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Deep Brain Stimulation; A Novel and Potential Approach for Simultaneous Management of Pain, Insomnia, and Depression Syndrome: A Narrative Review

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ABSTRACT

Chronic pain, insomnia, and depression syndrome (PIDS) are interconnected conditions that significantly reduce patients' quality of life. This narrative study examines the potential effectiveness of deep brain stimulation (DBS) as a treatment strategy for managing PIDS concurrently. By synthesizing existing literature, the research highlights the common neural pathways and brain structures linked to these disorders, illustrating their overlap. DBS operates by delivering electrical impulses to targeted brain regions, which may disrupt abnormal neural activity. This intervention could induce ionic and cellular changes that foster neuroplasticity, aiding in the restoration of balance in overactive neural circuits. By addressing the interconnected aspects of pain, sleep disturbances, and depressive symptoms, DBS offers a comprehensive therapeutic approach that may enhance patient outcomes. Nonetheless, the study recognizes the limitations of DBS, including the inherent surgical risks and variability in treatment efficacy among patients. Consequently, future research aims to refine targeting strategies through advanced imaging techniques and develop adaptive DBS systems capable of adjusting stimulation based on real-time feedback. Additionally, the exploration of combination therapies that integrate DBS with pharmacological or behavioral interventions could further enhance treatment effectiveness. Overall, this study underscores the necessity of developing integrated treatment approaches that consider the complex and multifaceted nature of PIDS, ultimately striving to improve therapeutic effectiveness and the quality of life for affected individuals.

Keywords: Deep Brain Stimulation, Chronic Pain, Insomnia, Depression, Brain Structure

Introduction

Pain, insomnia, and depression syndrome (PIDS) are considered a group of symptoms commonly observed in individuals with chronic nonmalignant pain (CNMP) (1, 2). According to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant experience that includes sensory and emotional dimensions and is

typically associated with actual or potential damage to body tissues. Chronic pain is characterized by pain lasting longer than three months and often extending beyond the expected healing period (3). Worldwide, the prevalence of pain is estimated to be 27.5% on average (4), with evidence indicating that chronic pain has reached epidemic proportions in both the United States and Europe (5).

Insomnia, considered one of the most common mental disorders (6), is characterized by difficulty initiating or maintaining sleep or waking early in the morning, occurring at least three times a week over three months. This condition results in clinically significant suffering and/or dysfunction. Insomnia is associated with a reduction in overall quality of life and represents a significant burden on individuals and healthcare systems worldwide, affecting multiple dimensions, including psychological, occupational, and economic factors. In the general population, the prevalence of insomnia symptoms is significantly increased, ranging from 30% to 48% when assessed by core features of the disorder (7).

Depression is a common psychological disorder characterized by reduced motivation, fatigue, anhedonia, sleep disturbances, difficulty concentrating, and a pervasive feeling of hopelessness (8). Depression is associated with reduced work productivity, family discord, substance abuse, and increased risk of suicide, and a shortened life expectancy (9). The World Health Organization identifies depression as the leading cause of disability worldwide. Low- and middle-income countries are particularly vulnerable to this burden. The global incidence of depression increased from 172 million cases in 1990 to 258 million in 2017, an increase of 49.8% (10).

Currently, the overall concept that insomnia, chronic pain, and depression are closely related is well established (11-16). Beyond the actual physical pain, patients often suffer from a variety of secondary consequences, particularly sleep disorders and depressive disorders (17). Indeed, pain is considered a risk factor for insomnia, as insomnia has been found to lower the pain threshold and increase pain intensity (18-21). Between 53% and 90% of individuals with chronic pain report clinically significant insomnia (22, 23), rendering them 18 times more likely to suffer from insomnia than those without chronic pain. The prevalence of sleep disorders in patients with chronic pain is approximately 44%, with insomnia being the most common condition (72%), followed by restless legs syndrome and obstructive sleep apnea at 32% each (23). Additionally, insomnia might contribute to the onset of depression, as insomnia is considered a symptom of depression (21).

In addition, chronic pain has increased the likelihood of depression, and depression is associated with adverse pain outcomes (24, 25). There is evidence that the presence of pain can hinder the accurate identification and effective treatment of depression (25) and that inadequate treatment of pain can lead to refractory depression or treatment-resistant depression (TRD), whereas inadequate treatment can lead to depression. Suboptimal pain regulation can lead to depression (24). The prevalence of major depression in patients with chronic pain ranges from 13 to 85%, depending on the clinical setting. Studies conducted in pain clinics or inpatient programs report an average prevalence of 52%, while psychiatric hospitals and primary care facilities have rates of 38% and 27%, respectively (26, 27). Individuals suffering from chronic pain are three to five times more likely to experience depression than those without pain, with the risk of depression increasing with the severity, frequency, duration, and number of pain symptoms experienced (24).

Currently, a multidisciplinary framework that integrates both pharmacological interventions (28- 30) and non-pharmacological therapies (NINPT) (29-31) is often used in the treatment of chronic pain, insomnia, and depression. These methods often focus on individual symptoms rather than recognizing their connections. For example, while cognitive behavioral therapy for insomnia (CBTI) is often recommended, many clinicians tend to view insomnia as a secondary symptom of depression, leading to inadequate treatment of sleep problems (32). Although CBT-I had the potential to alleviate both insomnia and depressive symptoms, challenges related to access and adherence remain (33). Likewise, the treatment of chronic pain often prioritizes pharmacologic treatments while overlooking the psychological factors that can exacerbate both pain and mood disorders (34). On the other hand, a significant proportion of patients do not respond to these methods (35). This highlights the importance of developing integrated treatment approaches that take into account the complex relationship between these diseases to improve overall patient outcomes (36).

Currently, neurostimulation methods are increasingly used either as an alternative to surgical lesions or in addition to existing medical treatments for various conditions, including Parkinson's disease (PD), dystonia, obsessivecompulsive disorder, and refractory pain (37). We aimed to investigate the use of deep brain stimulation (DBS) for the concurrent treatment of PIDS. The main aim of this research is not to generate new knowledge but to provide a contextualized synthesis of existing literature relevant to the topic of study. This article is based on previously conducted research.

Materials and Methods

This narrative review was designed to synthesize current knowledge on the application of DBS in the simultaneous management of chronic pain, insomnia, and depression—conditions that frequently co-occur and may share overlapping neurobiological mechanisms. The narrative format was selected to allow a flexible yet comprehensive integration of diverse findings from clinical and mechanistic studies.

A systematic literature search was carried out using PubMed, Scopus, Web of Science, and Google Scholar, targeting peer-reviewed published articles. Keywords and combinations included "Deep Brain Stimulation" or "DBS," along with "Pain management," "Neuropathic pain," "Insomnia," "Sleep disorders," "Depression," "Major depressive disorder," "Comorbidity," "Triad," "Multimodal treatment," and "Neuromodulation," using Boolean operators (AND, OR) to optimize the search. Additional sources were retrieved through manual screening of reference lists from key studies.

Inclusion criteria required studies to be peer-reviewed original research, systematic reviews, meta-analyses, or clinical trials written in English, focusing on the use of DBS for at least one of the target conditions—particularly those involving comorbid presentations—and providing data on clinical outcomes, mechanisms of action, or DBS target regions.

Exclusion criteria involved non-English publications, case reports with fewer than three patients, and conference abstracts or editorials lacking methodological detail. Data extraction followed a structured template including publication year, authorship, DBS target regions, patient characteristics and comorbidities, stimulation parameters (frequency, amplitude, pulse width), clinical

outcomes related to pain, sleep, and depression, and proposed mechanisms or neurophysiological effects. The findings were qualitatively synthesized to identify trends, overlaps, and research gaps, with emphasis on shared neural substrates such as the periaqueductal gray (PAG), ventral striatum, anterior limb of the internal capsule (ALIC), and subgenual cingulate cortex (Cg25), which are implicated in affective and sensory regulation.

As this review relied exclusively on previously published data, no ethical approval was required, and all sources were cited to maintain academic integrity.

Results

The literature search initially yielded 214 records. After removal of duplicates and title/abstract screening, 92 full-text articles were assessed for eligibility. Based on the predefined inclusion and exclusion criteria, a total of 66 studies were included in the final qualitative synthesis. The included studies span both human and animal models and cover diverse methodologies, from neuroimaging and molecular analyses to behavioral assessments and interventional trials (Fig. 1).

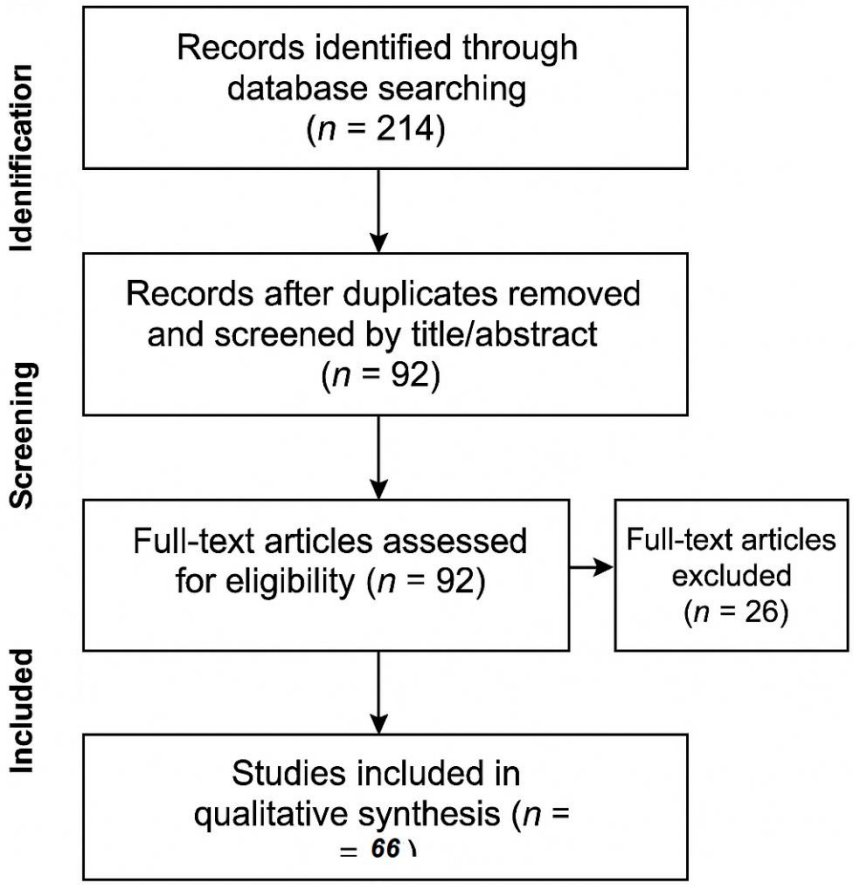

Fig. 1: Summary of Study Selection and Characteristics of Included Literature

Deep Brain Stimulation

The human brain consists of groups of neurons that form complexly linked networks displaying synchronized activity patterns. Disruptions in the synchronization of these brain networks can result in neurological disorders, which may be partially corrected through electrical stimulation. Dynamic brain rhythms arise from synaptic currents and the firing of neural action potentials, influencing interregional connections, circadian rhythms, and sleep patterns. Variations in rhythmic oscillatory neural activity have been associated with the accurate timing of neuronal action potentials, facilitating coordinated information transfer across distributed brain networks (38).

Therapeutic approaches, including DBS, can influence the identified pathological oscillatory circuit activity patterns and reduce associated symptoms (39). DBS is a neurosurgical procedure that involves delivering high-frequency electrical impulses to specific brain regions (40). DBS is regarded as an effective and accepted treatment for an expanding range of neurological and psychiatric disorders (41, 42) such as PD, essential tremor, dystonia, cerebellar outflow tremor, treatment-resistant major depressive disorder (MDD) (41), and different pain syndromes (35, 43, 44).

Technically, the DBS system uses a four-contact stimulating electrode that is stereotactically implanted into the specific area in the brain and connected via a subcutaneous wire to an implantable pulse generator (IPG), similar to a pacemaker, positioned under the collarbone on the chest wall. While electrodes are typically placed bilaterally, unilateral stimulation may also be used depending on clinical needs. Clinicians adjust stimulation parameters using a handheld device wirelessly connected to the IPG, optimizing stimulation to optimize symptom relief and reduce side effects (45).

The first proof of the electrical excitability of the brain was provided by Fritsch and Hitzig in 1870. Their experiment showed that applying electrical stimulation to the brain can produce motor responses that serve as the basis for DBS (46). DBS in Parkinson's patients not only replicated the positive results of ablative surgery but also offered the advantages of adaptability and reversibility in the face of adverse stimulation effects. Since then, this technique has paved the way for advances in the treatment of hyperkinetic disorders, pain, epilepsy, and certain neuropsychiatric disorders (47). As a clinical intervention, DBS presents several advantages compared to other surgical neuromodulation methods. These benefits include its nonlesional nature, the ability to adjust stimulation parameters to optimize therapeutic effects while minimizing side effects, and the capability to engage with the neural circuits that underlie observable symptoms directly. From a research perspective, DBS serves as a valuable tool for exploring the physiological mechanisms behind brain dysfunction, facilitating the identification and correction of abnormal neuronal patterns, which in turn fosters technological advancements and improves safety and clinical outcomes. Moreover, due to its precise targeting of anatomical regions typically within millimeters, DBS has advanced circuit theories of brain dysfunction by illustrating how localized impairments and interventions can significantly affect broader brain networks. This dual role of DBS as both an investigative probe and a modulator of neural circuitry has spurred research into its therapeutic applications across a wide spectrum of disorders, including those impacting motor, limbic, memory, and cognitive functions (48).

Simultaneous management of PIDS via DBS

Recognizing the interconnectedness of co-occurring symptoms suggests that treatment approaches could potentially address multiple symptoms simultaneously. There are several compelling reasons to consider that a single intervention might effectively target various symptoms within a symptom cluster. While symptoms within a cluster do not necessarily share a common etiology, they may indeed arise from a shared underlying cause. Consequently, focusing treatment on this underlying cause can alleviate or diminish the intensity of all associated symptoms. For instance, addressing hypercalcemia can concurrently mitigate both constipation and confusion. Moreover, a singular treatment may effectively address multiple symptoms; for example, employing benzodiazepines can alleviate both anxiety and sleep disturbances. This approach not only streamlines the treatment process but may also reduce the risk of adverse side effects and enhance cost-effectiveness. Additionally, the presence of one symptom can exacerbate others, as seen when pain leads to increased sleep difficulties. Therefore, managing the primary symptom can significantly lower the severity of its associated symptoms. Regardless of whether symptoms are treated collectively or individually, it is crucial to consider them holistically when developing treatment strategies. This comprehensive perspective allows for more effective and efficient management of interrelated symptoms, ultimately improving patient outcomes (49). As Williams asserts, it is crucial to consider symptoms that manifest in clusters as a cohesive entity when formulating management strategies (2).

Addressing chronic pain, insomnia, and depression simultaneously is key to improving overall wellbeing and quality of life. The hypothesis for the simultaneous management of chronic pain, insomnia, and depression through DBS is based on the shared interconnected neural pathways and structures involved in these conditions (50-54) including the prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, nucleus accumbens, periaqueductal gray matter, and other areas related to pain processing, emotional responses, and cognitive functions (55, 56).

Although the mechanisms underlying DBS are complex and not yet fully understood, available hypotheses and theories highlight that DBS disrupts abnormal activity in brain circuits. This disruption is mediated by stimulation effects at the ionic, protein, cellular, and network levels, leading to symptom improvement (57).

At the ionic level, the redistribution of charged particles from the implanted electrode generates an electric field that influences sodium channel activation, resulting in action potentials in the stimulated axons (58). This phenomenon is complemented by high-frequency stimulation (HFS) in DBS, which enhances synaptic filtering by suppressing low-frequency oscillatory activity within neural circuits. This suppression is particularly crucial for conditions such as chronic pain and mood disorders, which are often characterized by an excess of low-frequency activity. By diminishing these low-frequency signals, HFS can effectively alleviate symptoms related to overactive neural circuits (59, 60). Furthermore, HFS significantly reduces synchronized oscillatory activity in both the basal ganglia and cortical networks, which is associated with the mechanisms underlying various neurological disorders (61, 62). This reduction in abnormal rhythms may contribute to the therapeutic effects of DBS, enhancing emotional processing and alleviating symptoms of depression and chronic pain (63).

At the cellular level, DBS suppresses neuronal activity at the stimulation site, leading to reduced spike rates in critical regions such as the globus pallidus internus (GPi) and subthalamic nucleus (STN). This suppression can alleviate the hyperactivity associated with chronic pain and mood disorders (64, 65). Prolonged depolarization of neuronal membranes and increased potassium currents contribute to depolarization blockade, further diminishing maladaptive neural activity (35). Additionally, the activation of inhibitory presynaptic terminals and modulation of GABA release helps restore balance in overactive circuits related to these conditions. Importantly, while cell bodies near the electrodes are inhibited, axons and dendrites may exhibit increased action potentials, indicating that DBS can enhance beneficial neural activity while suppressing harmful oscillations. This dual action positions DBS as a promising intervention for addressing the interconnected challenges of chronic pain, insomnia, and depression, ultimately promoting both emotional and physiological well-being (66).

In key brain regions such as the STN and GPi, HFS effectively suppresses excessive neuronal firing, helping to restore balance in overactive pathways linked to chronic pain and mood disorders (64). By reducing abnormal activity, DBS alleviates symptoms associated with chronic pain and mood disorders while improving sleep patterns affected by hyperarousal (35). The dual capacity of DBS to inhibit and enhance excitatory neuronal activity enhances its therapeutic versatility, allowing for the activation of both local and distant neural circuits tailored to individual patient needs (66).

This multifaceted approach positions DBS as a compelling intervention for addressing the interconnected challenges of chronic pain, insomnia, and depression. In conditions like PD and dystonia, irregular firing patterns and altered discharge rates in areas such as the globus pallidus externus (GPe) and GPi can negatively impact motor control and emotional regulation (64, 65). By modulating these firing patterns, DBS can restore balance to overactive circuits, alleviating symptoms associated with chronic pain and mood disorders (35). The ability of DBS to influence both the rate and pattern of neuronal activity highlights its potential to improve not only motor function but also emotional stability and sleep quality (66).

HFS increases neuronal excitability and connectivity within cortico-basal ganglia circuits, thereby enhancing both motor function and emotional regulation (64). This comprehensive strategy tackles the interrelated issues of chronic pain, insomnia, and depression, facilitating personalized interventions according to individual responses to stimulation (67). DBS may utilize the "jamming theory" to address chronic pain, insomnia, and depression by creating high-frequency discharge patterns that prevent neurons from returning to abnormal firing states. This mechanism modifies pathological network activity rather than merely inhibiting it, which is especially advantageous in conditions like PD, where the GPi exhibits irregular activity (65, 66). HFS at approximately 130 pulses per second can normalize abnormal burst patterns in the GPi, improving thalamic responses and enhancing emotional regulation and sleep quality (64). This multifaceted approach highlights the versatility of DBS in tackling the interconnected challenges of chronic pain, insomnia, and mood disorders (67).

DBS may incorporate concepts from bursting theory to address chronic pain, insomnia, and depression. This theory highlights the significance of specific firing patterns, especially burst firing, in regulating motor control and alleviating symptoms associated with disorders such as PD. HFS can help

normalize irregular activity in the GPi, which is frequently associated with chronic pain and mood disorders (68, 69). Modulating GPi firing following STN DBS enhances typical thalamic responses, underscoring the therapeutic potential of this relationship (70). When administered at approximately 130 pulses per second, HFS aligns with the physiological oscillation frequencies within the basal ganglia-thalamic-cortex system, promoting improved emotional regulation and pain relief (71). This emphasizes DBS's potential as a flexible treatment approach for these interconnected conditions. DBS demonstrates considerable promise in managing chronic pain, insomnia, and depression through mechanisms such as electrotaxis and the enhancement of neuroplasticity. Electrotaxis refers to the movement of progenitor cells toward the electrical currents produced by DBS, which may aid in safeguarding and restoring neuronal health. This process can result in increased cerebral blood flow and neurogenesis, thereby fostering neuroplasticity at a molecular level (65, 72). Furthermore, DBS protects dopaminergic cells, with research showing the preservation of up to 24% of dopaminergic neurons in primate models following STN DBS (73).

These protective effects, along with the modulation of neural circuits, establish DBS as a comprehensive therapeutic approach that addresses the intricate relationships between chronic pain, insomnia, and depression, ultimately improving overall patient well-being (67).

DBS has demonstrated potential in addressing chronic pain, insomnia, and depression through its neuroprotective properties and ability to promote neuroplasticity. DBS, especially when aimed at regions such as the GPi, can enhance the release of glial cell-derived neurotrophic factor (GDNF), which may help slow the degeneration of dopaminergic cells, a key factor in disorders like PD (74). Additionally, DBS fosters neuroplasticity, as indicated by increased nerve proliferation found in post-mortem examinations, which is essential for recovery from neurological conditions (65). Moreover, DBS affects cortical activity by diminishing excessive coupling between beta oscillations and broadband activity, suggesting that its influence extends beyond just the basal ganglia (64). These mechanisms indicate that DBS not only offers immediate symptom relief but also fosters long-term enhancements in both emotional and physical wellbeing, making it a flexible treatment option for interconnected issues like chronic pain, insomnia, and depression (67).

DBS effectively manages these conditions through mechanisms such as the "information lesion" and the activation of astrocytes. HFS simulates a lesion effect by diminishing neuronal coding in regions such as the globus pallidus and ventrolateral thalamus, which can help alleviate symptoms related to chronic pain and mood disorders (65). Furthermore, DBS activates astrocytes, leading to enhanced neuroinhibition through increased extracellular adenosine levels, potentially improving emotional regulation and sleep quality (72). The "microlesion effect" suggests that symptom improvements can occur even prior to the initiation of HFS, highlighting the broad benefits of DBS (64). Additionally, DBS significantly modifies cortical activity by decreasing excessive coupling between beta oscillations and broadband activity, indicating that its effects reach beyond the basal ganglia (66).

DBS represents a promising therapeutic strategy for managing chronic pain, insomnia, and depression by inducing significant neurochemical alterations within targeted neural circuits. For example, DBS aimed at the anterior thalamus boosts adenosine release in the hippocampus, which may contribute to its antiepileptic and

potential antitremor effects (75). On the other hand, focusing on specific brain regions involved in pain processing, emotional regulation, and sleep pathway, DBS can effectively disrupt the maladaptive neural pathways that connect these symptoms. For example, the subcallosal cingulate gyrus has been recognized as a DBS target for treatment-resistant depression, with emerging evidence suggesting that stimulation of this area may improve mood and potentially reduce pain perception. Research suggests that patients undergoing DBS for depression often experience a reduction in pain symptoms, suggesting shared neural mechanisms between these disorders (70). Changes in neurotransmitter systems contribute to the neurobiological mechanisms underlying pain, insomnia, and depression (76, 77). Targeting the caudate nucleus with DBS leads to increased extracellular dopamine levels, an important factor in regulating mood and pain perception (65). Stimulation of areas such as the dorsal STN and zona incerta also raises dopamine levels, likely enhancing both emotional and pain-related responses (67). Furthermore, DBS can alleviate symptoms of PD, including dyskinesias and tremors, even in patients who do not respond to dopamine therapies, suggesting its effectiveness through dopamine-independent pathways (78). Additionally, stimulating the nucleus accumbens modifies monoamine signaling, impacting symptoms of depression and addiction (79). These neurochemical changes underscore the comprehensive benefits of DBS in addressing chronic pain, insomnia, and depression.

Limitations of DBS

DBS presents some notable limitations. First, as a neurosurgical intervention, DBS involves inherent surgical risks, including hemorrhage, infection, and anesthesia-related complications, which can be especially concerning for patients with comorbidities or those in vulnerable populations. Additionally, DBS is a resource-intensive treatment, necessitating significant financial investment and a multidisciplinary team for effective patient management, which can restrict accessibility, particularly in low-resource settings (80). Furthermore, patients face a lifelong commitment to the implanted devices, requiring regular battery replacements and potentially encountering hardware-related complications, a burden that can be particularly challenging for younger individuals (81). The efficacy of DBS can also be variable; not all patients experience significant symptom relief, and some may develop tolerance over time (82). Ethical considerations arise as well, particularly regarding informed consent, especially for vulnerable populations, with concerns about the long-term implications of altering brain activity on patient autonomy and
identity (83). These limitations underscore the necessity for continuous research aimed at optimizing DBS techniques, enhancing patient selection, and addressing ethical challenges associated with their use.

Future directions

Future directions for DBS as a novel approach for simultaneously managing pain, insomnia, and depression syndrome should prioritize personalized treatment protocols that leverage advanced neuroimaging techniques. This integration can optimize electrode placement, enhance understanding of patient-specific neural circuitry, and evaluate the effectiveness of multi-target stimulation. Research by Zhu et al. highlights the importance of individualized targeting in DBS for treatment-resistant depression, suggesting that precision in electrode placement can significantly improve outcomes (84). Additionally, examining the role of neuroplasticity and its modulation

through DBS could unveil mechanisms that facilitate symptom alleviation, aligning with findings from Alemany et al., which demonstrate long-term benefits of DBS in treatment-resistant depression (85). Long-term studies are crucial to assess the durability of therapeutic effects and potential side effects. Collaborative research efforts that merge clinical insights with neurobiological understanding will be vital for crafting comprehensive treatment strategies that effectively address the complex interplay of these co-occurring conditions.

Conclusion

DBS emerges as a promising therapeutic approach for addressing the intertwined challenges of PIDS. By leveraging the shared neural pathways and mechanisms underlying these conditions, DBS offers a unique opportunity for simultaneous intervention, potentially enhancing overall patient outcomes. The integration of DBS into a holistic treatment framework—one that recognizes the complex interrelationships between chronic pain, sleep disturbances, and depressive symptoms—could lead to improved quality of life for affected individuals.

Conflict of Interest

The authors declare that there is no conflict of interests.

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