Development of neuromodulation in the treatment of chronic pain and depression

Nursulu Mukhtar [1,*]

[1] Astana Medical University, Kazakhstan, Astana

Abstract. Neuromodulation techniques have emerged as promising therapeutic interventions for chronic pain and depression, conditions often characterized by complex neurophysiological dysfunctions and limited response to conventional treatments. Advances in understanding the neural circuits underlying these disorders have facilitated the development of diverse neuromodulation modalities, including transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS). These approaches target specific brain regions and neural pathways to modulate aberrant activity, alleviate symptoms, and restore functional balance. Clinical trials have demonstrated varying degrees of efficacy, with some modalities showing sustained symptom relief and improved quality of life. Despite challenges such as patient selection, optimization of stimulation parameters, and long-term safety, ongoing research continues to refine neuromodulation protocols and expand their applicability. This review summarizes the current state of neuromodulation in managing chronic pain and depression, highlighting recent technological advances, clinical outcomes, and future directions for integrative neurotherapeutic strategies.

1 Introduction

Chronic pain and depression are pervasive health conditions that contribute substantially to global morbidity, disability, and socioeconomic burden. Chronic pain affects approximately 20% of the adult population worldwide and is often refractory to conventional medical treatments, while depression is recognized as a leading cause of disability globally, frequently co-occurring with chronic pain and exacerbating its impact. The bidirectional relationship between these disorders involves complex neurobiological

*Corresponding author: Kureysh2562@gmail.com

and psychosocial interactions, including dysregulation of central nervous system pathways related to mood, cognition, and pain perception.

Conventional therapeutic approaches, including pharmacotherapy with analgesics, antidepressants, and psychotherapy, often fail to achieve adequate symptom control, leading to treatment-resistant cases and highlighting the urgent need for innovative treatment modalities. Neuromodulation, defined as the targeted electrical or magnetic modulation of neural activity, has gained increasing attention as a promising strategy to address the underlying pathophysiology of these disorders. By directly influencing dysfunctional neural circuits, neuromodulation aims to restore neurophysiological balance and improve clinical outcomes.

Over the past decades, a variety of neuromodulation techniques have been developed and refined. Non-invasive modalities, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), offer the advantages of safety and accessibility, making them suitable for broader clinical application. In contrast, invasive procedures like deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS) provide deeper and more precise modulation but require surgical implantation and carry associated risks. The choice of modality is often dictated by the severity of symptoms, patient characteristics, and therapeutic goals.

Recent advances in neuroimaging, electrophysiology, and computational modeling have enhanced understanding of the neural substrates involved in chronic pain and depression, guiding the optimization of neuromodulation targets and parameters. Clinical trials and meta-analyses have demonstrated the efficacy of several neuromodulation techniques in reducing pain intensity, alleviating depressive symptoms, and improving quality of life, although variability in response rates and long-term outcomes persists.

This review aims to provide a comprehensive overview of the current state of neuromodulation in treating chronic pain and depression, addressing mechanistic insights, clinical evidence, technological innovations, and future directions. By integrating multidisciplinary perspectives, it seeks to inform clinicians and researchers of the evolving role of neuromodulation as a viable therapeutic option in neuropsychiatry and pain management.

2 Methods and materials

This study is based on a comprehensive literature review and qualitative synthesis of current research focused on neuromodulation techniques applied to the treatment of chronic pain and depression. The literature search was conducted using major scientific databases including PubMed, Scopus, Web of Science, and Cochrane Library, covering publications from January 2000 to April 2025. The search strategy combined keywords and MeSH terms such as “neuromodulation,” “chronic pain,” “depression,” “transcranial magnetic stimulation,” “deep brain stimulation,” “spinal cord stimulation,” “vagus nerve stimulation,” and “clinical outcomes.” Inclusion criteria encompassed peer-reviewed original research articles, clinical trials, meta-analyses, systematic reviews, and relevant clinical guidelines published in English. Studies focusing on both invasive and non-invasive neuromodulation modalities were considered, provided they reported on therapeutic efficacy, safety, neurophysiological mechanisms, or technological developments. Exclusion criteria involved non-peer-reviewed articles, conference abstracts without full texts, case reports, and studies with insufficient methodological rigor. Data extraction included study design, sample size, patient demographics, neuromodulation technique and parameters, treatment duration, clinical outcomes (pain intensity reduction,

depression scale scores), adverse events, and follow-up periods. Quantitative and qualitative data were synthesized to identify common trends, challenges, and gaps in the field. Additionally, technical specifications and device innovations were reviewed through manufacturer documentation and regulatory agency reports to provide context on recent advancements in neuromodulation technology.

This integrative approach allowed for a comprehensive understanding of the current landscape of neuromodulation therapies in chronic pain and depression, supporting evidence-based conclusions and recommendations for future research and clinical practice.

3. Results

The reviewed literature reveals significant progress in the application of neuromodulation techniques for managing chronic pain and depression, with varying degrees of efficacy demonstrated across different modalities and patient populations.

Transcranial Magnetic Stimulation (TMS) has been extensively studied as a non-invasive method for modulating cortical excitability. Multiple randomized controlled trials (RCTs) have confirmed its efficacy in reducing depressive symptoms, leading to regulatory approval for treatment-resistant depression. Meta-analyses report response rates ranging from 40% to 60%, with sustained effects observed up to 12 months post-treatment. In chronic pain conditions such as neuropathic pain and fibromyalgia, TMS targeting the motor cortex has shown moderate analgesic effects, although variability in outcomes remains a challenge. Adverse effects are generally mild and transient, including scalp discomfort and headaches.

Deep Brain Stimulation (DBS), an invasive technique involving the implantation of electrodes into specific brain regions, has demonstrated promise particularly in refractory depression and certain chronic pain syndromes, such as neuropathic and cluster headaches. Target areas commonly include the subcallosal cingulate cortex for depression and the periaqueductal gray or thalamic nuclei for pain. Clinical studies show that DBS can achieve significant symptom reduction in patients unresponsive to conventional therapies; however, results are heterogeneous, and procedural risks such as infection and hemorrhage are non-negligible. Long-term follow-up data remain limited but suggest sustained benefits in selected cases.

Spinal Cord Stimulation (SCS) has established its role primarily in neuropathic and failed-back surgery syndrome-related pain. Advances in waveform technology, such as high-frequency and burst stimulation, have improved analgesic efficacy and patient tolerability. Prospective cohort studies indicate pain reduction of 50% or greater in up to 70% of patients. While SCS is not directly used for depression, improvements in mood are frequently reported secondary to pain relief. Device-related complications and the need for surgical revisions constitute notable limitations.

Vagus Nerve Stimulation (VNS), originally developed for epilepsy, has gained approval for treatment-resistant depression and is under investigation for pain modulation. Clinical trials indicate modest antidepressant effects, with response rates around 40%, and emerging evidence suggests potential analgesic benefits through autonomic regulation. Side effects primarily include voice alteration and cough. Newer non-invasive transcutaneous VNS devices are being explored to reduce invasiveness and improve accessibility.

Overall, the integration of neuromodulation into clinical practice reflects an evolving therapeutic landscape characterized by improved patient selection, parameter optimization, and combination with pharmacological and behavioral therapies. Nonetheless, heterogeneity in study designs, small sample sizes, and lack of standardized protocols pose

challenges to definitive conclusions. Further large-scale, longitudinal studies are warranted to establish long-term efficacy, optimize stimulation parameters, and identify biomarkers predictive of treatment response.

4. Discussion

The advancements in neuromodulation techniques for chronic pain and depression reflect a significant shift in therapeutic strategies, moving beyond traditional pharmacological and psychological interventions to more targeted modulation of dysfunctional neural circuits. The evidence from clinical trials and observational studies underscores the potential of these technologies to provide symptomatic relief and improve quality of life, particularly for patients who have exhausted conventional treatment options.

Transcranial magnetic stimulation (TMS) stands out as a widely adopted non-invasive approach with substantial evidence supporting its efficacy in treatment-resistant depression. Its safety profile and relative ease of application make it a favorable option, though variability in patient response highlights the need for further research into biomarkers that predict therapeutic outcomes. The application of TMS in chronic pain is promising but remains less established, necessitating standardized protocols and larger studies to validate its analgesic effects.

Deep brain stimulation (DBS) offers the advantage of precise targeting of deep brain structures implicated in mood and pain regulation. While DBS has demonstrated encouraging results, especially in refractory cases, the invasiveness of the procedure, potential surgical risks, and high costs limit its widespread use. The heterogeneity of clinical outcomes suggests that patient selection criteria and target site optimization require further refinement. Long-term safety and durability of benefit also remain areas of ongoing investigation.

Spinal cord stimulation (SCS) has a well-established role in managing neuropathic pain and chronic back pain syndromes. Innovations in stimulation paradigms, such as high-frequency and burst modes, have enhanced its efficacy and patient comfort. Although SCS does not directly target depression, its impact on mood through pain amelioration is clinically significant. The challenges of device-related complications and the need for repeat interventions necessitate improved device design and follow-up protocols.

Vagus nerve stimulation (VNS), both invasive and non-invasive, represents an emerging frontier in neuromodulation with dual applications in depression and pain. While the antidepressant effects are moderate, ongoing developments in transcutaneous VNS may expand accessibility and reduce adverse effects. Further research is needed to clarify its mechanisms in pain modulation and define optimal stimulation parameters.

Despite these advances, several overarching challenges impede the broader clinical integration of neuromodulation. These include variability in study methodologies, lack of standardized outcome measures, and insufficient long-term data. Moreover, the high costs and resource requirements associated with some invasive procedures raise concerns about equitable access, particularly in resource-limited settings.

Future research should prioritize the identification of predictive biomarkers to personalize neuromodulation therapies, the development of closed-loop systems for real-time modulation based on neural feedback, and the integration of multimodal approaches combining neuromodulation with pharmacological and behavioral interventions. Multidisciplinary collaboration among neurologists, psychiatrists, pain specialists, engineers, and rehabilitation experts will be essential to optimize treatment algorithms and maximize patient benefit.

In conclusion, neuromodulation represents a transformative and rapidly evolving modality in the management of chronic pain and depression. While significant progress has been made, continued innovation and rigorous research are imperative to fully harness its therapeutic potential and translate it into routine clinical practice.

3 Conclusion

Neuromodulation has emerged as a promising and innovative therapeutic avenue for the treatment of chronic pain and depression, particularly for patients who have demonstrated resistance to conventional therapies. Both non-invasive and invasive modalities have shown the capacity to modulate dysfunctional neural circuits, resulting in symptom alleviation and improved quality of life. Techniques such as transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS) offer diverse mechanisms of action tailored to specific pathophysiological targets.

Despite notable clinical successes, challenges remain in optimizing patient selection, standardizing stimulation protocols, and establishing long-term efficacy and safety profiles. Moreover, accessibility and cost-effectiveness continue to be important considerations for widespread adoption. Future advancements in neuroimaging, biomarker identification, and closed-loop neuromodulation systems hold the potential to enhance personalization and treatment responsiveness.

In summary, neuromodulation represents a transformative frontier in neurotherapeutics for chronic pain and depression. Continued multidisciplinary research and clinical innovation are essential to refine these technologies and integrate them effectively into comprehensive, patient-centered care paradigms.

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