Transcranial Ultrasound Stimulation in Neurology: A Systematic Review and Qualitative Meta-Analysis of Preclinical and Clinical Studies

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INTRODUCTION

Transcranial Ultrasound Stimulation (TUS) is an emerging non-invasive brain stimulation technique that uses focused ultrasound waves to interact with neural tissue. By modulating the intensity of stimulation, TUS can serve two distinct purposes: low-intensity neuromodulation, which modulates neuronal activity, and high-intensity ablation, which creates permanent lesions in targeted brain regions. Unlike electrical or magnetic approaches, TUS can reach deep brain structures with high spatial precision, without the need for craniotomy or implanted electrodes and avoiding all the common surgical risks, such as bleeding and infections. This dual capability sets TUS apart from other non-invasive methods. Ultrasound energy can be directed with millimetric accuracy, allowing selective intervention on structures such as the thalamus or the basal ganglia while preserving surrounding tissue. Moreover, TUS is fully compatible with neuroimaging, enabling its integration with real-time MRI guidance for both safety and precision.

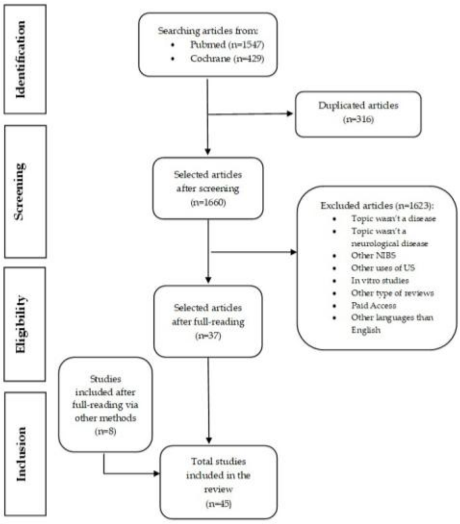
Clinically, TUS offers the possibility of safely modulating dysfunctional circuits in conditions like multi-drug-resistant-epilepsy, while also providing a non-surgical alternative for the treatment of movement disorders such as Parkinson's disease and essential tremor. In addition, recent research highlights its ability to transiently open the blood–brain barrier, introducing the potential for targeted drug delivery directly into the brain.

AIM

The purpose of this review was to evaluate the current evidence on the pre-clinical and clinical use of TUS in neurological diseases. We aimed to explore whether TUS can be considered a safe and effective alternative to invasive brain stimulation, and to clarify its potential applications both in neuromodulation and in therapeutic ablation, in both animals and human models.

METHODS

A systematic review of the literature was performed following PRISMA 2020 guidelines. Publications were searched in PubMed and the Cochrane databases. After screening 1976 articles, 45 articles fit in the inclusion criteria. Both animal and human studies were included, focusing on the therapeutic outcomes, safety profile, and technical aspects of TUS applications.



RESULTS

Neuromodulation: Animal studies

Animal studies consistently demonstrate efficacy across Alzheimer's, epilepsy, stroke, multiple sclerosis, traumatic brain injury, and vascular dementia.

Neuromodulation: Human studies

Promising but mixed results in Alzheimer's disease: with some studies reporting improved cognition when larger cortical areas were stimulated or when multiple sessions were applied.

In epilepsy, pilot studies suggested potential reduction of seizure frequency, though effects remain modest and require standardization of stimulation protocols.

There was only one paper on Parkinson disease and one on post-stroke cognitive impairment in which TUS showed in both of clinical improvement of neurological symptoms.

Ablation: Animal studies

Fewer in number, about arteriovenous malformations and Parkinson disease, but confirmed the feasibility of creating precise lesions in deep brain regions such as the basal ganglia

Ablative: Human studies

TUS led to clinically significant improvements in Parkinson's disease and essential tremor, with many patients experiencing long-term relief of symptoms.

General advantages of TUS:

- High spatial resolution compared to other non-invasive brain stimulation techniques.
- Ability to reach deep brain structures non-invasively.
- Flexible modulation depending on intensity and frequency, allowing both reversible modulation and permanent ablation.
- Overall safety confirmed by both animal and human evidence, with rare and mild adverse events.

CONCLUSION

Transcranial ultrasound stimulation (TUS) shows broad preclinical efficacy across major neurological disorders and emerging promise in human applications, ranging from cognitive enhancement in Alzheimer's disease to seizure reduction in epilepsy and symptom relief in movement disorders. Beyond neuromodulation, ablative approaches confirm the feasibility of creating precise, durable lesions in deep brain structures with sustained clinical benefit. The unique combination of high spatial resolution, non-invasive reach of deep targets, and the ability to flexibly induce either reversible modulation or permanent ablation distinguishes TUS from other non-invasive brain stimulation techniques. Supported by consistent safety evidence and mild adverse events, TUS is emerging as a versatile tool in both basic neuroscience and clinical neurology, bridging the gap between preclinical discoveries and therapeutic translation.

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