REVIEW ARTICLE

Focused Ultrasound for Movement Disorders: Evidence from a Systematic Review of Efficacy and Safety

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This systematic review evaluates the clinical efficacy and safety of focused ultrasound (FU) as a non-invasive neurosurgical modality for treating movement disorders, including Parkinson's disease (PD), essential tremor (ET), and dystonia. FU enables precise targeting of deep brain structures without incisions or implanted devices, using advanced imaging guidance to ablate or modulate dysfunctional neural circuits. Magnetic resonance-guided focused ultrasound (MRgFUS), the most widely adopted technique, is examined in detail to assess therapeutic outcomes and procedural characteristics.

Recent clinical studies consistently demonstrate that MRgFUS offers significant symptom relief, particularly in tremor reduction, with a favorable safety profile. Compared to conventional lesioning surgeries, MRgFUS produces smaller, more controlled lesions, minimizing adverse effects while preserving surrounding tissue integrity. In PD patients, improvements in tremors and bradykinesia have been observed following unilateral MRgFUS, which is currently considered the standard approach. However, bilateral applications remain under active investigation due to concerns regarding cumulative risk and long-term neurocognitive outcomes.

Overall, MRgFUS represents a promising and precise intervention for select movement disorders, with growing evidence supporting its integration into neurosurgical practice. Further longitudinal studies are warranted to refine patient selection criteria, optimize targeting strategies, and evaluate the durability of clinical benefits.

INTRODUCTION

Movement disorders, such as Parkinson's disease (PD), essential tremor (ET), and dystonia, significantly impact patients' quality of life. Essential tremor is hypothesized to result from neuronal hyperexcitability, particularly involving the ventral intermediate nucleus (Vim) of the thalamus, which plays a key role in symptom manifestation [1]. While Vim deep-brain stimulation (DBS) is a well-established treatment, its effectiveness varies among individuals, and questions remain regarding its optimal target in PD patients or whether alternative targets can provide superior outcomes.

While pharmacological therapy remains the first-line treatment for movement disorders, some patients experience limited symptom control or intolerable side effects [2]. Traditionally, DBS has been the primary surgical option; however, it carries risks such as neurostimulator malfunction, iatrogenic injuries, and complications in patients with high bleeding risks. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) has emerged as a promising non-invasive alternative with favorable therapeutic outcomes.

In 2015, Na YC and his colleagues conducted a study demonstrating that the subthalamic nucleus (STN) and globus pallidus internus (GPi) are compelling targets for intervention via the pallidothalamic tract. Their research indicated that Focused Ultrasound (FUS) treatment led to a 61% improvement in motor control among drug-resistant PD patients, with a 73% improvement following GPi ablation [3].

Purpose of the Study

The purpose of this systematic review is to identify and evaluate recent studies on Magnetic Resonance-guided Focused Ultrasound (MRgFUS) for treating movement disorders. This review aims to analyze the various applications of MRgFUS by examining key factors such as patient demographics, specific movement disorder diagnoses, targeted brain nuclei, and the overall success rate of the procedure. By synthesizing current research, this study seeks to provide a comprehensive understanding of MRgFUS's efficacy, safety, and clinical applicability in managing movement disorders.

Literature Review

Movement disorders, including Parkinson's disease (PD) and essential tremor (ET), pose significant therapeutic challenges due to their progressive nature and the limitations of conventional treatments such as pharmacotherapy and deep brain stimulation (DBS). However, High-Intensity Focused Ultrasound (HIFU) may offer a promising treatment option to aid in patients' recovery.

HIFU is an effective non-invasive ablation technique for soft tissues and has been used in a wide range of surgical procedures worldwide. This includes treatments for movement disorders, tumor removal, and cosmetic procedures. HIFU generates a focused ultrasound beam that can alter or destroy localized areas through the energy of the ultrasound waves. The ultrasound passes through the skin and underlying tissues without causing harm, focusing on areas about three to four centimeters in diameter. A cytotoxic level of temperature is delivered quickly to target tissues without damaging surrounding cells. The cellular reaction is measured by heat coagulation, which involves a change in the protein structure. This process disrupts the cellular structure and ultimately leads to cell death.

The ultrasound beam used in HIFU is nearly one millimeter in diameter and about ten millimeters long, which minimizes the risk of damage to surrounding tissues. When directed at a focal area, the heat generated can rapidly raise the temperature in the exposed tissue to over 60 degrees Celsius. This can lead to immediate and irreversible cell death in most tissues if the exposure lasts longer than one second. Over time, prolonged exposure and elevated temperatures may cause thermal damage or mechanical effects, such as cavitation. The ability to focus ultrasound energy and control temperature makes HIFU an exceptional treatment option. Currently, HIFU devices are approved by the Food and Drug Administration (FDA) and the Center for Devices and Radiological Health (CDRH).

It is important to consider the potential complications associated with HIFU. In some cases, damage to a vital blood vessel during ablation can lead to serious consequences. However, imaging technology plays a crucial role in facilitating surgeries, helping to prevent such incidents and minimizing risks. One emerging imaging modality that assists in visualizing structures and guiding procedures is magnetic resonance imaging (MRI). Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is a precise, non-invasive technique that targets specific brain nuclei, although its safety, efficacy, and clinical applications are still under investigation. This systematic review aims to evaluate the therapeutic potential of MRgFUS by assessing its effectiveness, safety profile, and clinical role in treating movement disorders.

Recent studies have illustrated the effectiveness of MRgFUS, demonstrating that it can be an effective treatment option for patients with drug-resistant PD-related tremors. A systematic review found significant improvement in limb tremors on the treated side, indicating its potential as a viable therapeutic approach. The safety of MRgFUS has also been a key focus in clinical evaluations. An open-label clinical trial assessing staged, bilateral-focused ultrasound thalamotomy in essential tremor patients reported that adverse events were mostly mild and often resolved, suggesting a favorable safety profile.

MRgFUS has been indicated for various neurological disorders, including epilepsy, Alzheimer's disease (AD), PD, and other movement disorders. Its capability to precisely target deep brain structures without the need for incisions has expanded its clinical utility. Recent reviews have underscored its application in treating conditions such as neuropathic pain and psychiatric disorders, showcasing its versatility in neurosurgical interventions. The benefits of MRgFUS have shown consistency over extended periods, approximately three to twelve months.

In conclusion, MR-guided focused ultrasound (MRgFUS) emerges as a groundbreaking non-invasive therapeutic approach for managing movement disorders. This innovative technique has shown significant effectiveness in alleviating symptoms while maintaining a commendable safety profile. As researchers continue to explore its full potential, further investigations are crucial to elucidate its clinical applications and refine strategies to enhance patient outcomes.

METHODOLOGY

To develop a nuanced and comprehensive literature review on the efficacy of focused ultrasound (FUS) techniques in treating various movement disorders, we meticulously categorized the research components into five primary areas of focus: the diagnosis of movement disorders, the specific target nuclei engaged during treatment, the associated success rates, methodology of outcome measures, and critical methodological considerations.

As a collaborative team, we established rigorous inclusion and exclusion criteria to curate a concise but comprehensive understanding of the existing literature relevant to both High-Intensity Focused Ultrasound (HIFU) and Magnetic Resonance-guided Focused Ultrasound (MRgFUS) applications for managing movement disorders.

To synthesize and illustrate our findings clearly and effectively, we aggregated individual research results into a unified PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, which provided a transparent overview of the collective data and insights (Table 1). Furthermore, to highlight the prevalence of movement disorders within the selected articles, we created a dedicated table that delineates the frequency and variety of these conditions as reported in the literature (Table 2). This structured approach enabled us to systematically present the diverse treatment outcomes and targeted nuclei involved, ultimately providing a thorough and insightful analysis of the effectiveness of Focused Ultrasound (FUS) therapies across a spectrum of movement disorders.

Search Strategy

A comprehensive literature search was systematically conducted utilizing a variety of reputable sources, including PubMed, Google Scholar, and the UT Dallas Library Database, to locate pertinent articles related to our research topic. In addition to these primary databases, we also consulted other valuable references sourced from the reference lists of key studies and authoritative websites, thereby broadening the scope of our investigation.

To ensure a rigorous selection process, we screened titles and abstracts independently, employing the Rayyan - Systematic Review Platform to facilitate the inclusion and exclusion process. Each identified article was meticulously categorized based on established inclusion criteria, allowing us to classify them as good, poor, or unrelated. All titles and abstracts that satisfied our criteria were subsequently selected for an in-depth, full-text review.

To minimize bias and enhance the reliability of our findings, each member of the research team independently reviewed and selected articles. We analyzed the data and addressed any discrepancies that arose through thorough discussion and consensus-building. Articles were excluded from our review if they did not provide full-text availability, if their content was not relevant to focused ultrasound (FUS), or if they were not published in the English language. Our final selection comprised a range of studies, including clinical trials and meta-analyses, that significantly contributed to our understanding of the topic.

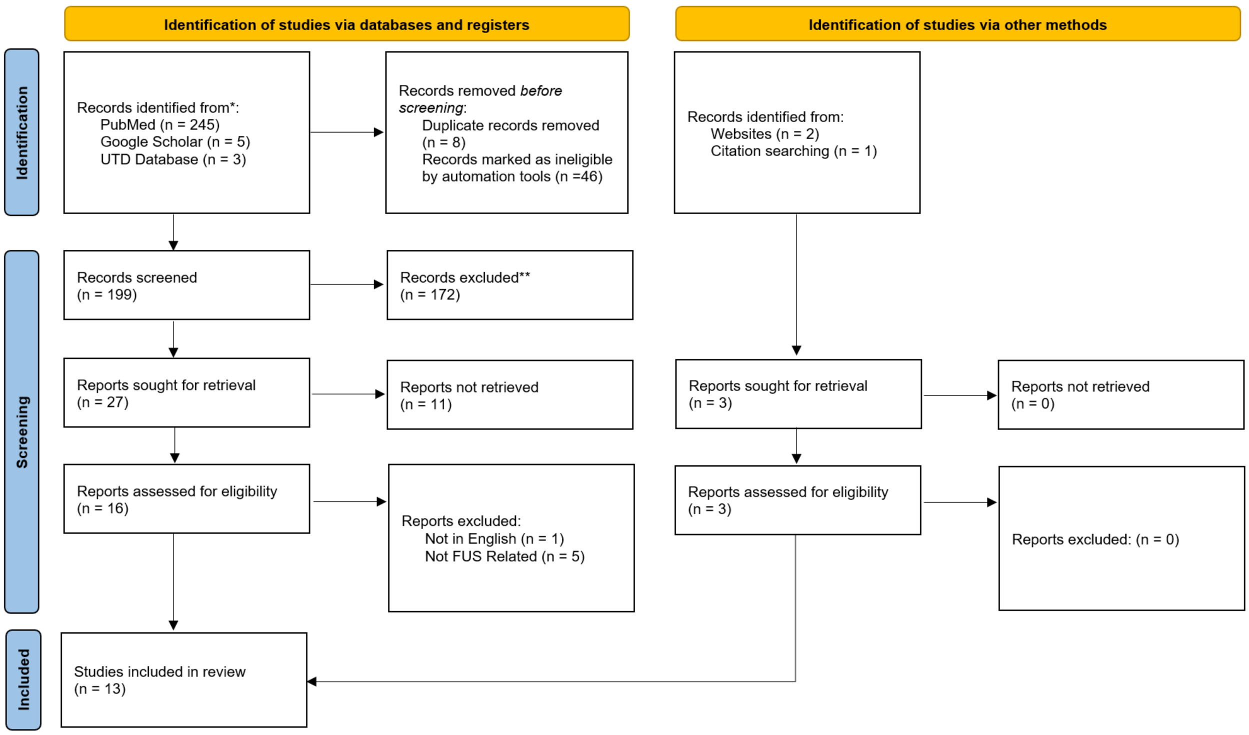

Table 1. PRISMA flow chart.

RESULTS

Cajigas and Halpern (2021) documented a case involving a single patient with essential tremor who was treated using magnetic resonance-guided focused ultrasound (MRgFUS) targeting the ventral intermediate nucleus of the thalamus [10]. The intervention resulted in a 95% reduction in tremor amplitude, as assessed by spiral drawing tests, with this improvement maintained over a three-year follow-up period. Notably, no adverse events were reported, indicating both the durability of the therapeutic effects and a favorable safety profile

Na et al. (2015) reported a case of unilateral MRgFUS pallidotomy targeting the globus pallidus internus (GPi) for a patient with Parkinson's disease, noting "symptom improvement" without specific quantification [3]. A subsequent multicenter open-label trial of unilateral MRgFUS pallidotomy for 20 Parkinson's disease patients reported adverse events that were generally mild and transient, including visual field deficit (n=1), dysarthria (n=4), cognitive disturbance (n=1), and fine motor deficit (n=2) [3].

Lin et al. (2021) conducted one-year multimodal imaging follow-ups for nine tremor-dominant Parkinson's disease patients undergoing unilateral MRgFUS thalamotomy [11]. Their findings revealed that MRgFUS not only abolished tremors but also significantly disrupted brain network topology. Network-based statistics identified a U-shape MRgFUS-sensitive subnetwork reflective of hand tremor recovery, accompanied by cerebral blood flow and gray matter alterations [11]. The researchers found that dopaminergic signatures were responsible for the preferential vulnerability associated with these architectural changes, with structural alterations significantly correlated with D1 and D2 receptors [11].

For GPi targeting in Parkinson's disease, Ito et al. (2020) reported stereotactic coordinates at 3.0 mm anterior, 1.5 mm inferior, and 20 mm lateral to the midpoint between the anterior and posterior commissure [12]. One case report of MRgFUS thalamotomy for Parkinson's disease noted that not only was right-side resting tremor and rigidity abolished immediately following treatment, but left-side symptoms also improved, suggesting potential bilateral effects from unilateral intervention [12].

Izadifar et al. (2020) described focused ultrasound as a non-invasive thermal ablation technique being developed as an alternative to standard therapies. Their systematic review emphasized that MRgFUS represents a novel non-invasive method that may serve as an alternative to open neurosurgical procedures for various brain disorders.

ear	First Author et al.	Title	Study Type	Sample Size (N)	Movement Disorder (Diagnosis)	Target Nuclei	Success Rate (%)	Outcome Measures	Follow-Up Duration	Adverse Events/Complications
2015	Na et al.	Unilateral magnetic resonance–guided focused ultrasound pallidotomy for Parkinson disease	Case Study	1	Parkinson's Disea	Globus Pallidus	Not specified	Symptom improvement	Not specified	Not specified
2018	Bretsztajn & Gedroyc	Brain-focused ultrasound: What's the "FUS" all about? A review of current and emerging neurological applications	Review	N/A	Various neurological conditions	Various	N/A	Overview of FUS applications	N/A	N/A
2020	Ito et al	Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: A systematic review	Systematic Review	8 studies included (total N ≈ 160)	Essential Tremor (ET)	Ventral intermediate nucleus (Vim) of the thalamus	~75–90% improvement in tremor reduction across studies	Tremor rating scales, Quality of life assessments	3 months to 1 year across studies	Gait disturbance, sensory disturbances, paresthesia ataxia (mostly transient)
2020	Izadifar et al.	An Introduction to High Intensity Focused Ultrasound: Systematic Review on Principles, Devices, and Clinical Applications	Systematic Review	N/A	Various neurological conditions	Various	N/A	Overview of FUS mechanisms & efficacy	N/A	N/A
2021	Halpern et al.	Providing Focused Ultrasound Therapy for the Treatment of Essential Tremor at Penn Medicine	Case Study	1	Essential tremors	Ventral intermediate nucleus of thalamus-MRgF US	95%	Tremors Reduced by 64 in 6 months	3 years	none
2021	Lin et al	Convergent structural network and gene signatures for MRgFUS thalamotomy in patients with Parkinson's disease	Observational Study	Not specified	Parkinson's Disease	Thalamus	Not specified	Structural network & genetic analysis	Not specified	Not specified

Table 2. Diverse aspects of treatment outcomes.

The absence of reported adverse events in the Cajigas and Halpern case over three years supports the potential safety of MRgFUS for essential tremors. However, comprehensive adverse event reporting was lacking in most studies. One case report noted an exacerbation of bradykinesia possibly caused by target-adjacent edema. Importantly, no visual-field defects were reported in focused ultrasound pallidotomy studies, unlike in traditional microelectrode-guided procedures [10].

The evidence has significant limitations, primarily the predominance of case reports over controlled trials. Sample sizes were small (n=1 for both case reports), and quantitative outcomes were inconsistently reported [10]. When standardized assessments were used, such as the Clinical Rating Scale for Tremor (CRST), they provided more reliable data. The lack of control groups or comparative analyses against established interventions (e.g., deep brain stimulation) represents a critical gap, as does the limited long-term safety and efficacy data beyond one year post-intervention.

DISCUSSION

A comprehensive analysis of clinical studies and randomized controlled trials assessing HIFU and MRgFUS for essential tremor, Parkinson's disease, and dystonia was conducted. Data on symptom improvement, adverse effects, and long-term efficacy were reviewed. There are physical limitations, emotional well-being, occupational impact, family dynamics, and the overall quality of life that is impacted by these movement disorders. However, HIFU may be a promising treatment to improve their quality of life in recovering from these disorders.

Focused Ultrasound (FUS) is a noninvasive technique that can transiently open the blood-brain barrier (BBB) in specific, targeted areas of the brain [2]. This is accomplished by delivering ultrasound waves in combination with systemically administered microbubbles. The interaction between the ultrasound waves and the microbubbles leads to their controlled oscillation or collapse, which temporarily disrupts the tight junctions of the BBB [2]. At higher energy levels, this process can also produce localized heating, resulting in thermal coagulation and the creation of precise lesions within the targeted tissue [4]. While the outcomes may vary depending on individual patient response and treatment parameters, FUS remains one of the safest and most promising methods for accessing the BBB, thereby enabling therapeutic delivery to otherwise restricted brain regions [4].

MRgFUS utilizes high-intensity ultrasound waves focused on a precise brain region to induce thermal coagulation, leading to selective tissue ablation. This process targets key brain structures such as Vim, GPi, and STN for movement disorder treatments. MRgFUS helps alleviate motor symptoms by disrupting overactive neural circuits to a larger extent [13]. Thermal coagulative necrosis is induced through the ultrasound waves, generating a rapid temperature rise, denaturing proteins, and causing localized cell death while preserving surrounding tissue [4,13]. The high energy waves converge at one point causing alterations of the neural activity and leading to diminishing the abnormal neuronal firing pattern (thereby, improving the tremors spontaneously). In addition, MRgFUS downregulates hyperactivity responsible for rhythmic involuntary movements. The drug delivery and neuromodulation enchantments permit MRgFUS to have shown potential in temporarily opening the blood-brain barrier (BBB), allowing for better drug penetration, and modulating neuronal function.

There are several advantages to MRgFUS and how sustained benefits have been demonstrated over the maximum period of 12 months [4]. MRgFUS are rapid relief of tremors and real-time MRI Feedback which ensures precise targeting and minimizes unintended damage by visualizing the localized site of choice. The lack of need for general anesthesia and the advantage of minimal recovery time, where patients typically experience rapid symptom relief with minimal post-procedure downtime. The rewards of patients being employed on an outpatient basis. There is a visual of spatial 3D images for sagittal, axial, and coronal images, which also provides benefits for surgeries. Lastly, there is no radiation exposure; compared to stereotactic radiosurgery, MRgFUS does not expose patients to ionizing radiation [4]. Unlike DBS, MRgFUS does not require surgical implantation, reducing infection and bleeding risks.

Considering the limitations and side effects present in MRgFUS, it is required to provide a full scope. In rare cases, patients may have experienced transient speech defects, headaches, dizziness, transient tremors, or hemorrhage if a blood vessel is affected [4]. In the matter of irreversibility of lesions, MRgFUS lesions are likely to remain persistent overall, contrary to DBS, where stimulation parameters can be adjusted. This long-term efficacy requires further study in more longitudinal studies to assess durability and long-term effects on neurological and non-neurological function.

CONCLUSION

MRgFUS is a revolutionary, non-invasive alternative to DBS that offers promising treatment options, especially for young patients in the early stages of their conditions, those who do not respond adequately to medications, or individuals hesitant to pursue DBS. Its efficacy in treating essential tremor and Parkinson's disease is well established, and ongoing studies are set to enhance its application for dystonia and other neurological disorders.

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