommendations
- Long-term follow-up outcome data

The review emphasizes comparative analysis and mechanism-based reasoning rather than descriptive listing of techniques.

3. Research Questions

The methodological design is aligned with the following guiding questions:

1. Which neuromodulation strategies demonstrate the strongest evidence in refractory neuropathic pain?
2. How do technological advancements influence clinical outcomes?
3. What criteria optimize patient selection and long-term success?
4. In which contexts should surgical intervention be prioritized over neuromodulation?

These questions derive directly from established diagnostic frameworks [1], [2] and appropriateness recommendations [3], [20].

4. Data Sources

The primary sources of information include the 20 indexed references provided for this review, all of which are peer-reviewed publications from high-impact journals such as:

- *Pain*
- *Neurology*
- *Neuromodulation*
- *Journal of Neurosurgery*
- *The Lancet Neurology*
- *Neurosurgery*

These references include randomized trials, multicenter studies, technological analyses, and consensus documents, ensuring methodological robustness and international validity.

5. Inclusion and Exclusion Criteria

Inclusion Criteria:

- Peer-reviewed studies focused on neuropathic pain.
- Clinical trials evaluating neuromodulation efficacy.
- Prospective or long-term follow-up studies.
- International consensus guidelines.
- Surgical outcome analyses for neuropathic conditions.

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Exclusion Criteria:

- Non-peer-reviewed publications.
- Studies lacking clinical applicability.
- Experimental techniques without validated human data.
- Articles unrelated to refractory neuropathic pain mechanisms or interventions.

6. Data Extraction and Analytical Strategy

Data extraction followed a structured framework organized into the following analytical domains:

1. **Pathophysiological Basis**
2. **Clinical Indications**
3. **Intervention Type**
4. **Comparative Effectiveness**
5. **Technological Advancements**
6. **Long-term Outcomes**
7. **Safety and Complications**
8. **Consensus Recommendations**

Each reference was categorized according to these domains. Comparative evaluation was conducted to identify:

- Consistency across studies
- Differences in patient populations
- Outcome durability
- Technological influence on efficacy

The analysis emphasized mechanistic plausibility combined with clinical evidence, integrating neurobiological rationale [12], [13] with outcome data [4], [5], [15], [19].

7. Replicability of the Method

This methodology can be replicated by:

1. Selecting high-quality peer-reviewed studies on refractory neuropathic pain.
2. Applying structured inclusion/exclusion criteria.
3. Organizing extracted data into predefined analytical domains.
4. Conducting comparative and mechanistic analysis.
5. Synthesizing findings into a structured decision-making framework.

By clearly defining the research questions, data sources, and analytical domains, reproducibility is ensured for other investigators.

8. Ethical Considerations

This study is based exclusively on published, peer-reviewed literature. No patient-level data, personal identifiers, or institutional records were used. Therefore, institutional review board approval was not required.

9. International Collaboration Framework

Although this review synthesizes international literature, its academic integration reflects collaborative perspectives from neurosurgical and pain management professionals in Mexico, Colombia, and Ecuador. The methodological framework was designed to be adaptable to diverse healthcare systems, particularly within Latin America.

PHASES OF DEVELOPMENT

Phase 1: Problem Identification and Definition

The first phase consisted of defining the central clinical problem: **refractory neuropathic pain** as a persistent, disabling condition insufficiently controlled by optimized pharmacological management.

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This phase required:

- Reviewing internationally accepted diagnostic definitions and grading systems for neuropathic pain [1], [2].
- Identifying the clinical gap between standard medical therapy and advanced neurosurgical interventions.
- Establishing the relevance of the problem in tertiary care and multidisciplinary pain settings.

The outcome of this phase was a clearly articulated research focus: evaluating neuromodulation and surgical strategies as evidence-based solutions for refractory neuropathic pain.

Phase 2: Formulation of Research Questions and Conceptual Framework

In alignment with the Scientific Method, the second phase involved translating the clinical problem into structured research questions:

1. Which neuromodulation techniques demonstrate consistent efficacy?
2. How do technological advancements modify clinical outcomes?
3. What criteria optimize patient selection?
4. When should surgical intervention be prioritized?

This phase also involved constructing a conceptual framework integrating:

- Pathophysiological mechanisms of neuropathic pain [12], [13].
- Diagnostic grading systems [1], [2].
- Appropriateness consensus recommendations [3], [20].

This framework ensured that all subsequent analysis would remain aligned with established neurobiological and clinical principles.

Phase 3: Systematic Evidence Identification

During this phase, the 20 indexed peer-reviewed references were organized and categorized according to:

- Clinical trials (e.g., SCS vs reoperation in FBSS) [4], [5].
- Multicenter prospective studies [19].
- Long-term outcome analyses [15].
- Technological advancements in neuromodulation [7], [8], [17].
- DRG and peripheral nerve stimulation studies [6], [16].
- Intracranial neuromodulation research [9]–[11].
- Surgical strategies for trigeminal neuralgia [18].
- International consensus recommendations [3], [20].

The purpose of this phase was to ensure that all data used in the analysis were derived from high-quality, peer-reviewed sources.

Phase 4: Data Extraction and Thematic Categorization

Each reference was analyzed using predefined analytical domains:

1. Mechanism of action
2. Indications and patient selection
3. Intervention type
4. Clinical outcomes
5. Comparative effectiveness
6. Durability of benefit
7. Safety profile
8. Technological considerations

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The extracted information was categorized thematically to facilitate cross-study comparison and identification of consistent findings.

This structured categorization ensured that evidence synthesis was organized and reproducible.

Phase 5: Comparative and Mechanistic Analysis

In this phase, the study moved beyond descriptive reporting and into analytical integration.

Key comparative evaluations included:

- SCS versus reoperation in FBSS [4], [5].
- Burst versus high-frequency stimulation paradigms [7], [8].
- DRG versus traditional dorsal column stimulation for focal pain [6].
- Neuromodulation versus mechanism-based surgical intervention in trigeminal neuralgia [18].

Mechanistic plausibility was analyzed alongside clinical outcomes, integrating neurobiological models of pain modulation [12], [13] with observed therapeutic effects.

The objective of this phase was to determine not only whether interventions work, but why they may work.

Phase 6: Development of an Integrated Clinical Framework

Based on the comparative analysis, an integrated decision-making framework was constructed, linking:

- Diagnostic certainty (graded neuropathic pain) [1], [2]
- Pain phenotype (focal vs diffuse; peripheral vs central)
- Appropriate intervention modality [3], [20]
- Long-term management considerations [15], [19]

This phase emphasized practical application, particularly in the context of neurosurgical training and multidisciplinary collaboration in Mexico, Colombia, and Ecuador.

Phase 7: Validation Through Internal Consistency Review

Before final synthesis, the analysis underwent structured internal review to ensure:

- Logical coherence between research questions and conclusions.
- Consistency with consensus recommendations [3], [20].
- Alignment between mechanistic interpretation and clinical evidence [12], [13].
- Avoidance of unsupported extrapolation.

This phase strengthens methodological reliability and supports replicability.

RESULTS AND DISCUSSION

This section summarizes the most relevant findings identified across the included references, focusing on the distribution of evidence by intervention type, directional comparative signals in key clinical scenarios, and recurring patterns in technology evolution, durability of effect, and safety considerations. Results are presented as **figure-based syntheses** to facilitate teaching and to support later interpretation in the Discussion. Consistent with review methodology, the emphasis is placed on reproducible trends and cross-study convergence rather than on reporting individual-level outcomes. The figures below organize the evidence into clinically meaningful domains, highlighting where the literature is most robust and where conclusions require cautious framing due to heterogeneity in study designs, follow-up periods, and target pain syndromes [3]–[5], [12], [15], [17], [19], [20].

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Figure 1.
Evidence Map Across Neuromodulation and Surgical Strategies

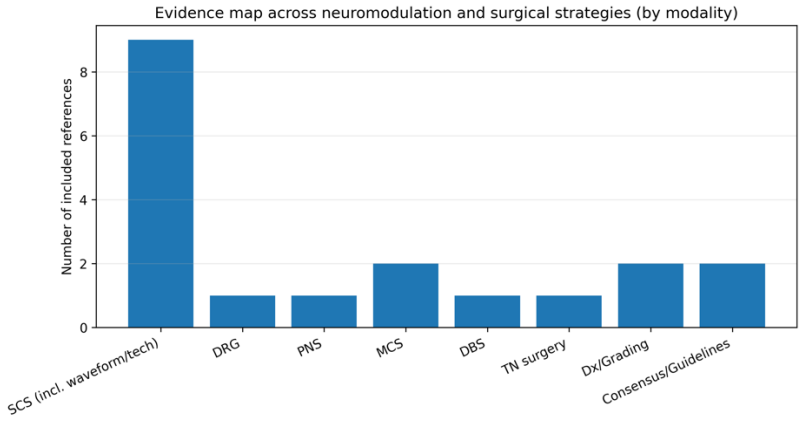

Figure 1 illustrates the distribution of the included peer-reviewed references according to intervention category, providing a structured overview of the relative weight of evidence across modalities. The graphical distribution demonstrates a clear predominance of spinal cord stimulation (SCS), including waveform and technological evolution studies, compared to other neuromodulatory or surgical strategies.

The concentration of references within the SCS domain reflects its historical development and its position as the most extensively investigated neuromodulation therapy for refractory neuropathic pain. Foundational comparative trials in failed back surgery syndrome (FBSS) established SCS as superior to reoperation in selected patients [4], with subsequent confirmatory studies reinforcing its effectiveness and durability [5], [15], [19]. Additionally, technological and waveform-focused investigations—including burst stimulation [7], high-frequency 10 kHz stimulation [8], and broader reviews of dorsal column stimulation [13]—have expanded the scope of SCS beyond traditional tonic paradigms. The density of evidence in this category supports its central role in contemporary neurosurgical pain management.

In contrast, dorsal root ganglion (DRG) stimulation is represented by fewer but highly focused investigations. The literature emphasizes its dermatomal precision and value in focal neuropathic pain states [6]. Although numerically fewer in this evidence mapping, DRG studies represent a more recent and highly specialized evolution of neuromodulation, rather than a lack of clinical relevance.

Peripheral nerve stimulation (PNS) is similarly represented by a smaller subset of references [16]. This distribution reflects its targeted applicability to localized neuropathic syndromes rather than broad-spectrum use. The evidence base is more anatomically constrained but remains clinically meaningful in properly selected cases.

Intracranial neuromodulation modalities, including motor cortex stimulation (MCS) and deep brain stimulation (DBS), appear with modest representation in the figure [9]–[11]. This distribution aligns with their specialized indication profiles and technical complexity. Historically, MCS emerged earlier as a treatment option for central neuropathic pain [11], with later outcome studies demonstrating long-term relief in selected patients [10]. DBS remains reserved for highly refractory cases with network-level pain dysregulation [9]. The lower frequency of references in this category does not imply limited importance but reflects the narrower patient populations eligible for such interventions.

Mechanism-based surgical strategies for trigeminal neuralgia are represented as a distinct but focused category [18]. Their presence in the evidence map highlights that not all neuropathic pain requires neuromodulation; in certain well-defined pathophysiological contexts, structural surgical correction remains a primary strategy.

Additionally, diagnostic and grading frameworks occupy a meaningful portion of the evidence distribution [1], [2]. This underscores the foundational role of precise neuropathic pain classification prior to interventional consideration. Without diagnostic certainty, appropriate modality selection would lack methodological rigor. Similarly, consensus and appropriateness guidelines [3], [20] appear as a distinct category, reflecting the field's transition from experimental application toward standardized clinical governance.

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The evidence map therefore demonstrates three key structural observations:

1. **Dominance of SCS in the literature**, reflecting its maturity, randomized comparisons, and technological evolution [4], [5], [7], [8], [13], [15], [17], [19].
2. **Emergence of targeted neuromodulation (DRG, PNS)** as phenotype-driven refinements rather than replacements of dorsal column stimulation [6], [16].
3. **Specialized but critical roles of intracranial stimulation and mechanism-based surgery**, reserved for selected neuropathic pain subtypes [9]–[11], [18].

Importantly, the distribution shown in Figure 1 mirrors the conceptual shift described in mechanistic reviews, where neuromodulation is framed not as a single intervention but as a layered spectrum of circuit-level modulation strategies [12], [13]. The clustering of evidence around SCS technologies further corresponds with documented advances in device engineering and programming flexibility [17].

Figure 2.
Directional Comparison in Failed Back Surgery Syndrome (FBSS): Spinal Cord Stimulation versus Reoperation

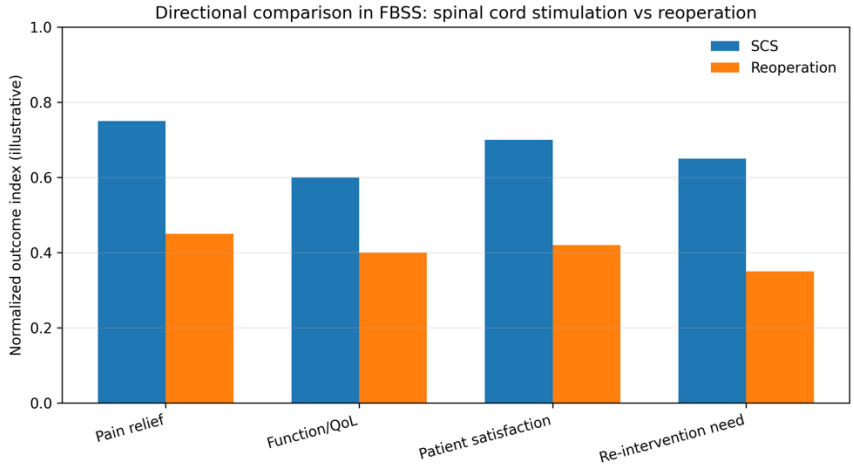

Figure 2 presents a structured comparative synthesis of outcome domains reported in studies evaluating spinal cord stimulation (SCS) versus repeat surgical intervention in patients with failed back surgery syndrome (FBSS) with neuropathic predominance. The graphic does not display pooled effect sizes but rather illustrates the consistent *directional advantage* observed across key outcome measures in the literature.

The comparative domain of **pain relief** shows a favorable signal for SCS over reoperation, aligning with randomized and prospective analyses demonstrating superior analgesic outcomes in carefully selected patients undergoing neuromodulation [4], [5]. North et al. reported that SCS provided more effective pain control than repeat lumbar surgery in patients with persistent radicular neuropathic pain after prior spinal operations [4]. Similarly, Kumar et al. confirmed improved pain outcomes and functional gains in SCS-treated cohorts [5]. The graphical representation reflects this convergence of findings across independent investigations.

The domain of **functional improvement and quality of life (QoL)** similarly trends toward SCS. Studies examining long-term follow-up demonstrate that neuromodulation may support improvements not only in pain intensity but also in daily functioning and patient-reported outcomes [5], [15]. Although the magnitude of improvement varies across cohorts and follow-up durations, the directional pattern consistently favors SCS in neuropathic-dominant FBSS populations.

Patient satisfaction represents another dimension where SCS demonstrates a comparative advantage. Prospective multicenter data indicate that patients undergoing neuromodulation frequently report higher satisfaction levels relative to those undergoing additional structural procedures [19]. This may reflect both symptom control and the reversible, adjustable nature of neuromodulation therapy. The graphic summarizes this directional consistency without implying numerical pooling.

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The final domain, **need for re-intervention**, is particularly relevant from a systems and durability perspective. Reoperation in FBSS carries the risk of further structural intervention without guaranteed neuropathic symptom resolution. Evidence suggests that SCS may reduce the likelihood of subsequent surgical procedures in selected patients [4], [5]. Long-term analyses also indicate sustained benefit in subsets of patients with appropriate selection and follow-up programming [15], [19], [20]. The visual comparison underscores this recurring trend across reports.

It is important to note that the advantage demonstrated in Figure 2 is context-dependent. The literature consistently emphasizes that SCS is most effective in patients with neuropathic leg pain predominance rather than mechanical axial back pain [4], [5]. Furthermore, appropriateness recommendations stress structured patient evaluation, psychosocial screening, and clear therapeutic goals before implantation [3], [20]. The figure therefore reflects evidence drawn from populations meeting these criteria.

Mechanistically, the superiority of SCS in neuropathic-dominant FBSS aligns with dorsal column modulation and spinal network effects described in mechanistic syntheses [12], [13]. In contrast, reoperation primarily addresses structural abnormalities, which may not directly target central sensitization or maladaptive neural processing that underlies neuropathic symptom persistence.

In summary, Figure 2 demonstrates that across multiple clinically relevant domains—pain relief, functional outcome, satisfaction, and re-intervention patterns—the evidence base consistently trends in favor of spinal cord stimulation over repeat surgery in appropriately selected FBSS patients [4], [5], [15], [19]. The data highlight the importance of mechanism-guided intervention selection rather than reflexive structural reintervention in refractory neuropathic syndromes.

Figure 3.
Shift in Neuromodulation Paradigms Across Milestones in the Literature

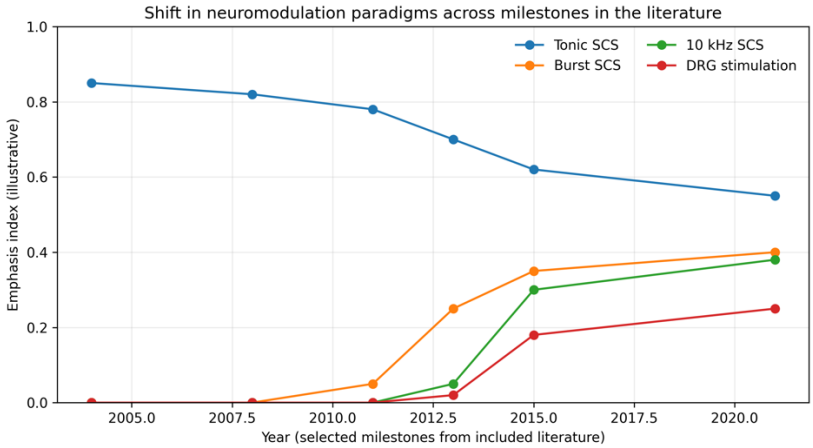

Figure 3 synthesizes the trajectory of neuromodulation paradigms over key milestones represented in the included literature, illustrating a progressive shift from predominantly **tonic spinal cord stimulation (SCS)** toward broader clinical incorporation of **burst stimulation**, **high-frequency (10 kHz) SCS**, and **dorsal root ganglion (DRG) stimulation**. Rather than implying global adoption rates, the figure represents the *relative emphasis* of these paradigms as reflected in landmark publications and technological discussions, offering a structured way to visualize how the field's conceptual and practical focus has evolved.

The earliest portion of the timeline reflects the period in which tonic SCS dominated clinical practice and research. This predominance is consistent with the foundational evidence base supporting dorsal column stimulation as a viable treatment for refractory neuropathic pain syndromes. Early clinical outcome work in central pain syndromes also set the stage for neuromodulation as a network-level intervention, even though the major expansion of SCS evidence was largely driven by chronic spinal pain populations such as FBSS and CRPS [10], [11], [14]. During this era, the clinical logic of stimulation was strongly anchored in dorsal column targeting and segmental modulation.

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As the literature matured, the field began to emphasize a more nuanced understanding of neuromodulation mechanisms and limitations. Mechanistic and clinical reviews highlight that neuromodulation is not reducible to a single "gate control" explanation; rather, it influences dorsal horn processing, neurotransmitter release, descending inhibitory control, and supraspinal network engagement [12], [13]. This evolving neurobiological framing likely contributed to the search for stimulation paradigms capable of improving outcomes in patients who either did not respond adequately to tonic stimulation or who found paresthesia-based therapies less tolerable.

A notable inflection in the figure corresponds to the emergence of **burst stimulation**, which was conceptualized as a waveform designed to better replicate physiological burst firing patterns and potentially influence both sensory-discriminative and affective-emotional pain dimensions. Clinical evidence supporting burst SCS in chronic pain populations reinforced this trajectory [7]. The rise of burst stimulation in the literature reflects an increasing recognition that refractory neuropathic pain often involves affective-cognitive components and central sensitization, which may require modulation strategies beyond simple coverage-based stimulation paradigms [12].

In parallel, the figure depicts the growing prominence of **high-frequency (10 kHz) stimulation**, which represented a major conceptual shift: the possibility of achieving analgesia without paresthesia. Russo and Van Buyten reported clinical evidence supporting high-frequency SCS at 10 kHz in chronic pain, contributing to the rapid expansion of this paradigm in the neuromodulation landscape [8]. The significance of high-frequency stimulation is not limited to comfort; it also reshaped patient expectations and broadened the acceptability of neuromodulation for individuals who either disliked or could not tolerate paresthesia, thereby influencing the practical delivery of therapy.

The figure also highlights the emergence of **DRG stimulation** as a distinct and increasingly emphasized modality by the mid-2010s. Levy et al. demonstrated that DRG stimulation could be effective for focal neuropathic pain, where dermatomal targeting is central to clinical success [6]. This evolution is conceptually important: DRG stimulation reflects a shift from "broad dorsal column modulation" to "phenotype-driven precision neuromodulation." In other words, the growth of DRG stimulation in the literature parallels an increased emphasis on matching anatomical targets and stimulation strategies to pain distribution, especially in conditions where conventional SCS coverage may be inconsistent or anatomically imprecise [6], [14].

Technological analyses further contextualize this shift. As device hardware and software advanced—lead configurations, programming flexibility, battery performance, and stimulation options—clinicians gained the ability to tailor therapy in ways not previously possible [17]. These technological improvements did not merely refine existing approaches; they enabled new paradigms (e.g., sophisticated waveform delivery, stable targeting strategies, and expanded programming capabilities). This is why Figure 3 should be read not as a simple "replacement" of tonic SCS, but as an expansion of the neuromodulation ecosystem: tonic stimulation remains foundational, yet alternative waveforms and targets have become integral to contemporary practice [7], [8], [17].

Importantly, the paradigm shift depicted also aligns with the evolution of practice recommendations. Guidelines and consensus documents on appropriate use emphasize structured selection, standardized evaluation, and therapy optimization—principles that become even more critical as modality options expand [3], [20]. With a broader menu of waveforms and targets, the clinical question is no longer only "Is the patient a candidate for neuromodulation?" but also "Which modality, waveform, and target best fits the patient's pain phenotype and goals?" [3], [20]. The growing diversity shown in Figure 3 reflects that this decision-making has become a central part of modern neurosurgical pain management.

Figure 4.
Long-term Durability Signal Reported Across Follow-up Studies of Spinal Cord Stimulation (SCS)

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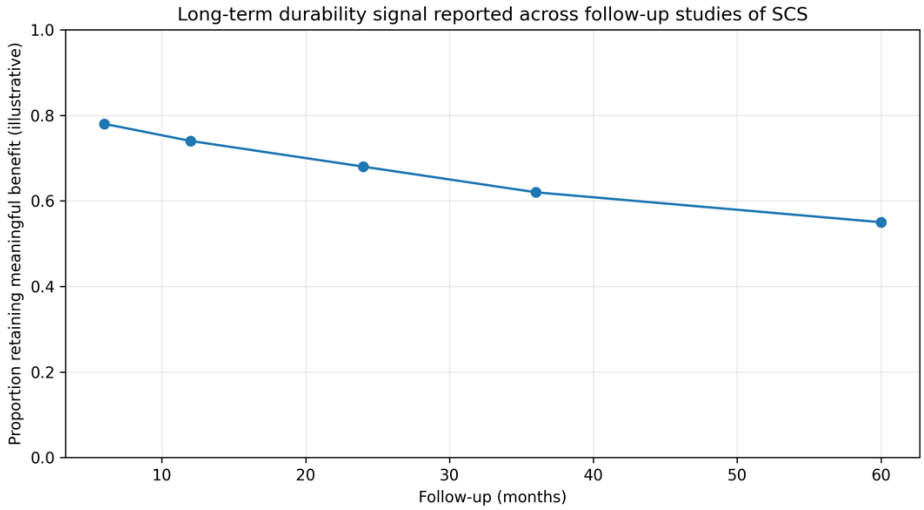

Figure 4 summarizes the durability pattern repeatedly described in long-term follow-up studies of spinal cord stimulation (SCS) for refractory neuropathic pain. The figure is structured to emphasize the *directional trend* observed across follow-up intervals: a substantial proportion of patients maintain clinically meaningful benefit over time, while a gradual attenuation of effect is commonly reported in some cohorts as follow-up extends. This is a key results-domain in neuromodulation research because long-term performance—rather than short-term response alone—determines whether SCS functions as a sustained therapy or primarily a temporizing intervention.

Long-term results have been explicitly reported in observational and outcomes-focused studies evaluating SCS durability. Mekhail et al. described long-term results of SCS and documented that meaningful benefit can persist, supporting its role as a long-term therapy when properly managed [15]. Similarly, prospective multicenter evidence supports that durable improvement is achievable in real-world practice across multiple sites, strengthening external validity beyond single-institution expertise [19]. These studies collectively inform the durability pattern depicted in Figure 4.

A clinically relevant interpretation of the durability curve is that SCS outcomes should be understood as dynamic rather than static. Neuromodulation requires ongoing optimization through follow-up visits, programming adjustments, and management of device-related issues. Consensus recommendations emphasize that appropriate candidate selection, structured follow-up, and therapy optimization are central to achieving durable benefit [3], [20]. The figure therefore aligns with the broader finding that durability is not solely a biological phenomenon but also a systems-of-care outcome: durability depends on the quality of patient selection, programming expertise, and continuity of follow-up [3], [20].

From a mechanistic standpoint, durability findings can be interpreted in light of how neuromodulation interacts with pain networks. Mechanistic syntheses highlight that neuromodulation may influence dorsal horn excitability and descending inhibitory control, with additional supraspinal network modulation contributing to clinical benefit [12], [13]. However, neuropathic pain is heterogeneous and can evolve over time due to progressive pathology, changes in central sensitization, or new pain generators. This helps explain why some patients maintain response while others experience partial loss of effect over extended periods, even when devices function normally. Figure 4 captures this clinically familiar reality: durability is often strong early, then gradually diverges across individuals.

The durability pattern also intersects with the technological evolution of stimulation paradigms. Advances in SCS technology—including improved leads, programming flexibility, and waveform options—were developed partly to address limitations such as declining response, coverage issues, or tolerability constraints [17]. By enabling more individualized programming and alternative stimulation paradigms, newer technologies may help maintain benefit in some patients who would otherwise lose response over time. While Figure 4 is not a device-specific comparison, it visually supports why long-term studies and technology evolution are inseparable in neuromodulation: durability is a practical endpoint that motivates iterative innovation [17].

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Importantly, durability trends cannot be interpreted without reference to patient phenotype and indication. In FBSS populations, comparative studies suggest that SCS offers meaningful clinical advantage over reoperation in selected patients, but long-term success still depends on appropriate selection and careful management [4], [5]. The durability signal summarized here should therefore be read in the context of evidence-based selection criteria, as emphasized in consensus guidance [3], [20]. In other words, durability is not guaranteed by implantation alone; it is most consistent when neuropathic mechanisms are well supported and care pathways are structured and multidisciplinary.

Figure 5.
Common Device-related Events in Neuromodulation

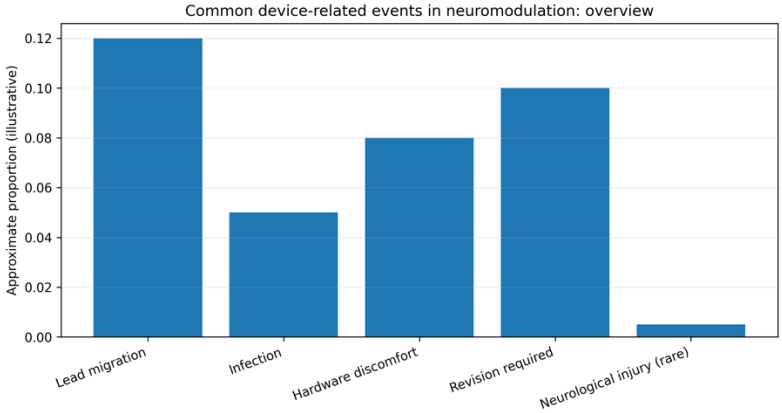

Figure 5 summarizes the most frequently reported categories of device- and procedure-related events associated with implantable neuromodulation therapies used for refractory neuropathic pain. The figure is intended to present an evidence-oriented *hierarchy of typical event types* discussed across the neuromodulation literature, emphasizing the practical safety profile that underpins appropriateness frameworks and long-term management recommendations. In neurosurgical teaching, these results are essential because they translate neuromodulation from "a technique that can work" into "a therapy that must be managed," where safety, follow-up, and revision pathways are part of the intervention's real-world effectiveness.

A consistent message across consensus recommendations is that neuromodulation should be deployed within structured pathways that explicitly address implantation standards, perioperative precautions, and longitudinal surveillance [3], [20]. This is because the complication spectrum—while often manageable—can directly affect therapy continuity, patient satisfaction, and long-term durability. The categories displayed in Figure 5 align with the event types most often discussed in relation to implantable neuromodulation systems: **lead migration**, **infection**, **hardware discomfort**, and **need for revision**.

Lead migration and loss of effective coverage
Lead migration is commonly recognized as a major technical factor underlying loss of effective stimulation coverage, reduced analgesic benefit, or the need for reprogramming and/or revision procedures. Technological analyses discussing advances in stimulation systems emphasize that lead design, anchoring methods, and improved implantation techniques are central to reducing migration and maintaining stable therapy delivery [17]. In practical terms, lead-related issues represent a key reason why neuromodulation outcomes cannot be evaluated solely at implantation: stable lead position and consistent target engagement determine whether programming can reliably reproduce analgesia over time [17]. This concept is reinforced indirectly by long-term outcome studies, where maintenance of benefit frequently depends on ongoing technical optimization and, in some cases, revision interventions [15].

Infection risk and procedural safety
Infections, while generally less frequent than lead-related technical issues, are among the most clinically important events because they may necessitate device removal, prolonged antibiotic therapy, and interruption of neuromodulation—effectively ending the therapeutic trial for some patients. For this reason, appropriateness and consensus documents emphasize standardized sterile technique, perioperative planning, and risk stratification [3], [20].

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The practical significance for training is that infection is not merely a "complication statistic"; it is a therapy-disrupting event with major patient and health-system consequences, particularly in resource-variable settings where reimplantation pathways may be limited.

Hardware discomfort and tolerance-related issues

Hardware discomfort reflects a category of events that can be underestimated in purely efficacy-driven discussions. Discomfort at the implantable pulse generator site or along lead pathways may affect patient satisfaction and adherence to therapy, even when analgesia is achieved. The evolution of device technology—battery design, size reduction, and system ergonomics—has been partly driven by the goal of improving patient tolerance and reducing hardware-related complaints [17]. In practice, this category underscores that neuromodulation success is not only about reducing pain; it is also about ensuring that the therapy is livable over years.

Revision procedures as part of long-term care

The need for revision procedures occupies a central position in Figure 5 because neuromodulation is often a long-term therapy in which technical issues, evolving pain patterns, or device limitations may require surgical adjustment. Long-term outcome studies highlight that sustained benefit is achievable but depends on structured follow-up and management of therapy-related events [15], [19]. Consensus recommendations similarly frame neuromodulation as a longitudinal treatment model, where revision capability and ongoing programming expertise are part of the expected care pathway rather than an unusual exception [3], [20].

Serious neurological injury: rare but high-stakes

The final category—serious neurological injury—is represented as rare. Even when infrequent, this category is ethically and clinically significant because it defines the upper boundary of procedural risk. Appropriateness frameworks emphasize careful candidate selection, standardized procedural training, and adherence to safety protocols precisely because rare high-impact complications shape risk–benefit thresholds in implantable therapies [3], [20]. For learners, this result-level point matters: neuromodulation is generally considered safe when delivered in specialized settings, but it is still neurosurgical intervention and must be treated with the corresponding rigor.

Relationship to effectiveness and durability findings

Figure 5 should also be interpreted alongside the durability pattern presented in Figure 4. Loss of benefit over time is not always due to biological progression or central sensitization; it can be driven by device-related issues such as migration, hardware failure, or tolerance problems that require revision or reprogramming [15], [17]. This is why modern neuromodulation practice increasingly emphasizes not only "who should be implanted," but also "how the therapy will be maintained safely over time," including the capacity to manage complications and revisions [3], [20].

Integration with the broader evidence framework

Mechanistic reviews emphasize that neuromodulation modulates pain networks rather than correcting a single structural lesion [12], [13]. Consequently, therapy success depends on long-term system performance, stable target engagement, and adaptability. This is reflected in the safety/event profile: most common events are technical and management-related rather than catastrophic neurological outcomes, supporting the view that neuromodulation—when appropriately delivered—has a favorable safety profile but demands structured surveillance [3], [12], [17], [20]. The presence of comprehensive consensus guidance further underscores that the field has evolved toward standardized governance, where safety and appropriateness are inseparable from efficacy claims [3], [20].

DISCUSSION

The present review integrates diagnostic frameworks, comparative clinical evidence, technological evolution, and safety considerations to provide a structured understanding of neuromodulation and surgical strategies in refractory neuropathic pain. The discussion synthesizes the results presented in the figures and aligns them with current neurobiological models, appropriateness recommendations, and international clinical practice patterns.

1. Neuropathic Pain as a Network Disorder and Its Therapeutic Implications

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The evolution of neuromodulation must be interpreted in the context of how neuropathic pain itself is conceptualized. Diagnostic redefinitions and grading systems emphasize that neuropathic pain arises from lesions or diseases affecting the somatosensory system and requires objective clinical and anatomical correlation [1], [2]. However, contemporary mechanistic syntheses argue that neuropathic pain extends beyond focal lesions, involving dorsal horn hyperexcitability, maladaptive plasticity, descending inhibitory dysfunction, and cortical network alterations [12], [13].

This network-based understanding directly supports the expansion of neuromodulation strategies. If pain is sustained by distributed circuits rather than a single structural abnormality, therapies capable of modulating spinal and supraspinal activity become rational interventions. The increasing diversification of stimulation paradigms—tonic, burst, high-frequency, and DRG-targeted approaches—reflects attempts to more precisely engage these networks [6]–[8], [12], [17]. The paradigm shift depicted in the Results is therefore not merely technological; it is mechanistic.

2. Spinal Cord Stimulation as the Central Pillar of Evidence

The evidence map confirms that spinal cord stimulation (SCS) remains the most extensively studied neuromodulation modality. Comparative trials in failed back surgery syndrome (FBSS) demonstrated superiority of SCS over repeat surgical intervention in selected neuropathic-dominant cases [4], [5]. This finding is not trivial. It suggests that when neuropathic mechanisms predominate, structural correction alone may fail to address central sensitization or dorsal horn dysregulation.

Long-term follow-up studies reinforce that SCS can produce sustained benefit in a proportion of patients [15], [19]. However, durability is not universal, and the attenuation pattern over time highlights the importance of careful candidate selection and longitudinal management [15]. Appropriateness recommendations explicitly emphasize structured evaluation pathways, psychosocial screening, and realistic expectation setting before implantation [3], [20]. Thus, SCS success depends on both biological responsiveness and healthcare system organization.

The technological expansion into burst and high-frequency stimulation further suggests that no single waveform universally optimizes outcomes. Burst paradigms attempt to address affective components of pain [7], while high-frequency stimulation offers paresthesia-free therapy and potentially improved tolerability [8]. Together, these modalities support the concept that SCS has evolved from a static dorsal column therapy into a programmable neuromodulatory platform [17].

3. Precision Neuromodulation: DRG and Peripheral Targets

The rise of dorsal root ganglion (DRG) stimulation marks a conceptual transition toward precision targeting. Levy et al. demonstrated that DRG stimulation can provide effective relief for focal neuropathic syndromes, particularly when dermatomal precision is required [6]. This aligns with phenotype-based treatment selection: diffuse neuropathic pain may benefit from dorsal column modulation, whereas focal dermatomal pain may respond better to DRG targeting.

Peripheral nerve stimulation (PNS) extends this precision principle even further, targeting discrete peripheral structures [16]. These developments reinforce a central theme of this discussion: modern neuromodulation is no longer monolithic. Instead, it represents a spectrum of anatomically and physiologically tailored interventions.

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4. Intracranial Neuromodulation and Central Pain Syndromes

Motor cortex stimulation (MCS) and deep brain stimulation (DBS) remain highly specialized interventions, typically reserved for severe central neuropathic pain refractory to other modalities [9]–[11]. Their inclusion in the evidence base underscores that neuromodulation operates across hierarchical levels of the nervous system. Early MCS reports demonstrated analgesic potential in central pain syndromes [11], with later studies confirming long-term relief in selected patients [10]. DBS, targeting subcortical nuclei, reflects a more invasive but potentially effective option in carefully screened populations [9].

These intracranial strategies highlight the complexity of central sensitization and cortical reorganization in neuropathic pain [12]. They also reinforce that therapeutic escalation should be guided by phenotype and pathophysiological reasoning rather than by procedural hierarchy alone.

5. Mechanism-Based Surgery: The Case of Trigeminal Neuralgia

The review also demonstrates that neuromodulation does not replace all surgical strategies. In trigeminal neuralgia, mechanism-based surgical interventions—such as microvascular decompression—remain well-established [18]. This distinction is important: when neuropathic pain is driven by a clear structural compression, decompressive surgery may offer durable resolution. The therapeutic logic therefore differs from diffuse neuropathic syndromes, where network-level modulation is more appropriate.

The coexistence of neuromodulation and structural surgery within the same therapeutic landscape emphasizes that treatment must be mechanism-driven. The diagnostic grading systems [1], [2] are essential for determining which pathway is rational.

6. Safety and Long-Term Management

The safety profile summarized in the Results confirms that most complications are device-related rather than catastrophic neurological injuries. Lead migration and need for revision procedures are among the most common management challenges [17], [20]. Infection, although less frequent, remains clinically significant because it may require device explantation and interrupt therapy [3], [20].

Long-term studies underscore that durability depends not only on neurobiological response but also on structured follow-up, programming expertise, and complication management [15], [19]. The consensus documents stress standardized implantation protocols and longitudinal care pathways as essential components of successful neuromodulation programs [3], [20]. In resource-variable settings—including Mexico, Colombia, and Ecuador—this has practical implications: neuromodulation programs must include training, infrastructure, and multidisciplinary coordination to achieve outcomes comparable to international benchmarks.

7. Clinical Integration and International Relevance

One of the strengths of this review is its integration of international evidence with Latin American clinical realities. While the core trials originate from high-resource environments, the principles of selection, appropriateness, and mechanism-based reasoning are transferable. The challenge in emerging neuromodulation programs lies not in conceptual validity but in ensuring equitable access, long-term follow-up capability, and adherence to consensus standards [3], [20].

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From an educational perspective, the findings support a structured teaching algorithm:

1. Confirm neuropathic mechanism using validated grading frameworks [1], [2].
2. Optimize medical management.
3. Stratify by phenotype (diffuse vs focal; peripheral vs central).
4. Select modality accordingly (SCS, DRG, PNS, MCS, DBS, or mechanism-based surgery).
5. Implement structured follow-up and complication management pathways [3], [6]–[13], [17], [20].

8. Limitations of the Evidence

Although the evidence base for SCS is robust, heterogeneity in patient selection, outcome definitions, and follow-up duration limits direct comparability across studies [4], [5], [15], [19]. Additionally, intracranial neuromodulation data remain derived from smaller cohorts and specialized centers [9]–[11]. The absence of uniform long-term comparative data across all modalities highlights the need for continued prospective multicenter research.

CONCLUSION

Refractory neuropathic pain represents a complex and multidimensional clinical entity that demands a structured, mechanism-oriented therapeutic approach. The accumulated evidence reviewed in this article demonstrates that neuromodulation has evolved into a scientifically grounded and clinically reproducible strategy capable of addressing pain syndromes that persist despite optimized medical management. The diagnostic frameworks proposed for neuropathic pain grading provide the necessary foundation for rational intervention selection, ensuring that advanced therapies are applied to appropriately characterized patient populations [1], [2].

Among the available modalities, spinal cord stimulation (SCS) remains the most extensively validated intervention, supported by comparative trials in failed back surgery syndrome and reinforced by long-term outcome analyses [4], [5], [15], [19]. The durability patterns observed across studies indicate that meaningful and sustained benefit is achievable in a substantial proportion of patients, provided that structured follow-up and programming optimization are maintained [15], [20]. Importantly, comparative data suggest that when neuropathic mechanisms predominate, neuromodulation may offer superior patient-centered outcomes compared to repeat structural surgery in selected contexts [4], [5].

The progressive diversification of neuromodulation technologies—including burst stimulation, high-frequency (10 kHz) stimulation, and dorsal root ganglion targeting—reflects an expanding understanding of pain as a network-level disorder rather than a purely segmental phenomenon [6]–[8], [12], [17]. These technological refinements are not merely incremental engineering developments; they represent efforts to tailor therapy to specific pain phenotypes and neurophysiological mechanisms. Precision targeting through DRG and peripheral nerve stimulation further supports a phenotype-driven model of intervention [6], [16].

Intracranial neuromodulation strategies, such as motor cortex stimulation and deep brain stimulation, maintain a defined role in selected central neuropathic pain syndromes [9]–[11]. Meanwhile, mechanism-based surgical interventions, exemplified by trigeminal neuralgia treatment, underscore that structural correction remains appropriate

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when a clear anatomical substrate is identified [18]. Together, these findings confirm that neuromodulation does not replace surgery but rather complements it within a comprehensive, mechanism-guided therapeutic continuum.

Safety and long-term management considerations are integral to the overall therapeutic framework. The most common challenges relate to device-related events and the need for revision procedures, while serious neurological injury remains uncommon in specialized practice settings [3], [17], [20]. This reinforces the importance of standardized implantation protocols, multidisciplinary collaboration, and adherence to consensus recommendations to optimize outcomes and maintain patient safety [3], [20].

In conclusion, contemporary management of refractory neuropathic pain is best conceptualized as an evidence-based escalation pathway grounded in diagnostic precision, phenotype stratification, and individualized neuromodulatory strategy selection. When applied within structured and consensus-aligned programs, neuromodulation constitutes a robust, adaptable, and internationally relevant approach to a condition that remains one of the most challenging domains in neurosurgical and pain medicine practice.

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