
Comparative Effectiveness of Focused Ultrasound Therapy for Movement Disorders

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and well-being; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the [ESP website](#). Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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DISCLOSURES

This report was prepared by the ESP Center located at the **VA Providence Health Care System**, directed by Eric Jutkowitz, PhD and James Rudolph, MD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Systems Research.

The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Main Report

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ABBREVIATIONS TABLE

Abbreviation	Definition
ANOVA	Analysis of variance
CRST	Fahn-Tolosa-Marín Clinical Rating Scale for Tremor
CTT	Cerebellothalamic tract
DBS	Deep brain stimulation
EQ-5D-5L VAS	5 level EQ-5D visual analog scale
ET	Essential tremor
FDA	US Food and Drug Administration
FUS	Focused ultrasound
GK	Gamma knife
GPi	Globus pallidus internus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIFU	High intensity focused ultrasound
IQR	Inner quartile range
KQ	Key question
MD	Mean difference
MRgFUS	Magnetic resonance-guided focused ultrasound
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NMD	Net mean difference
NR	Not reported
NRCS	Nonrandomized comparative studies
NRS-11	Numeric rating scale 11
PADRECC	Parkinson's Disease Research, Education, and Clinical Centers
PD	Parkinson's disease
PSA	Posterior subthalamic area
PTT	Pallidothalamic tract
QOL	Quality of life
QUEST	Quality of Life in Essential Tremor Questionnaire
RCT	Randomized controlled trials
RD	Risk differences
RF	Radiofrequency
RR	Risk ratio

Abbreviation	Definition
SD	Standard deviation
SMD	Standardized mean difference
SR	Stereotactic radiosurgery
SRDR+	Systematic Review Data Repository-Plus
STN	Subthalamus nuclear
TEP	Technical expert panel
TETRAS	Tremor Research Group Essential Tremor Rating Scale
UPDRS	Unified Parkinson's disease rating scale
VHA	Veterans Health Administration
VIM	Ventral intermedius
Vo	Ventro-oral
VOA	Ventro-oral anterior
VOP	Ventral oralis posterior
XPD	X-linked dystonia-parkinsonism
XDP-MDSP	X-linked dystonia-parkinsonism Movement Disorder Society of the Philippines

BACKGROUND

Movement disorders are a group of neurological conditions that cause problems with movement, including changes in movement frequency, speed, or control.¹ Typically, these disorders involve involuntary movements that present as either decreased or slowing of movement (hypokinesia) or increased or excessive movements (hyperkinesia).² Movement disorders result from damage or dysfunction in the brain due to neurodegeneration, stroke, autoimmune conditions, infections, or toxic/metabolic issues, among other causes.^{1, 3, 4} The most common movement disorders include Parkinson's disease (PD) and essential tremor (ET), which affect approximately 11.8 and 24.9 million people globally, respectively.^{5, 6} Other common movement disorders include dystonia (abnormal posture movements due to sustained or intermittent muscle contraction), ataxia (poorly coordinated movement), chorea (involuntary, jerky, irregular movements), and tic disorders.^{1, 2}

Veterans are at an increased risk for movement disorders compared to the general US population due to age, brain injuries, and exposure to chemicals (eg, Agent Orange).^{7, 8} To better serve Veterans, the VHA created six Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) in 2001 that specialize in the management of these movement disorders.⁹ The PADRECCs annually serve approximately 110,000 Veterans through education, interdisciplinary care, and research.⁹

Movement disorders can severely impact a person's physical and cognitive function, independence, and quality of life.^{10, 11} People with a movement disorder may encounter difficulties in activities of daily life including maintaining employment, driving, or self-care.^{12, 13} Movement disorders can also impact important non-motor functions including sleep patterns and can be associated with depression and anxiety.¹⁴⁻¹⁶ People diagnosed with movement disorders may require substantial caregiving from family, friends, or other caregivers,^{17, 18} and it is not uncommon for caregivers to experience stress and burnout.^{12, 13}

Treatment options for movement disorders include medications, neurorehabilitation therapy, surgical therapies such as deep brain stimulation (DBS), and more research-based interventions such as stem cell replacement or gene therapies.¹⁹⁻²³ Appropriate treatments vary by condition, patient and provider preferences, and individual responses to less invasive methods. More aggressive methods, such as invasive lesioning or stimulation therapies, are generally used as second- or third-line treatments after best medical management; however, aggressive therapies are associated with risks of serious adverse events (eg, infection, hemorrhage, stroke).²⁴ More recently, high intensity focused ultrasound (HIFU) therapy, a noninvasive technique for targeted tissue ablation, has been shown to be effective for treating a variety of health issues including pain, certain cancers, fibroids, and also movement disorders.²⁵ Magnetic resonance-guided focused ultrasound (MRgFUS) combines MRI and FUS to target and destroy tissue without damaging surrounding structures or requiring an open surgical approach.²⁶ MRgFUS has been approved by the US Food and Drug Administration (FDA) for the treatment of ET and PD,^{27, 28} and the FDA recently approved staged bilateral MRgFUS of the pallidothalamic tractotomy for PD.²⁹ At the time of this report, MRgFUS has not received FDA approval for the treatment of other movement disorders.

While side effects have been reported from MRgFUS, such as headache, ataxia, or paresthesia,^{30, 31} studies have also found improved outcomes for people with ET and PD treated with MRgFUS compared to sham or best medical management.³²⁻³⁴ Because of this, MRgFUS has already been approved by the FDA for ET and PD. While evidence for the FDA approvals come from RCTs that have compared MRgFUS to sham therapy, there is limited information about the comparative

effectiveness of MRgFUS to other surgical treatments (*eg*, DBS) or the comparison of ablating different anatomical targets. To our knowledge, there have been no systematic reviews on the use of MRgFUS for PD or ET that have focused exclusively on comparative studies. Existing systematic reviews have only reported on indirect comparisons of available treatments.^{35, 36} Generally, these have shown support for MRgFUS, but these vary by outcome, as well as condition and comparison of interest. There is minimal evidence about other comparative factors, such as anatomical target or unilateral versus bilateral treatments. Additionally, while MRgFUS is being explored for use in other movement-related conditions, such as dystonia, its efficacy to treat these conditions is still uncertain.

To help inform decisions about the use of MRgFUS within the VHA, the VA PADRECC requested a review of the available comparative evidence on the efficacy and safety of MRgFUS for movement disorders.

METHODS

REGISTRATION AND TOPIC DEVELOPMENT

A protocol for this review was registered on the PROSPERO international prospective register of systematic reviews (CRD42024611898). A draft version of this report was reviewed by external peer reviewers; their comments and author responses are provided in the Supplementary Materials.

Representatives from the VA PADRECC and a technical expert panel (TEP) were consulted to refine the key questions (KQ). We focused on studies that reported on the use of MRgFUS for the treatment of movement disorders in adults. For the purposes of this review, it was assumed that all FUS was MRI guided for the conditions of interest. Based on guidance from the TEP, it was determined that the effectiveness of MRgFUS versus sham is sufficiently established for the treatment of ET and PD. Therefore, KQ1 focuses on the comparative effectiveness of MRgFUS versus other surgical treatments. In contrast, the TEP and nominator noted that less is known about the benefits and harms of MRgFUS for other movement disorders of interest. Therefore, KQ2 focuses on the effectiveness of MRgFUS versus sham, best medical management, or no treatment.

While not originally part of our protocol, based on a request from our TEP members we also summarized the results of identified relevant systematic reviews, regardless of study designs included in these reviews.

KEY QUESTIONS

The following KQs were the focus of this review:

KQ Number	Key Question
Key Question 1a	What is the comparative effectiveness of high-intensity focused ultrasound therapy ^a versus other surgical treatments (eg, deep brain stimulation, stereotactic radiosurgery and other ablative treatments) applied to specific anatomic targets for the treatment of: <ul style="list-style-type: none"> • essential tremor? • Parkinson's disease?
Key Question 1b	Does the comparative effectiveness vary by patient characteristics (including treatment history) and anatomic targets?
Key Question 2a	What are the benefits and harms of high-intensity focused ultrasound therapy applied to specific anatomic targets for the treatment of: <ul style="list-style-type: none"> • other neurological conditions? • dystonia? • task-specific tremors? • other movement disorders?
Key Question 2b	Do benefits and harms vary by patient characteristics (including treatment history) and anatomic targets?

Notes. ^a Included studies that did and did not specify MRI-guided FUS.

SEARCHING AND SCREENING

We searched PubMed, EMBASE, Cochrane, and ClinicalTrials.gov (<http://clinicaltrials.gov>) from inception to August 26, 2024 (see [Appendix](#) for complete search strategies). We used medical subject

headings (MeSH) and free text terms specific to high intensity focused ultrasound, magnetic resonance imaging, and movement disorders (including *Parkinson's disease*, *essential tremor*, *dystonia*, and others). We ensured that known relevant publications were captured by our searches. Additional citations were sought from hand-searching reference lists of relevant systematic and non-systematic reviews and consultation with content experts.

Citations were uploaded into EndNote and deduplicated. We screened citations in Systematic Review Data Repository-Plus ([SRDR+](#)). A pilot round of 200 citations was run to ensure a common understanding of the eligibility criteria, where all team members screened the title and abstract of the same citations. The remaining citations were screened by 2 members of the research team and conflicts were resolved by group discussion. Abstracts accepted at the screening phase underwent full-text review by 2 independent reviewers. In the case of conflicts between reviewers during full text-review, an additional team member was consulted as necessary.

Table 1 lists the study eligibility criteria. For KQ1, we focused on individuals with ET or PD who were treated with MRgFUS ablation of brain tissue. Studies included randomized controlled trials (RCTs) and nonrandomized comparative studies (NRCS). Comparisons of interest included unilateral versus bilateral treatment (including different timing of treating the second side), different treatment procedures (DBS, stereotactic radiosurgery [SRS], gamma knife [GK], and other noninvasive or surgical ablations), and comparisons of anatomical targets. We required studies to include a minimum of 10 patients at baseline per arm. We excluded studies that compared people who received a treatment at a single target to those who received a second target due to initial failure of the first treatment. We also excluded studies that conducted only post hoc comparisons of target location. That is, studies that compared anatomical locations were required to have intentionally targeted different anatomical areas prospectively (rather than assess difference in outcomes based on where people were found to have lesions). For KQ1, we excluded studies that compared HIFU only with best medical management or sham comparators, non-comparative (*ie*, single group) studies, and studies that compared data from cohorts of different studies and did not include an adjusted analysis.

For KQ2, we focused on other neurological conditions that involved movement disorders (such as dystonia). Study designs included RCTs, NRCSs, and single group studies, since the overall benefits and harm of MRgFUS for these conditions are unknown. Comparators for KQ2 included those used for KQ1 in addition to best medical management or sham treatments, and studies comparing baseline to follow-up. Due to the expected sparseness of eligible studies, we required a minimum of 5 patients at baseline per arm for these studies (a lower threshold than for KQ1).

For both KQs, outcomes of interest included condition- or procedure-related outcomes (including tremor severity, required other treatments, and cost), patient-specific outcomes (*eg*, quality of life, patient satisfaction), and harms. Intermediate outcomes were not included. For both KQs, we excluded studies focused on atypical parkinsonism, since current evidence does not support use of MRgFUS in atypical parkinsonian syndromes which have different pathophysiologic mechanisms.^{37, 38} We also excluded modeling studies, case reports, case series, qualitative studies, non-systematic reviews, and studies that did not report results by condition and/or anatomical target.

Table 1. Eligibility Criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	<p>KQ1 & KQ2: Adults aged 18 and older</p> <p>KQ1: Essential tremor or Parkinson’s disease</p> <p>KQ2: Other movement related disorders, including dystonia, task-specific tremors, and other movement disorders</p>	<p>KQ1 & KQ2: Atypical parkinsonism</p>
Exposure	<p>KQ1 & KQ2: High-intensity focused ultrasound ablation of brain tissue, including unilateral, staged bilateral, non-staged bilateral</p>	
Comparator	<p>KQ1 & KQ2:</p> <ul style="list-style-type: none"> • Unilateral, staged bilateral, non-staged bilateral focused ultrasound ablation, including comparisons between these treatments, as well as comparisons between anatomical targets • Deep brain stimulation • Different timing of ultrasound (including timing of 2nd treatment for bilateral treatment) • Stereotactic radiosurgery • Gamma knife • Invasive or surgical ablations <p>KQ2:</p> <ul style="list-style-type: none"> • Any (eg, best medical management or sham treatment) or no comparator 	<p>KQ1: Studies comparing focused ultrasound to best medical management or sham treatment</p>
Outcomes	<p>KQ1 & KQ2:</p> <p>Disease/condition or procedural outcomes:</p> <ul style="list-style-type: none"> • Tremor severity • Required follow-up treatments for procedure • Required other treatments or change in other treatments • Recovery outcomes • Cost <p>Patient-Specific Outcomes</p> <ul style="list-style-type: none"> • Quality of life • Function • Patient satisfaction • Caregiving measures (reported in the specified studies) <p>Harms</p> <ul style="list-style-type: none"> • Adverse events/side effects • Complications from procedure • Cognitive decline or impairment 	<p>KQ1 & KQ2:</p> <ul style="list-style-type: none"> • Intermediate outcomes (eg, electroencephalogram readings, imaging measures) • Studies that do not report results by condition and anatomical target
Timing	<p>KQ1 & KQ2: Any</p>	

Domain	Inclusion Criteria	Exclusion Criteria
Setting	KQ1 & KQ2: Any	
Study Design	KQ1 <ul style="list-style-type: none"> • RCT • NRCS • Systematic reviews KQ2: <ul style="list-style-type: none"> • RCT • NRCS • Single group • Systematic reviews 	KQ1 & KQ2: <ul style="list-style-type: none"> • Modeling studies • Case reports or case series • Qualitative studies • Non-systematic reviews KQ1: Single group studies
Other	KQ1: ≥ 10 patients per arm (per condition) KQ2: ≥ 5 patients per arm (per condition)	

Notes. KQ=key question; NRCS=nonrandomized comparative studies; RCT=randomized controlled trials.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

Data were extracted into SRDR+. All data extraction was first completed by 1 reviewer and then confirmed by a second reviewer. Other team members were consulted if conflicts arose. For both KQs, we extracted the following data from eligible studies: study design, details of procedures used, sample size and population characteristics at baseline, and outcomes. Procedure outcomes included available details on anatomical targets, target coordinates, tractography used (visualization and mapping technique), number of sonications (or number of individuals treatment applications to a particular target tissue), ultrasound intensity, average and maximum temperature reached, and other available details. For studies that included comparative data, we extracted whether these were comparing treatments, target locations, or side of treatment. For adverse events, we did not extract severity data. For studies with multiple time points, we extracted data at a short-term and long-term time point (up to 24 months post procedure) for each outcome.

Study risk of bias was independently assessed by 1 reviewer using questions derived from the Cochrane Risk of Bias tool for RCTs and the Risk of Bias In Non-randomized Studies – of Interventions tool for other study designs (see Supplementary Materials). We also evaluated whether each article adequately defined patient eligibility criteria, interventions, and outcomes assessed, and whether it was free of discrepancies. Risk of bias assessments were confirmed by a second reviewer.

SYNTHESIS AND CERTAINTY OF EVIDENCE

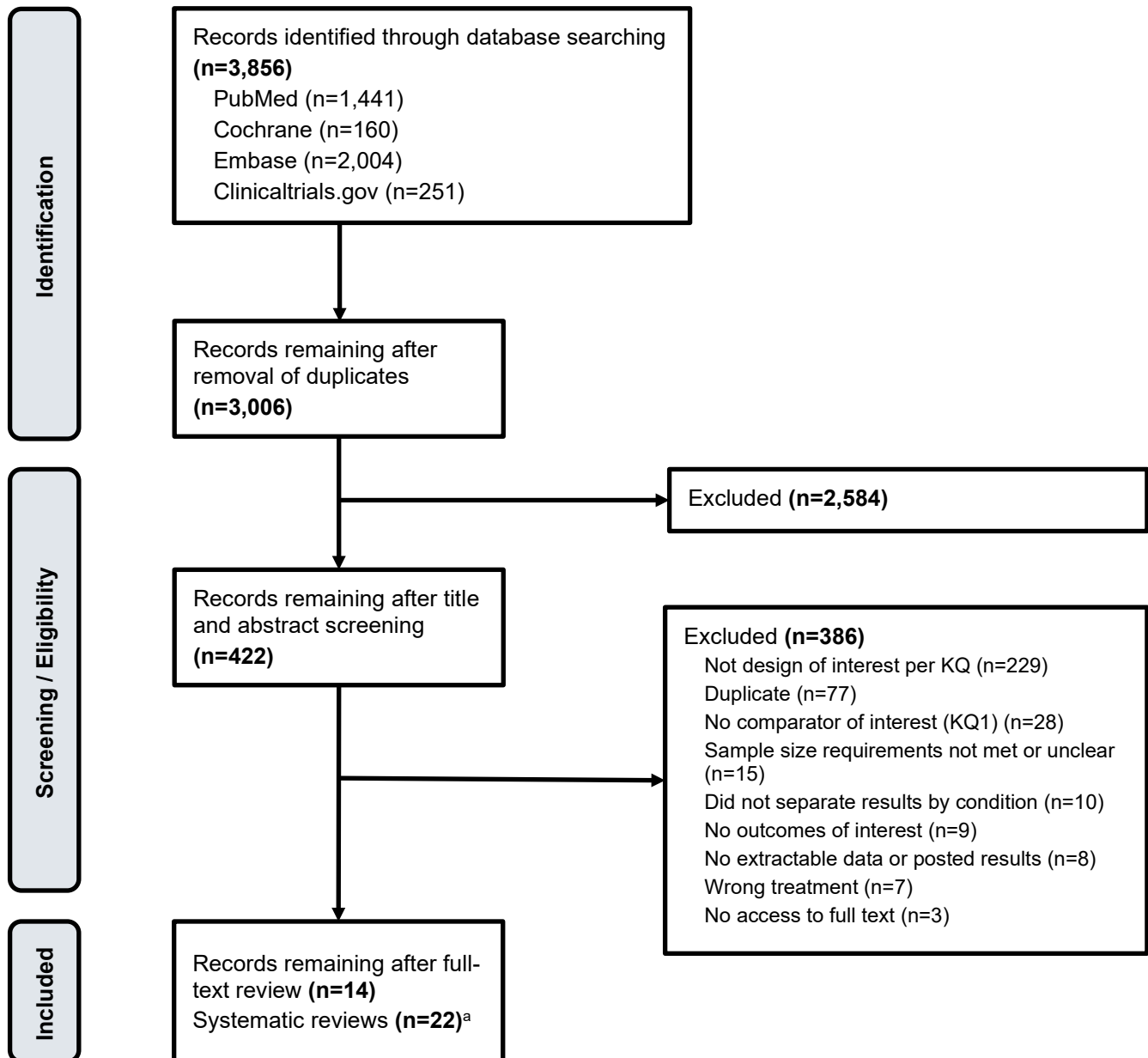
We conducted a narrative synthesis of the evidence. We aimed to meta-analyze quantitative data, but this was not feasible due to the variation in conditions and comparisons. Results in study groups were compared using risk ratios (RR) for dichotomous outcomes. When a study had 0 events in 1 group, we calculated risk differences (RD) instead. Continuous data were compared using mean differences (MD) between interventions or time points for single group studies. We assessed certainty of evidence following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.³⁹ The GRADE approach takes into account risk of bias, imprecision, inconsistency, indirectness, and other issues that the study may present in order to help synthesize results from a body of literature.^{40, 41} We assessed each of these aspects for each of the examined outcomes in order to

assess the confidence of our conclusions. Importantly, we considered the Fahn-Tolosa-Marín Clinical Rating Scale for Tremor (CRST) Part C scores as tremor-related outcomes (some studies described CRST Part C as quality of life [QOL] or function). We compiled evidence profiles based on key findings from the included literature, which provide the basis for determination of certainty of evidence and summary conclusions for outcomes. Within each outcome, we considered the study design, the number of studies and participants, methodological limitations, directness of the evidence, precision of the findings, consistency across studies, and other issues. For outcomes with insufficient evidence, the summary finding for that outcome is “no conclusion.” Although we summarize findings from existing systematic reviews, we do not include the findings of these systematic reviews as part of our GRADE approach.

RESULTS

LITERATURE FLOW DIAGRAM

The literature flow diagram summarizes the results of the study selection process. A full list of excluded studies is provided in the Supplementary Materials.



Notes. ^a References of identified systematic reviews were searched for potential additional primary studies, and we provide a narrative synthesis of the systematic reviews.

OVERVIEW OF INCLUDED STUDIES

Of 3,856 records screened, 422 records underwent full text screening. Of these, 385 were excluded for not being a design of interest per KQ1 ($N = 229$), being a duplicate ($N = 77$), having no comparator of interest (for KQ1) ($N = 28$), sample size requirements not met or unclear ($N = 15$), not reporting results by condition ($N = 10$), not reporting outcomes of interest ($N = 9$), having no extractable data or results ($N = 8$), not including a treatment of interest ($N = 7$), and not being able to retrieve full text ($N = 3$). Upon reviewing the full text of records, 14 primary studies were eligible and included for KQ1 and/or KQ2. Additionally, we identified 22 systematic review or meta-analysis that were related to our KQs and we summarized the evidence from these reviews.

The 14 primary studies were conducted between 1995 to 2024 and included 497 patients. Nine studies focused on patients with ET, 1 study focused on patients with PD, and 4 studies focused on patients with dystonia conditions. Four studies used a crossover NRCS design (eg, patients received a preplanned first treatment and were assessed, then received a second preplanned treatment and were assessed), 6 NRCS compared 2 or more groups of patients, and 4 studies used a single group design. In 9 studies, mean age ranged from 43.2 to 74.7 years, 1 study reported a median age of 56 years, and 4 studies did not report extractable data on patient age. Males represented 53.0 to 87.0% of patients in 10 studies (4 studies did not report sex), and no studies reported patient race/ethnicity data. In 6 studies, the mean skull density ratio (which can impact energy transmission and focusing of the ultrasound wave⁴²) ranged from approximately 0.37 to 0.58, 1 study reported a median skull density ratio of 0.50, and 7 studies did not report skull density ratio. Mean disease duration ranged from 9.8 to 38 years in 5 studies, and 1 study reported a median of 35 years. Three studies reported the mean number of sonications ranging from 7.1 to 11, and 2 studies listed median sonications of 5.5 and 10. Six studies reported maximum temperature ranging from 50 to 62 degrees Celsius. Across all studies, 12 specified the use of MRgFUS and 2 indicated FUS without specifying MRI guidance. Table 2 provides select study details by condition of interest. Full details of the baseline characteristics, design details, and procedure characteristics for the studies can be found in the Supplementary Materials.

Table 2. Select Primary Study Details

Domain	Study Details	ET (N=9)	PD (N=1)	Other Conditions (N=4)
	<i>Patients, N (Range)</i>	407 (10–98)	40 (NA)	50 (6–24)
Study design	Crossover NRCS	4	0	0
	NRCS	5	1	0
	Single group	0	0	4
Comparator	Unilateral vs bilateral	3	0	0
	Left vs right side	1	0	0
	Target location vs target location	2	1	0
	MRgFUS vs other treatment	3	0	0
	None	0	0	4

Domain	Study Details	ET (N=9)	PD (N=1)	Other Conditions (N=4)
Outcomes	Tremor related	7	3	2
	Quality of life	3	0	1
	Function	2	0	1
	Adverse events	4	0	3
	Other	3	1	2

Abbreviations. ET=essential tremor; MRgFUS=magnetic resonance-guided focused ultrasound; NRCS=nonrandomized comparative study; PD=Parkinson's disease.

We identified 22 systematic reviews or meta-analyses published between 2017 and 2024 (see Supplementary Materials). These 22 systematic reviews or meta-analyses included 491 individual studies, with significant overlap in the studies included. Seven reviews focused exclusively on ET, 7 focused exclusively on PD, and 8 included multiple conditions (eg, PD, ET, MS, dystonia, rubral tremor). Importantly, most of the systematic reviews included single group studies, and most relied on indirect comparisons of MRgFUS to other treatments. These reviews reported on tremor-related outcomes ($N = 19$), quality of life ($N = 10$), function ($N = 4$), adverse events ($N = 14$), or other outcomes ($N = 9$). Of note, CRST Part C scores were used to assess both function and quality of life across these reviews. Only 2 systematic reviews used GRADE methodology to synthesize the evidence.^{43, 44}

ESSENTIAL TREMOR

Comparative of Effects of MRgFUS for ET from Primary Studies

Nine studies (4 crossover NRCS and 5 NRCS) reported results for 407 patients with ET (see Supplementary Materials). The studies were conducted the US ($N = 4$), Canada ($N = 3$), Korea ($N = 1$) and the UK ($N = 1$) between 1995 and 2022. Three crossover studies compared unilateral to bilateral MRgFUS treatment, 3 NRCS compared MRgFUS to other treatments, 2 NRCS (1 NRCS and 1 crossover NRCS) compared target locations (eg, ventral intermedialis [VIM] versus posterior subthalamic area [PSA]), and 1 NRCS compared side of treatment (ie, left versus right).

Four studies (all crossover NRCS) had no concerns (therefore, low risk of bias). The other 5 NRCS had high risk of bias due to use of crude analyses ($N = 5$), lack of or unclear blinding of the assessor ($N = 4$), concerns about comparator representativeness ($N = 3$), unclear representativeness of the cohort ($N = 2$), and concerns about adequacy of description of the intervention, lack of clear eligibility criteria, and lack of clear reporting ($N = 1$).

Comparative Effectiveness of Unilateral versus Bilateral

Three studies compared unilateral to bilateral MRgFUS treatment. In summary (Table 3), bilateral treatment compared to unilateral treatment was associated with improved tremor-related outcomes (moderate confidence), and there were no differences in functional outcomes between unilateral and bilateral treatments (low confidence). There were no conclusions for quality of life, adverse events, and other outcomes (insufficient evidence).

Tremor-Related Outcomes

Three crossover NRCS reported tremor-related outcomes for patients receiving unilateral then bilateral treatment. One study examined tremor-related outcomes post-first side treatment and post-second side treatment of MRgFUS in 10 patients.⁴⁵ In this study, the first side (unilateral) was performed at 7 to 56 months before the second (bilateral) (median of 9 months). The study reported significant improvements in CRST A+B after treatment to the second side compared to first side (MD = -17.2, $p < 0.001$). There was also an improvement in CRST C (functional disability) scores at 3 months post-treatment on the second side compared to post (unclear time point) first side treatment (MD = -4.2, 95% CI [-6.8, -1.6], $p = 0.005$).

Another crossover NRCS included 51 patients who received MRgFUS on 1 side and then a second side.⁴⁶ Mean time between treatments was 2.2 (standard deviation [SD] = 1.6) years. Tremor (CRST parts A and B tremor / motor function score) improved at 3 months and 12 months post-treatment on the second side compared to post-treatment (unclear time point) on the first side (3-month MD = -11.00, 95% CI [-12.47, -9.53], $p < 0.001$ and 12-month MD = -10.40, 95% CI [-11.91, -8.90], $p < 0.001$). Similarly, for CRST parts A (upper extremity posture tremor score), tremor improved at 3 months (MD = -1.90, 95% CI [-2.13, -1.67]), $p < 0.001$ and 12 months (MD = -1.90, 95% CI [-2.12, -1.68], $p < 0.001$) post-treatment on the second side compared to post-treatment on the first side. The same study reported that head tremor scores improved at 3 months (MD = -0.70, 95% CI [-0.95, -0.45]) and 12 months (MD = -0.90, 95% CI [-1.07, -0.73]) post-treatment on the second side compared to post-treatment on the first side. The study reported an improvement in CRST part C scores (functional disability) at 3 months (MD = -8.1, 95% CI [-9.22, -6.98], $p < 0.001$) and 12 months (MD = -7.9, 95% CI [-9.02, -6.78], $p < 0.001$) post-second side treatment compared to post-treatment on the first side. Finally, the study reported that head tremor scores improved at 3 months (MD = -0.70, 95% CI [-0.95, -0.45]) and 12 months (MD = -0.90, 95% CI [-1.07, -0.73]) post-treatment on the second side compared to post-treatment on the first side.

A third study reported on 16 patients who received MRgFUS on 1 side and then a second side. Bilateral treatment was performed within 1 year of the first side (unilateral). The study found that CRST scores improved after each treatment in the targeted hand ($p < 0.001$), while the untargeted tremor had not significantly changed.⁴⁷

Quality of Life Outcomes

One crossover NRCS examined quality of life outcomes post-first side treatment and post-second side treatment of MRgFUS in 10 patients.⁴⁵ Quality of Life in Essential Tremor Questionnaire (QUEST) scores declined (*ie*, an improvement) at 3 months post-treatment on the second side compared to post-treatment (unclear time point) on the first side treatment (MD = -19.7, 95% CI [-31.4, -8.0], $p = 0.004$). Similarly, EQ-5D-5L VAS improved at 3 months post-second side treatment compared to post-first side treatment (MD = 6.9, 95% CI [1.8, 11.6], $p = 0.013$).

Functional Outcomes

Two crossover NRCS comparing unilateral to bilateral treatment reported on functional outcomes. One study compared function post-first side treatment and post-second side treatment of MRgFUS in 10 patients.⁴⁵ This study reported no significant difference in blinded evaluators' assessment of patients' ability to walk based on a repeated measures ANOVA from baseline (post-first procedure), and 2 hours, 1 month, and 3 months post-second procedure ($F_{3,27} = 1.777$, $p = 0.176$). Similarly, the authors

found no significant differences in patients' self-reported ability to walk ($F_{1,349,12.145} = 0.199$, $p = 0.735$) or speak ($F_{3,27} = 1.855$, $p = 0.161$) across these same time periods. The study reported a significant increase in missteps in a 6-m tandem walk across these same time periods ($F_{3,27} = 0.629$, $p < 0.0005$), and significant improvements in blinded evaluators' assessment of speech using the NRS-11 ($F_{3,27} = 7.364$, $p = 0.001$). There were significant reductions in gait after treatment on the second side versus post-treatment on the first side impairment (RR = 0.25, 95% CI [0.07, 0.90]).

Another study of 16 patients who received MRgFUS on 1 side and then a second side reported no significant differences in processing speech ($p = 0.271$), attention/working memory ($p = 0.250$), executive function ($p = 0.896$), language ($p = 0.991$), verbal memory ($p = 0.803$), or visuospatial perception ($p = 0.614$) between treatment of the second side versus first side.⁴⁷

Adverse Events

One crossover NRCS reported adverse events post-first side treatment and post-second side treatment of MRgFUS in 10 patients.⁴⁵ There were significant reductions in dysesthesia after treatment on the second side versus post-treatment on the first side (RD = 0.30, 95% CI [0.02, 0.58]). There were no significant differences in any other reported adverse events.

Other Outcomes

One crossover study of 10 patients reported that 100% of patients indicated they would receive a second side treatment again by answering "given what I know now, I would do the second side again."⁴⁵

Table 3. Summary of Findings for Essential Tremor: Comparative Effectiveness of Unilateral versus Bilateral

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	3 (77); Crossover NRCS	Low	Direct	Imprecise ^a	Consistent	N/A	All 3 studies reported significant improvements for bilateral vs unilateral	Moderate
Quality of life outcomes	1 (10); Crossover NRCS	Low	Direct	Imprecise ^b	N/A ^c	Single study	Significant improvement for bilateral vs unilateral	Insufficient
Functional outcomes	2 (26); Crossover NRCS	Low	Direct	Imprecise ^a	Inconsistent ^d	N/A	Overall, no clear difference in outcomes	Low
Adverse events	1 (10); Crossover NRCS	Low	Direct	Imprecise ^b	N/A ^c	Single study	Significant reduction in dysesthesia after bilateral vs after unilateral	Insufficient
Other outcomes	1 (10); Crossover NRCS	Low	Direct	Imprecise ^b	N/A ^c	Single study	All patients would have second side treatment again	Insufficient

Notes. ^a Two of the studies had $N < 20$; ^b Study only included 10 patients; ^c Single study; ^d One study reported mixed results and the other reported no difference.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Comparative Effectiveness of Treatment Sides

Only 1 NRCS compared outcomes by treatment side. This study of 98 patients reported no significant difference in the proportion of patients who had $\geq 30\%$ improvement in ipsilateral sub-score between those who received MRgFUS on the left side versus MRgFUS on the right side (RR = 1.26, 95% CI [0.33, 4.75]).⁴⁸ Evidence was insufficient to make any conclusions (Table 4). No other outcomes were reported for this study.

Table 4. Summary of Findings for Essential Tremor: Comparative Effectiveness of Side

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quality of life outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Other outcomes	1 (100); NRCS	High ^a	Direct	Precise	N/A	Single study	No difference in ipsilateral sub score between left vs right side	Insufficient

Notes. ^a High risk of bias due to lack of blinding of assessor, unclear representativeness of cohort and comparison group, and lack of adjustment for confounders.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Comparative Effectiveness of Target Locations

Two NRCS compared target locations for MRgFUS in ET. In summary (Table 5), there was greater improvement in tremor-related outcomes for MRgFUS targeting the PSA or targets with PSA compared to VIM (low confidence). The studies provide insufficient evidence differences in adverse events between target locations (no conclusion). No other outcomes were reported for this comparison.

Tremor-Related Outcomes

Two NRCS compared MRgFUS for ET targeting 2 separate locations in the brain. One study compared 10 patients who received treatment targeted 1.2–1.5 mm superior to the AC-PC plane with FUS lesion extension into PSA (Group 1) to 10 other patients whose treatment targeted the standard 2.0 mm superior to AC-PC without FUS lesion extension into the PSA (Group 2).⁴⁹ This study reported significantly greater improvement in Tremor Research Group Essential Tremor Rating Scale (TETRAS) postural tremor (NMD = -1.20, 95% CI [-1.71, -0.69]), kinetic tremor (NMD = -1.05, 95% CI [-1.57, -0.53]), and Archimedes spiral scores (NMD = -1.00, 95% CI [-1.58, -0.42]) for those who received treatment with extension in the PSA (Group 1) compared to those who did not (Group 2).

A second study was a crossover NRCS that compared tremor outcomes of 13 patients who received MRgFUS treatment at the VIM/ventral oralis posterior (VOP) to treatment in the PSA.⁵⁰ The study reported a 30.1% improvement in BFS score from post anterior-VIM/VOP to post-PSA ablation ($p < 0.001$).

Adverse Event Outcomes

One NRCS compared 10 individuals who received treatment with lesion extension into PSA (Group 1) to 10 other individuals who received treatment without FUS lesion extension into the PSA (Group 2). The study reported no significant differences between groups in transient imbalance (RR = 2.00, 95% CI [0.64, 6.25]) or numbers at 3 weeks post-treatment (RD = -0.10, 95% CI [-0.29, 0.09]).⁴⁹

No other outcomes were reported for studies comparing target locations.

Table 5. Summary of Findings for Essential Tremor: Comparative Effectiveness of Target Locations

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	2 (23); 1 Crossover NRCS; 1 NRCS	Moderate ^a	Direct	Imprecise ^b	Consistent	N/A	PSA targets or targets with PSA had greater improvement compared to VIM alone	Low
Quality of life outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events	1 (10); NRCS	High	Direct	Imprecise ^c	N/A ^d	Single study	No difference in transient imbalance or numbness between targets	Insufficient
Other outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Notes. ^a One was rated as low and the other was rated as high; ^b Two of the studies had $N < 20$; ^c Study only included 10 patients; ^d Single study.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Comparative Effectiveness of Treatments

Three NRCS reported outcomes comparing MRgFUS to other treatments for people with ET. In summary (Table 6), tremor-related outcomes and quality of life improved for patients who received bilateral DBS compared to unilateral MRgFUS, but confidence was low given baseline differences between groups. No conclusions were made for adverse events of other outcomes for studies that compared treatments (insufficient evidence), and no studies reported on functional outcomes.

Tremor-Related Outcomes

Two NRCS reported tremor-related outcomes for patients who received MRgFUS versus DBS. One study compared unilateral MRgFUS to bilateral DBS in 55 patients.⁵¹ This study reported significantly better total CRST scores in the DBS group compared to MRgFUS after surgery (timeframe not specified; $p < 0.01$), and larger improvement in scores for those in the DBS group compared to the MRgFUS group (NMD = 20.3, p NR). Importantly, baseline scores were better for those in the MRgFUS group. Significantly better total CRST scores were reported post-treatment for the DBS group compared to the MRgFUS group ($p < 0.01$), and larger improvements were reported for the DBS group when comparing follow-up scores to baseline (NMD = 12.05, p NR). Again, baseline scores were better in the MRgFUS group. CRST part B scores were significantly better after surgery (timeframe not specified) in the DBS group compared to the MRgFUS group ($p < 0.01$). This study also reported no significant differences between CRST C disabilities subscore after treatments (MD = 0.8, $p = 0.34$). Baseline scores for subscales were not reported. No differences were reported in hand tremor scores between unilateral FUS treatment (5.5 [treated hand score]) and bilateral DBS (4.6 and 3.9, $p = 0.26$ and 0.45).

A second NRCS compared unilateral MRgFUS to unilateral and bilateral DBS in 85 individuals with ET.⁵² This study reported significant improvements on total CRST scores from baseline to follow-up for all treatments ($p < 0.005$ for all, mean follow-up = 13.1, 8.6, and 11.8 months for bilateral DBS, unilateral DBS, and FUS, respectively). Changes were greater in the unilateral DBS (NMD = 6.5, p NR) and bilateral DBS (NMD = 14, p NR) compared to MRgFUS. Baseline scores were lower (better) for the MRgFUS group compared to people receiving other treatments. This study also reported significant improvements from baseline to post-treatment in CRST observed tremor scores for all treatments ($p < 0.005$ for all). Changes were greater in the unilateral DBS (NMD = 6, p NR) and bilateral DBS (NMD = 13.6, p NR) compared to MRgFUS. Baseline scores were lower (better) at baseline in the MRgFUS group compared to the other treatments. For CRST task scores, this study reported significant improvements from baseline to post-treatment for all treatments ($p < 0.005$ for all). Changes were greater in the unilateral DBS (NMD = 0.4, p NR) and bilateral DBS (NMD = 4.4, p NR) compared to MRgFUS. Baseline scores were lower (better) at baseline in the MRgFUS group compared to the bilateral DBS group.

There was no significant difference in change from baseline to follow-up for CRST axial score in the MRgFUS group (mean follow-up 11.8 months). There were significant improvements in CRST axial score from baseline to post-treatment for both unilateral and bilateral DBS ($p < 0.005$ for both, mean follow-up = 13.1 months for bilateral and 8.6 months for unilateral DBS). Changes were greater in the unilateral DBS (NMD = 2.9, p NR) and bilateral DBS (NMD = 5.5, p NR). Baseline scores were lower (better) at baseline in the MRgFUS group compared to the other treatments.

This study reported significant improvements in CRST disability scale scores from baseline to follow-up for all treatment groups ($p < 0.05$ for all, mean follow-up = 13.1, 8.6, and 11.8 months for bilateral

DBS, unilateral DBS, and FUS, respectively. Changes were slightly greater in the unilateral DBS (NMD = 0.3, *p* NR) and bilateral DBS (NMD = 2.2, *p* NR) compared to MRgFUS.

For CRST scores in the treated hand, the study also reported significant improvements from baseline to post-treatment for all treatments ($p < 0.005$ for all). Changes were greater in the MRgFUS group compared to unilateral DBS (NMD = -1.8, *p* NR) but just slightly better in the bilateral DBS compared to MRgFUS (NMD = 0.5, *p* NR). Scores were lower (better) at baseline in the MRgFUS group compared to the other treatments. For the untreated hand, improvements from baseline to follow-up were only seen in the bilateral DBS group ($p < 0.05$). Changes were greater in the unilateral DBS (NMD = 9.5, *p* NR) and bilateral DBS (NMD = 21.1, *p* NR). Baseline scores were lower (better) at baseline in the MRgFUS group compared to the other treatments.

Quality of Life Outcomes

Two NRCS reported quality of life outcomes. One NRCS compared unilateral MRgFUS to bilateral DBS in 55 patients.⁵¹ This study reported improvements in QUEST scores from baseline to post-treatment for both groups (*p* NR). The change was greater in the bilateral DBS group compared to MRgFUS group (NMD = 13.5, *p* NR). Importantly, baseline scores were lower (better) for patients in the MRgFUS group.

A second NRCS compared unilateral MRgFUS to unilateral and bilateral DBS in 85 individuals with ET,⁵² but only reported quality of life scores for the MRgFUS versus bilateral DBS. This study reported significant improvements in total QUEST scores from baseline to follow-up for both groups ($p < 0.05$ for both, mean follow-up = 13.1 for bilateral DBS and for FUS). The change was greater in the bilateral DBS group compared to the MRgFUS group (NMD = 10.6, *p* NR), but scores were lower (better) at baseline for the MRgFUS group. Similar results were seen for QUEST work, hobbies, and physical and social subscales. There was no significant difference on communication subscales from baseline and follow-up for the MRgFUS group.

Functional Outcomes

No studies reported on functional outcomes.

Adverse Event Outcomes

One NRCS compared unilateral MRgFUS to unilateral and bilateral DBS in 85 individuals with ET.⁵² A significantly greater proportion of patients experienced paresthesia at 3 months post-treatment in the unilateral MRgFUS versus unilateral DBS group (RR = 12.53, 95% CI [1.75, 89.56]) or bilateral DBS group (RR = 26.73, 95% CI [6.36, 112.26]). At 12 months post-treatment, there was only a significant difference in the proportion of patients who experienced paresthesia between the MRgFUS versus bilateral DBS (RR = 11.36, 95% CI [1.39, 92.64]).

There were no significant differences in the proportion of patients with dysarthria at 3 months between groups, but there were significantly more cases of dysarthria in the bilateral DBS group compared to the MRgFUS group (RD = -0.11, 95% CI [-0.18, -0.03]) at 12 months post-procedure.

At 3 months follow-up, the proportion of people with gait instability was higher among those who received unilateral DBS compared to unilateral MRgFUS (RR = 0.39, 95% CI [0.17, 0.90]) but not at 12 months. No significant differences were seen between bilateral DBS and unilateral MRgFUS.

There were significantly higher proportions of headache (RD = 0.60, 95% CI [0.35, 0.85]), lightheaded/dizziness (RD = 0.73, 95% CI [0.51, 0.96]), and nausea/vomiting (RD = 0.53, 95% CI [0.28, 0.79]) in the MRgFUS group compared to unilateral DBS at 3 months follow-up, but no significant difference by 12 months follow-up.

Similarly, there were significantly higher proportions of headache (RD = 0.60, 95% CI [0.35, 0.85]) lightheaded/dizziness (RD = 0.73, 95% CI [0.51, 0.96]) and nausea/vomiting (RD = 0.53, 95% CI [0.28, 0.79]) in the MRgFUS group compared to bilateral DBS at the 3 month follow-up, but no significant difference by 12 months follow-up.

There were no significant differences in hemorrhage, flushed warmth, mental health status, weakness, dysphagia, or hardware-related MRI burn, lead erosion, or infection between any groups at any time point.

One NRCS compared unilateral MRgFUS to unilateral DBS and unilateral radiofrequency (RF) in 59 individuals with ET.⁵³ A significantly larger proportion of people in the RF group compared to the MRgFUS group had an adverse event (defined as intracerebral hemorrhage near the lesion, cognitive deterioration, mild dysarthria, impaired eye movement, mild facial paresis, hypesthesia, loss of taste, balance problems, or muscle twitching) at 1 month follow-up (RR = 0.22, 95% CI [0.07, 0.68]). There were no significant differences in adverse events at 12 months. No significant difference was reported between unilateral DBS and MRgFUS groups. Further, no significant differences were reported between groups for any individual adverse event examined.

Other Outcomes

One NRCS compared unilateral MRgFUS to unilateral DBS and unilateral RF in 59 individuals with ET.⁵³ No differences were reported between groups at 1 month or 12 months follow-up in the proportion of people with successful treatment or complete remission.

Table 6. Summary of Findings for Essential Tremor: Comparative Effectiveness of Treatments

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	2 (140); NRCS	High ^a	Direct	Precise	Consistent	N/A	Bilateral DBS had better improvement compared to Unilateral MRgFUS	Low
Quality of life outcomes	2 (140); NRCS	High ^a	Direct	Precise	Consistent	N/A	Bilateral DBS had better improvement compared to Unilateral MRgFUS	Low
Functional outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events	2 (144); NRCS	High ^a	Direct	Imprecise ^b	Consistent ^c	N/A	Greater AEs in MRgFUS group within 3 months of procedure, but generally no difference by 12 months post-procedure	Insufficient
Other outcomes	1 (59); NRCS	High	Direct	Precise	N/A ^d	Single study	Greater remission in Unilateral RF at 0-3m but no difference by 12 months	Insufficient

Notes. ^a Both rated as high; ^b Confidence intervals for several measures were wide; ^c Measures varied across studies and were not consistent; ^d Single study.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Results from Systematic Reviews for ET

Seven systematic reviews examined MRgFUS for ET. Overall, MRgFUS for ET may improve tremor-related symptoms, quality of life outcomes, and functional outcomes, but comparative effectiveness results were mixed, particularly when compared to DBS. Adverse event outcomes also showed mixed results. However, cost outcomes favored MRgFUS over DBS and RF.

Pre-Post

Four systematic reviews reported change in outcomes from before to after MRgFUS.^{30, 43, 54, 55} All 4 systematic reviews concluded that there were improvements in tremor-related outcomes and quality of life (1 review using GRADE methodology concluded low certainty of evidence for tremor severity and very low certainty of evidence for recurrence).⁴³ One of the 4 reviews also reported an improvement in function from before to after treatment.⁴³

Another systematic review reported that a significant proportion of patients pooled across 9 individual studies experienced adverse events including in-procedure dizziness (pooled estimate = 43.4%), nausea/vomiting (pooled estimate = 26.8%). In addition, a significant proportion of patients across 9 studies experienced paresthesia or ataxia at 0 to 3 months (pooled estimates = 25.1% and 32.8%, respectively) or 12 months after treatment (pooled estimates = 15.3% and 10.5%, respectively).⁵⁵

MRgFUS versus Deep Brain Stimulation

Four systematic reviews compared MRgFUS to DBS with mixed findings.^{35, 43, 44, 56} One systematic review of 9 studies reported no difference in tremor outcomes between MRgFUS and DBS (GRADE: very low)⁴³ Another systematic review of 45 studies reported worse tremor-related outcomes for MRgFUS compared to DBS (pooled average % improvement tremor severity, DBS = 60.1% [SD = 9.7] vs FUS = 55.6% [SD = 8.2], p NR).³⁵ The same review reported significantly better outcomes for bilateral DBS compared to those receiving unilateral MRgFUS (pooled average % improvement tremor severity, bilateral DBS = 60.2% [SD = 5.2] vs FUS = 55.6% [SD = 8.2], $p < 0.001$). There was no significant difference in tremor-related outcomes for MRgFUS compared to unilateral DBS (pooled average % improvement tremor severity, unilateral DBS = 56.4% [SD = 9.7] vs FUS = 55.6% [SD = 8.2], $p = 0.198$).³⁵ One systematic review of 46 articles narratively reported mixed results for tremor-related outcomes.⁵⁶ Another systematic review of 32 studies reported significantly better tremor outcomes for those receiving MRgFUS versus DBS ($p < 0.001$).⁵⁷

Two systematic reviews reported quality of life outcomes. One systematic review of 9 studies found better quality of life for MRgFUS compared to DBS (GRADE: very low), and the other systematic review of 45 studies found significantly better quality of life in the FUS group (percent improvement = 61.9% [SD = 7.9]) compared to the DBS group (52.5% [SD = 16.2], $p < 0.001$).³⁵

One systematic review reported no difference in function or complications between MRgFUS and DBS (GRADE: very low for both).⁴³ One review of 45 studies reported that a significantly higher proportion of patients experienced gait disturbances and/or muscle problems, paresthesia, and nausea for patients with ET after MRgFUS compared to any DBS ($p < 0.001$ for all). The same review reported significantly higher gait disturbances/muscle problems for patients who received MRgFUS compared to only those receiving unilateral DBS ($p = 0.003$). Those receiving any DBS (unilateral or bilateral) had a significantly higher prevalence of speech disturbances and local adverse symptoms ($p < 0.001$ for both). No deaths were reported in the MRgFUS group, while 1 surgery-related death was

reported in the DBS group. There were more persistent complications in the MRgFUS group than in the DBS cohort (with persistent defined as present at the latest follow-up, with average follow-up of 16.6 [SD = 16.4] in the DBS group and 14.4 [SD = 7.3] in the MRgFUS group).³⁵

Two systematic reviews reported lower costs for FUS compared to DBS.^{43, 57} One reported that MRgFUS neurosurgery has a mean cost of \$23,507 and a mean quality-adjusted survival of 3.69 quality-adjusted life-years, while the DBS group had mean costs and quality-adjusted life-years of \$57,535 and 3.94 (HQO). The other review estimated a mean cost of treatment to be lower with MRgFUS (\$20,593 [SD = \$1,402]) versus DBS without staging (\$27, 906 [SD = \$524], *p* NR) or DBS with staging (\$45,107 [SD = \$614], *p* NR) (overall DBS vs MRgFUS *p* < 0.001).⁵⁷

MRgFUS versus Other Treatments

One systematic review of 9 studies compared MRgFUS to RF. The review reported no difference in tremor-related outcomes between RF and MRgFUS (GRADE: very low). The same review reported lower total mean costs for patients who received MRgFUS compared to RF, and higher complications for RF compared to MRgFUS (GRADE: very low for both).⁴³

One systematic review reported significantly better quality of life for FUS compared to SRS for quality of life effect and duration of effect (*p* < 0.001), but no significant difference in cost outcomes (*p* = 0.654).⁵⁷ One systematic review compared FUS to “other” treatments and narratively reported favorable results for those treated with FUS.⁴³

One systematic review reported improved CRST Part C scores and quality of life for patients who received MRgFUS compared to sham based on 1 RCT (GRADE: high for both).⁴³

PARKINSONS DISEASE

Comparative of Effects of MRgFUS for PD from Primary Studies

One NRCS compared MRgFUS targeted at either the VIM or the pallidothalamic tract (PTT) in people with Parkinson’s disease (see Supplementary Materials).⁵⁸ The 40-person study was conducted between 2020–2022 in Russia. Median follow-up time was 109.0 (inner quartile range [IQR] = 53, 231) days, with a maximum of 625 days. The full study included patients whose treatments were either telemedicine-proctored treatment (*N* = 27) or whose treatments were conducted independently without proctor supervision (*N* = 40). However, the study only reported results by target for those whose treatments were conducted independently; therefore, only these patients were included in this review. The median age of all participants in the independently treated group was 63.0 (IQR = 58.5, 69.5) years and 72.5% were male. The median skull density ratio for the independently treated group was 0.5 (IQR = 0.4, 0.6) and the median disease duration was 6.0 years (IQR = 5.0, 11.2). Patient characteristics were not reported by treatment target group. Importantly, 30 patients received treatment in the VIM nucleus target, and 25 of these patients received treatment in the PTT target, but 15 of the patients in the PTT group received treatment in both targets. Overall, patients received approximately 6.0 sonications (median; IQR = 5.0, 9.0).

The study was high risk of bias due to concerns about comparator representativeness, use of crude analyses, and lack of clarity for blinding of an outcome assessor and representativeness of the cohort (see Supplementary Materials).

The study only reported 1 outcome (recurrence of tremor) for the comparison of anatomical targets. Specifically, a smaller proportion of patients had recurrence of tremor 1 year after treatment for the PTT target group compared to the VIM target group (12% vs 22%, p NR). No other outcomes were reported for the comparison of anatomical targets in this group. We conclude that there was insufficient evidence to make conclusions about the effect of MRgFUS targeted at VIM or PTT in patients with Parkinson's disease (Table 7).

Table 7. Summary of Findings for Parkinson’s Disease ^a

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quality of life outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional outcomes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Recurrence of tremor	1 (40); NRCS	High ^b	Direct	N/A ^c	N/A ^c	N/A	No conclusion	Insufficient

Notes. ^a Comparing target location; ^b Rated as high risk of bias due to unclear blinding of assessor, unclear representativeness of cohort, and concerns about comparator and use of crude analyses; ^c Single study.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Results from Systematic Reviews for PD

Seven systematic reviews focused on PD patients treated with MRgFUS. Four reviews reported changes in outcomes from before FUS to after FUS. Two reviews looked at FUS more generally, while the rest focused specifically on MRgFUS. Three systematic reviews reported on tremor-related outcomes.

Overall, for tremor-related outcomes for PD, MRgFUS appeared to show benefit from before to after treatment. However, results were mixed when compared to RF of DBS. Results were mixed for quality of life, but 1 review showed improvement in function compared to sham. Results for adverse events compared with sham, RF, or no comparator were mixed.

Pre-Post

One systematic review of 5 studies reported significant improvements in tremor-related outcomes using the Unified Parkinson's Disease Rating Scale (UPDRS)-II, III, IV, and Unified Dyskinesia Rating Scale (UDysRS) after FUS compared to before (pooled $p < 0.001$ for all).⁵⁹ Another systematic review of 11 studies narratively reported favorable outcomes after FUS compared to before using the UPDRS-III.⁶⁰ Another systematic review that included 20 studies reported favorable results or no difference in tremor outcomes (UPDRS-III) from before to after MRgFUS compared to baseline for those “on” medication (pooled standardized mean differences [SMDs] of 12.88 (95% CI [5.32, 20.44]) at 1 month and 20.65 (95% CI [12.15, 29.14]) at 1 year. Similar findings were reported when comparing people who received MRgFUS to those “off” medication (SMD = 11.45; 95% CI [-3.50, -26.40]) and SMD = 22.28 (95% CI [15.26, 29.30]) for those “off” medication).⁶¹

For adverse events, 1 systematic review of 5 studies reported a significant occurrence of dysarthria ($p = 0.038$) but no other significant adverse events after MRgFUS.⁵⁹ Two other reviews provided information on adverse events from before to after, but no conclusions were made.^{60, 61}

One systematic review of 11 studies narratively reported favorable quality of life outcomes after compared to before MRgFUS.⁶⁰ Of note, CRST Part C scores were included as part of the quality of life assessments in this review. Another review of 2 studies narratively reported that the only significant cognitive changes seen over time were visual memory and verbal fluency, but that otherwise there were minimal cognitive declines.⁶²

A systematic review of 24 studies reported significant improvement in efficacy (defined as UPDRS III and UPDRS III items 20 and 21) after MRgFUS of the globus pallidus internus (GPi) (MD = 13.46, 95% CI [2.46, 25.10]).³⁷

MRgFUS versus Other Treatments

A systematic review of 2 studies compared MRgFUS to sham and found significantly favorable tremor-related (pooled SMD = -1.20, 95% CI [-2.06, -0.34]) and functional outcomes (SMD = -0.86, 95% CI [-1.41, -0.32]), but no difference in quality of life (SMD = -0.43, 95% CI [-0.96, 0.10]) or “other” indications (pooled SMD NR). This same review reported that dizziness was significantly more common for people who received MRgFUS (OR = 4.68, 95% CI [1.20, 18.23]) but there were no other differences in adverse events.⁶³

One systematic review included 40 studies (3 of these using FUS) to compare FUS with RF.³⁶ This review reported a lower failure rate for RF compared to FUS (14% vs 24%, p NR), and no difference

in post treatment UPDRS-III scores between RF and FUS (pooled MD = -1.1, 95% CI [-9.6, 7.4]). This same review reported mixed results for adverse events, with RF having significantly higher cognitive deficits ($p = 0.004$), but MRgFUS having significantly worse “other” adverse events ($p < 0.001$).

One systematic review of 24 studies generally found no significant difference in efficacy (defined as UPDRS III and UPDRS III items 20 and 21) between MRgFUS of the GPi or MRgFUS of the VIM to each other or DBS with various targets. However, significant differences were seen between DBS of the GPi compared to MRgFUS of the GPi (MD = -9.21, 95% CI [-16.44, -2.28]) or compared to MRgFUS of the VIM (MD = -9.23, 95% CI [-18.19, -0.11]) for total UPDRS III scores who were “on medications.”³⁷

OTHER CONDITIONS

Effects of MRgFUS for Dystonia Conditions from Primary Studies

Four single group studies reported results for 50 patients with dystonia conditions that were treated with MRgFUS. Conditions included dystonic tremor ($N = 2$), focal hand dystonia (FHD) ($N = 1$), and X-linked dystonia-parkinsonism (XDP) ($N = 1$) (see Supplementary Materials). The studies were conducted in Italy, Australia, Japan, and the Philippines between 2017 and 2024, and follow-up ranged from 12 to 36 months. The primary targets included the VIM ($N = 2$), ventro-oral (Vo) nucleus ($N = 1$), and the PTT ($N = 1$). Of note, 1 of the VIM studies noted that all patients received treatment in the VIM, but that some patients also received treatment at another target (PSA and/or ventro-oral anterior [VOA]). The mean number of sonications ranged from 7.1 to 11, and the average maximum temperature ranged from 56.6 to 60.3 degrees Celsius across the 4 studies.

In 2 studies, the average age of patients was 43.2 (SD = 9.8) and 70.9 (SD = 10.6), while the median age in a third study was 56 (IQR = 44, 66). In 3 studies, males comprised 62 to 90% of the study population, and none of the studies reported information on patient race/ethnicity. A fourth study did not report age of patients for those with XPD (Khu). In 2 studies, the mean skull density ratio of patients was 0.37 and 0.41, and a third study reported a median skull density ratio of 0.5. Mean disease duration was 9.8 and 20.5 years in 2 studies, and median disease duration was 35 years in a third study.

All studies were single group designs with no true comparator. Three were moderate risk of bias for having unclear or high risk of blinding of the outcome assessor, high risk of incomplete outcome data, or unclear representativeness of the cohort. The other study was low risk of bias (see Supplementary Materials).

In summary, there was insufficient evidence to make any conclusions about the use of MRgFUS in patients with dystonia conditions (Table 8).

Tremor-Related Outcomes

Three single group studies reported tremor-related outcomes. One single group study reported on patients with dystonic tremor who received MRgFUS targeted at the VIM, and potentially additional sonications in the PSA and/or VOA if tremor persisted after 3 treatments of the VIM. This study reported a significant reduction (improvement) in hand tremor score based on CRST Parts A & B at 1 month and 24 months compared to baseline (1-month aMD = -14.5, 95% CI [-17.7, -11.3], $p < 0.001$; 24-month aMD = -12.2, 95% CI [-15.6, -8.9], $p < 0.001$). The same study also reported a significant

reduction (improvement) in total CRST scores at 1 month and 24 months compared to baseline (1-month aMD = -31.4, 95% CI [-38.1, -24.8], $p < 0.001$; 24-month aMD = -24.8, 95% CI [-32.5, -17.1]; $p < 0.001$).⁶⁴

One single group study of patients with focal hand dystonia who received MRgFUS targeted at the Vo nucleus reported a significant decrease (improvement) in Writer's Cramp Rating Scale at 12 months compared to baseline (MD = -4.3, 95% CI [-7.17, -1.43], $p = 0.011$). The same study also reported a significant increase (improvement) in Tubiana Musician's Dystonia Scale scores at 1 month and 12 months follow-up compared to baseline (1-month MD = 3.4, 95% CI [2.7, 4.1]; 12-months MD = 3.6, 95% CI [3.2, 4.0], $p < 0.0001$). There was also a significant increase (improvement) on the Arm Dystonia Disability Scale scores at 1 month and 12 months compared to baseline (1-month MD = 29.2, 95% CI [18.3, 40.1]; 12-months MD = 22.9, 95% CI [6.2, 39.6], $p = 0.025$).⁶⁵

A third single group study of patients with X-linked dystonia-parkinsonism received MRgFUS targeted at the PTT and reported a 14.1% to 15.3% improvement in X-linked dystonia-parkinsonism Movement Disorder Society of the Philippines (XDP-MDSP) total scores from baseline to a mean follow-up of 19.1 months (p NR).⁶⁶

Quality of Life Outcomes

One single group study reported quality of life outcomes for patients with dystonic tremor who received MRgFUS targeted at the VIM or potentially sonications in the PSA and/or VOA if tremor persisted after 3 treatments of the VIM. This study reported a significant decrease (improvement) in QUEST scores at 1 month and 24 months compared to baseline (1-month aMD = -39.3, 95% CI [-53.4, -25.2], $p < 0.001$; 24-months aMD = -22.4, 95% CI [-40.3, -4.4], $p < 0.05$).⁶⁴

Functional Outcomes

One single group study of patients with dystonic tremor reported functional outcomes related to MRgFUS targeted at the VIM. There were significant reductions (improvements) in activities of daily living (MD = -16.67, 95% CI [-21.71, -11.62], $p < 0.001$), total performance scores (MD = -6.33, 95% CI [-11.68, -0.99], $p < 0.01$), and performance scores on the treated side (MD = -7.67, 95% CI [-9.59, -5.74], $p < 0.001$) at 12 months compared to baseline, all assessed using the TETRAS. There was no significant difference in axial performance scores at 12 months compared to baseline (MD = -1.67, 95% CI [-4.13, 0.80], p NR).⁶⁷

Adverse Events

Three single group studies reported on adverse events related to MRgFUS targeted at the VIM. One single group study of 10 patients with dystonic tremor reported 1 instance of imbalance and 1 instance of dysarthria during the first 12 months after treatment, but neither persisted after 12 months. The study reported no instances of limb ataxia, oral paresthesia, or hand paresthesia.⁶⁷

Another single group study of 10 patients with focal hand dystonia who received MRgFUS targeted at the Vo nucleus reported several adverse events that resolved by 12 months. Reported adverse events including periorbital edema (1 patient) unsteady gait (2 patients), facial palsy (2 patients), occipital sensory loss (3 patients), and nausea (3 patients). Headache related to stereotactic frame occurred in all 10 patients, as well as headache related to sonication, but all were resolved by the 12 month follow-up point. Dysarthria occurred in 3 patients, with 1 of these cases persisting after 12 months. One suicide attempt was reported but was likely unrelated to treatment.⁶⁵

One single group study of patients with X-linked dystonia-parkinsonism who received MRgFUS targeted at the PTT reported that 1 out of 6 patients reported right side weakness 3 months post-procedure.⁶⁶ This study indicated that there were no interoperative adverse events in these patients.

Other Outcomes

One single group study of patients with focal hand dystonia who received MRgFUS targeted at the Vo nucleus reported that 4 of 5 patients who were unemployed at baseline had returned to work by 12 months. The same study reported that 3 of 10 patients had symptom recurrence at 3 months.⁶⁵

Another single group study of patients with X-linked dystonia-parkinsonism reported that all 6 patients reported symptom improvement after receipt of MRgFUS targeted at the PTT.⁶⁶

Table 8. Summary of Findings for Dystonia Conditions

Result	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Tremor-related outcomes	3 (40); Single group	Moderate ^a	Direct	Imprecise ^b	Consistent	All single group	All 3 studies reported improvements (2 significant; significance could not be assessed in the third based on reported data)	Insufficient
Quality of life outcomes	1 (24); Single group	Low	Direct	Imprecise ^b	N/A ^c	Single study	Significant decrease (improvement) in QUEST scores	Insufficient
Functional outcomes	1 (10); Single group	Moderate	Direct	Imprecise ^b	N/A ^c	Single study	Significant improvement in 3/4 scale measures of function	Insufficient
Adverse events	3 (26); Single group	Moderate ^d	Direct	Imprecise ^b	Consistent	All single group	Occur in approximately 10-30% of patients for most adverse events (though higher for headache), and generally resolve by 12 months post procedure	Insufficient
Other outcomes	2 (16); Single group	Moderate ^d	Direct	Imprecise ^b	Inconsistent ^e	All single group	4/5 patients who were not working at baseline were working at 12 months follow-up 3/10 had symptoms recurrence All (6/6) patients reported symptom improvement	Insufficient

Notes. ^a Two rated as moderate risk, 1 as low risk of bias; ^b Due to small sample size; ^c Single study; ^d All studies rated as moderate; ^e Variety of outcomes so consistency not applicable.

Abbreviations. N/A=not applicable; NRCS=nonrandomized comparative study.

Results from Systematic Reviews for Mixed or Other Conditions

Eight systematic reviews reported on multiple conditions. Six reviews focused on MRgFUS and 2 reviews reported on FUS more generally. Two of the 8 reviews included patients with just ET and PD^{68,69} and 6 included patients with a general combination of conditions (eg, PD, ET, multiple sclerosis [MS], dystonia, rubral tremor).

In summary, for mixed conditions, MRgFUS generally showed improvements in tremor-related outcomes, but no differences were seen when compared to RF, GK, DBS, or other lesioning surgeries based on 2 reviews, and 1 review reported favorable results for MRgFUS compared to SR. Two reviews reported that quality of life results favored MRgFUS over DBS, sham, or without a comparator group. One review reported no difference in function after MRgFUS. Overall adverse event outcomes were mixed.

ET and PD

One systematic review of 9 studies narratively found favorable results for tremor-related outcomes, quality of life, adverse events, and patient satisfaction after compared to before MRgFUS for patients with ET and PD (p NR).⁶⁸ Of note, CRST part C scores were included as part of the quality of life measures. The other systematic review included mostly ET patients but noted that some PD patients were incidentally included within these studies. This review included 18 studies examining efficacy and 34 examining adverse events. The review found significant improvement in tremor-related outcomes for patients who received FUS compared to SRS (pooled net mean difference = 1.31, 95% CI [-2.96, 5.99]).⁶⁹ However, the same review reported significantly more adverse events in the FUS group, including imbalance/gait disturbances (10.5% vs 0%, p NR) and sensory disturbances (8.3% vs 1.1%, p NR). This review also reported significantly higher imbalance/gait disturbances for people who received FUS in modified coordinates compared to classic coordinates ($p = 0.0005$).

Mixed Conditions

Two systematic reviews included patients with mixed conditions and reported changes in outcomes from before to after MRgFUS. One review of 8 studies reported no significant differences in functional outcomes from before to after MRgFUS ($p = 0.39$ to 0.81).⁴⁴ One systematic review of 42 studies (16 include MRgFUS, as well as 15 DBS and 13 GK studies) just reported data about the procedures (eg, MRgFUS) and did not report treatment-related outcomes.⁷⁰

One systematic review of 17 studies that compared MRgFUS to DBS in patients with ET, PD, and dystonia narratively reported that costs were higher for both unilateral and bilateral DBS compared to MRgFUS.⁷¹

One systematic review of mixed conditions (15 studies, 2 of which included MRgFUS) reported favorable results for tremor-related (SMD = 1.31; 95% CI [0.83, 1.80]) and quality of life outcomes (SMD = 1.25; 95% CI [0.75, 1.74]) for patients who received MRgFUS compared to sham.⁷² There were no significant differences in cognitive or neuropsychiatric function. Of note, CRST Part C scores were used as part of the quality of life assessments. The same systematic review found no significant difference in tremor-related outcomes between MRgFUS compared to DBS (p NR) but significantly greater quality of life for patients who received MRgFUS compared to DBS ($p = 0.014$). There was no difference in tremor-related outcomes between MRgFUS and other lesioning surgeries (p NR).

One systematic review that included patients with ET, PD, MS, and rubral tremor compared MRgFUS targets as well as different treatments.⁷³ There were significant improvement in tremor-related outcomes after MRgFUS of the cerebellothalamic tract (CTT) (MD = -2.35, 95% CI [-2.51, -2.19]) and the VIM for patients with ET (MD = -2.08, 95% CI [-2.77, -1.39]). The same review found no significant differences in tremor outcomes for ET patients who received MRgFUS of either target to each other, or to RF of the VIM, or GK of the VIM. There were no significant differences in speech or swallowing difficulties (both defined as adverse events) for ET patients who received MRgFUS of the VIM compared to CTT (p NR). A higher proportion of ET patients who received MRgFUS of the VIM compared to CTT had sensory changes (not defined). There were no differences in adverse events between ET patients who received MRgFUS of the CTT compared to RF of the VIM. For MRgFUS of the VIM compared to RF of the VIM, there was no difference in speech or swallowing difficulties, but a higher percentage of sensory changes (not defined) in the MRgFUS of the VIM. MRgFUS of the CTT for ET patients had more favorable adverse event outcomes than GK of the VIM (significance not assessed), but MRgFUS of the VIM showed mixed results for adverse events.

The same systematic review narratively concluded that there were fewer adverse events for PD patients who received MRgFUS of the VIM compared to RF of the VIM. Similarly, the systematic review narratively found either fewer adverse events or no difference in adverse events for PD patients who received MRgFUS of the VIM compared to RF of the subthalamic nucleus (STN) or pallidum. The systematic review also narratively found no differences in adverse events between PD patients who received MRgFUS of the VIM compared to GK of the VIM.

A final systematic review of 25 studies reported results for the use of FUS for tremor with ataxia, multiple sclerosis, mixed tremor, post-stroke tremor, tremor plus dystonia, isolated and combined dystonia without tremor, subthalamotomy for PD, CTT-FUS for ET, and PTT-FUS for PD.⁷⁴ The systematic review narratively concluded that there were improvements in tremor-related outcomes for all conditions except post-stroke after FUS compared to before.

DISCUSSION

We identified 14 primary studies that reported on the comparative use of MRgFUS for the treatment of movement disorders. Nine of these were comparative studies focusing on ET, 1 was a comparative study focusing on PD, and 4 were single group studies that focused on other movement disorders. In addition, we identified 22 systematic reviews that reported on the use of MRgFUS for the treatment of movement disorders. Importantly, for ET and PD we focused only on studies that compared treatments, target locations, and laterality, or side. For other movement disorders, less is known about the effect of MRgFUS or FUS, so we included comparative and single group studies.

Key findings include the following:

KEY FINDINGS

ET:

MRgFUS versus Other Treatments (3 Comparative Studies)

- ▶ Bilateral DBS compared to unilateral MRgFUS may provide better improvement of tremor-related outcomes and quality of life (low confidence).
- ▶ There was insufficient evidence to assess adverse events or other outcomes for studies that compared treatments (no conclusions), and no studies reported on functional outcomes.

Unilateral versus Bilateral MRgFUS (3 Comparative Studies)

- ▶ Bilateral treatment compared to unilateral treatment may provide better improvement of tremor-related outcomes (moderate confidence).
- ▶ There were no differences in functional outcomes between unilateral and bilateral treatments (low confidence).
- ▶ There is insufficient evidence for quality of life, adverse events, and other outcomes (no conclusions).

Target Location (2 Comparative Studies)

- ▶ MRgFUS targeting the PSA or targets with PSA compared to VIM alone may provide better improvement of tremor-related outcomes (low confidence).
- ▶ There is insufficient evidence for adverse events between target locations (no conclusion).
- ▶ No other outcomes were reported for this comparison.

Left versus Right Side Treatment (1 Comparative Study)

- ▶ Evidence was insufficient to make any conclusions about the effect of treatment side on tremor-related outcomes (no conclusion).
- ▶ No other outcomes were reported.

Results from the Systematic Reviews (7 Studies)

- ▶ MRgFUS for ET improves tremor-related symptoms, quality of life, and functional outcomes (single group and comparative data), but overall it was not clear how MRgFUS compared to other treatments for these outcomes (certainty of evidence not assessed).
- ▶ Results (single group and comparative data) were mixed for the effects of MRgFUS on adverse event for ET (certainty of evidence not assessed).

PD:

- ▶ Only 1 comparative study reported comparative data for PD. There was insufficient evidence to make any conclusions about the use of MRgFUS in these patients.

Results from the Systematic Reviews (7 studies)

- ▶ MRgFUS for PD improved tremor-related outcomes (single group and comparative data), but results were mixed when compared to other treatments (certainty of evidence not assessed).
- ▶ Results (single group and comparative data) were mixed for the effects of MRgFUS for PD on quality of life and adverse events (certainty of evidence not assessed).

Other Movement Disorders (4 Single Group Studies):

- ▶ Single group studies showed improvements in several outcomes of interest, but there was insufficient evidence to make any conclusions about the use of MRgFUS in patients with dystonia conditions.

Results from the Systematic Reviews (8 studies)

- ▶ MRgFUS improved tremor-related outcomes in cohorts of people with mixed conditions (single group and comparative data), but no differences were seen when compared to other treatments (certainty of evidence not assessed).
- ▶ For mixed condition studies, reviews favored MRgFUS over other treatments for quality of life, but adverse event outcomes were mixed (certainty of evidence not assessed).

Overall, bilateral compared to unilateral MRgFUS appears to improve tremor-related outcomes for people with ET. This finding may be because unilateral treatment only treats the contralateral side, so treating the other side may offer further benefit. In addition, targeting the PSA versus VIM alone is associated with improved tremor-related outcomes, and other studies have shown that the PSA target may also be superior for DBS in ET.⁷⁵ Importantly, at present, bilateral MRgFUS is generally not recommended by the American Society for Stereotactic and Functional Neurosurgery, which may be due to concerns of increased risk of side effects.^{76,77} The current review concluded that there was insufficient evidence to assess differences in adverse events between unilateral and bilateral treatment for ET. There were sparse data on the effect of MRgFUS compared to other active treatments. Importantly, 1 meta-analysis of single group studies indirectly compared bilateral DBS to unilateral MRgFUS. The authors concluded that bilateral DBS may be more beneficial for tremor control though

less so for post-operative quality of life, but again this was an indirect comparison and there were important baseline differences between patient groups.³⁵ Although evidence was insufficient to draw conclusions about adverse events, 2 primary studies included in our review noted that adverse events were more common for MRgFUS compared to bilateral DBS or unilateral RF.^{52, 53} By 12 months there were no meaningful differences in adverse events between MRgFUS and bilateral DBS or unilateral RF.

For PD, only 1 study directly compared target locations.⁵⁸ This study found lower recurrence in individuals who received treatment of the PTT target compared to VIM. In this study, some individuals in the PTT group also received treatment of the VIM, making it challenging to interpret the findings. For the systematic reviews identified, overall the studies showed benefit of MRgFUS comparing baseline to follow-up data or comparing MRgFUS to sham.⁶³ As a result, there is limited information on comparisons of MRgFUS to other treatments, use of different treatment targets, or other similar comparisons.

For other movement disorders, it appears that MRgFUS improves tremor-related outcomes, quality of life, and function, and that adverse effects generally dissipate by 12 months post-procedure. However, overall these studies were small, did not include comparison groups, and included a variety of conditions. Standard treatments for idiopathic dystonia, for example, include medications including botulinum toxin injections or other therapies, such as DBS.⁷⁸ We identified no studies fitting our criteria that compared MRgFUS to other therapies. Several of the identified systematic reviews made indirect comparisons between MRgFUS and other treatments for patients with other movement disorders. Overall, these reviews showed varied results.^{69, 71, 72}

Importantly, across all conditions and comparisons of interest, there was either no evidence or insufficient evidence to be able to assess differences in adverse events, which is a crucial component when considering appropriate treatment. Some of the systematic reviews we identified, which incorporated single group studies, may shed additional light on the evidence for differences in adverse events between treatment groups. For instance, the review by Giordano et al reported more gait disturbances, paresthesia, and nausea in patients who received MRgFUS compared to DBS, but fewer speech disturbances and local adverse symptoms. However, based on the larger literature base of single group studies and MRgFUS compared to sham, some side effects, such as head pain, dizziness, ataxia, and paresthesia, may be common in patients treated with MRgFUS.^{30, 31} Individualized discussions with patients will be important when considering potential adverse events related to treatments.

Finally, costs were a prioritized outcome for this review, but none of the identified primary studies reported or compared costs between treatments. Three of the systematic reviews we identified indicated that MRgFUS compared to DBS may cost less. In addition, 1 systematic review indicated no difference in costs between SRS and MRgFUS,⁵⁷ and another systematic review indicated that RF may be less costly than MRgFUS.⁴³ It is difficult to act on the cost data without comparative data on clinical and patient centered outcomes.

STRENGTHS AND LIMITATIONS OF THE SYSTEMATIC REVIEW PROCESS

This review employed rigorous methodology to capture studies that aligned with the key questions. However, there are several important limitations to the current review that should be considered. First, because MRgFUS has already been shown to be effective for ET and PD, for these conditions we focused only on studies that provided comparative results based on treatment, target location, or

laterality. As a result, the literature base for these conditions was small and did not include several pivotal trials that compared MRgFUS to sham or best medical management.^{34, 79-81} Much of the literature includes single group studies, and many of the systematic reviews and meta-analyses “compared” results from these single group studies. By focusing on comparative studies, we excluded single group studies that may have offered insight into potential adverse effects that may occur from MRgFUS. While single group studies were not included in our analyses of primary studies, we did provide a summary of identified systematic reviews that included single group studies. Notably, the systematic reviews concluded that adverse events were resolved by 12 months post-treatment.

Second, we also chose to only include studies that intentionally and prospectively targeted different treatment locations in the brain. We excluded several studies that conducted post hoc retrospective analyses of people who received treatments in different locations. We opted to exclude these studies due to a high concern of selection bias and unobserved confounding. While this helped to ensure intentionality in differing treatment targets, the omitted studies that examined lesion location post hoc may offer further insight into the outcome differences based on lesion location.

For comparisons of side or unilateral verses staged bilateral treatments, it was not explicitly stated across studies how side or laterality was determined. While there may be some assumption this could have been based on tremor severity, we could not confirm this information. From a clinical perspective, patient preference and safety decisions made by the surgeon would be the main factors.

Finally, for conditions other than ET and PD, we included single group studies. Data from single group studies did offer some insight into effectiveness of treatment; however, data from single group studies do not offer information on how treatment may compare to other treatments including usual medical management. Additionally, we only included a subset of conditions that cause secondary movement disorders as part of our search, so other studies on secondary movement disorders may not have been included.

STRENGTHS AND LIMITATIONS OF THE LITERATURE BASE AND FUTURE RESEARCH NEEDS

Overall, the evidence base has several limitations. First, the available research made it challenging to directly examine comparisons of interest (*eg*, target locations, use of different treatments) due to potential difference in baseline patient risk factors or reasons for treatment allocation. No RCTs compared treatments, target location, laterality, or side for ET and PD. Nor were there any RCTs that compared MRgFUS to other treatments for all other movement disorders. Historical evolution of RCTs for surgical procedures is important to consider. When treatments are shown to be clinically beneficial, and as surgeons’ skills improve over time with improved patient outcomes, often they eventually become accepted as standard surgical procedures, which differs compared to drug trials. There can be ethical issues, patient preferences in the case of elective surgeries, and safety issues at the time of the procedure that are factors in the development of such trials. As a procedure matures, the expectation would be an increase in controlled and comparative trials, which reflects the typical trajectory of surgical intervention. Future studies should consider conducting RCTs to inform these questions when increased numbers of patients and better understanding of target physiology allow. In the interim, NRCS can provide valuable information, but they need to adjust for confounders such as patient characteristics and availability of treatment options and infrastructure.

Second, many included studies mentioned that slight target adjustments were made during procedures to ensure lesioning was effective. While this may be typical for treatment, this also may lead to inaccuracies when comparing treatment target locations. When treatment modality is dynamic and patient-centered outcomes including safety are the goals, these adjustments are likely unavoidable. Future studies should document when and how adjustments are made and consider approaches to control for adjustments in the analysis.

Third, given the limited number of studies included, we were also unable to examine outcomes based on patient characteristics that might be important for treatment, such as skull density ratio. Relatedly, the studies included in this review consisted of a heterogeneous group of disorders, all with smaller sample sizes. This makes it challenging to generalize results to any 1 disorder of interest. In addition, in studies that looked at different treatments, there were significant differences in baseline scores for a variety of outcomes, making it challenging to directly compare the changes in scores between these groups.

Finally, there were limited data surrounding the effects of different treatment comparators on adverse events. This is problematic, as it limits the ability to understand the full scope of treatments. While this may have been somewhat a reflection of the scope of the current review, limiting studies to only those that directly compare treatments of interest, future studies should focus on reporting adverse events in comparative studies. These studies should also consider potential differences in timing of adverse events that may arise from different treatment types. Since our literature search was conducted, several new studies on MRgFUS have been published.⁸²⁻⁸⁴ These and other future studies may be able to help lend additional evidence to differences in adverse events among comparators of interest.

CONCLUSIONS

MRgFUS has emerged within the last decade as a viable and less invasive alternative for the treatment of movement disorders. For ET, bilateral DBS compared to unilateral MRgFUS may provide better improvement of tremor-related outcomes and quality of life; however, we cannot rule out that these differences are not based on unobserved patient characteristics, since comparative studies did not conduct adjusted analyses. We were unable to assess differences between other treatments and MRgFUS for tremor-related outcomes. Staged bilateral MRgFUS compared to unilateral treatment may improve tremor-related outcomes. MRgFUS treatments that target or include the PSA compared to VIM alone may improve tremor-related outcomes. There was insufficient evidence to assess adverse events or other outcomes for the above comparisons. Systematic reviews of single group studies and comparative data indicate that MRgFUS improves tremor-related symptoms, quality of life, and functional outcomes, but it was not clear how these outcomes compare to other treatments.

For PD, the single comparative study found insufficient evidence to make any conclusions regarding the use of MRgFUS when the VIM and/or PTT were targets. There were no direct head-to-head comparisons of MRgFUS targeting the subthalamus nuclear versus the globus pallidus internus for PD. However, systematic reviews of single group and comparative data indicate improved tremor-related outcomes but with mixed results when compared to other treatments for effects on quality of life and adverse events.

For other movement disorders—mainly dystonic conditions—single group studies showed improvements in several outcomes of interest, but there was insufficient evidence to make any conclusions about use of MRgFUS in patients with dystonia conditions. Systematic reviews of single

group and comparative data indicate improved tremor-related outcomes in those with mixed conditions, but no differences were seen when compared to other treatments. MRgFUS was favored over other treatments for quality of life, but adverse event outcomes were mixed.

Future NRCS should adjust for baseline patient characteristics such as skull density ratios and tremor laterality and distribution. Adverse events have been reported in the larger literature of single group studies of MRgFUS and those of MRgFUS compared to sham. Evidence on adverse events from the comparative studies for the specific diseases discussed was insufficient to draw definitive conclusions. There is a need for well-designed RCTs that compare MRgFUS to other treatments and to understand the effect of different anatomical targets as well as longer-term outcomes of unilateral and bilateral procedures. As MRgFUS establishes itself in the treatment of movement disorders, these suggestions may allow for more robust studies to better guide patient care and improve outcomes.

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