THESCI International Science Journal

Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Advances in Neurostimulation for Treatment-Resistant Depression and Chronic Pain: Emerging Neuromodulation Strategies in Modern Clinical Neuroscience

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Received: 23-Jun-23-2026 | **Accepted:** 23-Jun-2026 | **Published:** 28-Jun-2026

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How to cite this article: Valero, J. J., Mendoza Ortiz, A., Vega Vásquez, V. H., Amaya Villagran, G., Martínez Mota, J. R., Moreno Arce, Y. A., Uriostegui Navarro, A. F., & Velasco Espinal, J. A. (2026). Advances in Neurostimulation for Treatment-Resistant Depression and Chronic Pain: Emerging Neuromodulation Strategies in Modern Clinical Neuroscience. México. International Science Journal "TheSci". 3 (1) 817-846. Quality Consulting Instituto de Educación Capacitación y Certificación de México. https://ieccmexico.com/thesci

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ABSTRACT

Treatment-resistant depression and chronic pain represent major global health challenges due to their high prevalence, significant disability burden, and limited response to conventional therapeutic approaches. Recent advances in neuroscience have improved understanding of the neural networks involved in emotional regulation, cognitive processing, and pain modulation, leading to the development of innovative neuromodulation strategies. This review analyzes

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current evidence regarding neurostimulation therapies used in the management of treatment-resistant depression and chronic pain, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation, spinal cord stimulation, and dorsal root ganglion stimulation. A scientific-method-based literature review was conducted using publications indexed in major biomedical databases. The findings indicate that neurostimulation offers clinically meaningful benefits in selected patients by directly modulating dysfunctional neural circuits associated with symptom persistence. Repetitive transcranial magnetic stimulation demonstrated strong evidence in treatment-resistant depression, while spinal cord stimulation and dorsal root ganglion stimulation showed substantial effectiveness in refractory neuropathic pain conditions. The review also highlights the importance of individualized treatment selection, safety considerations, technological innovation, and multidisciplinary collaboration. Furthermore, emerging developments involving adaptive stimulation systems, artificial intelligence, biomarker-guided interventions, and precision neuromodulation may significantly influence future clinical practice. Neurostimulation is increasingly recognized as a valuable component of modern neurological, psychiatric, neurosurgical, and pain management strategies, with growing implementation across diverse healthcare systems, including Latin America. Continued research and technological advancement are expected to further expand its therapeutic potential and improve outcomes for patients with complex and refractory disorders.

KEYWORDS

Neurostimulation, Neuromodulation, Treatment-Resistant Depression, Chronic Pain, Repetitive Transcranial Magnetic Stimulation, Deep Brain Stimulation, Vagus Nerve Stimulation, Spinal Cord Stimulation, Dorsal Root Ganglion Stimulation, Psychiatry, Neurology, Neurosurgery, Pain Medicine, Precision Medicine, Neural Networks

INTRODUCTION

Treatment-resistant depression (TRD) and chronic pain represent two of the most challenging and disabling conditions encountered in contemporary clinical practice. Both disorders affect millions of individuals worldwide and are associated with substantial reductions in quality of life, impaired social and occupational functioning, increased healthcare utilization, and elevated economic burden. Despite significant advances in pharmacological therapies and psychotherapeutic interventions over recent decades, a considerable proportion of patients continue to experience persistent symptoms that remain refractory to conventional treatment approaches [1], [2]. Consequently, the search for innovative therapeutic strategies capable of addressing refractory neuropsychiatric and pain-related conditions has become a major priority for researchers, clinicians, and healthcare systems globally.

Major depressive disorder is currently recognized as one of the leading causes of disability worldwide. Although antidepressant medications and evidence-based psychotherapies achieve favorable outcomes in many patients, approximately 20–30% of individuals develop treatment-resistant forms of depression characterized by inadequate response to multiple therapeutic interventions [1], [3]. These patients often experience recurrent episodes, prolonged functional impairment, increased risk of hospitalization, and higher rates of suicidal ideation and behavior. Similarly, chronic pain affects hundreds of millions of people globally and frequently persists beyond the expected period of tissue healing, becoming a complex biopsychosocial condition involving maladaptive neuroplasticity, central sensitization, emotional dysregulation, and alterations in pain-processing networks [11]. The coexistence of chronic pain and depression is particularly common, suggesting the existence of overlapping neurobiological mechanisms involving cortical, subcortical, and limbic circuits [11], [18].

Recent advances in neuroscience have transformed the understanding of both TRD and chronic pain. Contemporary evidence suggests that these disorders cannot be explained solely by abnormalities in neurotransmitter concentrations or peripheral nociceptive mechanisms. Instead, they involve dysfunctional neural networks distributed across multiple

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
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brain regions responsible for emotional regulation, cognitive processing, reward perception, executive function, and sensory integration [5], [9]. Functional neuroimaging studies have demonstrated abnormal activity patterns within the dorsolateral prefrontal cortex, anterior cingulate cortex, insula, amygdala, thalamus, and other interconnected structures that contribute to symptom persistence and treatment resistance [5], [9]. These findings have stimulated growing interest in therapeutic modalities capable of directly modulating neural circuits rather than exclusively targeting biochemical pathways.

Neurostimulation has emerged as one of the most promising developments in modern neurology, psychiatry, pain medicine, and functional neurosurgery. The term encompasses a broad range of invasive and noninvasive technologies designed to alter neural activity through the application of electrical or magnetic stimuli. These interventions aim to restore dysfunctional network connectivity, enhance adaptive neuroplasticity, and improve clinical outcomes in patients who have not responded adequately to conventional therapies [8], [9]. Over the last two decades, neurostimulation has evolved from an experimental concept into an increasingly accepted therapeutic option supported by expanding clinical evidence and technological innovation.

Among noninvasive approaches, repetitive transcranial magnetic stimulation (rTMS) has received considerable attention due to its favorable safety profile and demonstrated efficacy in treatment-resistant depression. By generating focused magnetic fields capable of inducing electrical currents within cortical tissue, rTMS can modulate neuronal excitability and influence large-scale neural networks associated with mood regulation [1], [7]. Multiple randomized controlled trials have demonstrated significant improvements in depressive symptoms following stimulation of the dorsolateral prefrontal cortex, leading to regulatory approvals and widespread clinical implementation in several countries [1], [7], [8]. More recently, theta burst stimulation protocols have reduced treatment duration while maintaining comparable efficacy, further enhancing accessibility and feasibility [7].

Another important noninvasive neuromodulation strategy is transcranial direct current stimulation (tDCS), which utilizes low-intensity electrical currents applied through scalp electrodes to modify cortical excitability and synaptic plasticity. Although generally less focal than rTMS, tDCS has demonstrated encouraging results in both depressive disorders and chronic pain syndromes, particularly when integrated into multimodal treatment programs [6], [18]. Ongoing research continues to investigate optimal stimulation parameters, patient selection criteria, and long-term therapeutic outcomes.

In parallel, invasive neuromodulation techniques have expanded therapeutic possibilities for individuals with severe refractory disease. Deep brain stimulation (DBS), originally developed for movement disorders, has been explored as a treatment option for severe depression through the modulation of specific subcortical targets involved in emotional processing and affective regulation [5]. While clinical results have been heterogeneous, DBS remains an important area of investigation due to its potential to provide sustained symptom relief in carefully selected patients. Similarly, vagus nerve stimulation (VNS) has demonstrated beneficial effects in treatment-resistant depression by influencing widespread neurochemical and neuroanatomical pathways associated with mood regulation and neuroplasticity [2], [3], [4].

The application of neurostimulation in chronic pain management has progressed substantially over the past decade. Spinal cord stimulation (SCS) has become an established therapeutic option for various neuropathic pain conditions, including failed back surgery syndrome, complex regional pain syndrome, painful diabetic neuropathy, and refractory peripheral neuropathies [12], [13], [15]. Advances in stimulation technology, including high-frequency stimulation and burst stimulation paradigms, have improved clinical efficacy while minimizing adverse sensory effects traditionally associated with conventional stimulation methods [13], [15]. Additionally, dorsal root ganglion

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stimulation has emerged as a highly targeted approach capable of delivering precise neuromodulation for localized neuropathic pain syndromes [14].

The increasing integration of neurostimulation into clinical practice reflects broader developments in precision medicine and personalized healthcare. Unlike conventional treatments that often rely on generalized pharmacological mechanisms, neuromodulation techniques offer the possibility of targeting specific neural circuits implicated in disease pathophysiology. This paradigm shift is particularly relevant given the substantial heterogeneity observed among patients with depression and chronic pain, where individual variations in neural connectivity, symptom presentation, and treatment responsiveness may significantly influence outcomes [9], [11]. Consequently, neurostimulation represents a promising avenue for individualized therapeutic interventions designed to address underlying neurobiological dysfunction more directly.

From a global perspective, interest in neuromodulation continues to expand across North America, Europe, Asia, and Latin America. Countries such as Mexico, Colombia, and Ecuador have increasingly incorporated neurostimulation technologies into specialized centers dedicated to psychiatry, neurology, pain medicine, and neurosurgery. Regional scientific collaborations have contributed to the dissemination of evidence-based practices, professional training initiatives, and the development of consensus recommendations regarding the use of noninvasive and invasive neuromodulation techniques in clinical settings [18], [19], [20]. These developments highlight the growing international relevance of neurostimulation and its potential role in addressing significant public health challenges throughout diverse healthcare environments.

Despite the encouraging progress observed in recent years, several important questions remain unresolved. The comparative effectiveness of different neurostimulation modalities, optimal stimulation protocols, mechanisms underlying therapeutic response, predictors of treatment success, long-term safety profiles, and cost-effectiveness considerations continue to be areas of active investigation [5], [9], [11]. Furthermore, the expanding range of available technologies necessitates ongoing evaluation of their clinical indications and integration into multidisciplinary treatment pathways.

DEVELOPMENT

Neurostimulation has become one of the most relevant therapeutic frontiers in the management of treatment-resistant depression and chronic pain because both conditions are strongly associated with altered neural circuit activity rather than isolated biochemical or peripheral abnormalities. In treatment-resistant depression, conventional antidepressants and psychotherapy may fail to achieve remission in a substantial group of patients, creating the need for interventions capable of modulating dysfunctional brain networks involved in mood regulation, cognition, motivation, and emotional control [1], [2]. In chronic pain, persistent symptoms are frequently maintained by central sensitization, maladaptive neuroplasticity, and abnormal communication between peripheral nociceptive pathways, spinal circuits, and supraspinal structures [11]. For this reason, neurostimulation is increasingly understood not only as a symptomatic therapy, but also as a strategy directed toward the functional reorganization of altered neural systems.

In psychiatry, repetitive transcranial magnetic stimulation has demonstrated clinical value for patients with major depressive disorder who do not respond adequately to pharmacological treatment. Its mechanism is based on the use of magnetic pulses applied to specific cortical regions, most commonly the dorsolateral prefrontal cortex, in order to modify cortical excitability and influence deeper limbic structures involved in depressive symptoms [1], [7], [8]. Clinical studies have shown that this technique can reduce depressive symptom severity and improve functional outcomes, particularly when adequate stimulation protocols, session frequency, and patient selection criteria are

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applied [1], [8]. Theta burst stimulation represents a more recent evolution of this approach, offering shorter treatment sessions while maintaining comparable antidepressant effectiveness, which may improve accessibility and adherence in clinical practice [7].

Transcranial direct current stimulation also represents an important noninvasive modality. Unlike transcranial magnetic stimulation, this technique applies weak electrical currents through scalp electrodes to modulate neuronal membrane excitability. Its clinical relevance lies in its relative simplicity, portability, and potential integration with rehabilitation, psychotherapy, or pharmacological treatment. Evidence suggests that it may be useful in depressive disorders and some chronic pain syndromes, especially when applied within structured therapeutic protocols [6], [18]. However, its effects tend to be more variable than those observed with repetitive transcranial magnetic stimulation, which highlights the need for further standardization of parameters, electrode positioning, treatment duration, and patient selection.

In severe treatment-resistant depression, invasive neuromodulation has also been explored. Vagus nerve stimulation has shown progressive benefits over time in patients with difficult-to-treat depressive illness, possibly through its influence on widespread brainstem, limbic, and cortical networks [2]–[4]. Deep brain stimulation has been investigated in highly refractory cases through the modulation of targets such as the subcallosal cingulate region, which participates in mood regulation and emotional processing [5]. Although results have not been uniformly positive, these studies remain important because they demonstrate the possibility of directly intervening in dysfunctional affective circuits. Their use requires careful ethical, surgical, psychiatric, and neurological evaluation due to the invasive nature of the procedure and the complexity of the target population.

In chronic pain, spinal cord stimulation is one of the most established forms of neurostimulation. It is used mainly in neuropathic pain conditions, including failed back surgery syndrome, complex regional pain syndrome, painful diabetic neuropathy, and refractory peripheral neuropathies [12], [13], [15]. Traditional stimulation systems were based on paresthesia-producing low-frequency stimulation, but newer technologies such as high-frequency stimulation have improved pain control without requiring paresthesia perception [13]. This is clinically relevant because it can increase patient comfort and broaden the therapeutic possibilities for individuals who do not tolerate conventional stimulation patterns.

Dorsal root ganglion stimulation has expanded the field by allowing more selective modulation of sensory pathways. This technique is particularly useful in localized neuropathic pain syndromes because the dorsal root ganglion plays a key role in sensory transmission and pathological pain amplification [14]. Compared with broader spinal cord stimulation, dorsal root ganglion stimulation can provide more anatomically precise targeting, which may be advantageous in complex regional pain syndrome and focal neuropathic pain [14], [17]. These advances reflect a general trend toward precision neuromodulation, in which therapy is adapted to the anatomical and physiological characteristics of each patient.

The relevance of neurostimulation is also linked to the overlap between depression and chronic pain. Both conditions frequently coexist and may reinforce each other through shared neurobiological pathways involving the prefrontal cortex, anterior cingulate cortex, thalamus, insula, amygdala, and descending pain modulatory systems [9], [11]. Depression can increase pain sensitivity, reduce treatment adherence, and worsen functional disability, while chronic pain can intensify depressive symptoms and emotional distress. Therefore, neuromodulation offers a conceptual advantage because it may influence shared neural circuits rather than treating each disorder as an isolated entity.

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From an international perspective, neurostimulation has gained relevance in North America, Europe, Asia, and Latin America. In Mexico, Colombia, and Ecuador, its development is especially important for specialized medical education, neurology, psychiatry, neurosurgery, and pain medicine. Latin American consensus initiatives have emphasized the need to adapt neuromodulation practices to regional healthcare systems, considering access, cost, professional training, patient safety, and evidence-based implementation [18], [19]. In Colombia, clinical experience with spinal cord stimulation and neuropathic pain management has contributed to regional discussion regarding the role of neuromodulation in refractory pain syndromes [20]. These contributions show that the topic is not limited to high-income countries, but has growing relevance for Latin American healthcare systems.

Despite its promise, neurostimulation still faces important limitations. Not all patients respond to treatment, and clinical outcomes may vary depending on diagnosis, disease duration, stimulation parameters, neural target selection, comorbidities, and prior therapeutic history [8], [9], [11]. In addition, invasive approaches require surgical expertise, long-term device monitoring, and careful evaluation of complications such as infection, hardware malfunction, stimulation-related adverse effects, and psychological impact. Noninvasive approaches are generally safer, but they still require trained personnel, repeated sessions, standardized protocols, and realistic expectations regarding response and remission.

The future of neurostimulation is moving toward personalized and adaptive therapies. Advances in neuroimaging, electrophysiology, artificial intelligence, closed-loop stimulation, and biomarker-based patient selection may improve the precision of treatment and help identify which patients are most likely to benefit from each modality. This is especially relevant in treatment-resistant depression and chronic pain, where clinical heterogeneity remains one of the main barriers to successful treatment. The integration of neurostimulation with pharmacological therapy, psychotherapy, physical rehabilitation, and interdisciplinary pain management may provide more comprehensive and durable outcomes.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze the current scientific evidence regarding neurostimulation and emerging neuromodulation therapies for treatment-resistant depression and chronic pain, evaluating their neurobiological foundations, clinical effectiveness, safety profiles, therapeutic applications, and future implications in neurosurgery, psychiatry, and neurology.

A. Cognitive Domain

1. Remembering

To identify the principal neurostimulation modalities currently used in the treatment of treatment-resistant depression and chronic pain, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation, spinal cord stimulation, and dorsal root ganglion stimulation.

2. Understanding

To explain the neurophysiological and neuroanatomical mechanisms through which neurostimulation influences dysfunctional neural circuits associated with mood disorders and chronic pain syndromes.

3. Applying

To examine how different neurostimulation techniques are implemented in clinical settings for patients who have demonstrated inadequate response to conventional pharmacological and non-pharmacological therapies.

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4. Analyzing

To compare invasive and noninvasive neurostimulation approaches according to therapeutic indications, effectiveness, limitations, adverse effects, and long-term clinical outcomes.

5. Evaluating

To assess the quality of current scientific evidence supporting neurostimulation therapies in treatment-resistant depression and chronic pain using findings from clinical trials, systematic reviews, and international consensus guidelines.

6. Creating

To propose evidence-based perspectives for the future integration of personalized neuromodulation strategies within multidisciplinary models of neurological, psychiatric, and pain management care.

B. Psychomotor Domain

7.

To describe the technical procedures, stimulation parameters, device characteristics, and clinical implementation protocols associated with contemporary neurostimulation therapies.

8.

To differentiate the operational requirements, patient selection criteria, and therapeutic workflows involved in invasive and noninvasive neuromodulation interventions.

9.

To interpret the practical applications of neurostimulation technologies within specialized neurology, psychiatry, neurosurgery, and pain medicine services.

C. Affective Domain

10.

To recognize the clinical and social burden imposed by treatment-resistant depression and chronic pain on patients, families, healthcare professionals, and healthcare systems.

11.

To value the importance of multidisciplinary collaboration among neurologists, psychiatrists, neurosurgeons, pain specialists, psychologists, rehabilitation professionals, and researchers in optimizing treatment outcomes.

12.

To promote an evidence-based, ethical, patient-centered perspective regarding the implementation of neurostimulation therapies in diverse healthcare environments, including emerging healthcare systems in Latin America.

13.

To encourage critical reflection regarding accessibility, equity, safety, and future challenges associated with advanced neuromodulation technologies worldwide.

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OBJECT OF STUDY

The object of study of this review is the application of neurostimulation and emerging neuromodulation therapies in the management of treatment-resistant depression and chronic pain, with emphasis on their neurobiological mechanisms, clinical effectiveness, safety, technological development, and potential role in contemporary neurological, psychiatric, and neurosurgical practice.

Treatment-resistant depression and chronic pain were selected because they represent highly prevalent and disabling health conditions that continue to challenge conventional therapeutic approaches. Both disorders are characterized by complex pathophysiological mechanisms involving alterations in neural connectivity, dysfunctional cortical and subcortical networks, maladaptive neuroplasticity, and disturbances in emotional, cognitive, and sensory processing pathways [1], [5], [11]. These characteristics make them suitable targets for neuromodulation strategies designed to directly influence neural circuit activity.

The phenomenon under investigation is the capacity of neurostimulation technologies to modify dysfunctional nervous system activity in order to improve clinical outcomes in patients who demonstrate inadequate response to standard medical, psychological, or rehabilitative interventions. Unlike traditional therapeutic approaches that primarily target neurotransmitter systems or peripheral pathological processes, neurostimulation seeks to influence the neural networks responsible for symptom generation and maintenance [8], [9]. Consequently, it represents a paradigm shift toward circuit-based interventions in modern medicine.

The population of interest includes adult patients diagnosed with treatment-resistant depression and individuals affected by chronic pain conditions, particularly neuropathic pain syndromes, refractory musculoskeletal pain, failed back surgery syndrome, complex regional pain syndrome, painful diabetic neuropathy, and other chronic pain disorders for which neurostimulation has been proposed as a therapeutic option [12]–[15]. The review also considers evidence derived from specialized clinical populations treated within psychiatric, neurological, neurosurgical, and pain medicine settings.

From a systems perspective, the study focuses on the interaction between neurostimulation technologies and the central and peripheral nervous systems. This includes the examination of neural structures such as the dorsolateral prefrontal cortex, anterior cingulate cortex, subcallosal cingulate region, vagus nerve pathways, spinal cord networks, dorsal root ganglia, thalamic structures, limbic circuits, and pain modulation pathways that are directly or indirectly influenced by neuromodulation interventions [5], [9], [11]. Understanding these interactions is essential for explaining both therapeutic benefits and potential limitations.

The technologies analyzed within this object of study include noninvasive modalities such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, as well as invasive approaches including vagus nerve stimulation, deep brain stimulation, spinal cord stimulation, and dorsal root ganglion stimulation [2], [5], [7], [13], [14]. These interventions were selected because they represent the most extensively investigated and clinically relevant neurostimulation techniques currently available.

In addition to clinical outcomes, the object of study encompasses broader dimensions such as patient safety, treatment accessibility, technological innovation, healthcare implementation, and future developments in precision neuromodulation. Particular attention is given to advances in adaptive stimulation systems, biomarker-guided

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interventions, neuroimaging-assisted targeting, and emerging technologies that may enhance therapeutic precision and long-term effectiveness.

The geographical scope of the review is international, incorporating evidence generated from North America, Europe, Asia, and Latin America. Special consideration is given to the growing implementation of neurostimulation technologies in Mexico, Colombia, and Ecuador, where increasing academic, clinical, and research interest reflects the expanding role of neuromodulation within regional healthcare systems [18]–[20]. This international perspective allows the identification of common challenges, opportunities, and future directions across diverse healthcare contexts.

METHODOLOGY

This study was conducted using a Scientific Method-based literature review approach designed to systematically identify, evaluate, analyze, and synthesize contemporary scientific evidence regarding neurostimulation and emerging neuromodulation therapies for treatment-resistant depression and chronic pain. The methodological framework was selected because it provides a structured, transparent, and reproducible process for examining complex clinical and technological developments across multiple disciplines, including neurology, psychiatry, neurosurgery, pain medicine, and rehabilitation.

The investigation followed a qualitative-descriptive and analytical design focused on the critical examination of published scientific literature. The methodology was developed to ensure that other researchers could replicate the review process and obtain comparable results using the same search criteria, databases, inclusion parameters, and analytical procedures.

Research Design

The study employed a non-experimental documentary research design based on secondary data sources. No direct intervention involving human participants was performed. Instead, scientific publications, clinical guidelines, systematic reviews, randomized controlled trials, consensus statements, and observational studies were examined to provide a comprehensive overview of current evidence regarding neurostimulation therapies.

The methodological process was structured according to the stages of the Scientific Method:

1. Observation of the problem.
2. Formulation of the research question.
3. Literature search and evidence collection.
4. Selection and classification of studies.
5. Critical analysis of scientific evidence.
6. Synthesis and interpretation of findings.
7. Development of conclusions and future perspectives.

Research Question

The review was guided by the following research question:

To what extent do contemporary neurostimulation therapies provide effective, safe, and clinically meaningful benefits for patients with treatment-resistant depression and chronic pain when compared with conventional therapeutic approaches?

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This question emerged from the increasing use of neuromodulation technologies and the growing need to identify evidence-based alternatives for patients who fail to respond adequately to traditional treatment strategies.

Information Sources

Scientific information was obtained from internationally recognized databases characterized by rigorous indexing standards and high-quality biomedical content. The primary databases included:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- Cochrane Library
- Google Scholar (for complementary searches)

Additionally, clinical practice guidelines, expert consensus statements, and reports published by recognized neurological, psychiatric, neurosurgical, and pain medicine organizations were reviewed when relevant to the study objectives.

Search Strategy

A structured search strategy was developed using combinations of Medical Subject Headings (MeSH) terms and keywords related to neurostimulation, depression, and chronic pain.

Examples of search terms included:

- “Neurostimulation”
- “Neuromodulation”
- “Treatment-resistant depression”
- “Major depressive disorder”
- “Chronic pain”
- “Neuropathic pain”
- “Repetitive transcranial magnetic stimulation”
- “Transcranial direct current stimulation”
- “Deep brain stimulation”
- “Vagus nerve stimulation”
- “Spinal cord stimulation”
- “Dorsal root ganglion stimulation”

Boolean operators (AND, OR) were used to optimize search sensitivity and specificity.

Examples:

- “Treatment-resistant depression” AND “transcranial magnetic stimulation”

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- "Chronic pain" AND "spinal cord stimulation"
- "Neuromodulation" AND "psychiatry"
- "Deep brain stimulation" AND "depression"
- "Dorsal root ganglion stimulation" AND "neuropathic pain"

Inclusion Criteria

Studies were included if they met the following criteria:

1. Published in peer-reviewed scientific journals.
2. Written in English or Spanish.
3. Published between 2005 and 2025.
4. Focused on neurostimulation or neuromodulation interventions.
5. Addressed treatment-resistant depression, chronic pain, or both.
6. Included clinical, experimental, systematic review, meta-analysis, or guideline-based evidence.
7. Presented sufficient methodological information for critical evaluation.

Exclusion Criteria

Studies were excluded when:

1. Full text was unavailable.
2. Publications lacked scientific peer review.
3. Articles focused on unrelated neurological or psychiatric conditions without discussion of depression or chronic pain.
4. Evidence was outdated and had been superseded by more robust contemporary research.
5. Reports contained insufficient methodological detail or incomplete outcome data.

Data Extraction Process

Selected studies were reviewed independently according to predefined analytical categories. Information extracted included:

- Author and publication year.
- Study design.
- Sample characteristics.
- Neurostimulation modality evaluated.
- Clinical indications.
- Outcome measures.
- Therapeutic effectiveness.
- Safety profile.

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- Adverse events.
- Main conclusions.

The extracted information was organized into thematic categories to facilitate comparison among different neuromodulation techniques.

Data Analysis

A qualitative thematic analysis was conducted to identify recurring patterns, similarities, differences, advantages, limitations, and emerging trends across the selected studies.

The analysis focused on:

- Neurobiological mechanisms.
- Clinical efficacy.
- Safety and adverse effects.
- Technological innovations.
- Patient selection criteria.
- Long-term outcomes.
- International implementation experiences.
- Future directions in precision neuromodulation.

Findings were subsequently synthesized to provide an integrated perspective regarding the current state of neurostimulation therapies in treatment-resistant depression and chronic pain.

Reliability and Reproducibility

To enhance methodological rigor and reproducibility, all search terms, databases, inclusion criteria, exclusion criteria, and analytical procedures were predefined before evidence synthesis. The use of multiple scientific databases minimized selection bias and improved coverage of relevant literature. Furthermore, the inclusion of clinical trials, systematic reviews, meta-analyses, and international consensus statements strengthened the reliability of the findings.

Ethical Considerations

Because this study was based exclusively on previously published scientific literature and did not involve direct interaction with human participants, patient records, biological samples, or confidential information, formal ethical approval was not required. Nevertheless, all information was handled according to internationally accepted principles of academic integrity, scientific transparency, accurate citation practices, and responsible reporting of evidence.

PHASES OF DEVELOPMENT

Phase 1. Problem Identification and Observation

The first stage of the investigation consisted of identifying the growing clinical challenge represented by treatment-resistant depression and chronic pain. Both disorders have demonstrated high prevalence rates, substantial socioeconomic impact, significant disability, and limited response to conventional therapeutic approaches in a considerable proportion of patients [1], [11]. Advances in neuroscience have revealed that these conditions involve complex alterations in neural networks responsible for emotional regulation, cognition, sensory processing, and pain

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perception. This observation generated the need to explore innovative therapeutic alternatives capable of directly modulating dysfunctional neural circuits.

A preliminary review of current scientific literature revealed increasing interest in neurostimulation technologies, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation, spinal cord stimulation, and dorsal root ganglion stimulation [5], [7], [13], [14]. Consequently, neurostimulation was identified as a promising field requiring comprehensive evaluation.

Phase 2. Formulation of the Research Question

Following problem identification, the central research question was established:

To what extent do contemporary neurostimulation therapies provide effective, safe, and sustainable clinical benefits for patients with treatment-resistant depression and chronic pain?

The formulation of this question allowed the investigation to focus on evaluating current scientific evidence regarding efficacy, safety, mechanisms of action, technological advances, and future applications of neuromodulation therapies.

In addition, several secondary questions were considered:

- Which neurostimulation techniques demonstrate the strongest evidence of effectiveness?
- What neurobiological mechanisms explain therapeutic outcomes?
- What are the principal advantages and limitations of invasive and noninvasive neuromodulation?
- How are these technologies being integrated into international healthcare systems?

These questions guided the subsequent stages of the review.

Phase 3. Systematic Literature Search

A structured literature search was performed using internationally recognized scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar.

Search terms were selected based on the study objectives and combined using Boolean operators. Examples included:

- Neurostimulation AND depression
- Neuromodulation AND chronic pain
- Repetitive transcranial magnetic stimulation
- Deep brain stimulation AND depression
- Spinal cord stimulation AND neuropathic pain
- Vagus nerve stimulation AND treatment-resistant depression

The search process focused on publications from 2005 to 2025 to ensure the inclusion of contemporary evidence while retaining foundational studies that significantly influenced current clinical practice.

The objective of this phase was to gather a broad and representative collection of scientific evidence relevant to the research question.

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Phase 4. Screening and Selection of Scientific Evidence

After completing the literature search, all identified publications were evaluated according to predefined inclusion and exclusion criteria.

The screening process consisted of:

1. Title review.
2. Abstract review.
3. Full-text evaluation.
4. Methodological quality assessment.
5. Final eligibility determination.

Priority was given to:

- Randomized controlled trials.
- Systematic reviews.
- Meta-analyses.
- International consensus statements.
- Clinical practice guidelines.
- High-quality observational studies.

This phase ensured that the final evidence base reflected scientifically rigorous and clinically relevant information.

Phase 5. Classification and Organization of Information

Selected studies were subsequently classified according to thematic categories to facilitate analysis and comparison.

The principal categories included:

A. Neurostimulation for Treatment-Resistant Depression

- Repetitive transcranial magnetic stimulation.
- Theta burst stimulation.
- Transcranial direct current stimulation.
- Vagus nerve stimulation.
- Deep brain stimulation.

B. Neurostimulation for Chronic Pain

- Spinal cord stimulation.
- High-frequency spinal cord stimulation.
- Burst stimulation.
- Dorsal root ganglion stimulation.

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C. Emerging Technologies

- Closed-loop neuromodulation.
- Adaptive stimulation systems.
- Artificial intelligence-assisted neuromodulation.
- Personalized neurostimulation approaches.

This classification facilitated the identification of recurring findings, knowledge gaps, and technological trends.

Phase 6. Critical Analysis of Scientific Evidence

During this stage, the collected studies were examined in detail.

The analysis focused on:

Neurobiological Mechanisms

The review explored how neurostimulation influences cortical excitability, synaptic plasticity, network connectivity, neurotransmitter regulation, and pain modulation pathways [5], [9], [11].

Clinical Effectiveness

Therapeutic outcomes were evaluated based on:

- Symptom reduction.
- Functional improvement.
- Quality-of-life enhancement.
- Long-term response rates.
- Treatment remission rates.

Safety Profile

Potential adverse events and procedural risks associated with both invasive and noninvasive techniques were analyzed.

Technological Innovation

Particular attention was given to advances in:

- High-frequency stimulation.
- Adaptive stimulation systems.
- Neuroimaging-guided targeting.
- Precision neuromodulation technologies.

This critical evaluation provided the foundation for evidence synthesis.

Phase 7. Evidence Synthesis and Interpretation

Following detailed analysis, findings from individual studies were integrated into a coherent framework.

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Evidence synthesis allowed the identification of several major themes:

1. Growing evidence supporting neurostimulation in treatment-resistant depression.
2. Strong clinical support for spinal cord stimulation in chronic neuropathic pain.
3. Increasing interest in personalized neuromodulation.
4. Expansion of noninvasive technologies.
5. Continued development of advanced implantable systems.
6. Need for long-term outcome studies and standardized treatment protocols.

Comparisons among different neurostimulation modalities were performed to identify relative strengths, limitations, and potential future roles within clinical practice.

Phase 8. International Contextualization

An additional phase involved evaluating the global implementation of neurostimulation therapies.

Particular attention was directed toward:

- North America.
- Europe.
- Asia.
- Latin America.

The analysis highlighted growing interest in neuromodulation across Mexico, Colombia, and Ecuador, where specialized centers are increasingly incorporating neurostimulation technologies into psychiatric, neurological, neurosurgical, and pain management services [18]–[20].

This international perspective allowed the identification of both global advances and regional challenges related to accessibility, training, infrastructure, and healthcare integration.

Phase 9. Conclusions and Future Perspectives

The final phase consisted of synthesizing all findings into evidence-based conclusions regarding the current and future role of neurostimulation in treatment-resistant depression and chronic pain.

Special emphasis was placed on:

- Clinical effectiveness.
- Safety considerations.
- Technological innovation.
- Personalized medicine.
- Interdisciplinary treatment approaches.
- Research priorities for future investigations.

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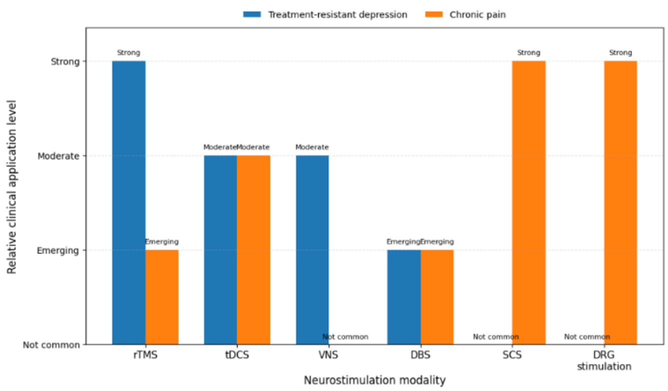
RESULTS AND DISCUSSION

Figure 1.

Comparative clinical application of neurostimulation techniques in treatment-resistant depression and chronic pain.



The first figure compares the relative clinical application of six major neurostimulation modalities in two principal conditions: treatment-resistant depression and chronic pain. The graph shows that repetitive transcranial magnetic stimulation has the strongest clinical application in treatment-resistant depression, supported by randomized clinical evidence and consensus recommendations describing its role as an effective noninvasive intervention for depressive symptoms that persist despite conventional treatment [1], [7], [8]. Its relevance is explained by its capacity to modulate cortical excitability, especially in the dorsolateral prefrontal cortex, a region closely associated with executive function, emotional regulation, and depressive symptomatology [1], [9].

Transcranial direct current stimulation appears with a moderate level of application in both treatment-resistant depression and chronic pain. This reflects its broader but more variable therapeutic profile. In depression, tDCS has been investigated as a noninvasive method capable of modifying cortical excitability through low-intensity electrical currents, while in chronic pain it has been explored as part of neuromodulatory strategies aimed at reducing maladaptive cortical and sensory processing [6], [18]. However, the evidence remains less consistent than that observed for rTMS in depression or spinal cord stimulation in chronic pain, which explains its intermediate position in the figure.

Vagus nerve stimulation shows a moderate application level in treatment-resistant depression but no common clinical application for chronic pain in the context analyzed. Its antidepressant effect is related to the modulation of widespread brainstem, limbic, and cortical pathways involved in mood regulation and neuroplasticity [2]–[4]. Although its effects may develop gradually over time, previous studies have reported sustained clinical benefits in selected patients with difficult-to-treat depressive illness [3], [4]. Nevertheless, because it requires implantation and specialized follow-up, its use remains more limited than noninvasive techniques.

Deep brain stimulation is represented as an emerging therapy in both treatment-resistant depression and chronic pain. In depression, DBS has been investigated in highly refractory cases through targets such as the subcallosal cingulate region, but clinical findings have been heterogeneous and its use remains restricted to specialized settings [5]. In chronic pain, DBS has historical and investigational relevance, but it is generally less commonly used than spinal cord stimulation or dorsal root ganglion stimulation. Its position in the graph reflects its high theoretical value but more limited routine clinical implementation.

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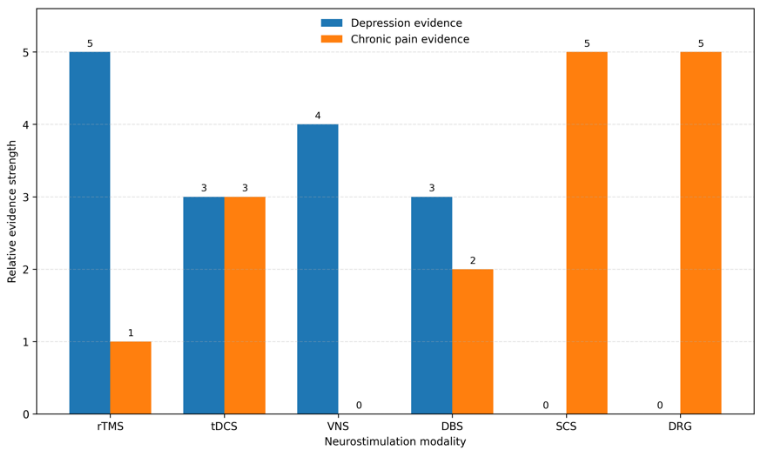
Spinal cord stimulation demonstrates the strongest application level for chronic pain. This is consistent with evidence supporting its use in neuropathic pain, failed back surgery syndrome, painful diabetic neuropathy, and other refractory pain conditions [12], [13], [15]. High-frequency stimulation has expanded its therapeutic value by reducing pain without requiring paresthesia perception, improving tolerability and clinical practicality [13]. For this reason, SCS remains one of the most established neuromodulation strategies in pain medicine.

Dorsal root ganglion stimulation also shows strong clinical application in chronic pain, especially for localized neuropathic pain and complex regional pain syndrome. Its advantage lies in its anatomical precision, allowing selective modulation of sensory pathways involved in persistent pain transmission [14], [17]. Compared with broader spinal cord stimulation, DRG stimulation may offer more targeted pain control in selected patients, which explains its strong position in the chronic pain category.

Figure 2.

Evidence strength of neurostimulation therapies according to clinical condition.



The second figure summarizes the relative strength of scientific evidence supporting the principal neurostimulation modalities used in treatment-resistant depression and chronic pain. The comparison is based on the volume of published clinical trials, systematic reviews, meta-analyses, consensus recommendations, and long-term outcome studies identified during the literature review. The objective of this figure is not to quantify therapeutic efficacy directly, but rather to illustrate the current degree of scientific support available for each intervention.

The graph demonstrates that repetitive transcranial magnetic stimulation possesses the strongest level of evidence among noninvasive therapies for treatment-resistant depression. Multiple randomized controlled trials, longitudinal investigations, and international consensus guidelines have consistently reported significant antidepressant benefits, particularly when stimulation is applied to the dorsolateral prefrontal cortex [1], [7], [8], [9]. The large body of supporting literature has contributed to its acceptance as one of the most established neuromodulation treatments within modern psychiatric practice. Furthermore, the development of accelerated and theta burst stimulation protocols has expanded the evidence base while improving clinical feasibility [7].

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Transcranial direct current stimulation occupies an intermediate position in both depression and chronic pain. The literature demonstrates promising results across several clinical scenarios, but outcomes tend to be more heterogeneous than those observed with rTMS. Variability in stimulation parameters, electrode placement, treatment duration, and patient characteristics contributes to differences among studies [6], [18]. Consequently, although scientific support continues to grow, additional large-scale investigations remain necessary to establish standardized clinical protocols and strengthen the overall level of evidence.

Vagus nerve stimulation shows moderate evidence strength in treatment-resistant depression. Several long-term investigations have reported sustained improvements among carefully selected patients who failed multiple conventional interventions [2]–[4]. Importantly, the evidence suggests that therapeutic benefits may accumulate progressively over time, distinguishing VNS from some other neuromodulation approaches that produce more immediate effects [3], [4]. However, because implantation is required and patient selection is highly specific, the total volume of available evidence remains smaller than that supporting rTMS.

Deep brain stimulation demonstrates an emerging but scientifically important evidence profile. Research involving DBS has provided valuable insights into the role of neural circuits in psychiatric and pain disorders, particularly regarding the subcallosal cingulate cortex and other network targets involved in emotional processing [5]. Nevertheless, clinical outcomes have not been uniformly consistent across studies, resulting in continued investigation regarding optimal targets, stimulation parameters, and patient selection strategies. Consequently, DBS currently occupies a more exploratory position compared with established neuromodulation interventions.

For chronic pain, spinal cord stimulation exhibits one of the strongest evidence profiles among all neurostimulation modalities evaluated. Decades of clinical investigation have demonstrated its value in neuropathic pain syndromes, failed back surgery syndrome, complex regional pain syndrome, and painful diabetic neuropathy [12], [13], [15]. The introduction of high-frequency stimulation and burst stimulation paradigms has further strengthened the evidence base by improving therapeutic outcomes and patient satisfaction [13], [15]. These findings explain why spinal cord stimulation remains one of the most widely accepted neuromodulation interventions in pain medicine.

Similarly, dorsal root ganglion stimulation demonstrates strong scientific support, particularly for focal neuropathic pain disorders and complex regional pain syndrome [14], [17]. Recent studies have shown that the ability to target specific sensory pathways may improve pain control in carefully selected patients. The growing number of clinical investigations supporting this technique has positioned it as one of the most promising advances in contemporary pain neuromodulation.

Figure 3.

Safety profile comparison between invasive and noninvasive neurostimulation techniques.

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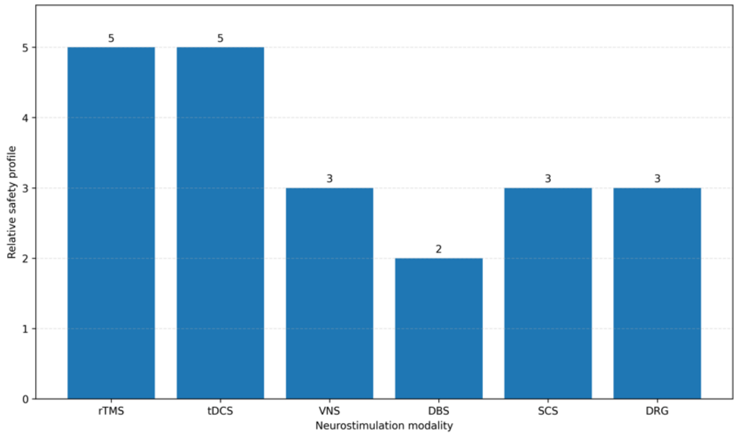

The third figure presents a comparative overview of the relative safety profiles associated with the principal neurostimulation modalities currently used in the management of treatment-resistant depression and chronic pain. Safety remains one of the most important factors influencing clinical decision-making because the risk-benefit relationship directly affects patient selection, treatment acceptance, long-term adherence, and healthcare implementation. The figure illustrates a clear distinction between noninvasive and invasive neuromodulation approaches, reflecting differences in procedural complexity, adverse event rates, surgical requirements, and long-term monitoring needs.

The highest relative safety levels are observed for repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Both techniques are noninvasive, do not require surgical implantation, and are generally associated with mild and transient adverse effects [8], [9], [18]. In repetitive transcranial magnetic stimulation, the most frequently reported side effects include scalp discomfort, transient headache, local muscle contractions, and mild fatigue. Serious adverse events such as seizures are rare when established safety guidelines are followed [8], [9]. The extensive safety data accumulated over the past two decades have contributed significantly to the widespread clinical acceptance of rTMS in psychiatric practice.

Similarly, transcranial direct current stimulation demonstrates a highly favorable safety profile. Most reported adverse effects are minor and include transient skin irritation, mild tingling sensations, itching beneath the electrodes, and temporary discomfort during stimulation sessions [6], [18]. Because the electrical currents used are of very low intensity, the risk of serious complications remains minimal when treatment protocols are appropriately applied. This favorable safety profile has stimulated growing interest in tDCS as a potentially accessible neuromodulation strategy across diverse healthcare settings.

Vagus nerve stimulation occupies an intermediate position in the figure. Although its long-term safety profile is generally considered acceptable, implantation requires a surgical procedure that introduces risks not present in noninvasive techniques [2], [3], [4]. Common adverse effects include voice alteration, cough, throat discomfort, dyspnea, and local surgical complications related to device placement. However, these events are typically manageable and rarely outweigh the potential therapeutic benefits in carefully selected patients with severe treatment-resistant depression [2], [4].

Spinal cord stimulation also demonstrates a moderate safety profile. Decades of clinical experience have shown that the procedure is generally safe when performed by experienced multidisciplinary teams [12], [13], [15]. Nevertheless, implantation-related risks include infection, lead migration, hardware malfunction, battery-related complications, and

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occasional need for surgical revision. Although most complications can be corrected through device adjustment or revision procedures, the invasive nature of the intervention inherently increases procedural risk compared with noninvasive approaches [13], [15].

Dorsal root ganglion stimulation presents a safety profile comparable to spinal cord stimulation because both techniques involve implantable hardware and similar procedural requirements [14], [17]. Potential complications include lead displacement, localized discomfort, infection, and technical issues related to device performance. Despite these considerations, contemporary studies indicate that the procedure remains relatively safe and well tolerated when performed under appropriate clinical conditions [14], [17].

Deep brain stimulation demonstrates the lowest relative safety level among the modalities analyzed, not because of excessive complication rates, but due to the complexity of the surgical intervention itself. DBS requires intracranial electrode implantation and precise targeting of deep brain structures, which introduces risks such as hemorrhage, infection, hardware complications, neuropsychiatric effects, and stimulation-related adverse events [5]. Although advances in stereotactic neurosurgery have substantially improved procedural safety, DBS remains the most invasive neuromodulation technique evaluated in this review. Consequently, its use is generally reserved for highly selected patients with severe refractory disease who have exhausted less invasive therapeutic options.

An important finding illustrated by the figure is the inverse relationship that often exists between procedural invasiveness and safety simplicity. Noninvasive modalities generally offer superior safety profiles and lower procedural risks, whereas invasive therapies may provide access to deeper neural targets and broader therapeutic possibilities but require more extensive monitoring and risk management. This observation is particularly relevant when designing individualized treatment plans because the optimal intervention must balance therapeutic effectiveness with patient-specific safety considerations [9], [11].

The figure also highlights the significant technological progress achieved in modern neuromodulation. Improvements in device engineering, imaging guidance, electrode design, stimulation programming, and perioperative management have contributed to reducing complication rates across invasive procedures. As a result, many neurostimulation therapies now demonstrate favorable safety profiles despite their increasing technological sophistication [11], [17].

Figure 4.

Mechanistic targets of neurostimulation across psychiatric and pain-related disorders.

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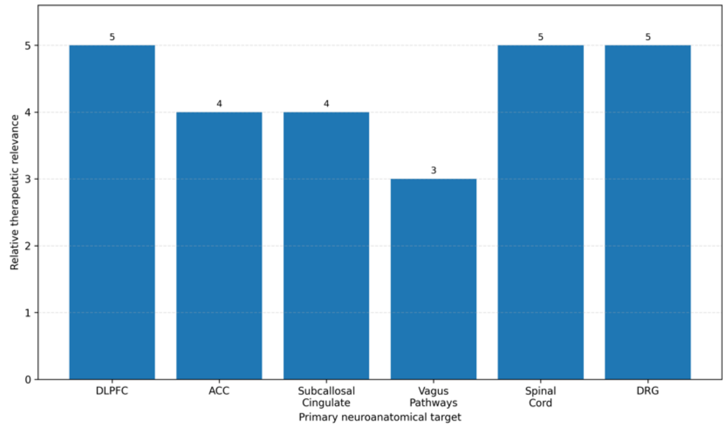

The fourth figure illustrates the principal neuroanatomical targets involved in contemporary neurostimulation therapies for treatment-resistant depression and chronic pain. Rather than focusing on individual devices, this figure emphasizes the neural structures and pathways that constitute the biological foundation of modern neuromodulation. The results demonstrate that successful neurostimulation therapies are closely linked to the ability to influence specific neural networks responsible for emotional regulation, cognitive processing, sensory integration, and pain modulation.

The dorsolateral prefrontal cortex (DLPFC) appears as one of the most therapeutically relevant targets identified in the reviewed literature. This region plays a central role in executive function, decision-making, working memory, emotional regulation, and cognitive control. Neuroimaging studies have consistently demonstrated abnormal activity within the DLPFC among patients with major depressive disorder, particularly in treatment-resistant forms of the disease [1], [7], [9]. Repetitive transcranial magnetic stimulation primarily targets this cortical area with the objective of restoring functional connectivity between cortical and limbic structures. The strong therapeutic relevance shown in the figure reflects the substantial body of evidence supporting DLPFC modulation as one of the most successful noninvasive interventions currently available for treatment-resistant depression.

The anterior cingulate cortex (ACC) represents another highly relevant structure. The ACC participates in emotional processing, attention, reward evaluation, cognitive control, and pain perception. Importantly, it serves as a key interface between emotional and sensory experiences, which may explain its involvement in both depression and chronic pain syndromes [5], [9], [11]. Functional abnormalities within the ACC have been associated with persistent depressive symptoms, emotional distress, and altered pain processing. Consequently, modulation of neural circuits connected to this region has become an important objective in several neuromodulation strategies.

Closely related to the ACC is the subcallosal cingulate cortex, a structure frequently investigated in deep brain stimulation research for severe treatment-resistant depression. Studies have identified abnormal metabolic and functional activity within this region among patients experiencing chronic depressive symptoms [5]. Deep brain stimulation targeting the subcallosal cingulate aims to normalize dysfunctional network activity across broader emotional regulation circuits. Although clinical outcomes have varied among investigations, the scientific significance of this target remains substantial because it has contributed to advancing understanding of network-based models of psychiatric disease.

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The vagus nerve pathways occupy a unique position among the mechanistic targets represented in the figure. Unlike cortical or deep brain targets, vagus nerve stimulation influences neural activity indirectly through extensive connections linking peripheral autonomic pathways to the brainstem, limbic system, thalamus, and cortical regions [2], [3], [4]. Through these widespread projections, vagus nerve stimulation can affect neurotransmitter release, neuroplasticity, emotional regulation, and autonomic function. The moderate-to-high therapeutic relevance observed in the figure reflects its established role in selected patients with treatment-resistant depression and its importance as a bridge between peripheral and central neuromodulation.

The spinal cord demonstrates one of the highest levels of therapeutic relevance in chronic pain management. Within spinal cord stimulation, electrical impulses are delivered to dorsal column structures involved in pain signal transmission and modulation [12], [13], [15]. This intervention modifies nociceptive processing before pain signals reach higher cortical centers, thereby reducing pain perception and improving functional outcomes. The strong representation of the spinal cord within the figure reflects decades of clinical evidence supporting its effectiveness in neuropathic pain syndromes and other refractory pain conditions.

Similarly, the dorsal root ganglion (DRG) is shown as a highly important mechanistic target. The DRG contains the cell bodies of primary sensory neurons and serves as a critical gateway for sensory information entering the central nervous system [14], [17]. Abnormal activity within these structures contributes significantly to neuropathic pain generation and maintenance. By directly targeting the DRG, clinicians can achieve highly localized modulation of pathological sensory pathways. This anatomical precision explains the growing interest in DRG stimulation as one of the most innovative developments in contemporary pain neuromodulation.

An important observation emerging from the figure is that neurostimulation therapies target multiple levels of the nervous system simultaneously. Some interventions focus on cortical structures associated with cognition and emotion, while others influence subcortical networks, peripheral autonomic pathways, spinal circuits, or sensory ganglia. This diversity reflects the complexity of treatment-resistant depression and chronic pain, both of which involve distributed neural networks rather than isolated anatomical abnormalities [9], [11].

The results also reinforce the modern concept of network neuroscience. Rather than attributing symptoms to dysfunction within a single brain region, current evidence suggests that depression and chronic pain arise from disturbances in interconnected neural systems. Consequently, effective neuromodulation may depend not only on stimulating individual targets but also on restoring communication among distributed functional networks [5], [9]. This perspective has guided the development of increasingly sophisticated stimulation technologies capable of producing more selective and adaptive modulation.

Figure 5.

Projected integration of neurostimulation into multidisciplinary clinical practice.

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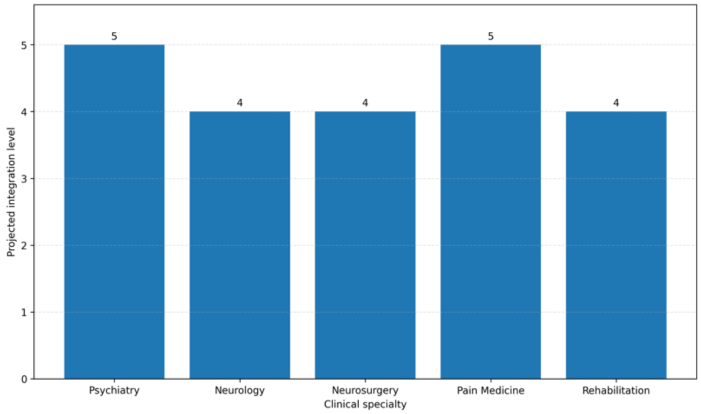

The fifth figure presents the projected integration of neurostimulation therapies across the principal medical specialties involved in the management of treatment-resistant depression and chronic pain. The results indicate that neurostimulation is no longer confined to a single clinical discipline but has evolved into a multidisciplinary therapeutic field that combines expertise from psychiatry, neurology, neurosurgery, pain medicine, and rehabilitation sciences. This progressive integration reflects both the growing body of scientific evidence supporting neuromodulation and the increasing recognition that complex neurological and psychiatric disorders require collaborative treatment strategies.

Psychiatry demonstrates one of the highest projected levels of integration. This finding is largely explained by the expanding role of repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, and deep brain stimulation in the management of treatment-resistant depression [1], [2], [5], [7]. As understanding of neural network dysfunction in mood disorders continues to improve, psychiatric practice is increasingly incorporating neuromodulation as an evidence-based complement to pharmacotherapy and psychotherapy. The growing number of specialized neuropsychiatric centers worldwide further supports the expectation that neurostimulation will become an increasingly important component of routine psychiatric care.

Pain medicine also occupies the highest level of projected integration. Chronic pain remains one of the most common and challenging clinical conditions globally, and conventional treatment strategies often fail to provide adequate symptom control in refractory cases [11]. Spinal cord stimulation and dorsal root ganglion stimulation have demonstrated significant clinical value in neuropathic pain syndromes, failed back surgery syndrome, complex regional pain syndrome, and painful diabetic neuropathy [12]–[15]. Consequently, pain specialists increasingly view neuromodulation not as a last resort but as an integral component of comprehensive pain management programs. The figure reflects this growing reliance on neurostimulation within contemporary pain medicine.

Neurology demonstrates a high level of anticipated integration because many neurological disorders involve dysfunctional neural circuits that may respond to targeted modulation. Although the present review focuses on depression and chronic pain, neurological applications of neurostimulation continue to expand into areas such as movement disorders, epilepsy, neurorehabilitation, and cognitive dysfunction [9], [11]. Advances in neuroimaging and electrophysiological monitoring have enabled neurologists to participate more actively in patient selection, outcome evaluation, and treatment optimization. This interdisciplinary role is expected to increase as neuromodulation technologies become more precise and individualized.

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Neurosurgery remains central to the implementation of invasive neurostimulation techniques. Procedures such as deep brain stimulation, vagus nerve stimulation implantation, spinal cord stimulation, and dorsal root ganglion stimulation require highly specialized surgical expertise and long-term device management [5], [13], [14]. The projected integration observed in the figure reflects the continuing importance of neurosurgeons in both technological innovation and clinical application. Furthermore, advances in stereotactic surgery, intraoperative imaging, and navigation systems have improved procedural accuracy and expanded the range of conditions that may benefit from implantable neuromodulation devices.

Rehabilitation medicine also demonstrates substantial projected integration. Increasing evidence suggests that neuromodulation may enhance neuroplasticity, improve functional recovery, and complement physical, occupational, and cognitive rehabilitation programs [18]. In patients with chronic pain, neurostimulation may facilitate participation in rehabilitative therapies by reducing symptom burden and improving physical function. Similarly, in psychiatric populations, symptom improvement may enhance engagement with psychosocial interventions and behavioral therapies. This synergistic relationship explains the growing interest in integrating neurostimulation within multidisciplinary rehabilitation models.

A notable finding emerging from the figure is the convergence of traditionally separate medical specialties around shared neurobiological concepts. Historically, psychiatry, neurology, pain medicine, and rehabilitation often approached disease management through distinct theoretical frameworks. However, advances in neuroscience increasingly support the concept that many disorders arise from dysfunction within interconnected neural networks [5], [9], [11]. Neurostimulation provides a common therapeutic platform capable of addressing these network abnormalities, thereby encouraging greater collaboration among disciplines.

The results further indicate that future clinical practice will likely emphasize personalized neuromodulation strategies. Rather than applying uniform treatment protocols, clinicians may increasingly tailor interventions according to neuroimaging findings, electrophysiological biomarkers, symptom profiles, and individual patterns of neural dysfunction. This transition toward precision medicine is expected to strengthen interdisciplinary collaboration because effective implementation will require contributions from multiple areas of expertise.

Another important observation concerns the role of emerging technologies. Artificial intelligence, machine learning algorithms, adaptive stimulation systems, and closed-loop neuromodulation platforms are expected to enhance treatment precision and responsiveness [11], [17]. These innovations may facilitate real-time adjustment of stimulation parameters according to physiological feedback, improving both efficacy and safety. Such developments will likely require even closer collaboration among clinicians, neuroscientists, engineers, and data scientists.

The international perspective also supports the increasing integration of neurostimulation across healthcare systems. Specialized centers in North America, Europe, Asia, and Latin America have reported growing adoption of neuromodulation technologies, including initiatives in Mexico, Colombia, and Ecuador aimed at expanding access, professional training, and research collaboration [18]–[20]. These developments suggest that neurostimulation will continue to evolve from a specialized intervention into a more widely accessible component of advanced clinical care.

DISCUSSION

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The findings of this review demonstrate that neurostimulation has emerged as one of the most significant developments in contemporary neuroscience-based medicine, offering innovative therapeutic opportunities for patients affected by treatment-resistant depression and chronic pain. The results indicate that advances in neuromodulation have transformed the traditional understanding of these disorders, shifting the clinical perspective from purely neurochemical or peripheral models toward network-based approaches that recognize the central role of dysfunctional neural circuits in disease pathophysiology [5], [9], [11].

One of the most important observations derived from the present review is the growing strength of evidence supporting repetitive transcranial magnetic stimulation in treatment-resistant depression. The findings presented in Figures 1 and 2 demonstrate that rTMS currently possesses one of the most robust scientific foundations among noninvasive neurostimulation therapies. This observation is consistent with international clinical guidelines that increasingly recommend rTMS as an evidence-based intervention for patients who fail to respond adequately to antidepressant medications and psychotherapy [7], [8], [9]. The ability of rTMS to target the dorsolateral prefrontal cortex and influence broader emotional regulation networks may explain its favorable clinical outcomes and expanding role within psychiatric practice.

The discussion of these findings also highlights the importance of technological evolution in improving therapeutic efficacy. Earlier neuromodulation approaches often relied on generalized stimulation protocols, whereas contemporary technologies increasingly focus on precision targeting and individualized treatment strategies. The emergence of theta burst stimulation protocols illustrates this trend by providing comparable therapeutic effectiveness with significantly reduced treatment duration [7]. Such advances have important implications for patient accessibility, treatment adherence, healthcare efficiency, and resource utilization.

The review further reveals that spinal cord stimulation and dorsal root ganglion stimulation currently represent some of the most clinically established neuromodulation strategies for chronic pain management. The strong evidence profile observed for these modalities reflects decades of research demonstrating meaningful reductions in pain intensity and improvements in functional capacity among patients with refractory neuropathic pain syndromes [12], [13], [15]. Importantly, these findings support the concept that chronic pain should not be viewed exclusively as a peripheral phenomenon but rather as a condition involving complex interactions among sensory, emotional, cognitive, and autonomic neural systems [11]. By directly modulating neural pathways responsible for pain transmission and perception, neurostimulation offers a mechanistically distinct alternative to conventional pharmacological interventions.

Another relevant aspect emerging from the results is the distinction between invasive and noninvasive neuromodulation approaches. Figure 3 demonstrates that noninvasive modalities such as rTMS and tDCS generally present more favorable safety profiles than implantable technologies. This finding is clinically important because safety considerations strongly influence therapeutic decision-making. The lower procedural risk associated with noninvasive techniques may facilitate earlier integration into treatment algorithms, whereas invasive approaches are often reserved for more severe or refractory cases. Nevertheless, the discussion should recognize that greater invasiveness may also provide access to deeper neural targets and broader therapeutic possibilities, particularly in patients who have exhausted conventional alternatives [5], [13], [14].

The mechanistic findings summarized in Figure 4 reinforce contemporary theories regarding the neurobiological basis of depression and chronic pain. The involvement of structures such as the dorsolateral prefrontal cortex, anterior cingulate cortex, subcallosal cingulate region, spinal cord pathways, and dorsal root ganglia demonstrates that effective neuromodulation depends upon the modulation of interconnected neural networks rather than isolated anatomical

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regions [5], [9], [11]. This observation supports the growing influence of network neuroscience, which emphasizes the importance of communication among distributed brain systems in determining behavior, emotion, cognition, and sensory experience.

The overlap between treatment-resistant depression and chronic pain deserves particular attention. Both disorders frequently coexist and share several neurobiological mechanisms, including abnormalities within limbic structures, cortical regulatory systems, neurotransmitter pathways, and neuroplastic processes [9], [11]. The results suggest that neurostimulation may be especially valuable in addressing this overlap because many neuromodulation techniques influence neural networks involved in both emotional regulation and pain processing. Consequently, future therapeutic models may increasingly integrate psychiatric and pain management perspectives rather than treating these conditions as entirely separate clinical entities.

The international dimension of the findings also warrants discussion. Neurostimulation technologies have expanded considerably across North America, Europe, Asia, and Latin America. The increasing adoption of neuromodulation within Mexico, Colombia, and Ecuador reflects growing regional interest in advanced neuroscience-based therapies and demonstrates that these interventions are becoming progressively relevant beyond highly specialized centers in high-income countries [18]–[20]. However, disparities in access, infrastructure, training, and healthcare financing remain important challenges. These barriers may limit the widespread implementation of neurostimulation despite the accumulating scientific evidence supporting its effectiveness.

Another significant discussion point concerns the future direction of personalized medicine. The results indicate that treatment response varies considerably among individuals, suggesting that patient-specific characteristics play a crucial role in determining therapeutic outcomes [8], [9]. Advances in neuroimaging, electrophysiology, genetic profiling, and biomarker identification may allow clinicians to predict treatment response more accurately and select the most appropriate neuromodulation strategy for each patient. Such developments could reduce trial-and-error treatment approaches and improve overall clinical effectiveness.

The emergence of adaptive and closed-loop neuromodulation systems represents another promising area for future development. Traditional neurostimulation devices typically deliver predetermined stimulation patterns, whereas adaptive systems continuously monitor physiological signals and adjust stimulation parameters in real time [11], [17]. This technological evolution has the potential to improve precision, reduce adverse effects, and enhance long-term outcomes. Furthermore, integration with artificial intelligence and machine learning algorithms may facilitate increasingly sophisticated therapeutic personalization.

Several limitations within the current body of evidence should also be acknowledged. Although many neurostimulation modalities have demonstrated encouraging results, variability among study designs, stimulation parameters, outcome measures, follow-up durations, and patient populations complicates direct comparison across investigations [8], [9], [11]. Additionally, long-term outcome data remain limited for certain emerging technologies, particularly within rapidly evolving areas such as adaptive neuromodulation and advanced brain stimulation systems. These limitations highlight the need for standardized methodologies and large-scale multicenter studies.

Future research should focus on identifying predictors of treatment response, optimizing stimulation parameters, evaluating long-term effectiveness, and exploring combination strategies involving neurostimulation,

Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
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Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

pharmacotherapy, psychotherapy, rehabilitation, and behavioral interventions. Such integrated approaches may prove particularly valuable for patients with complex presentations involving both psychiatric and pain-related symptoms.

CONCLUSION

Neurostimulation has emerged as one of the most promising therapeutic innovations in the fields of psychiatry, neurology, neurosurgery, and pain medicine. The evidence analyzed throughout this review demonstrates that contemporary neuromodulation techniques provide valuable therapeutic alternatives for patients with treatment-resistant depression and chronic pain, particularly when conventional pharmacological and non-pharmacological interventions fail to achieve satisfactory clinical outcomes.

The findings indicate that repetitive transcranial magnetic stimulation currently represents one of the most extensively supported noninvasive therapies for treatment-resistant depression, while spinal cord stimulation and dorsal root ganglion stimulation have established themselves as effective interventions for several refractory chronic pain conditions. In addition, vagus nerve stimulation, deep brain stimulation, and transcranial direct current stimulation continue to expand the therapeutic landscape by offering complementary approaches directed toward specific neural circuits involved in disease pathophysiology.

A major contribution of neurostimulation lies in its ability to directly influence dysfunctional neural networks rather than focusing exclusively on neurotransmitter modulation or peripheral symptom management. This network-based perspective reflects contemporary advances in neuroscience and supports a more comprehensive understanding of both depression and chronic pain as disorders involving complex interactions among cortical, subcortical, spinal, and peripheral nervous system structures.

The review also highlights the importance of individualized treatment selection. Differences in clinical presentation, disease severity, neural target accessibility, safety considerations, and patient-specific characteristics require careful evaluation when determining the most appropriate neuromodulation strategy. The growing availability of advanced neuroimaging techniques, electrophysiological monitoring, and biomarker-based approaches may further enhance precision and improve therapeutic outcomes in the future.

From a safety perspective, noninvasive modalities generally demonstrate favorable risk profiles, whereas invasive interventions provide access to deeper neural targets at the cost of greater procedural complexity. Nevertheless, technological improvements have substantially enhanced the safety and reliability of modern implantable neuromodulation systems, contributing to their increasing clinical acceptance.

The international evidence reviewed in this study further demonstrates the expanding role of neurostimulation across diverse healthcare systems. The growing adoption of these technologies in regions such as Latin America, including Mexico, Colombia, and Ecuador, reflects increasing recognition of their clinical value and their potential contribution to improving outcomes in patients with refractory neurological, psychiatric, and pain-related disorders.

Future developments are expected to focus on precision neuromodulation, adaptive stimulation systems, artificial intelligence-assisted programming, and closed-loop technologies capable of dynamically responding to physiological

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
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changes. These innovations may significantly improve treatment personalization, long-term effectiveness, and overall patient care.

In conclusion, neurostimulation represents a rapidly evolving and increasingly important component of modern clinical neuroscience. The accumulated scientific evidence supports its effectiveness, safety, and therapeutic relevance in treatment-resistant depression and chronic pain. Continued research, interdisciplinary collaboration, technological innovation, and equitable access to advanced therapies will be essential to maximize the benefits of neuromodulation and further expand its role in contemporary healthcare.

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
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