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Evidence Brief: Factors that Optimize Therapy with Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Major depressive disorder is one of the most common mental disorders in the general and Veteran populations. The one- to two-thirds of MDD patients who do not respond to the first antidepressant prescribed, and the 15% to 33% who do not respond to multiple drugs are defined as having treatment-resistant depression (TRD). Repetitive transcranial magnetic stimulation (rTMS) is one of many possible options for treating TRD. It is supported by two FDA-cleared protocols and acceptable acute efficacy based on a recent Comparative Effectiveness Review conducted by the RTI-UNC EPC. This Evidence Brief synthesizes the literature on factors that optimize rTMS therapy in patients with TRD.

WHICH PATIENTS HAVE THE BEST CHANCE OF SUCCESS WITH rTMS?

Whether the effectiveness of rTMS treatment differs by sex or in young (age 18-37 years) or older adults (age ≥ 65 years) is unclear. But evidence suggests that patients with unipolar or bipolar depression, with more or less stringently defined TRD, and who are treated with rTMS as monotherapy or as augmentation to pharmacotherapy, have similar chances of success with LHF-DLPFC rTMS. A major limitation of rTMS studies is that they generally exclude patients with medical and psychiatric comorbidities.

WHAT ARE THE OPTIMAL rTMS TREATMENT PROTOCOLS AND PARAMETERS?

High-frequency rTMS applied to the left dorsolateral prefrontal cortex is the most well-studied approach and it includes a FDA-cleared protocol that has been shown to improve quality of life. But no particular protocol has been shown to have any advantages over others in head-to-head trials. In terms of dose for LHF-DLPFC, 2 large multicenter RCTs support using 10 Hz, 120% RMT, 5 days a week for 3-6 weeks to guarantee adequate stimulation. Intensities down to 100% may also be effective in certain patients. The effects of variability in coil geometry, coil placement, session duration, timing, or number of sessions remain unclear.

WHAT IS KNOWN ABOUT CONTINUATION AND MAINTENANCE TREATMENT IN RESPONDERS?

Available evidence is inadequate for determining the value of maintenance rTMS in general and for defining optimal treatment parameters.

CONCLUSIONS

There is a great need to determine the effects of rTMS in TRD patients with medical and psychiatric comorbidities and to determine the long-term durability of rTMS response. Although the optimum protocols and parameters have not yet been determined, the best evidence available supports use of the FDA-cleared LHF-DLPFC protocol. However, nearly all of this evidence was developed in experimental settings. In order to collect meaningful data from clinical experience, the VA should increase standardization of rTMS delivery. In the meantime, rTMS has acceptable acute efficacy and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought.

INTRODUCTION

A 2014 Department of Veterans Affairs (VA) Memorandum states, "Before rTMS can be incorporated into clinical practice guidelines or treatment algorithms for depression, more research is needed to address a number of questions including who may benefit, under what treatment protocol, and how treatment outcomes will be measured."[1,2] Important components of coverage policy design include identifying which subpopulations will benefit the most, which protocol is ideal, and the long-term efficacy of an intervention. To answer these questions, the VA is undertaking a number of research efforts. First, the VA's Office of Research and Development has implemented a large-scale ongoing cooperative study of rTMS compared with sham in Veterans with treatment-resistant depression and possible comorbid post-traumatic stress disorder (PTSD) and/or a history of substance abuse (CSP #556, NCT01191333). Second, the VA has proposed evaluating data from their own accumulating experience with rTMS on a system-wide basis. Third, the Mental Health Operations (10NC5) and Mental Health Services (10P4M) in the Office of Patient Care Services requested that the VA Evidence-based Synthesis Program Coordinating Center (ESP CC) conduct an Evidence Brief to synthesize the literature on factors that optimize therapy with rTMS in patients with TRD.

BACKGROUND

Major depressive disorder (MDD) continues to be one of the most common mental disorders in the United States. In the general population, roughly 5 to7% have had an episode of depression in the past 12 months and 13% have had an episode at some point in their life.[3,4] The estimated prevalence of depression is higher among recently deployed service members compared with the general US population; 11% to 17% of soldiers returning from Afghanistan or Iraq meet current criteria for depression.[5-7] Among Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) Veterans entering VA health care from 2001 to 2010, 17% to 22% were diagnosed with depression.[6,8] Another survey of US Army soldiers and National Guard infantry brigade combat teams estimated the prevalence of depression ranged from 12% to 16% following deployment.[5]

OIF and OEF Veterans also have a greater burden of comorbid mental health conditions compared with the general population. OIF and OEF Veterans entering VA health care from 2002 to 2008 had 4 to 5 times greater 12-month prevalence of 2 (29% vs 5.8%) and 3 or more (27% to 33% vs 6%) comorbid DSM-IV disorders than for the general population.[4]

Treatment-resistant depression (TRD) is defined as depression resistant to antidepressant medications. Between one- and two-thirds of MDD patients will not respond to the first antidepressant prescribed, and 15% to 33% will not respond to multiple drugs.[9,10] Among clinical studies, case definitions of TRD differ in:

- The number of antidepressant treatment failures: one, 2, or more than 2[11]
    - For a failed antidepressant trial, what constitutes a "sufficient" length of time or an "adequate dose";[12,13]
    - With or without a change in antidepressant class;[11]

- The degree of effect: from non-response (< 25% symptom reduction from baseline) to response without remission (50% or greater symptom reduction from baseline without achieving remission);[13]
- Whether antidepressant treatment failed in the current episode or in a past episode.[14]

Some have suggested that patients with TRD should be classified to differentiate those resistant to all first-line interventions (including antidepressant medication and psychotherapy) from those resistant to one type of first-line intervention (for example, SSRI-TRD).[11]

Options for treating patients with TRD include various pharmacologic and nonpharmacologic strategies. Pharmacologic options include optimization of current treatment, combination of antidepressants, switching to a different antidepressant, and augmentation of antidepressants with neuromodulator drugs.[12] Non-pharmacologic options include psychotherapy, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS).[12]

Over the last decade, research on rTMS as a potential treatment for TRD has gained momentum. Using an electromagnetic coil system, rTMS delivers short, repeated pulses of magnetic energy intended to activate cortical nerve cells within the area of interest and indirectly stimulate the limbic system, the area of the brain that influences emotion.[2] An rTMS system consists of a treatment chair, mobile console and touchscreen display, and an electromagnetic coil. The patient sits in the treatment chair and wears a helmet connected to an apparatus holding the electromagnetic coil. The patient's resting motor threshold, defined as the stimulator setting that moves the patient's thumb 50% of the time, is determined in the first session of rTMS using single magnetic pulses over the motor cortex. Resting motor threshold (RMT) is used to determine the treatment level that will be used to minimize seizure risk and to determine the amount of stimulation needed to penetrate the cortex.[2] rTMS can be administered in an outpatient or inpatient setting, and facilities providing rTMS require additional staffing, infrastructure, and credentialing/training resources aside from the cost of obtaining an rTMS system.[2] A licensed psychiatrist prescribes and oversees treatment and a psychiatrist or trained staff member administers treatment and ensures patient safety.[2] System operators must complete the appropriate trainings before using any rTMS therapy system, including system efficacy and safety, general information on clinical use, hands-on training in determining motor threshold, identifying treatment location(s), and moving and seating the treatment coil.[2] Training is typically provided by the manufacturer and through appropriate non-vendor courses and certifications required by many insurance companies and health systems, including the VHA.[2]

TMS encompasses a wide spectrum of treatments. Aside from a single TMS stimulation, repetitive TMS, and deep TMS, strategies for using rTMS vary based on types of coils, region of the brain stimulated (*ie*, left or right dorsolateral prefrontal cortex, or bilateral), "dose" (*eg*, intensity, percent of resting motor threshold (% RMT)), speed of pulses (*ie*, Hz, pulses per second), pulse train duration, inter-train interval, trains per session, total number of pulses,* number of weekly sessions, duration (*ie*, 2 to 6 weeks), and total number of sessions.

To date, the US Food and Drug Administration has granted 510(k) marketing clearance to 2 specific rTMS protocols and devices for use in TRD.[15,16] The first was in October 2008 for the

NeuroStar TMS device (manufactured by Neuronetics, Inc.) for use specifically in patients who failed one, but no more than one, adequate antidepressant medication trial. The protocol reviewed by the FDA is 3,000 high-frequency (10 Hz) pulses administered to the left dorsolateral prefrontal cortex at 120% of motor threshold on a schedule of 5 sessions per week for 4-6 weeks (60,000 to 90,000 total pulses). The reason for the limitation to one previous treatment failure was that the initial data submitted by the manufacturer showed no efficacy among patients who had failed two or more antidepressant trials.[17] In 2014, in response to the results from another multicenter sham-controlled RCT, sponsored by the National Institutes of Health (NIH),[18] the clearance was expanded to include patients who had failed one or more prior antidepressant medications in the current episode.[19]

In 2013, the FDA cleared a second device, the Brainsway Deep TMS System, for use in adult patients who failed to achieve satisfactory improvement from one or more courses of antidepressant medication treatment in the *current* episode of major depression. The specific cleared deep TMS parameters include an intensity of 120% of resting motor threshold, a frequency of 18 Hz, 1980 pulses per session, on a schedule of 5 daily sessions for 4 weeks (39,600 total pulses).

The American Psychiatric Association (APA) recommends ECT as a treatment of choice for patients with severe MDD that is not responsive to psychotherapeutic and/or pharmacological interventions.[20] The recommendation was based on older meta-analyses of clinical trials which found remission rates of 70% to 90% for major depression and demonstrated that ECT is more effective and works faster than other therapies with which it has been compared, including rTMS.[21,22] Although a 2014 meta-analysis confirmed these older findings about the superiority of ECT for severe or resistant major depression *overall*,[23] findings from other recent meta-analyses that focused exclusively on TRD suggest there may be less of a difference between ECT and rTMS in TRD subgroups in response (range, 20% to 64% vs 20% to 58%) and remission (range, 15% to 53% vs 9% to 43%).[14,24,25] ECT requires general anesthesia and is associated with transient episodes of hypertension, tachycardia, and arrhythmia, is still socially stigmatized, has high relapse rates (> 60%), and, in a community-based setting, may have more modest remission rates than expected.[26]

Several professional societies have issued clinical practice guidelines on the use of rTMS for treating depression, including the American Psychiatric Association (APA),[20] World Federation of Societies of Biological Psychiatry Task Force (WFSBPTF),[27] the Canadian Network for Mood and Anxiety Treatments (CANMAT),[28] the National Collaborating Centre for Mental Health (NCCMH) in the UK,[29] and, most recently, the International Federation of Clinical Neurophysiology.[30] All but the NCCMH regard rTMS as a clinically relevant technique to treat major depression, including treatment-resistant depression. The NCCMH recommends that TMS should only be performed in research studies designed to investigate factors that might increase the procedure's clinical efficacy.[29]

Total pulses=(Hz)x(pulse train duration)x(trains per session)x(total number of sessions). For example, the total number of pulses for 40 15-Hz trains of 2-s duration given 5 times a week for 2 weeks would be given by the following calculation: (15 Hz)*(2 s/train)*(40 trains/session)*(10 total sessions)=12,000 total pulses. The total number of pulses for 20 20-Hz trains of 4-s duration given twice a week for 4 weeks would be given by the following calculation: (20 Hz)*(4 s/train)*(20 trains/session)*(8 total sessions)=12,800 total pulses. This is how the total number of pulses was calculated throughout this review.

Several recent systematic reviews have examined the efficacy of rTMS compared with sham specifically for treatment-resistant depression.[14,24,25,31-33] Among these, the Agency for Healthcare Research and Quality's (AHRQ) Comparative Effectiveness Review (CER) conducted by the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC)[14,24] and a health technology assessment completed by the University of Calgary conducted to inform the Alberta Health Technologies Decision Process[25] are the two highest quality and most comprehensive. Across 31 TRD RCTs overall (N=1377), regardless of definition of TRD, the University of Calgary reported that the average short-term response rate was over 2 times greater after rTMS compared with sham (30% vs 12%) with a number needed to treat (NNT) of 6 to benefit one additional patient, and that the average short-term remission rate was over 2 times greater with rTMS (20% vs 7%), with an NNT of 8. Gains were even greater among the subset of 15 RCTs (N=642) using the most stringent definition of TRD, based on the RTI-UNC EPC CER findings of high-strength evidence that the average short-term response rate was over 3 times greater after rTMS compared with sham (29% vs 8%) with an NNT of 5 to benefit one additional patient, and that the average short-term remission rate was over 5 times greater with rTMS (28% vs 5%), with an NNT of 5. The RTI-UNC EPC also noted the response and remission rates for rTMS were consistent with other standard pharmacologic next-step options for TRD, including switching to a different antidepressant or adding a second antidepressant. However, they also concluded that there is only low-strength evidence that rTMS improves short-term health-related outcomes (*eg* quality of life, health status, and daily functioning) and insufficient evidence regarding short-term withdrawals due to adverse events and maintenance of remission.

Insurance coverage of rTMS treatment is mixed, and to help make coverage decisions, several health plans have conducted their own reviews.[34-36] The BlueCross BlueShield Technology Assessment Program published an updated assessment on the effect of TMS therapy on depression in early 2014.[34] The assessment relied on results from 2 published trials,[17,18] FDA documents, extension studies, and 7 meta-analyses, and concluded that, while the mechanism by which TMS might improve depression is biologically plausible, large trials and meta-analyses do not provide convincing evidence of improved health outcomes.[34] In 2013, United Healthcare published a medical policy on TMS that stated "there is insufficient evidence that transcranial magnetic stimulation (TMS) is beneficial for health outcomes in patients with major depression."[36] Anthem (Wellpoint) covers rTMS for major depression with one of the 2 FDA-cleared devices for patients meeting very strict criteria.[35] CMS has not issued a coverage policy on rTMS; however, a number of Medicare contractors have issued Local Coverage Determinations regarding rTMS coverage. Cahaba Government Benefit Administrators®, LLC (L32834), Palmetto GBA (L34170), Novitas Solutions, Inc. (L32055 and L33660), and First Coast Service Options, Inc. (L33676) cover rTMS for patients diagnosed with resistant depression with some requirements on the definition of resistance and limitations on which patients can safely receive rTMS treatment. Conversely, National Government Services, Inc. (L32038), Wisconsin Physicians Service Insurance Corporation (L32220), and Noridian Healthcare Solutions, LLC (L33495) have issued non-coverage policies, concluding that rTMS is not medically necessary.

SCOPE

An evidence brief differs from a full systematic review in that the scope is narrowly defined and the traditional review methods are streamlined in order to synthesize evidence within a shortened timeframe. An evidence brief does not outline the full context in which the information is to be used and does not present a comprehensive assessment of knowledge on the topic. Brief or rapid review methodology is still developing and there is not yet consensus on what represents best practice.

The objective of this Evidence Brief is to synthesize the literature on factors that optimize therapy with rTMS in patients with TRD. The ESP CC investigators and representatives of the Mental Health Operations (10NC5) and Mental Health Services (10P4M) in the Office of Patient Care Services worked together to identify the population, comparator, outcome, timing, setting, and study design characteristics of interest. The Mental Health Operations (10NC5) and Mental Health Services (10P4M) in the Office of Patient Care Services approved the following key questions and eligibility criteria to guide this review:

KEY QUESTIONS

- Key Question 1: For adults with TRD, how do the benefits and harms of treatment with rTMS differ in subpopulations based on age, gender, TRD symptom subtypes, comorbid mental health conditions, complicating medication conditions, and definitions of treatment resistance?
- Key Question 2: For adults with TRD, how do the benefits and harms of treatment with rTMS differ based on variation in rTMS treatment protocol (*eg*, coil geometry, coil placement, stimulus parameters, duration of a treatment session, timing and number of sessions, *etc*)?
    - Key Question 2a: What defines an adequate course of treatment?
- Key Question 3: For adults with TRD, what is the evidence about early predictors of rTMS treatment benefit?
- Key Question 4: What is known about the need for and effectiveness of continuation or maintenance treatment to prevent relapses or recurrences in patients who have responded to rTMS?

INCLUSION CRITERIA

The ESP CC included studies that met the following criteria:

- *Population*: Adults with treatment-resistant depression, defined as some history of treatment failure. We expect that studies will vary in how treatment resistance is defined. We will accept any definition that refers to a history of treatment failure, even if not well-characterized, and will analyze results based on variation found.
- *Intervention*: Repetitive transcranial magnetic stimulation, given as a single treatment or part of a combination treatment.

- *Comparator*: Any pharmacologic, nonpharmacologic, or sham interventions.
- *Outcomes*:
    - *Benefits*: Response, remission, maintenance of response or remission (*eg*, preventing relapse or recurrence) quality of life, functional capacity.
    - *Harms*: Withdrawals due to adverse events, seizures, cognitive dysfunction.
- *Timing*: Any duration of follow-up.
- *Setting*: Any setting.
- *Study design*: Systematic reviews, technology assessments, controlled clinical trials, and intervention series with well-defined inclusion criteria.

METHODS

The protocol for this Evidence Brief was published on the PROSPERO register (CRD42014009579). To identify articles relevant to the key questions, our research librarian searched MEDLINE (1946-April 2014), PsychINFO (1806-April 2014), and the Cochrane Library using the terms *repetitive transcranial magnetic stimulation* and *treatment-resistant depression* (see Supplemental Materials for complete search strategies). Additional citations were identified from hand searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles, abstracts, and full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus.

Due to the volume of literature encountered, we added a post-hoc requirement that, in order to be included in this report, studies must report both benefits and harms of rTMS. In the absence of RCTs reporting both benefits and harms or multicenter trials, we used a best-evidence approach.[37] Further, we only rated the internal validity (quality) of multicenter trials and systematic reviews. We used the Cochrane Collaboration's Risk of Bias Tool to rate the internal validity of all multicenter trials based on adequate sequence generation, allocation concealment, blinding, assessment of incomplete data, outcome reporting bias, and other sources of bias.[38] We used the AMSTAR tool to assess the quality of included systematic reviews.[39] We abstracted data for each outcome from selected studies (available from the authors upon request). All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

For meta-analysis, we used random-effects models to estimate pooled effects. Forest plots graphically summarize results of individual studies and of the pooled analysis. The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies. Meta-analyses were conducted using StatsDirect statistical software (StatsDirect Ltd. 2013. Altrincham, UK). Due the time limitations of this Brief, we did not formally rate the Strength of Evidence. Instead we informally applied the principles recommended by the AHRQ Methods Guide for Comparative Effectiveness Reviews (risk of bias (includes study design and aggregate quality), consistency, directness, and precision) to interpret the evidence and commented on relevant limitations in these domains.[40]

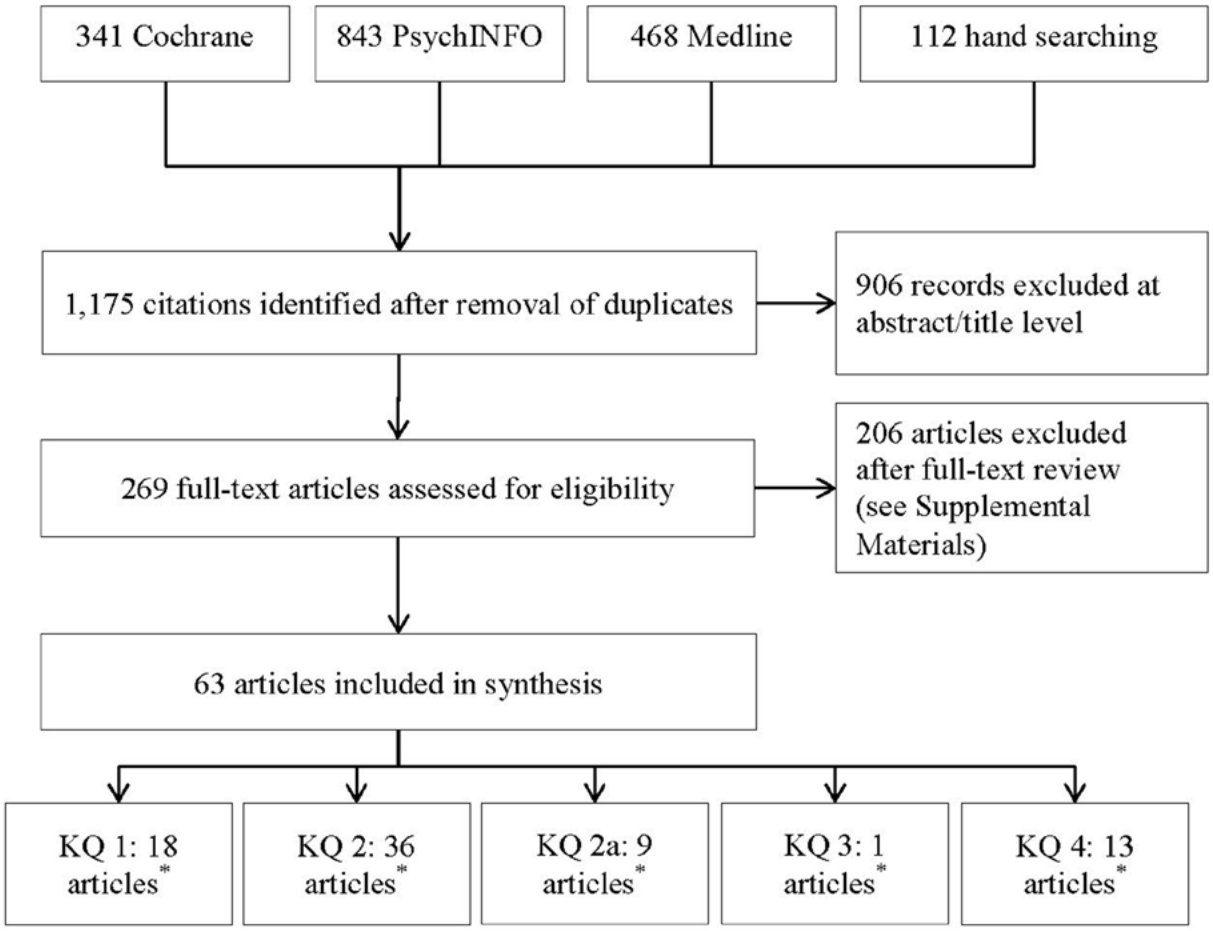
A previous version of this Evidence Brief was reviewed by 4 invited peer reviewers. The peer review disposition table can be found in the Supplemental Materials.

RESULTS

OVERVIEW

Figure 1 provides the results of the study selection process. A full listing of all studies excluded at the full-text level is provided in the Supplemental Materials.

Figure 1: Literature Flow Chart



The Agency for Healthcare Research and Quality's (AHRQ) Comparative Effectiveness Review (CER) conducted by the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC)[14,24] and the health technology assessment completed by the University of Calgary conducted to inform the Alberta Health Technologies Decision Process[25] provide the best source of evidence to answer some of our Key Questions. Table 1 summarizes all relevant findings from the RTI-UNC EPC and University of Calgary reviews. After Table 1, we describe findings from all other systematic reviews and original studies we reviewed to supplement gaps in the RTI-UNC EPC and University of Calgary reviews.

Table 1: Summary of all relevant findings from the RTI-UNC EPC and University of Calgary reviews

RTI-UNC EPC-University of Calgary

KQ1: Benefits/harms in subpopulations

Age: None-None

Sex: None

Bipolar Depression: rTMS was as effective in patients who had bipolar depression as in patients with major depression. This conclusion was based on a comparison of the results of rTMS versus sham for response (5.40, 95% CI 1.88 to 15.50 compared with 3.38, 95% CI, 2.24 to 5.10) or remission (15.19, 95% CI, 2.13 to 108.47 compared with 5.07, 95% CI, 2.50 to 10.30) for patients with major depression versus studies that had a mix of patients with bipolar or unipolar depression.

Depression Severity: Since nearly all patients in the included RCTs were severely depressed, no difference in treatment outcomes by severity of depression could be detected.

Comorbid psychiatric and medical conditions: None

Concomitant medications: Due to the small number of studies and great variability between them, no difference in rTMS outcomes could be detected by pharmacotherapy strategy.

TRD Definition: Classified studies based on whether they defined TRD as failure 2 or more prior antidepressant courses of adequate dose and duration (Tier 1); 1 or more antidepressant failures (Tier 2), or did not report the number of failures (Tier 3). They found no clear difference between the pooled estimates of rTMS versus sham for the Tier 1-only and combined Tiers analyses for response (3.38, 95% CI, 2.24 to 5.10 compared with 2.62, 95% CI 1.93 to 3.56) or remission (5.07, 95% CI, 2.50 to 10.30 compared with 2.76, 95% CI, 1.79 to 4.26). Relative risk of remission in Tier 1 subgroup may be overestimated due to reporting bias; remission only reported in 7 of 18 trials. It would be clinically useful to consider whether rTMS effects vary based on type of previous treatments (eg, which antidepressant drugs), rather than just on how many. They could not evaluate this because the studies did not provide adequate detail on the specific types of previous failed treatments.

KQ2. Differences in benefits/harms based on variation in rTMS protocol	
Did not perform subgroup analyses because the number of studies was too limited.	**High Frequency versus Low Frequency:** "The optimal frequency of rTMS is unclear. There is a trend towards high frequency rTMS being more effective to achieve both clinical response and remission than low frequency."
	Meta-analysis results: Response: RR=1.19 (95% CI: 0.97, 1.46); remission: RR=1.29 (95% CI: 0.75, 2.22).
	Comment: These results do not isolate the effect of frequency because this analysis merged data from varying protocols without adjusting for differences (eg, left vs right).
	Unilateral versus Bilateral: "The optimal location of treatment for rTMS is unclear. There is a trend towards bilateral rTMS being more effective to achieve both clinical response and remission than bilateral."
	Meta-analysis results: response: RR=1.15 (95% CI: 0.85, 1.56); remission: RR=1.18 (95% CI: 0.71, 1.96)
	High Intensity versus Low Intensity: "The optimal intensity of rTMS is unclear. There is a trend towards high intensity rTMS being more effective to achieve both clinical response and remission than low intensity."
	Meta-analysis results: response: RR=1.15 (95% CI: 0.54, 2.41); remission: RR=1.72 (95% CI: 0.89, 3.33).
	Various Other rTMS Protocols: "Active research is ongoing with the use of image-guided techniques, scheduling of treatment, timing of treatment, and deep brain stimulation. None of these research areas are developed enough to clarify the role of these variables in the effective use of rTMS."
KQ2a. Definition of adequate course of rTMS treatment	
None	None
KQ3. Early predictors of rTMS benefit	
None	None
KQ4. Continuation/maintenance treatment	
Found that no sham-controlled RCTs assessed rTMS outcomes beyond a week following acute treatment.	None

KEY QUESTION 1: For adults with TRD, how do the benefits and harms of treatment with rTMS differ in subpopulations based on age, gender, TRD symptom subtypes, comorbid mental health conditions, complicating medical conditions, concomitant medications, and definitions of treatment resistance?

Age

Whether the effectiveness of rTMS treatment differs in young (age 18-37 years) or older adults (age ≥ 65 years) is unclear; these populations have been underrepresented in controlled trials.[14]

LHF-DLPFC rTMS

Two small trials that recruited patients 40 years and older[41,42] and subgroup analyses of sham-controlled trials[43] and a single-site, single-arm study[44] are frequently cited to support the assertion that older patients are less likely to respond to LHF-DLPFC rTMS when it is used at stimulation intensities of 80% to 120% RMT. Some experts have suggested that higher stimulation intensities of LHF-DLPFC rTMS are needed in older adults to overcome selective prefrontal atrophy.[45] However, important methodological limitations prevent firm conclusions based on this evidence.

Two single-site sham-controlled RCTs that specifically recruited older adults (n=44)[41,42] found that LHF-DLPFC rTMS at 80% to 100% RMT, and 4,000-16,000 total pulses did not significantly increase response over sham (Table 2). In contrast, in one single-site sham-controlled RCT in younger patients,[46] LHF-DLPFC rTMS at 110% RMT for 60,000 total pulses significantly increased response compared with sham in younger adults, but not in older adults. However, since the dose of rTMS was higher in the RCT of younger adults, it is not possible to attribute the difference in response rates to age alone.

Table 2: Sham-controlled trials with varying age of participants

Author Year Sample size	Stimulation parameters Comparator	Mean patient age	Response	Remission	Adverse event withdrawals
Manes 2001[41] N=20	LHF-DLPFC, 80% RMT, 20 Hz, 4,000 total pulses vs sham	60.5 vs 60.9 years	30% vs 30%	20% vs 20%	NR
Mosimann 2004[42] N=24	LHF-DLPFC, 100% RMT, 20 Hz, 16,000 total pulses vs sham	60.0 vs 64.4 years	27% vs 0%; *P*=0.089	NR	NR
Zheng 2010[46] N=34	LHF-DLPFC, 110% RMT, 15 Hz, 60,000 total pulses vs sham	26.9 vs 26.7	63% vs 7%; *P*<0.001	NR	NR

A pooled analysis of 5 RCTs and one open-label study (N=195) cited in the APA Practice Guideline[20] found a small negative association between age and response (OR=0.95; 95% CI: 0.92-0.99) and remission (OR=0.94; 95% CI: 0.90-0.98) after rTMS treatment.[43] But this study has 2 main weaknesses. First, it is unclear how this subset of studies was selected for inclusion among the larger body of similar evidence. Second, 3 of the 6 studies included are unpublished, so data and methods of these studies cannot be verified.

A subgroup analysis of an uncontrolled single-site study of LHF-DLPFC rTMS at 110% RMT and 10Hz in 56 adults found a numerically lower response rate in 22 adults aged 65 years and above, compared those aged less than 65 years (23% compared with 56%); however, we cannot rule out that this difference is due to chance alone due to the small sample sizes or due to other confounding factors such as baseline depression severity and type.[44]

Finally, in an uncontrolled single-site study of 18 older adults (mean age 61.2 years),when rTMS was administered at higher intensities (range, 103% to 141% RMT, mean of 114%) that were individually tailored to account for MRI-measured prefrontal atrophy, response and remission rates were 28% and 22%, respectively.[45] However, head-to-head trials are needed to compare the effects of using individually-tailored intensity levels compared to the more widely-used method of not adjusting for prefrontal atrophy.

RLF-DLPFC or bilateral rTMS in older adults

Although subgroup analyses from 3 recent RCTs consistently found that age was not significantly associated with RLF-DLPFC rTMS or bilateral rTMS response, this may have been due to the lack of variation in age of the study participants.[47-49] Two multicenter head-to-head trials performed secondary analyses to identify predictors of response to treatment and concluded that age was not significantly associated with response to rTMS treatment.[47,48] The earlier head-to-head trial (N=130) compared the benefits and harms of 10 sessions of 1-Hz and 2-Hz RLF-DLPFC[48] while the later trial (N=219) compared 2 forms of bilateral stimulation to RLF-DLPFC.[47] In both trials, mean age was under 50 years old, most patients were female, and besides alcohol or substance dependence, there were no restrictions on concurrent Axis I psychiatric disorders. Neither trial reported differences in response or remission among groups receiving different simulation parameters. Upon multivariate logistic regression analysis, age was not significantly associated with response to rTMS treatment ($P>0.05$). In one small trial (N=34), although the significant difference in HDRS percent change from baseline between older (>45 years) and younger (≤45 years) patients was emphasized, there was not a significant difference in the proportion of responders and remitters in each group ($P>0.05$).[49]

Sex

The proportion of female participants in meta-analyses of RLF-DLPFC,[32] LHF-DLPFC,[33]and bilateral[31] rTMS ranged from 54.4% to 66.4%. Sex was not significantly associated with response in two multicenter head-to-head trials of bilateral versus RLF-DLPFC rTMS treatment (N= 219 and N=130, respectively).[47,48] But we did not identify any analyses of response or remission rates by sex among studies of LHF-DLPFC rTMS.

Bipolar Depression

Findings from earlier meta-analyses that focused on either RLF-DLPFC rTMS[32] or LHF-DLPFC[33] were consistent with RTI-UNC EPC (see Table 1). There was no significant difference in response or remission rates between RCTs including subjects with unipolar depression only and those including mixed samples of subjects with unipolar and bipolar depression.

Treatment-resistance definition

The RTI-UNC EPC CER is the best source of evidence about the differential effects of rTMS based on variation in TRD definitions and its findings are summarized in Table 1 above.

Comorbid mental health and medical conditions

Most studies of rTMS excluded patients with comorbid mental health conditions, such as substance abuse and post-traumatic stress disorder, as well as medical comorbidities. This prevented us from adequately evaluating how rTMS may differ in various patient subpopulations with comorbidities. However, consistent findings from 3 trials provide some preliminary evidence that rTMS can produce a clinically significant response in patients with comorbid posttraumatic stress disorder (PTSD).[47,48,50] One trial from the Partial Hospitalization Program and Post Traumatic Stress Disorder Clinic of the Mental Health Service Line at the Department of Veterans Affairs Medical Center in Washington, DC included 12 patients with TRD and combat PTSD who remained depressed after a minimum of one month on antidepressant therapy (100% male; mean age of 55 years).[50] After 2 weeks of fast (5 Hz) and slow (1 Hz) frequency left-sided rTMS, response rates were 67% and 83%, respectively. Additionally, subgroup analyses based on 139 patients with concurrent Axis I psychiatric disorders from 2 trials found that response to rTMS did not differ based on the presence of various comorbid anxiety disorders, including PTSD.[47,48]

We are aware of a multi-site, sham-controlled VA Cooperative Study of rTMS that is currently enrolling Veterans with TRD and possible comorbid disorders and/or a history of substance abuse (NCT01191333, CSP #556). This study will provide findings that are directly applicable to the Veteran population and has the potential to provide more general insights about how comorbidities may affect rTMS treatment. This VA study plans to enroll 360 Veterans across 9 VA Medical Centers and the estimated completion date is November 2017.

Overall illness morbidity

Compared to the findings of controlled trials of patients with typically narrow ranges of symptomatology and comorbidity, response and remission rates (58% and 37%, respectively) were similar in one multisite, naturalistic, uncontrolled observational study of 307 outpatients that were selected using less stringent eligibility criteria.[52] In particular, patients in the observational study had a higher incidence of prior inpatient psychiatric hospitalizations (44%) and a greater number of failed antidepressant trials (2.5) than patients in controlled trials. However, only 15% of patients had comorbid anxiety disorders and rates of other comorbidities were not reported. Also, because there was no sham control group in this study, the observed improvements may have been a result of being part of the study, including the remuneration patients received for completing the study procedures.

Concomitant medications

Evidence from the Berlim 2014 meta-analysis of sham-controlled LHF-DLPFC rTMS RCTs suggest that patients who are treated with rTMS as monotherapy or as augmentation to pharmacotherapy have similar response (29% vs 10%; 19% vs 5%) and remission (34% vs 13%; 24% vs 6%) rates compared to sham (response: Q=0, df=1, *P*=0.95, remission: Q=0.01, df=1, *P*=0.91).[33]

It is unknown whether the benefits of RLF-DLPFC rTMS differ in subpopulations based on use of concomitant medications. Results of the Berlim 2013 meta-analysis of sham-controlled trials suggest a greater chance of response (Q=5.99; df=1; *P*=0.014) when used as monotherapy (OR=27.94; 95% CI: 4.3-181.53) versus an augmentation strategy (OR=2.32; 95% CI: 1.17-4.6).[32] But the problem with the RLF-DLPFC monotherapy therapy evidence is that it has unclear applicability to patients with stringently defined TRD because patients either were *not* treatment resistant[53] or were only required to have failed at least one antidepressant in *either* the current or previous episode.[54]

KEY QUESTION 2: For adults with TRD, how do the benefits and harms of treatment with rTMS differ based on variation in rTMS treatment protocol (*eg,* coil geometry, coil placement, stimulus parameters, duration of a treatment session, timing and number of sessions, *etc)*?

Overview

Head-to-head trials provide the most direct evidence of how benefits and harms of treatment with rTMS differ based on variation in rTMS treatment protocols. When the University of Calgary combined data from head-to-head trials, they found no statistically significant differences based on frequency, intensity, or on use of bilateral protocols (Table 1); however, their meta-analyses did not adjust for the potentially confounding effects of variation in other parameters (*eg*, left vs right). To try to better isolate the effects of individual stimulation parameters, we sought to create more homogenous subgroupings of head-to-head trials based on whether they compared (1) different LHF-DLPFC protocols; (2) RLF-DLPFC versus LHF-DLPFC; (3) bilateral versus unilateral protocols; or (4) involved other rTMS protocol variations such as the use of priming, stimulating other regions of the brain, image guidance, etcetera.

However, the wide variation in rTMS protocols we encountered in the literature, and probably reflected in clinical practice, makes it almost impossible to determine how to achieve the best result. High-frequency rTMS applied to the left dorsolateral prefrontal cortex is the most well-studied approach and it includes a FDA-cleared protocol that has been shown to improve quality of life. Head-to-head trials have not found any particular protocol to have any advantages over others. In terms of dose for LHF-DLPFC, 2 large multicenter RCTs support using 120% RMT to guarantee adequate stimulation intensity. Intensities down to 100% may also be effective in certain patients. LFR-DLPFC has primarily been used as augmentation at 1 Hz and intensity ranging from 90% to 110% and has shown higher levels of response with more than 1200 total pulses per session. We found no reviews that have evaluated the effects of variability in coil

geometry, coil placement, session duration, timing or number of sessions. Most studies have used the figure-eight coil and the 5-cm technique for coil placement. rTMS has most commonly been delivered daily during the week, for 2 to 4 weeks, with each session ranging in duration from 10 to 40 minutes. In order to collect meaningful data from clinical experience, the VA should increase standardization of rTMS delivery.

Standard LHF-DLPFC rTMS

General efficacy of LHF-DLPFC rTMS

The rTMS protocol that is FDA-cleared is the only one that has been studied in 2 published multisite studies.[17,18] It is comprised of administration to the left dorsolateral prefrontal cortex (DLPFC) at a speed of 10 pulses per second, an intensity of 120% motor threshold, with 3,000 pulses delivered per session, and one session conducted per day in 5-day sequences for 3-6 weeks. The first of these multisite trials was Neuronetics' pivotal trial which led to the 2008 FDA clearance.[17] This trial randomized 325 medication-free outpatients with major depression who had previously failed one to 4 adequate antidepressant trials, were medically healthy, and who were without additional psychiatric comorbidity (*eg*, PTSD).[17] When response was defined as at least a 50% improvement in HAMD24 total score, rates were statistically significantly greater for rTMS at both 4 weeks (19.4% vs 11.6%; $P<0.05$) and 6 weeks (23.9% vs 15.1%; $P<0.05$). The advantage of rTMS over sham in remission rates (HAMD24 Total Score < 11) did not reach statistical significance until week 6 (17.4% vs 8.2%; $P<0.05$). rTMS was also found to modestly improve quality of life, based on significant improvements in the Q-LES-Q total score (+4.8 points vs 2.8 points; $P=0.035$) and in the SF-36 mental component score (+6.3 points vs +3.6 points; $P=0.043$).[55] Discontinuation due to adverse events was similar (4.5% vs 3.4%; *P* not reported) and there were no deaths or seizures.

The second multisite trial was sponsored by the NIH and had similar results to the Neuronetics' pivotal trial, thus strengthening the therapeutic profile of this particular rTMS protocol.[18] The NIH multisite trial involved a similar rTMS protocol and a similar patient population, but included a few notable methodological advances, including an effort to improve the blinding by better simulating the rTMS somatosensory experience in the sham condition and a formal assessment of patients, raters, and treaters to assess the adequacy of the blind. The rate of correctly guessing treatment assignment was 60% for patients, 65% for treaters, and 48% for raters. Patients were generally moderately to extremely confident in their guesses, whereas treaters and raters were generally not at all to moderately confidence in their guesses. At 3 weeks, there was a significant effect of rTMS on the proportion of remitters (primary outcome, HAMD ≤ 3 or 2 consecutive HAMD scores < 10; 14% vs 5%; OR 4.2, 95% CI, 1.32-13.24; $P=0.02$) and responders (≥ 50% decrease in HAMD; 15% vs 5%; $P=0.009$). Rates of withdrawal due to adverse events were 5.4% for rTMS and 0 for sham (*P* not reported). No seizures or suicides were reported.

Head-to-head trials of different LHF-DLPFC protocols

Eight eligible head-to-head trials compared different variations in LHF-DLPFC protocols. All are small (N≤54), single-site studies. Three compared different intensities (Table 1 and 3),[56-58] 5 compared different speeds (Table 4),[48,50,54,59,60] and one compared daily treatments to less than daily treatments (N=12).[61] None compared the protocol used in the multisite trials described

above to any other protocol and all used lower doses than the FDA-cleared protocol. These trials didn't demonstrate any obvious dose-response relationship, but comparison among these studies is difficult due to clinical diversity (*eg*, patient characteristics, whether rTMS was used as an augmentation strategy or as monotherapy, rTMS stimulation parameters) and methodological diversity (*eg*, how treatment resistance was defined). Our finding of no frequency or intensity-related differences in head-to-head trials of different LHF-DLPFC protocols is consistent with those of University of Calgary, even though their meta-analyses combined a broader set of head-to-head trials. A meta-regression based on 29 sham-controlled trials of 1,371 patients also found no significant association between variation in rTMS speed, intensity, total number of sessions, or total number of pulses and response or remission.[33,25]

In general, the findings of the head-to-head trials are most applicable to women in their mid-forties to early sixties, who are medically healthy, and do not have any Axis I comorbidities. A fair-quality head-to-head trial of 12 Veterans found statistically comparable response rates for 1 Hz and 5 Hz rTMS after 2 weeks (67% vs 83%).[50] When the Veterans were followed for an additional 2 months after treatment discontinuation to monitor the durability of the rTMS effects, a slight relapse of symptoms was noted, with the response rate dropping to 50% in both groups. The sample came from the Partial Hospitalization Program and Post Traumatic Stress Disorder Clinic of the Mental Health Service Line at the Department of Veterans Affairs Medical Center in Washington, DC, who had treatment-refractory depression and combat PTSD, and who remained depressed after a minimum of one month on antidepressant therapy (100% male; mean age of 55 years). Table 4 describes the characteristics of the rTMS protocol used in this trial and its results at the end of rTMS treatment. The magnitude of response in both treatment groups was considerably greater than that seen in other studies. This may have been due to the trial's open design in which neither patients nor raters were blinded to treatment.

Only one trial evaluated re-treatment with left-sided high-frequency PFC rTMS of patients who failed to response to a previous course of right-sided low-frequency PFC rTMS.[48] This trial reported a response rate almost 5 times greater with 10-Hz compared with 5-Hz left-sided PFC rTMS, but the difference was not statistically significant, likely due to the small sample size. Limitations of this study are that the between-group comparability of important baseline characteristics is unknown and no information was collected on the integrity of the blind.

Table 3: Trials comparing different LHF-DLPFC intensities

Author, Year Sample size	Intensity comparisons	Speed	Total pulses	Response	Remission	Adverse event withdrawals
Bakim 2012[56] N=35	110% vs 80% vs sham	20 HZ	24,000	73% vs 83% vs 17%	55% vs 25% vs 9%	NR
Rossini 2005[58] N=54	100% vs 80% vs sham	15 Hz	6,000	61% vs 28% vs 6.2%	NR	None
Padberg 2002[57] N=31	100% vs 90% vs sham	10 Hz	15,000	30% vs 20% vs 0	20% vs 10% vs 0	NR

Table 4: Trials comparing different LHF-DLPFC frequencies (Hz)

Author Year Sample Size	CC AD meds?	Hz comparison	Intensity (% RMT)	Total pulses	Response	Remission	Adverse event withdrawals
George 2000[59] N=32	N	20 vs 5 vs sham	100%	16,000	30% vs 60% vs 0	NR	0% vs 20% vs 0%
Su 2005[60] N=30	Y	20 vs 5 vs sham	100%	16,000	60% vs 60% vs 10%	50% vs 50% vs 0	NR
Fitzgerald[a] 2006[48] N=30	Y	10 vs 5	100%	15,000	28% vs 6%; *P*=0.16	NR	NR
Stern 2007[54] N=45	N	10 vs 1 vs sham	110%	16,000	60% vs 0 vs 0	40% vs 0 vs 0	0% vs 50% vs 30%
Rosenberg 2002[50] N=12	Y	5 vs 1	90%	6,000	83% vs 67%	NR	1, group NR

[a]Non-responders to 1- or 2-Hz rTMS over the R-DLPFC

Deep LHF-DLPFC rTMS

We did not identify any study that has directly compared deep LHF-DLPFC TMS to any standard rTMS protocol. However, in January 2013 the FDA determined deep rTMS, administered at an intensity of 120% of motor threshold and a frequency of 18 Hz for 1,980 pulses per session on a schedule of five daily sessions for 4 weeks, to be substantially equivalent to the FDA-cleared standard rTMS protocol described above.[15] The FDA determination of substantial equivalence appears to be based on indirect evidence from an unpublished, multisite, international sham-controlled trial of 229 patients with TRD (NCT00927173).[15] Results of per-protocol analyses, which excludes 31 subjects who "did not receive the adequate DTMS treatment regimen," found significantly greater rates of response (38.4% compared with 21.4%; *P*=0.0138) and remission (32.6% compared with 14.6%; *P*=0.0051) in the deep TMS group compared with sham, but the differences were not statistically significant in the ITT analysis set. Information about the balance of benefits and harms is not available, however, as rates of withdrawals due to adverse events were not reported. Also, the quality of this trial is unknown, as essential information about the randomization and allocation concealment methods and the balance of important patient

characteristics at baseline is not available. We contacted the principal investigators to request additional information, but had not received any response at the time of this report. A 2013 review of deep rTMS identified an additional 7 uncontrolled trials, but no other sham-controlled trials.[62]

Right low-frequency dorsolateral prefrontal cortex (RLF-DLPFC) protocols

The most widely studied alternative rTMS strategy to the LHF-DLPFC approach is low frequency stimulation over the right DLPFC (RLF-DLPFC). The proposed advantages to the low frequency stimulation are lower risk of seizure induction and a lesser degree of scalp discomfort. It has been hypothesized that RLF-DLPFC could be a potential alternative in people with risk factors for seizure. Our finding of no frequency or intensity-related differences in head-to-head trials that compared RLF-DLPFC to LHF-DLPFC protocols or compared different RLF-DLPFC protocols is consistent with those of University of Calgary, even though their meta-analyses combined a broader set of head-to-head trials.

General efficacy of RLF-DLPFC rTMS approaches

Many small, single-site clinical trials have investigated the benefits and harms of RLF-DLPFC, but it has not yet been studied in a large, multicenter trial, such as has been done for LHF-DLPFC. A 2013 systematic review by Berlim and colleagues synthesized data from 8 randomized trials totaling 263 patients.[32] rTMS frequency was 1 Hz in all the studies. Intensity did not vary much and was 110% of resting motor threshold in 6 trials and 100 and 90% in each of the remaining 2 trials. Total pulses ranged quite a bit, though, from 1,200 to 24,000. rTMS was used as augmentation in the majority of trials. Results of their meta-analysis found that RLF-DLPFC produced higher response (38.2% vs 15.1%; OR 3.35 (95% CI, 1.34-8.02); NNT=5; I^2=34.18) and remission rates (34.6% vs 9.7%; OR 4.76; 95% CI, 2.13-10.64; NNT=5; I^2=0) than sham, with no worsening of overall withdrawals (5.3% vs 11.28; P=0.22). Sensitivity analyses found that protocols that delivered greater than 1200 total pulses were associated with higher response rates (OR 6.9; 95% CI, 2.39 to 19.92). The greatest weakness of this systematic review is that the authors did not formally assess the quality of the included studies. The authors expressed an intent to increase their reliability by restricting their inclusion criteria to only studies that used random allocation and were double-blind, but they did not assess how well those methodologies were carried out.

Head-to-head comparisons of RLF-DLPFC to LHF-DLPFC

Eight small, single-site clinical trials (N=338) have directly compared RLF-DLPFC to LHF-DLPFC approaches (Table 5).[63-70] The response, remission, and adverse event withdrawal profiles of the RLF-DLPFC approaches were all comparable to the LHF-DLPFC approaches, but the LHF-DLPFC approaches used in these trials were all of lower dose than those FDA-cleared or studied in multicenter trials.

Table 5: Head-to-head comparisons of RLF-DLPFC to LHF-DLPFC

Author Year Sample Size	RLF: Hz, % RMT, pulses per session	LHF: Hz, % RMT, pulses per session	Total # sessions (given 5 days/wk)	Response (≤ 50% reduction in MADRS or HAMD, unless otherwise specified)	Remission	Adverse event withdrawals
Fitzgerald 2003[64] N=60	1, 100%, 300	10, 100%; 1,000	Phase 1=10, 5 d/wk, Phase 2: responders continued another 10 sessions	≤ 20% decrease in MADRS: 35% vs 40%	NR	None
Fitzgerald 2009[63] N=27	Hz NR; 110%; pulses per session unclear	Hz NR; 100%; pulses per session unclear	20	44% vs 45%	19% vs 36%	NR
Fitzgerald 2007[65] N=26	1, 110%, 720	10; 110; 1,500	15	≤ 30% decrease in MADRS: 54% vs 60%	NR	NR
Isenberg 2005[69] N=28	1, 110%, 120	20, 80%, 2,000	≤ 20	29% vs 36%	14% vs 21%	NR
Rossini 2010[66] N=74	1, 100%, 600	15, 100%, 600	10	57% vs 66%	NR	None
Richieri 2012[70] N=61	1, 120%, 360	10, 120%, 2,000	20	≤ 50% reduction in BDI: 54.5% vs 28.6%	NR	None
Triggs 2010[67] N=48	5, 100%, 2,000	5, 100%, 2,000	10	31% vs 22%	NR	None
Eche 2012[68] N=14	1, 100%, 120	10, 100%, 2,000	10-20	MADRS < 15: 2 weeks: 25% vs 50% 4 weeks: 50% vs 67%	NR	None

Head-to-head comparisons of different RLF-DLPFC protocols

Clinical trials that have evaluated RLF-DLPFC protocols have predominantly used 1.0 Hz stimulation speed. We only identified one eligible clinical trial that compared alternative RLF-DLPFC protocols.[48] This multisite, double-blind randomized trial compared the benefits and harms of 10 sessions of 1-Hz and 2-Hz RLF-DLPFC in 130 inpatients. Stimulation intensity was 110% RMT. Total number of pulses was 900 in the 1 Hz group and 1,800 in the 2 Hz group. Mean age was 49 years and most patients were female. Current alcohol or substance dependence was excluded, but there were no other restrictions on concurrent Axis I psychiatric disorders, and 14% had anxiety disorders. Mean number of failed antidepressant trials was 5.5. This trial found that a double dose of RLF-DLPFC (2-Hz) offered no advantages over 1-Hz RLF-DLPFC

in terms of proportion of patients who met response (27% vs 32%) or remission (7% vs 16%) criteria or withdrawals due to adverse events. The main limitations of this trial are that it may have been underpowered and it did not collect information on the integrity of the blind.

Bilateral dorsolateral prefrontal cortex (DLPFC) protocols

The second most widely studied alternative rTMS strategy is bilateral stimulation to the right and left-side DLPFC. The proposed advantage to bilateral stimulation is that it could maximize the likelihood of improvement in any individual patient who may have left-side or right-side resistance.[31]

General efficacy of bilateral DLPFC protocols

No bilateral DLPFC protocol has yet been studied in a large, multicenter trial. A 2013 systematic review by Berlim and colleagues synthesized data from 7 randomized, sham-controlled trials totaling 279 patients.[31] Right DLPFC protocol parameters included primarily 1 Hz frequency, percent of resting motor thresholds of 90 to 120, total pulses ranging from 4,200 to 27,000, and number of sessions ranging from 10 to 15. Ranges of left DLPFC protocol parameters included 10 to 20 Hz for frequencies, 90 to 120 for percent of resting motor thresholds, 7,500 to 27,000 for total pulses, and 10 to 15 for total sessions. rTMS was used as an antidepressant medication augmentation strategy in 6 of 7 trials. Six of 7 trials administered the left- and right-sided stimulations sequentially. Results of their meta-analysis found that RLF-DLPFC produced higher response (24.7% vs 6.8%; OR 4.3, 95% CI, 1.95-9.52; NNT=6; I^2=0) and remission rates (19% vs 2.6%; OR 6, 95% CI, 1.65-21.8; NNT=7; I^2=0) than sham, with no worsening of overall withdrawals (7.15% vs 13.4%; P=0.19). The greatest weakness of this systematic review is that the authors did not formally assess the quality of the included studies. The authors expressed an intent to increase their reliability by restricting their inclusion criteria to only studies that used random allocation and were double-blind, but they did not assess how well those methodologies were carried out.

Head-to-head comparisons of bilateral to unilateral protocols

The University of Calgary systematic review pooled data from 5 studies comparing bilateral and unilateral LHF-DLPFC stimulation and reported no significant difference in response, remission, or side effects (Table 1).

Clinical trials that have compared bilateral rTMS approaches to unilateral LHF-DLPFC approaches have predominantly given left-sided stimulation first, followed by stimulation on the right side. So far, only one single center trial of 62 patients has investigated whether the order of bilateral sequential rTMS stimulation makes a difference, but found similar rates of response (28% compared with 12%) and remission (12% compared with 0%), regardless of whether fast left stimulation or slow right was given first.[71]

Other comparisons with bilateral DLPFC protocols

A few other trials of bilateral DLPFC protocols combining high and low frequencies have found no differences based on variation in treatment schedule or when compared to either unilateral left-sided DLPFC stimulation at alternating low and high frequencies or bilateral stimulation at low frequency on both sides.

Clinical trials of bilateral rTMS have predominantly used a daily treatment schedule. However, results from one single-site trial of 77 patients has shown that giving treatment 3 days a week for 6 weeks has the potential of achieving similar rates of response (43% compared with 43%) and remission (33% compared with 31%) compared with giving treatments daily for 4 weeks.[72]

Response rates were not statistically significantly different between groups that received a bilateral DLPFC protocol that combined high and low frequency stimulation (50%) or a unilateral left-sided DLPFC protocol that also combined (10 Hz) high and low (1 Hz) frequency stimulation (67%) in a trial of 36 inpatients at a single site in Austria.[73]

We also identified one multisite randomized controlled trial that compared 2 forms of bilateral stimulation to RLF-DLPFC in 219 inpatients.[47] Mean age was 47 years and most patients were female. Mean number of failed antidepressant trials was 5.5. Current alcohol or substance dependence was excluded, but there were no other restrictions on concurrent Axis I psychiatric disorders and 40% had anxiety disorders. Stimulation intensity was 110% of resting motor threshold and total number of pulses was 900 in all groups. Stimulation speed was 1 Hz in the unilateral right group, 1 Hz on the right side followed by 10 Hz on the left side in the sequential bilateral group, and 1 Hz on the right side followed by 1 Hz on the left side in the low-frequency sequential bilateral group. There were no significant differences between the right unilateral, sequential bilateral, or low-frequency sequential bilateral groups in response (56% , 49%, and 55%; P=0.61) or remission (35%, 29%, 31%; P=0.71), or withdrawals due to adverse events (1%, 1%, 3%, P not reported).

Other rTMS protocol variations

Future trends in rTMS research include protocol variations such as: (1) enhancement of RLF-DLPFC protocols by "priming" them with a preceding period of higher frequency stimulation provided at low intensity[74,75]; (2) exploring stimulation in different regions of the brain[76]; (3) improving the stimulus location by using structural MRI-guided[77,78] or PET-guided[79] navigation; and (4) individualizing stimulus timing parameters based on background EEG activity.[80] As most of these alternatives would require even more resources, however, more research in larger samples is still needed to confirm their value.

KEY QUESTION 2A: What defines an adequate course of treatment?

In contrast with the drug development process, dose response assessment has not been an integral component of establishing the effectiveness and safety of rTMS treatment. We are aware that surrogate markers of brain activity have been examined to infer the minimum dose needed to interact with brain circuits,[81-83] but this evidence was outside of the scope of this evidence brief. We discuss the use of biomarkers in Key Question 3. We did not find any prospective dose-ranging study that used a factorial design to directly and simultaneously compare the effects of multiple stimulation parameters in isolation from one another (*eg*, intensity, quantity of pulses, duration). In the absence of definitive direct data on minimally effective rTMS dose, we looked across sham-controlled trials to indirectly examine the effects of variable dose intensities. However, a limitation of relying on sham-controlled trials for evidence on dose response is that the generalizability of their findings is limited to narrower ranges of dose and patient characteristics than are encountered in typical VA clinical practice settings.

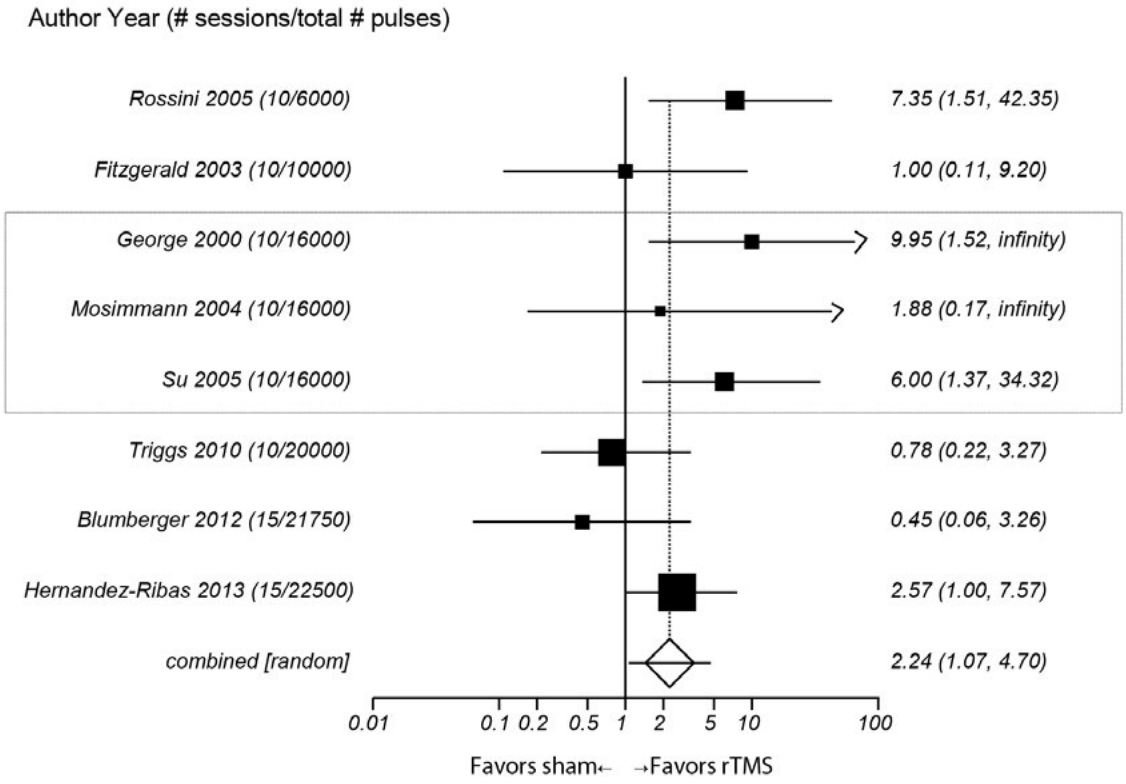
The best evidence from 2 large multicenter RCTs supports using 120% RMT to guarantee an adequate stimulation intensity.[17,18] Using data from the 2014 systematic review by Berlim and colleagues of 29 sham-controlled trials of high-frequency left-sided PFC rTMS at lower intensities, 80% to 110%,[33] we found that intensities down to 100% may also be effective in patients primarily under 50 years of age without Axis I comorbidities and past substance abuse.[33] When we grouped trials by % RMT for 80%, 90%, 100%, and 110% (Table 6), we found that the relative risks for response gradually increased with increasing % RMT. The 100% RMT was the lowest level at which the higher response rate for rTMS versus sham reached statistical significance. However, within any 100% RMT regimen, there are still the questions of how many sessions and how many total pulses are minimally effective. Among the 8 trials of 100% RMT, the number of sessions ranged from 10 to 15 and the total number of pulses ranged widely, from 6,000 to 22,500. Likely because most regimens were represented by only a single trial with a small sample size, when examining the plot of relative risks (Figure 2), we found no clear dose response pattern based on escalating numbers of sessions and total number of pulses. However, when we pooled the 3 trials that used the same stimulation regimen of 100% RMT in 10 sessions of 16,000 total pulses, we found a statistically significant increased response for rTMS, and this did not appear to be at the expense of increased withdrawals.[42,59,60]

Although the systematic review by Berlim and colleagues did not report withdrawals due to adverse events, we pooled their data for overall withdrawals, which includes withdrawals due to adverse events. Overall withdrawal rates did not consistently escalate as a function of increasing rTMS intensity. We did not attempt to evaluate dose response for low-frequency right-sided PFC rTMS due to the smaller number of trials available.[32]

Table 6: Pooled analyses of response rates from sham-controlled trials from Berlim 2014 grouped based on % RMT for examining dose

% RMT	# sessions	Total # pulses	# RCTs/ Total N	Response rates, Relative Risk (95% CI), I^2	Overall withdrawals, Relative Risk (95% CI), I^2
80%	10	8,000	4/105	11% vs 6%; RR 1.39 (95% CI, 0.44 to 4.40), I^2=0%	2% vs 13%; 0.29 (0.06 to 1.38); I^2=0%
90%	10	8,000-16,000	3/87	44% vs 21%; RR 1.88 (95% CI, 0.74 to 4.79); I^2=43.4%	11% vs 5%; 2.08 (0.75 to 5.75), I^2=0%
100%	10-15	6,000-22,500	8/266	31% vs 10%; RR 2.24 (95% CI, 1.07 to 4.70); I2=18.5%	13% vs 10%; 1.41 (0.70 to 2.87), I^2=0%
100%	10	16,000	3/84	40% vs 3%; RR 5.40 (95% CI, 1.34 to 21.76)	7% vs 5%; 1.10 (0.22 to 5.40); I2=0%
110%	10-20	10,000-60,000	9/313	41% vs 12%; RR 2.78 (95% CI, 1.67, 4.63); I2=13%	6% vs 9%; 0.71 (0.30 to 1.66); I^2=0%
110%	10	16,000	3/63	39% vs 14%; RR 2.39 (95% CI, 0.50 to 11.39), I2=48.8%	5% vs 12%; 0.50 (0.07 to 3.71)
110%	20	30,000	2/66	42% vs 21%; RR 2.00 (95% CI, 0.95 to 4.23)	6% vs 6%; 1.00 (0.15 to 6.69)

Figure 2: Relative risk (random effects) of response for rTMS 100% RMT versus sham (95% confidence interval) in order of escalating number of sessions and total number of pulses



KEY QUESTION 3: For adults with TRD, what is the evidence about early predictors of rTMS treatment benefit?

Early prediction of treatment benefit can be based on clinical or physiological factors that are established *before* treatment, such as age and gender, and those that may change early *in response to* treatment, such as neurochemical or hormonal biomarkers. Key Question 1 focused on a number of pre-specified subpopulations based on factors established *before* treatment. Here we focus on factors that may change early *in response to* treatment. The minimally acceptable study would prospectively test the ability of a tool, designed a priori, to predict treatment benefit based on multiple factors. We did not identify any such studies. Factors that have been preliminarily examined as predictors of rTMS outcomes in primarily retrospective, uncontrolled studies include neuroimaging (fMRI, SPECT, PET, MRS, and NIRS), electrophysiological (EEG, TMS-indexed cortical excitability, and saccadic eye movements), and neuroimmunoendocrine (cortisol, THS, BDNF, ILs, and sexual hormones) biological markers.[81] Some of these factors have been shown to be associated with clinical outcomes, but due to small, heterogeneous samples and uncontrolled confounders, drawing definitive conclusions about their use is impossible at this time.[81]

KEY QUESTION 4: What is known about the need for and effectiveness of continuation or maintenance treatment to prevent relapses or recurrences in patients who have responded to rTMS?

No sham-controlled RCTs assessed rTMS outcomes beyond a week following acute treatment.[14] In an older review[84] cited in the APA guideline for MDD treatment,[20] a pooled analysis of 14 studies that tested patients 2 weeks after acute rTMS treatment showed that the effect of rTMS treatment on remission had disappeared. We included 13 nonrandomized studies of relapse or recurrence.[85-97]

Persistence of benefit following end of acute treatment

For patients with TRD, response to ECT or various antidepressant medications is often transient.[98] Six studies examined the persistence of benefit in patients who had achieved remission or response during RCTs of acute rTMS treatment (Table 7).[85,87,89,93,95,97] These studies lasted from 3 months to 1 year and reported widely varying rates of relapse. The largest study included 76 remitters in a naturalistic setting followed for one year, 30% of which relapsed mostly during the first 6 months.[97] Among the 44 responders, 42% did not sustain their response during follow-up. In another year-long study, recurrence was experienced by 1 of 4 remitters, 1 of 2 responders, and 2 of 3 who had a partial response at the end of acute rTMS treatment.[89] Three studies followed patients for 6 months after the end of acute rTMS treatment and found relapse rates of 10% among patients who at least partially responded,[93] 20% among 21 patients who achieved response (identical to the relapse rate in the ECT group),[87] and 77% among 204 patients who achieved remission during acute rTMS treatment.[85] In the 6-month study of remitters, upon multivariate analysis younger age (P=0.003) and additional rTMS treatment sessions (P=0.027) were statistically significantly associated with increased duration of remission.[85] Finally, a follow-up of a RCT and an open-label trial reported that after 3 months, 5 out of 37 (14%) patients had relapsed and the mean time to relapse was 7.2 weeks.[95] This study was a follow-up of the multisite NIH trial reviewed in Key Question 2.[18]

Table 7: Extension studies of persistence of benefit following end of acute rTMS treatment

Author Year Sample size Duration	Population	Continuation, maintenance therapy	Outcomes
Dell'Osso 2011[89] N=11 1 year	Responders (BD)	Pharmacotherapy	Recurrence: 17% responders, 0% remitters, 67% partial responders
Cohen 2009[85] N=204 6 months	Remitters (MDD)	Pharmacotherapy	Relapse: 77%
Dannon 2002[87] N=21 6 months	ECT or rTMS responders (MDD)	Pharmacotherapy	Relapse: rTMS: 19%; ECT: 20%
Janicak 2010[93] N=99 6 months	At least partial responders (MDD)	Pharmacotherapy	Relapse: 10% after a mean of 164 days

Mantovani 2012[95] N=37 3 months	Remitters (MDD)	Pharmacotherapy	Relapse: 14% after mean of 7.2 weeks
Dunner 2014 N=76[97] 12 months	Remitters (MDD)	Varied	Relapse: 30% mostly during first 6 months
Dunner 2014 N=44[97] 12 months	Responders (MDD)	Varied	Did not sustain response: 42%

Long-term rTMS maintenance therapy strategies for relapse prevention

We identified 4 uncontrolled studies of 4 different rTMS maintenance therapy strategies for preventing relapse among responders to acute rTMS treatment (Table 8).[86,92,94,96] None of the strategies has been directly compared in any head-to-head trials and while relapse rates in these studies ranged widely, it is difficult to attribute this variation to different maintenance strategies given the heterogeneity in follow-up time, type of acute rTMS treatment, and patient populations. In 2 studies of weekly rTMS maintenance, relapse rates ranged from 50%[96] to 57%[94] after a mean of 24 weeks. A retrospective cohort examining tapered rTMS maintenance reported 62% of patients maintained response at 6 months.[86] Finally, a recent RCT follow-up examining clustered rTMS maintenance reported that 71% relapsed after an average of 10.2 months.[92]

Table 8: Extension studies of rTMS continuation or maintenance therapy

Author Year Sample size Duration	Population	Continuation, maintenance therapy	Outcomes
Connolly 2012[86] N=42 6 months	Responders (MDD and BD)	Tapered rTMS: 1 per week for 4 weeks, 2 per month for 2 months, and 1 per month for 3 months	Response duration: 62%
Fitzgerald 2013[92] N=35 50 months	Responders (MDD and BD)	Clustered rTMS: 5 sessions over 2.5 days every 4 weeks	Relapse: 71% Withdrew: 11% Remained in treatment: 17%
Li 2004[94] N=7 1 year	Responders (BD)	Weekly rTMS	Completed f-u: 43% Multiple relapse: 57% after mean of 24 weeks
O'Reardon 2005[96] N=10	Responders (MDD)	Weekly rTMS	Relapse or recurrence: 50%

rTMS retreatment following relapse

Four uncontrolled studies examined retreatment with rTMS following relapse in patients who responded to an initial acute course of rTMS (Table 9).[90,91,93,97] Rates of re-achievement of response ranged from 50 to 100%, but as with the studies of long-term rTMS maintenance

strategies, we cannot attribute the apparent variation in rates of re-achievement of response to retreatment parameters, due to the heterogeneity in study design and patient populations. In one multisite naturalistic study, among those who received rTMS introduction, 20%, 21%, 44%, and 66% of non-responders, partial responders, responders, and remitters did not experience a later relapse.[97] A follow-up of a RCT reported that patients received an average of 4 rescue treatments, with a mean treatment interval of 4.9 months, and after 4 years, 50% of patients sustained their response.[90] Another RCT follow-up reported that of the patients that received one rescue treatment, 63% responded; of the patients that received a second treatment, 57% responded; and 100% of patients that received a third or fourth rescue treatment responded.[91] A final RCT follow-up reported that of the patients that were reintroduced to rTMS after symptom worsening, 84% benefited from treatment, 40% experienced a second instance of symptom worsening, and 13% experienced a third instance of symptom worsening.[93] This study was a follow-up of Neuronetics' pivotal trial which led to the 2008 FDA clearance.[17]

Table 9: Extension studies of rTMS rescue treatment

Author Year Sample size Duration	Population Response, remission definition	Rescue treatment	Outcomes
Demirtas-Tatlidede 2008[90] N=14 4 years	Responders (MDD)	Mean treatments: 4 Mean interval: 4.9 months	Sustained response: 50%
Fitzgerald 2006[91] N=19 3 years	At least partial responders (MDD and BD)	Mean interval: 1st re-treatment: ~11 months 2nd: ~12 months 3rd: ~9 months 4th: 6 months	Response: 1st re-treatment: 63% 2nd re-treatment: 57% 3rd re-treatment: 100% 4th re-treatment:100%
Janicak 2010[93] N=38 6 months	At least partial responders (MDD)	2 sessions/week for 2 weeks followed by 5 sessions/week for up to 4 more weeks	84% benefited and continued
Dunner 2014[97] N= 15 (non-responders), 19 (partial responders), 27 (responders), 32 (remitters) 12 months	Non-responders Partial responders Responders Remitters	Varied	Did not experience relapse: Non-responders: 20% Partial responders: 21% Responders: 44% Remitters: 66%

SUMMARY OF MAIN FINDINGS

- **Which patients have best chances of success with rTMS?** Whether the effectiveness of rTMS treatment differs by sex or in young (age 18-37 years) or older adults (age ≥ 65 years) is unclear. But evidence suggests that patients with unipolar or bipolar depression, with more or less stringently defined TRD, and who are treated with rTMS as monotherapy or as augmentation to pharmacotherapy have similar chances of success with LHF-DLPFC rTMS. However, the strength of this evidence is low due to small sample sizes, resulting in limitations in precision and methodological quality of the studies (*eg*, single center, inconsistent assessment of blinding integrity). Also, as subgroup analyses tended to focus on benefits only, it was not possible to assess the balance of benefits and harms in subpopulations. For example, it is possible that populations that are traditionally susceptible to lower tolerability of treatments in general, such as elderly patients, may be less likely to succeed with rTMS, but this has not yet been explored in the literature.
    - A major limitation of rTMS studies is that they generally excluded patients with medical and psychiatric comorbidities. However, consistent findings from 3 trials provide some preliminary evidence that rTMS can produce a clinically significant response in TRD patients with comorbid posttraumatic stress disorder (PTSD).
- **What are the optimal rTMS treatment protocols/parameters?** Evidence suggests that more intensive protocols are not uniformly more effective, and it is not yet clear which parameters matter the most. The effects of variability in coil geometry, coil placement, session duration, timing, or number of sessions remain unclear.
    - **LHF-DLPFC protocols:** This is the most well-studied approach and it includes a FDA-cleared protocol that has been shown to improve quality of life, but head-to-head trials and meta-regressions of sham-controlled trials have not yet demonstrated any particular LHF-DLPFC protocol to have any advantages over another.
        - To guarantee adequate stimulation, 2 large multicenter RCTs support using standard rTMS at 10 Hz, 120% RMT, 3,000 pulses per session, 5 days per week for 3 to 6 weeks. Intensities down to 100% may also be effective in patients primarily under 50 years of age without Axis I comorbidities and past substance abuse.
            - Deep rTMS, applied to the left DLPFC and administered at an intensity of 120% of motor threshold and a frequency of 18 Hz, for 1980 pulses per session on a schedule of 5 daily sessions for 4 weeks, is also FDA-cleared, but we identified no published sham-controlled trials that provided evidence to assess the balance of its benefits and harms in general. It is also unknown how its benefit/harm profile *directly* compares to established standard rTMS protocols as we did not identify any head-to-head trials.

  - Low-frequency rTMS applied to the right DLPFC (RLF-DLPFC) at a speed of 1 pulse per second, intensities of 90 to 110%, and total pulses over 1,200 appears to be an additional viable approach. Although the *theoretical* advantages of lower risk of seizure induction and a lesser degree of scalp discomfort than LHF-DLPFC have not yet been proven in any multicenter clinical trials, it may be worth a try in patients with risk factors for seizure since it seems to provide comparable response and remission rates to LHF-DLPFC when given using parameters up to a speed of 10 pulses per second, an intensity of 100% motor threshold, with 2,000 pulses delivered per session (lower than FDA-cleared protocol). It has not yet been directly compared to the FDA-cleared LHF-DLPFC protocol.
  - Bilateral rTMS stimulation, sequentially targeting both the left and right DLPFC, is more effective than sham in improving response and remission. But since head-to-head trials have not yet demonstrated any significant advantage of bilateral rTMS stimulation over unilateral LHF-DLPFC or RLF-DLPFC, the value of the more complicated, time-consuming approach is not yet clear.

- **Early prediction of benefit:** We did not identify any evidence on a risk prediction tool for the early detection of rTMS treatment benefit.
- **Continuation/maintenance treatment in rTMS responders:** Available evidence is inadequate for determining the value of maintenance rTMS in general and for defining optimal treatment parameters. No studies have directly compared different rTMS maintenance strategies head-to-head and uncontrolled studies are limited by small sample sizes and heterogeneity in duration, acute rTMS parameters, and population characteristics. Rates of relapse during maintenance treatment ranged from 38% at 6 months (when rTMS was administered once weekly for 4 weeks, twice monthly for 2 months, and once monthly for 3 months), to 71% in a mean of 10.5 months (using a form of "clustered" maintenance, whereby rTMS was applied in monthly maintenance sessions of 5 treatments over a 2-day period).
  - Limited evidence suggests that rTMS retreatment following relapse may have some value, as rates of re-achievement of response ranged from 50% to 100%.

DISCUSSION

As stated in a Memorandum dated March 20, 2014, in order to consider whether to make rTMS more broadly available to Veterans and/or consider developing detailed clinical guidance, the VA is seeking more research on a number of questions about who may benefit, under what treatment protocol, what the predictors of benefit are, and what the longer term outcomes are. Except for providing some low-strength guidance on parameters for using LHF-DLPFC rTMS, when to consider RLF- DLPFC rTMS, and on who may benefit, this Evidence Brief found that currently available evidence is still falling short of addressing all of the VA's questions.

The most important limitation of the included rTMS studies is that they generally excluded patients with medical and psychiatric comorbidities or did not report their prevalence. This particularly limits the generalizability of the evidence in this Brief to Veterans, who are known to have a greater burden of comorbid mental health conditions compared with the general population. While we identified some evidence that rTMS can produce a clinically significant response in patients with comorbid PTSD (KQ 1), it is unclear if the benefits and harms of rTMS treatment would differ among MDD patients with other comorbidities. A multi-site, sham-controlled VA Cooperative Study of rTMS that is currently enrolling Veterans with treatment resistant depression and possible comorbid disorders and/or a history of substance abuse will provide findings that are directly applicable to the Veteran population and have the potential to provide more general insights about how comorbidities may affect rTMS treatment (NCT01191333, CSP #556). This VA study plans to enroll 360 Veterans across 9 VA Medical Centers and the estimated completion date is November 2017. The results from this study may answer many outstanding questions regarding the use of rTMS among TRD patients with comorbidities.

Another major limitation is the heterogeneous definition of TRD throughout the literature on rTMS treatment for depression. We included studies that used a variety of definitions of TRD, which may have affected the conclusions in this report and lessened the apparent benefit of rTMS. If the VA wishes to evaluate their own data on rTMS, a uniform definition of TRD should be adopted.

A search of Clinicaltrials.gov identified an additional 16 ongoing clinical trials focusing on rTMS and depression (see Supplemental Materials). Three are multicenter trials and another trial is comparing clustered versus tapered maintenance rTMS over 2 years. Interventions for the ongoing trials identified are consistent with interventions acknowledged throughout this review, including high- versus low-frequency rTMS, deep TMS, accelerated TMS, and rTMS versus selective serotonin reuptake inhibitors. One ongoing clinical trial (NCT02080507) is recruiting patients that meet the criteria for ECT and will shed light on the effects of rTMS in this population. Two additional studies are focusing on theta burst rTMS, which consists of applying short, high frequency trains repeated at intervals of 200ms.[99] However, due to the high frequency bursts delivered, there is a higher risk of seizure with TBS than with other rTMS protocols.[99]

We attempted to extend the results from several recent systematic reviews of sham-controlled trials by seeking additional evidence from head-to-head randomized trials that directly compared different rTMS parameters and from observational studies. Unfortunately, these additional sources of evidence generally suffered from the same limitations as in the sham-controlled trials,

including use of small sample sizes from single centers. Despite their limitations, we included data from a number of head-to-head trials of different rTMS parameters for Key Question 2, as it offered the most direct evidence to address this question. However, we did not identify any observational studies with a concurrent control group, and none of the numerous small uncontrolled before-after studies clearly filled gaps in the trial evidence.

In the March 20, 2014 VA Memorandum on rTMS, one of the stated goals is to evaluate their own accumulating experience with rTMS on a system-wide basis to inform policy and practice. We agree that doing so could make an important contribution to the existing body of observational evidence by including a larger sample of patients across multiple sites and patients with a greater number of risk factors such as medical and psychiatric comorbidities and possible suicidality. As there is a great need to determine the durability of rTMS reponse, monitoring of outcomes after treatment should be included in this effort. Considering the high resource and time investments required with rTMS treatment, evaluation of its effects on reducing hospitalizations could be very useful. Clarifying whether response to rTMS differs based on level of social support,[67] type of failed pharmacotherapy approaches, number of past episodes of TRD, and history of ECT failure could also help guide selection of Veterans who may be better candidates for rTMS.

Aside from the limitations we encountered in the literature described above, there are a number of methodological limitations with our review. An evidence brief differs from a full systematic review in that the scope is narrowly defined and the traditional review methods are streamlined in order to synthesize evidence within a shortened timeframe. Rapid review methodology is still developing and there is not yet consensus on what represents best practice. Methodological limitations of this Evidence Brief include the exclusion of studies published in languages other than English. Second, rather than generalizing from the broader base of all rTMS studies in major depression, we focused on a narrower subgroup of studies specifically in patients with TRD. However, we believe that enough evidence has accumulated for TRD to stand on its own, and findings from other recent reviews suggest that generalizing from all rTMS studies could *underestimate* the effects of rTMS in TRD on HAM-D change scores (37% in all MDD trials vs 48% in TRD trials)[100] and on response (34% in all MDD trials and 43% in TRD) and remission (49% in all MDD trials and 58% in remission).[23,25] Third, we considered a narrower range of outcomes than may be of interest to some stakeholders, such as cost-effectiveness, mean change in symptom scales, or patient satisfaction. Fourth, given the time constraints on completing this Evidence Brief and the large volume of literature encountered, we only included studies that reported both benefits and harms and were only able to perform quality assessment on multicenter trials. Finally, given the time constraints, we could not conduct a broad search for unpublished studies. However, in our search of Clinicaltrials.gov, we did identify 4 studies that were completed at least a year ago and still have not been published (see Supplemental Materials for details). Two of these studies had potential publication matches, but only one of these was included in the review. Lack of access to these unpublished trials is a potential limitation of this review.

In summary, rTMS represents a wide spectrum of treatments, many variations of which are still not well-studied. The specific LHF-DLPFC protocols cleared by the FDA have the strongest evidence of efficacy, with response and remission rates that are at least as good or

better than those in the third and fourth acute treatment steps in the STAR*D trial, as well as of improvements in quality of life, and no major safety concerns have been uncovered. However, nearly all of this evidence was developed in experimental settings. Also, decisions to use rTMS must be weighed by consideration of the uncertainty about the maintenance of its benefits beyond the first 4-6 weeks of treatment and of the potential difficulty of implementing a 5-day per week intervention. The current VA/DoD Clinical Practice Guidelines (2009) support ECT as the recommended somatic treatment strategy for patients who have failed multiple other treatment strategies on management of Major Depressive Disorder and does not address rTMS.[101] Since the sections of the 2009 VA/DoD CPG on MDD management appear outdated in their statement that TMS is not FDA-approved, we suggest the VA/DoD update the CPG to consider the two FDA clearances and the AHRQ findings of high-strength evidence about rTMS' acute efficacy that have emerged since 2009. In the meantime, rTMS has acceptable acute efficacy, and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought.

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