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MR-Guided Focused Ultrasound for Blood-Brain Barrier Disruption in Neurodegeneration: A Systematic Review and Meta-Analysis of Clinical Safety

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202580025

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 August 2025 and was last updated on 8 August 2025.

INTRODUCTION

Review question / Objective The primary objectives are to: (1) systematically review the evidence on the safety and feasibility of MRgFUS-BBBD in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS); (2) perform the first meta-analysis of procedure-related adverse events to provide a pooled quantitative estimate of risk; and (3) critically appraise the quality of the evidence for this emerging technology.

Rationale The blood-brain barrier (BBB) prevents most drugs from reaching the central nervous system, hindering treatment for neurodegenerative diseases. Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive technology that can transiently and focally disrupt the BBB to allow therapeutic delivery. While early trials have established initial safety, the field is rapidly evolving, with recent studies suggesting therapeutic effects even without drugs. A comprehensive, cross-pathology synthesis is needed to establish an overarching safety profile and contextualize emerging mechanistic insights. This review addresses this need by providing a robust appraisal of the current clinical evidence.

Condition being studied This review focuses on the application of a therapeutic delivery technology in patients with neurodegenerative diseases, specifically Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. The core challenge being addressed is the restrictive nature of the blood-brain barrier (BBB), a neurovascular interface that protects the brain but also blocks nearly all large-molecule biologics and the vast majority of small-molecule drugs from entry, representing a major obstacle for treating these conditions.

METHODS

Search strategy A comprehensive search will be conducted in PubMed, Embase, Scopus, the

Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Web of Science for studies published from January 2018 to January 2025. The search strategy will combine controlled vocabulary (e.g., MeSH, Emtree) and keywords related to focused ultrasound, the blood-brain barrier, and the specified neurodegenerative diseases. The full search strategy will be provided as a supplementary appendix in the final publication.

Participant or population Adult patients (≥18 years) with a clinical diagnosis of Alzheimer's disease (including mild cognitive impairment due to AD), Parkinson's disease (including Parkinson's disease dementia), or amyotrophic lateral sclerosis.

Intervention MR-guided focused ultrasound used to induce transient disruption of the BBB, with or without an adjunctive therapeutic agent.

Comparator No comparator is required. Single-arm, pre-post interventional studies will be included to assess safety and feasibility.

Study designs to be included Interventional clinical trials (e.g., Phase I, Phase II, single-arm, or controlled trials) will be included.

Eligibility criteria Exclusion criteria include: case reports, reviews, preclinical studies, conference abstracts without full-text data, and studies of FUS used for thermal ablation.

Information sources The intended information sources are the electronic databases PubMed, Embase, Scopus, CENTRAL, ClinicalTrials.gov, and Web of Science. In addition, the reference lists of included articles and relevant narrative reviews will be manually screened to identify any further studies.

Main outcome(s) The primary outcomes are safety and feasibility. Safety outcomes include the incidence and severity of all adverse events, with a focus on radiological findings like asymptomatic T2* hypointensities. Feasibility is determined by the radiological confirmation of BBB opening via contrast-enhanced MRI and its subsequent closure within 48 hours.

Additional outcome(s) Secondary outcomes include preliminary efficacy measures, such as changes in disease-specific biomarkers (e.g., amyloid-β PET signal) and changes on clinical rating scales.

Data management All identified records will be imported into a reference management software to remove duplicates[cite: 58]. Data from included studies will be extracted by one reviewer using a standardized data extraction form and subsequently verified by a second reviewer to ensure accuracy.

Quality assessment / Risk of bias analysis The risk of bias in included non-randomized interventional studies will be assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies – of Interventions) tool. Two reviewers will independently apply the tool, with disagreements resolved by consensus. The results will be presented in a summary "traffic light" plot.

Strategy of data synthesis A dual approach will be used. A narrative synthesis will summarize study characteristics and findings, structured by disease. For quantitative synthesis, a meta-analysis of the incidence of key adverse events will be performed using a random-effects generalized linear mixed model (GLMM) with a binomial distribution. Heterogeneity will be assessed with the I^2 statistic.

Subgroup analysis No subgroup analyses are planned for this review.

Sensitivity analysis A sensitivity analysis for the meta-analysis of adverse event rates will be performed using the more traditional DerSimonian and Laird random-effects model to compare results with the primary GLMM analysis.

Language restriction No language restrictions will be applied during the search to minimize bias.

Country(ies) involved Russian Federation.

Other relevant information This protocol has been registered retrospectively. This step was taken to enhance transparency and create a permanent, citable record of the review's pre-specified methods, in line with modern evidence synthesis standards designed to guard against reporting biases.

Keywords Alzheimer disease; amyotrophic lateral sclerosis; blood-brain barrier; focused ultrasound surgery; meta-analysis; neurodegenerative diseases; Parkinson disease.

Dissemination plans The findings of this systematic review and meta-analysis will be disseminated through publication in a peer-

reviewed academic journal. The results will also be presented at relevant scientific conferences.

Contributions of each author

Author 1 - Suhail Ahmed Khan - Author 1: Contributed to the conception and design of the work, the acquisition and analysis of data, and drafted the manuscript.
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Author 2 - Ekaterina Vladimirovna Mandra - Author 2: Contributed to the conception and design of the work, the interpretation of data, and revised the manuscript critically for important intellectual content.
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