Washington State Health Care Authority

March 17, 2023 Meeting Materials
Health Technology Clinical Committee

Transcranial magnetic stimulation for treatment of selected conditions

Contents

- ☐ HTCC clinical expert information
- ☐ Agency Medical Director presentation
- ☐ Scheduled public comments presenters and presentations
- ☐ TMS evidence presentation
- ☐ HTCC decision aid
- ☐ TMS final key questions

Tuesday Burns, MD

Education

8/1995-5/1999	**Sc.B. Neuroscience, Brown University**	**Providence, RI**
8/1999-5/2003	**M.D., Mount Sinai School of Medicine**	**New York, NY**

Clinical Experience

3/2022–Present **Associate Professor, Attending Psychiatrist** **Seattle, WA**
University of Washington Medical Center

- Attending Psychiatrist, Outpatient Psychiatric Clinic, University of Washington
- Associate Clinical Professor, University of Washington Medical Center
- 1.0 FTE, outpatient clinical time alongside rotating call at UWMC
- In addition to clinical work at OPC, I supervise psychiatry residents in their 2nd, 3rd and 4th years
- I carry my own caseload of patients being followed for medication management, supportive psychotherapy and DBT
- I offer expert, second opinion consultation around treatment-resistance, gender affirming care, hormonally-mediated psychiatric conditions and neuromodulation
- I offer consultation to Washington State providers through the PCL service at UW
- I carry 3 Caseload Supervision groups of residents in the outpatient clinic
- I offer psychiatric supervision to residents and fellow DBT providers at OPC

5/2020–2/2022 **Medical Director** **Seattle, WA**

THIRA Health

- Supervising Psychiatrist overseeing the care of PHP and IOP patients struggling with severe depression, anxiety, disordered eating, emotion dysregulation, self-harm and suicidal ideation (ages 13-65)
- Managing a caseload of 30-70 female identifying and female-aligned patients while supervising 3 nurse practitioners
- With 20 direct reports, I manage our RNs, CNAs, ARNPs, PAs, RDs and Diet Techs
- Offering medication management and DBT-informed therapy alongside medical education groups to PHP patients
- Navigating executive leadership decisions alongside the CEO, CMO, CCO and CFO
- Offering training and supervision to all members of our Integrated DBT Team
- Support intake, utilization review, compliance, finance and other administrative departments
- Creating and refining standard operating procedures and P&P across the COVID-19 pandemic and as our in-person PHP has grown from 20 to more than 40 patients in the past year
- Offering skillful and effective crisis management to actively suicidal patients; triaging and addressing acute medical concerns related to non-suicidal self-injury

9/2015–Present **Founding Partner** **Seattle, WA**
Behavioral Health Collaborative

- Clinical Psychiatrist specializing in Women's Mental Health
- Offered assessments, second opinion consultations and ongoing care to women across the life cycle (ages 16 and up)
- Areas of expertise include: PMDD, anxiety disorders, bipolar disorder, pregnancy/postpartum, menopause, eating disorders, gender dysphoria and gender affirming care
- This inclusive practice focuses on collaboration with referring providers (PCPs, OB/GYNs, NDs and therapists)

10/2012–9/2015 **Associate Psychiatrist**
Seattle, WA Seattle Neuropsychiatric Treatment Center

- Provided consultation to treatment-refractory outpatients and inpatients
- Performed initial assessments and delivered ongoing treatment
- Managed chronic depression, bipolar disorder, anxiety and OCD as well as acute episodes of suicidal depression, mania and psychosis
- Cared for patients with chronic self-injury related to borderline personality disorder
- Delivered both ECT and TMS to the treatment-refractory population

7/2011-7/2012 **Attending Psychiatrist, Assistant Professor** **New York, NY**
NYU Department of Psychiatry and Behavioral Health

- Faculty, Consultation-Liaison Psychiatry Service, Tisch Hospital
- Provided psychiatric coverage to the NYUMC Emergency Department
- Attending ECT physician, delivered ECT to both inpatients and outpatients
- Brain stimulation and 2nd opinion consultation to treatment refractory inpatients
- Direct supervision of NYU psychosomatic fellows - Resident and medical student supervision and teaching

1/2010-7/2011 **Attending Psychiatrist, Assistant Professor** **Norfolk, VA**
Eastern Virginia Medical School

- Provided consultation and medication management to a full outpatient caseload
- Provided short-term mindfulness-based therapy
- Supervised psychiatry residents
- Lecturer to 1st and 2nd year medical students
- Course Director for the Human Development course
- Covered the inpatient psychiatric unit and C/L service on a rotating basis
- Director, Electroconvulsive Therapy Service
- Co-Director, Division of Therapeutic Brain Stimulation
- Faculty Consultant to the Department of OB/GYN

7/2009-1/2010 **Psychopharmacologist** **Hampton, VA**
Riverside Behavioral Health Center

- Full-time, staff psychiatrist in outpatient services
- Performed initial evaluations and offered ongoing medication management of mood disorders, anxiety disorders and substance use disorders
- Collaborated with and supervised LCSWs and other mental health clinicians
- Bi-weekly on-site consultation at affiliated academic OB/GYN practice with ongoing management of patients struggling with infertility, PMDD, pregnancy and issues related to the postpartum period

7/2008-7/2009 **Associate Psychiatrist, Clinical Instructor** **Boston, MA**
Outpatient Psychiatry Department, Brigham and Women's Hospital

- Performed initial evaluations and pharmacologic consultations
- Responsible for ongoing psychopharmacologic management
- Offered ongoing, insight-oriented and cognitive behavioral therapy to patients
- Provided urgent and crisis level assessments to patients of BWH - Supervised the intakes and caseloads of psychiatry residents

Residency Training

6/2004-7/2008 **Harvard Longwood Psychiatry Residency Training Program** **Boston, MA**

Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Children's Hospital Boston
Massachusetts
Mental Health Center Faulkner Hospital

7/2007-7/2008 **Chief Psychiatry Resident** **Boston, MA**
Brigham and Women's Hospital
Harvard Medical School

Fellowship Training

7/2008-7/2009 **Women's Mental Health Fellow** **Boston, MA**
The Fish Center for Women's Health, Brigham and Women's Hospital
Harvard Medical School

January, 2010 **Visiting Fellowship in Electroconvulsive Therapy** **New York, NY**
Columbia University Medical Center

April, 2010 **Visiting Fellowship in in Transcranial Magnetic Stimulation** **New York, NY**
Columbia University Medical Center

Appointments and Accreditation

7/2006 – 7/2008 Brigham and Women's Hospital Graduate Medical Education Committee
7/2006 – 7/2009
Curriculum Committee, Harvard Longwood Psychiatry Residency Training Program
8/2009 – 1/2010 Chair, Education Committee, Riverside Behavioral Health Center
12/2009 – 7/2011 Psychiatry Residency Training Committee, EVMS
1/2010 – 7/2011 Emergency Psychiatry Training Committee, EVMS
1/2010 – 7/2011 Strategic Planning Committee, EVMS
1/2010 – 7/2011 Clinical Advisory Committee, EVMS
11/2012 – 10/2015 Behavioral Health Pathways Committee, Swedish Hospital
4/2014 – 10/2015 Department of Health and Joint Commission re-certification, Swedish Hospital
1/2021 - present Department of Health and Joint Commission initial accreditation, THIRA Health

Teaching

7/2007 -6/2008 Co-Leader, Introduction to Psychotherapy Seminar, Brigham and Women's Hospital

7/2008-7/ 2009 Faculty, Patient-Doctor I Course, Harvard Medical School

7/2007- 7/2009	Faculty, Patient-Psychiatrist Course, HLPRTP
1/2010 – 7/2011	Faculty, Clinical Assessment Course, EVMS
1/2010 – 6/2011	Lecturer, Introduction to Psychopathology, EVMS
3/2010 – 3/2011	Course Director, Human Development Course, EVMS
5/2010 – 7/2011	Course Director, Therapeutic Brain Stimulation Course, EVMS
12/2012 – 9/2014	Facilitator, ECT psychoeducation and support group, Swedish Hospital
12/2012 – 7/2018	Supported UW psychiatry resident education during ECT rotations, Swedish Hospital
5/2020 - present	Lecturer, Biologic Basis of Psychiatric Illness, THIRA Health

Licensure and Certification

7/2009- 12/2012	Full License in Washington
4/2009 - Present	Board Certified in Psychiatry, ABPN (re-certification completed 12/2019)

Research Experience

7/2008 – 7/2009	Investigator, The Health Study, Brigham and Women's Hospital
3/2010 – 7/2011	Investigator, Biomarkers of Postpartum Depression, EVMS
3/2010 – 7/2011	Investigator, Transcranial Magnetic Stimulation, Mechanisms of Action, EVMS

Publications

Burns TE and Kolodziej M. 2008. Diagnosis and Treatment of Depression in the ICU Patient. In R.S. Irwin, F.B. Cerra, J.M. Rippe (Eds), Irwin and Rippe's Intensive Care Medicine (6th Ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Gul R, Okwara L, Burns T, Neumann S. 2014. Transcranial Magnetic Stimulation (TMS) Efficacy in Treating Visual Hallucinations Associated with Obsessive Compulsive Disorder. Brain Research. 1659: 302-313.

Professional Society Memberships

5/2007 -	American Psychiatric Association
10/2010 -	The Marcé Society
10/2012 -	Postpartum Support International
10/2012 -	Washington State Psychiatric Association

Personal Interests

Spending time with family, volunteering at The Evergreen School, fiction writing and long-distance running

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

As stewards of public funds, the practicing clinicians who serve (or apply to serve) on the Committee strive to uphold the highest standards of transparency and impartiality. Identifying financial, professional, and other interests contribute to the effective management of perceived, potential, and/or real conflicts of interest/bias that could affect Committee determinations. (WAC 182-55)

This Conflict of Interest form must be completed by an applicant for appointment to the State of Washington Health Technology Clinical Committee (HTCC) or appointment to any of its subcommittees or work groups.

A member of the HTCC or any of its subcommittees or work groups may not participate in discussions or deliberations of any class of drugs, health technology, or any agenda item for which a conflict of interest is identified and may not vote on any such matter.

If a conflict of interest is so great as to make it difficult for any member to participate meaningfully in the work of the HTCC, that member may be asked to resign.

1 Applicant information

First name: Tuesday

Middle initial:

Last name: Burns

Phone number:

Email:

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.

Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

Use these categories to indicate the nature of the financial interest:

A. Payment from parties with a financial or political interest in the outcome of work as part of your appointment or activity.

B. Employment including work as an independent contractor, consultant, whether written or unwritten.

C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.

D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.

E. Participating on a company's proprietary governing boards.

F. Participating in a speakers bureau.

G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topics(s):

No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topics(s):

No

Could a coverage determination based on a Committee decision conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying committee staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership.

To sign this request, do **not** use the "Fill & Sign" function; instead, simply click in the signature field to add your signature.

Signature

Date

1/25/2023

Submit

or return form to **shtap @hca.wa.gov**

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Health Technology Clinical Committee Application for Membership

Washington State Health Care Authority

Clear form

1 Contact information

First name: Tuesday

Middle initial:

Last name: Burns

Address:

Phone number:

Best method, time to reach you: Cell phone

Email:

Today's date: 1/25/2023

2 Personal information (optional)

Gender:

☐ Male ☑ Female ☐ X/non-binary[1]

Pronouns (select all that apply)

☑ She/her ☐ He/him ☐ They/them ☐ Other (subj./obj.):

Race or Ethnicity

☐ American Indian or Alaska Native

☐ Asian or Pacific Islander American

☐ Black/ African American

☐ Latino, Hispanic, Spanish

☑ White/ Caucasian

☐ Other:

3 Professional training

Education (list degrees): ScB (Brown University), MD (Mount Sinai School of Medicine)

Health care practitioner licenses: WA MD 603 191 64

Professional affiliations: Associate Professor, University of Washington

Board certifications, formal training, or other designations: ABPN, 2009 and re-certification in 2019; Psychiatry Residency and Fellowship , Harvard Medical School

Current position (title and employer): Attending Psychiatrist and Associate Clinical Professor, UW OPC

Current practice type and years in practice: Attending Psychiatrist, Outpatient Clinic (3/2022 -)

Total years as an active practitioner: 15

Location of practice (city): University of Washington, Seattle, WA

1 *Non-binary (X) is an umbrella term used to describe those who do not identify as exclusively male or female. This includes but is not limited to people who identify as genderqueer, gender fluid, agender, or bigender.*

4 Experience

Provide a brief explanation (up to 150 words each) addressing the following:

1) Why you would like to serve on the clinical committee;

I have enjoyed treating treatment-resistant conditions such as depression, bipolar disorder, OCD and trauma across my time in practice. I hope to increase knowledge, access and availability to brain stimulation techniques in Washington state as I have seen the impact therapies such as ECT and TMS can have on patient care and wellbeing.

2) The value of informing health policy decisions with scientific evidence, including any examples incorporating new evidence into your practice;

I have been privileged to be able to participate in IRB-driven research and policy development in all levels of psychiatric care. Serving in academic hospital settings, small community health centers, private practice and in PHP and IOP levels of care has offered a keen view of standards of practice in various settings and allowed me to observev areas in need of innovation. I find supervising and teaching medical students and residents to be the most authentic and enjoyable motivvator when it comes to understanding, adhering to and improving "Best Practice".

3) How your training and experience will inform your role on the committee

I have specialized training in both ECT and TMS and was able to study and learn from neuromodulation experts in New York, Boston and Virginia across my career. I have spent time directing ECT services both locally and on the east coast and founded a neuromodulation service in SE Virginia where we were able to offer TMS clinically and collect data for IRB-approved research endeavors. My experience using both ECT and TMS and working with treatment-resistant patients across the country has offered me a full and in-depth perspective on the impact these illnesses can have on an individual's quality of life and the cost burden TRD can pose on society as a whole.

4) Treating populations that may be underrepresented in clinical trials: women, children, elderly, or people with diverse ethnic and racial backgrounds, including recipients of Medicaid or other social safety net programs?

My fellowship training focused on Women's Mental Health and I went on to study the use of TMS and ECT in pregnancy and postpartum. Having worked in may diverse academic settings, I have had the privilege of learning from and treating patients from a broad swath of SES and cultural backgrounds. Given the marked disparities in treatment options and treatment delivery with underserved populations, ensuring that treatment modalities are well studies and equitably offered to all-comers is central to my values as a physician.

5 Ability to serve

Are you able to participate in all-day meetings, an estimated six times per year? ✔ Yes ☐ No

Are you willing to commit to the responsibilities of a committee member, including:

- Attending meetings prepared for the topics of the day;
- Actively participating in discussions;
- Making decisions based on the evidence presented and the public interest[1]? ✔ Yes ☐ No

Could you, or any relative, benefit financially from the decisions made by the HTCC? ☐ Yes ✔ No

6 References

Provide three professional references:

1.

First name: James
Last name: Lolley
Relationship: Previous colleague
Title: PsyD
Contact email:
Phone number:

2.

First name: Amanda
Last name: Focht
Relationship: Peer
Title: MD, Medical Director, OPC (UW)
Contact email:
Phone number:

3.

First name: Ryan
Last name: Kimmel
Relationship: Peer
Title: MD, Chief of Service, UW
Contact email:
Phone number:

Please return:

✓ Completed application ✓ curriculum vitae ✓ **conflict of interest disclosure**

Submit to send via email to: **shtap@hca.wa.gov**

OR mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

1 *Detailed in Washington Administrative Code (WAC) and committee bylaws*

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Washington State Agency Medical Directors' Group Comments

Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Health Disorders

Gary Franklin, MD, MPH
Medical Director, Washington State Department of Labor and Industries
Research Professor, University of Washington
March 17, 2023

Behavioral Health Disorders

- Over 14 million adults (14.2%) are estimated to have serious mental illness in the past year. [2020 national survey]
- Disease-specific prevalence
  - Depression and Anxiety: 8.1% over age 20 and 15.6% over age 18.
  - OCD: 2-3% of the U.S. population
  - PTSD: 7% (23% in a veteran population)
- Treatment-resistant depression
  - Twice as likely to be hospitalized.
  - Direct medical costs 2-6 times higher compared to treatment-responsive depressive disorder
  - Mean quality of life 25-40% lower than individuals with treated depression.
- Over 47 million U.S. adults (19%) used any commercial tobacco product in 2020.
- Substance use with growing numbers of drug-related deaths.

TMS for Treatment of Selected Behavioral Disorders

- **Major Depressive Disorder (MDD)**
- Obsessive-Compulsive Disorder (OCD)
- Posttraumatic Stress Disorder (PTSD)
- Generalized Anxiety Disorder (GAD)
- Substance Use Disorder (SUD)
- Smoking Cessation

Treatments

- Current treatments for behavioral health disorders
  - Pharmacotherapy
  - Psychotherapy
  - Electroconvulsive therapy (ECT) – for unipolar major depression, bipolar depression or mania
- Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulation technique that has been cleared (all 510(k)) by the FDA for some behavioral health and neurologic conditions:
  - MDD, OCD, smoking cessation, anxiety symptoms in those with depression, and acute and prophylactic treatment of migraine with aura.
- TMS is not currently cleared by the FDA for treating these conditions:
  - GAD, PTSD, and SUD

Transcranial Magnetic Stimulation (TMS)

- TMS is an electromagnetic device that non-invasively delivers a rapidly pulsed magnetic field focally to the cerebral cortex.
- TMS is claimed to activate neurons.
- There are several types of TMS device cleared by the FDA for marketing
  - Repetitive TMS or rTMS (*e.g.,* NeuroStar TMS Therapy System)
  - Theta Burst Stimulation or TBS (*e.g.,* MagVita TMS Therapy System w/Theta Burst Stimulation)
  - deepTMS or dTMS (*e.g.,* Brainsway Deep TMS system)
- Treatment protocols are different

2014 HTCC Review

- Nonpharmacological Treatments for Treatment-resistant Depression (TRD)
  - Repetitive Transcranial Magnetic Stimulation (rTMS) is a covered benefit for Treatment-resistant Depression.
  - The coverage determination (wa.gov)

Topic: Nonpharmacological Treatments for Treatment-resistant Depression
Meeting Date: March 21, 2014
Final Adoption: May 16, 2014

Meeting materials and transcript are available on the HTA website at:
www.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.aspx

Number and Coverage Topic:

20140321A – Nonpharmacological Treatments for Treatment-resistant Depression (TRD)

HTCC Coverage Determination:

Nonpharmacological Treatments for Treatment-resistant Depression are **covered benefits with conditions** consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination:

Limitations of Coverage

Electroconvulsive Therapy is a **covered benefit.**
Repetitive Transcranial Magnetic Stimulation is a **covered benefit.**

Non-Covered Indicators

Deep Brain Stimulation is **not covered.**
Transcranial Direct Current Stimulation is **not covered.**

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TMS for Selected Behavioral Health Disorders: 2023 HTCC re-review

- Why the TMS topic is selected for re-review
  - There is a growing evidence base on TMS, which has led to growing interest in applying TMS to a broader set of conditions, such as:
    - Obsessive-compulsive disorder (OCD);
    - Generalized anxiety disorder (GAD);
    - Post-traumatic stress disorder (PTSD);
    - Tobacco use disorder; and
    - Substance use disorder (SUD)

Agency Medical Director Concerns

Safety = Low/Medium

Efficacy = Medium/High

Cost = Medium/High

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Current State Agency Policies

- TMS for the treatment of treatment-resistant depression:

Agency	Policy
ERB*/UNIFORM MEDICAL PLAN (UMP)	Covered per HTCC determination
MEDICAID	Covered per HTCC determination
LABOR AND INDUSTRIES	Covered per HTCC determination

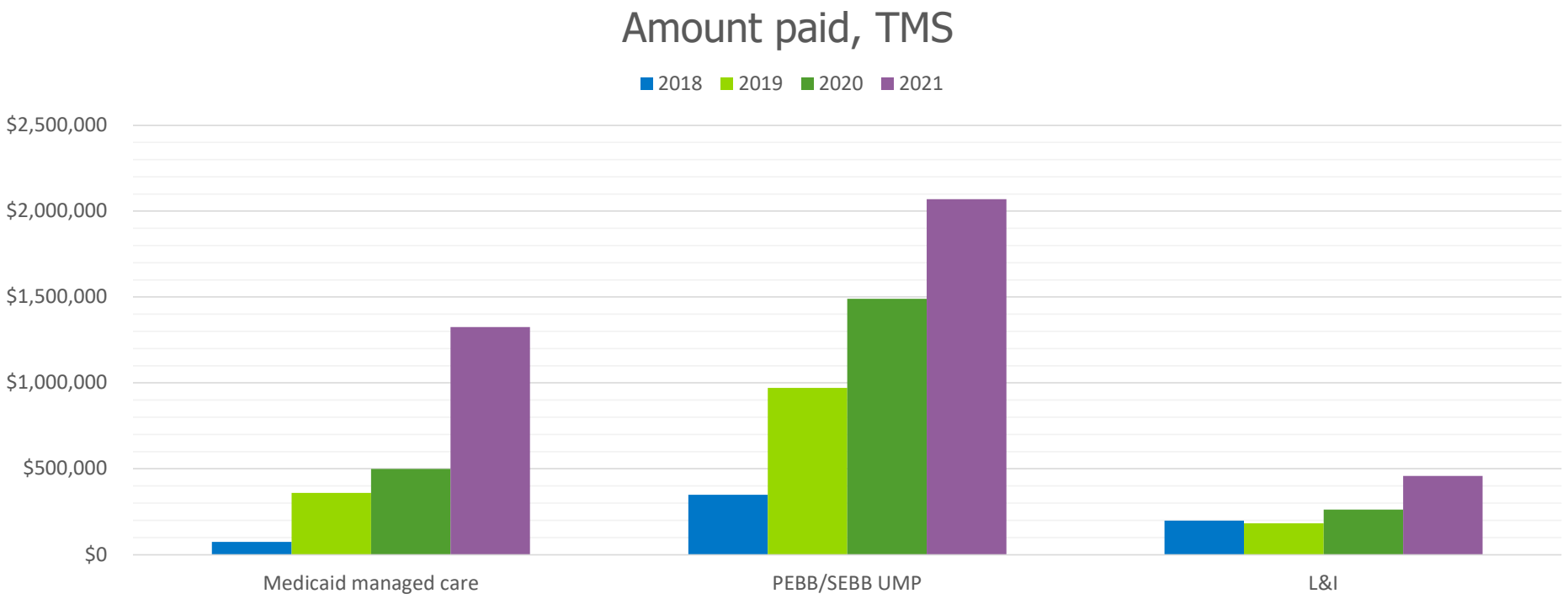
*Employee and Retiree Benefits (ERB), the HCA program encompassing the Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB)

Current State Agency Policies (cont.)

- TMS for the treatment of other behavioral health disorders:

Indication	ERB*/Uniform Medical Plan (UMP)	Medicaid	Labor and Industries
OCD	Investigational	Not Medically Necessary	Investigational
PTSD	Investigational	Not Medically Necessary	Investigational
GAD	Investigational	Not Medically Necessary	Investigational
Smoking cessation	Investigational	Not Medically Necessary	Investigational
SUD	Investigational	Not Medically Necessary	Investigational

Agency Cost 2018-2021



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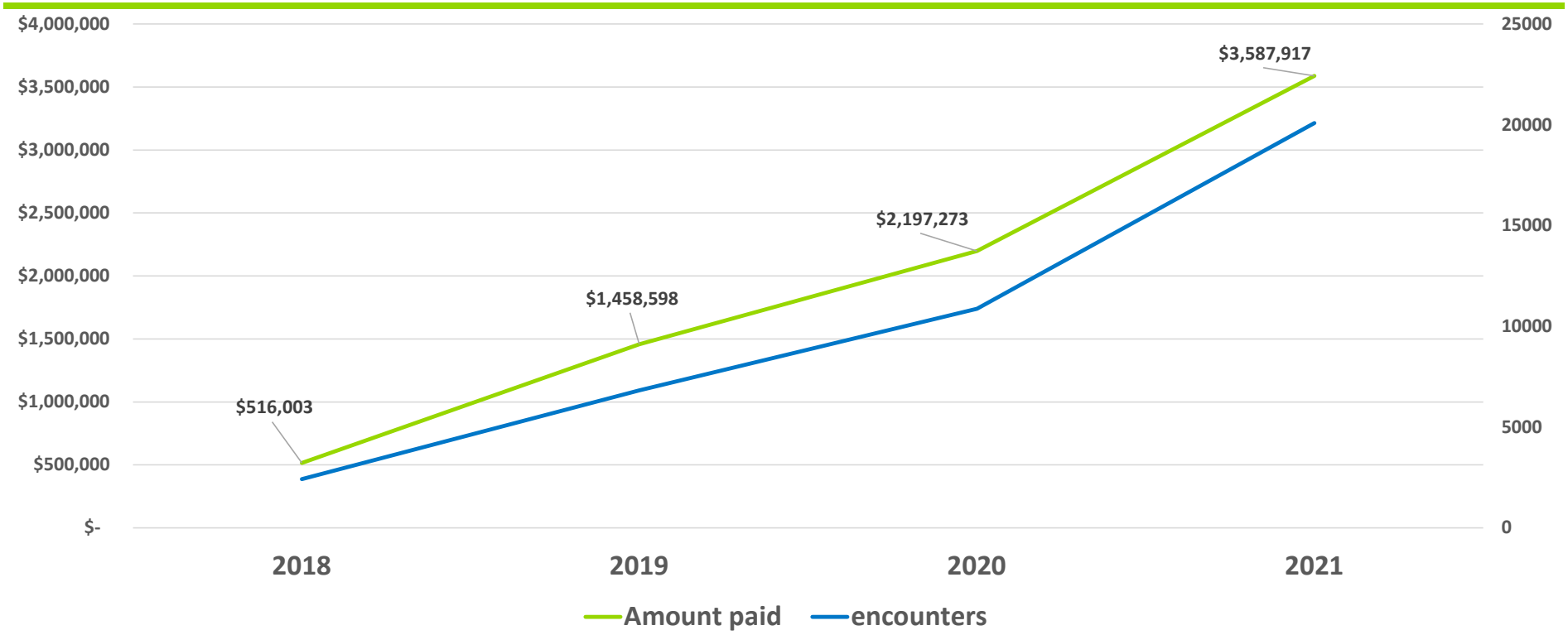
Agency Utilization Combined: Cost and Encounter: 2018-2021



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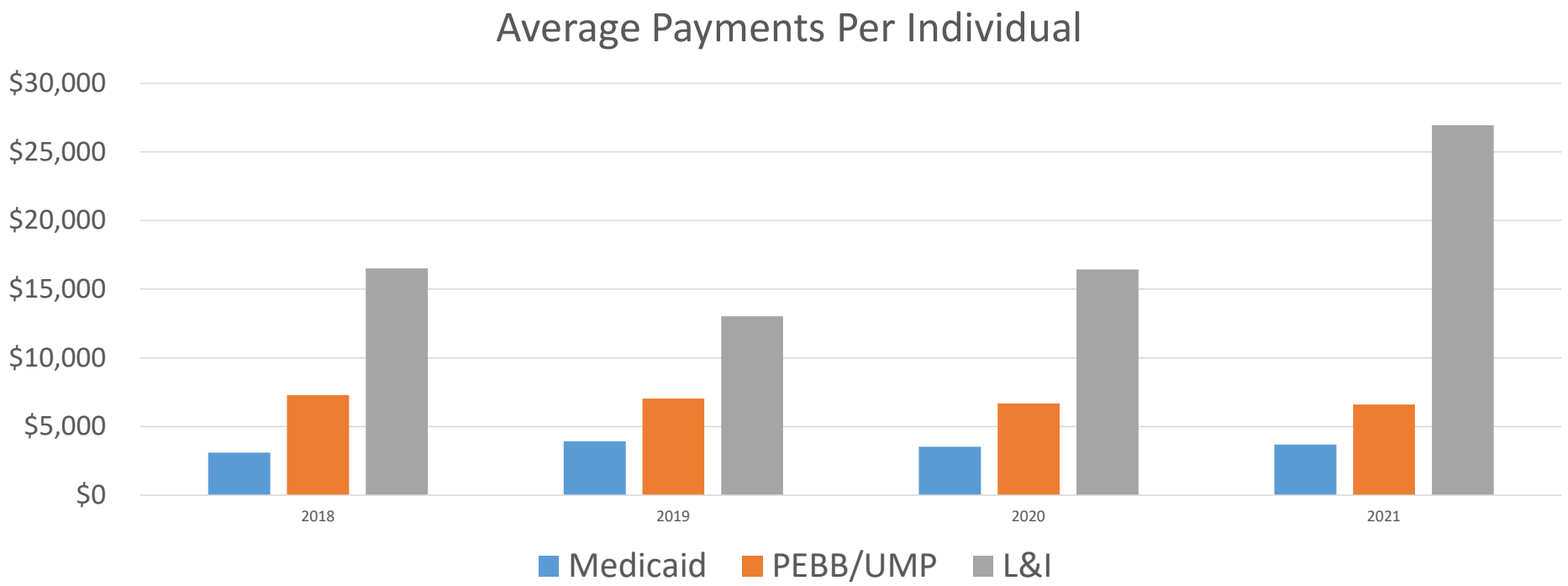
Payment Per Individual: 2018-2021



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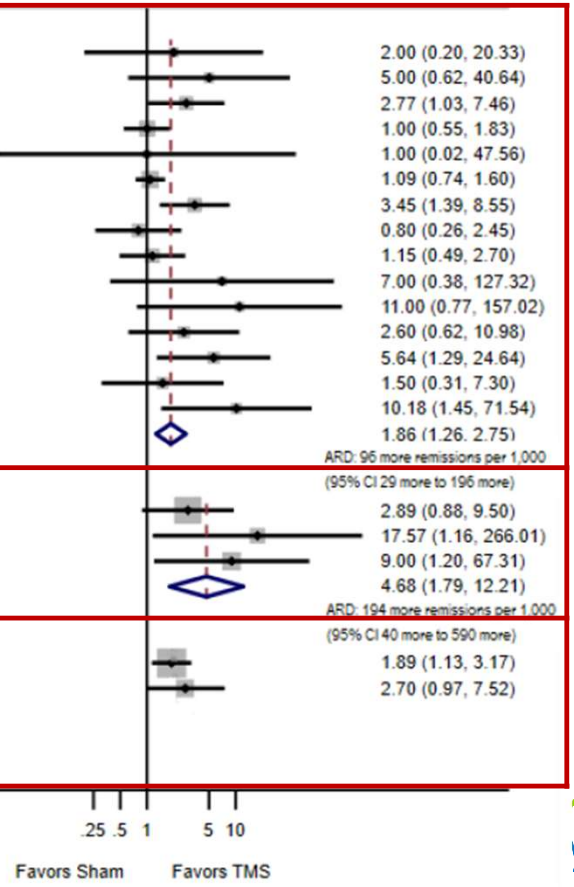
Efficacy: MDD Remission

Type of TMS and Author, Year	TMS Treatment	Remission Definition	Sessions (N)	Follow-up	Intervention Events (N)/Total N (%)	Sham Events (N)/Total N (%)	Risk Ratio (95% CI)
rTMS							
Pallanti, 2010	Bilateral rTMS	HAMD28 ≤8	15	3 w	2/20 (10.0)	1/20 (5.0)	2.00 (0.20, 20.33)
Li, 2020	HF-rTMS	HAMD17 ≤ 7	10	2 w	5/35 (14.3)	1/35 (2.9)	5.00 (0.62, 40.64)
George, 2010	HF-rTMS	HAMD24 ≤ 3[a]	15	3 w	13/92 (14.1)	5/98 (5.1)	2.77 (1.03, 7.46)
Croarkin, 2020	HF-rTMS	NR	30	6 w	14/48 (29.2)	16/55 (29.1)	1.00 (0.55, 1.83)
van Eijndhoven, 2020	HF-rTMS	HAMD17 ≤ 7	20	5 w	0/15 (0)	0/16 (0)	1.00 (0.02, 47.56)
Yesavage, 2018	HF-rTMS	HAMD24 ≤ 10	30	4 to 11 w	33/81 (40.7)	31/83 (37.3)	1.09 (0.74, 1.60)
Rossini, 2005	HF-rTMS	HAMD21 ≤ 8	10	2 w	18/49 (36.7)	5/47 (10.6)	3.45 (1.39, 8.55)
Taylor, 2018	HF-rTMS	MADRS < 10	20	4 w	4/16 (25)	5/16 (31.3)	0.80 (0.26, 2.45)
O'Reardon, 2007	HF-rTMS	HAMD17 < 8	36	4 w	11/155 (7.1)	9/146 (6.2)	1.15 (0.49, 2.70)
Padberg, 2002	HF-rTMS[b]	HAMD < 9	10	2 w	3/20 (15.0)	0/20 (0)	7.00 (0.38, 127.32)
Stern, 2007	HF-rTMS, LF-rTMS[c]	HAMD21 ≤10	10	2 w	4/30 (13.3)	0/45 (0)	11.00 (0.77, 157.02)
Blumberger, 2012	HF-rTMS/Bilateral rTMS	HAMD17 ≤ 10	15 to 30	3 or 6 w	10/48 (20.8)	2/25 (8.0)	2.60 (0.62, 10.98)
Blumberger, 2016	HF-rTMS/Bilateral rTMS	HAMD17 ≤ 7	15 to 30	3 or 6 w	11/80 (13.8)	2/82 (2.4)	5.64 (1.29, 24.64)
Kim, 2019	LF-rTMS	HAMD17 < 8[d]	20	4 w	3/11 (27.3)	2/11 (18.2)	1.50 (0.31, 7.30)
Januel, 2006	LF-rTMS	HAMD17 < 9	16	4 w	7/11 (63.6)	1/16 (6.3)	10.18 (1.45, 71.54)
Subgroup, DL (I^2 = 38.1%, p = 0.067)							1.86 (1.26, 2.75)
							ARD: 96 more remissions per 1,000 (95% CI 29 more to 196 more)
TBS							
Chou, 2020	cTBS	HAMD21 < 8	10	4 w	9/27 (33.3)	3/26 (11.5)	2.89 (0.88, 9.50)
Cole, 2022	iTBS	MADRS ≤ 10	50	1 w	8/14 (57.1)	0/15 (0)	17.57 (1.16, 266.01)
Li, 2020	iTBS	HAMD17 ≤ 7	10	2 w	9/35 (25.7)	1/25 (2.9)	9.00 (1.20, 67.31)
Subgroup, DL (I^2 = 0.0%, p = 0.378)							4.68 (1.79, 12.21)
							ARD: 194 more remissions per 1,000 (95% CI 40 more to 590 more)
dTMS							
Levkovitz, 2015	dTMS	HAMD21 < 10	20	5 w	31/101 (30.7)	18/111 (16.2)	1.89 (1.13, 3.17)
Kaster, 2018	dTMS	HAMD24 ≤ 10[e]	20	4 w	10/25 (40.0)	4/27 (14.8)	2.70 (0.97, 7.52)

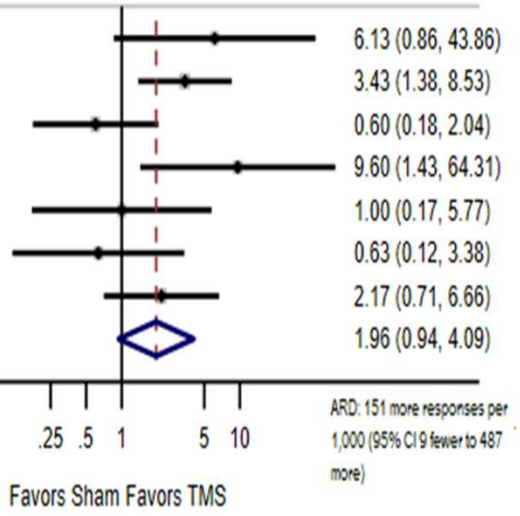


Evidence Considerations: MDD

- Small sample sizes
- Short follow-up times → Durability of treatment effect?
- Varying degree of evidence based on technology (rTMS, TBS, dTMS)
- Different TMS protocols (number of sessions, duration, target locations, etc.)
- 11/15 of rTMS RCTs showed no difference compared to sham.
- Funding sources: 3 fully funded and 9 partially funded by industry, 7 did not report on study sponsorship.
- Risk of bias: 9 trials high, 24 some concerns and 3 low risk of bias.
- Varying definitions of response, remission, and treatment resistance.
- Unclear effect of underlying comorbid psychiatric conditions.
- Few studies including special populations or subgroups.

Evidence: OCD

Author, Year	TMS Treatment	Response Definition	Sessions (N)	Follow-up	Intervention Events (N)/Total N (%)	Sham Events (N)/Total N (%)	Risk Ratio (95% CI)
Carmi, 2018	dTMS	Reduction YBOCS ≥ 30%	25	5 weeks	7/16 (43.8)	1/14 (7.1)	6.13 (0.86, 43.86)
Carmi, 2019	dTMS	Reduction YBOCS ≥ 30%	29	6 weeks	16/42 (38.1)	5/45 (11.1)	3.43 (1.38, 8.53)
Harika-Germaneau, 2019	cTBI	Reduction YBOCS ≥ 25%	30	6 weeks	3/14 (21.4)	5/14 (35.7)	0.60 (0.18, 2.04)
Hawken, 3716	LF-rTMS	Reduction YBOCS ≥ 25%	25	6 weeks	8/10 (80.0)	1/12 (8.3)	9.60 (1.43, 64.31)
Kang, 2009	LF-rTMS	Reduction YBOCS ≥ 25%	10	4 weeks	2/10 (20.0)	2/10 (20.0)	1.00 (0.17, 5.77)
Pelissolo, 2016	LF-rTMS	Reduction YBOCS ≥ 25%	20	4 weeks	2/20 (10.0)	3/19 (15.8)	0.63 (0.12, 3.38)
Seo, 2016	LF-rTMS	Reduction YBOCS ≥ 25%	15	3 weeks	7/14 (50.0)	3/13 (23.1)	2.17 (0.71, 6.66)
Overall, DL (I^2 = 47.1%, p = 0.078)							1.96 (0.94, 4.09)



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Evidence Considerations: OCD

- Small sample sizes
- Short follow-up times
- Outcomes are mostly Rx vs Sham post-hoc
- Some confusion Re treatment resistance
- Bias from industry conflict of interest –e.g., OCD example
- 5/7 of the RCTs showed no difference compared to sham
- Pooled result is not statistically significant

Evidence Considerations: OCD (cont.)

- Carmi, Tendler, et al, 2019
  - Dr. Carmi has received research and travel support from Brainsway. Dr. Tendler serves as the chief medical officer of and has a financial interest in Brainsway, and he has ownership interest in Advanced Mental Health Care, Inc.

Evidence Considerations: Other Behavioral Health Conditions

- PTSD, GAD, Substance abuse disorder, Smoking cessation
- Limited data with **insufficient** to low strength of evidence (SOE) on efficacy and safety.
- Systematic reviews of TMS for GAD, OCD, and PTSD often included study designs that were ineligible for HTA (comparative effectiveness research, open-label studies, uncontrolled studies, sample sizes fewer than 10 per study arm)
- No studies reported cost-effectiveness outcomes.
- General low quality of evidence in studies with various methodology.

Safety

- Long-term safety evidence is lacking
- The quality of evidence on short-term safety is low or very low.
- Adverse events:
  - Common: headache, scalp pain, treatment site discomfort, facial twitching
  - Rare: hearing loss and vasovagal syncope
- Few SAEs were reported for either active or sham TMS
  - Seizure is a rare but serious adverse event. Safety protocols include offering hearing protection and potentially having anti-epileptics and oxygen on hand.

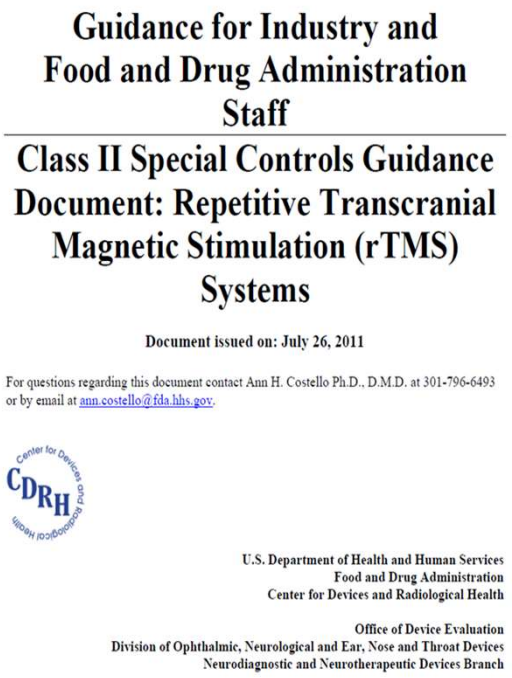
TMS and Seizure Risk

- Risk factors for TMS seizure
  - **"Seizures can occur within safety guidelines, even in patients who present with no known risk factors."** (McClintock et al., J Clin Psychiatry 2018)
  - Focal or generalized encephalopathy, severe head trauma
  - Non-treated epilepsy, family history of epilepsy in first-degree relatives
  - Heavy alcohol use, cocaine use, severe cardiac disease
  - Medications that lower seizure threshold, other epileptogenic drugs
- Risks of a seizure with TMS
  - General: <1/30,000 (Rossi et al. 2009)
  - TBS: 0.02% (Oberman et al. 2011)
  - Figure-8 coil: 3/1000 (Carpenter et al. 2012)
  - Brainsway H1-Coil: 0.087% (Tendler et al. 2018)
- Most seizures occur during or around the time of treatment
- Among seizure incidents, seizure occurred on first exposure to TMS (62%) or within the first three treatment (75%).

Stultz et al., Neuropsychiatric Disease and Treatment 2020

Seizures, Technical Specifications and Treatment Protocols

- Seizure is one of the main risks identified by the FDA associated with the use of TMS systems.
- The treatment protocols cleared by the FDA should be followed strictly to avoid seizures.
- TMS is delivered as a series of magnetic pulses called a pulse train; Some of the stimulation parameters are frequency, MT intensity, train duration, inter-train interval, and number of trains per session.
- Motor Threshold(MT) intensity: The motor threshold level is the minimum stimulator setting that induces an observable motor response by the patient in 50% of the applied pulses, usually as observed by movement of the thumb. The MT level is used as a reference point for setting TMS treatment intensity, usually expressed as a percent multiple of the MT level, e.g. 120% MT.
- Pulse train durations that are above certain limits increase the risk of seizures. A maximum safe train duration is determined with magnetic pulse frequency and MT intensity.



Guidance for Industry and Food and Drug Administration Staff

Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems

Document issued on: July 26, 2011

For questions regarding this document contact Ann H. Costello Ph.D., D.M.D. at 301-796-6493 or by email at ann.costello@fda.hhs.gov.

CDRH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of Device Evaluation
Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices
Neurodiagnostic and Neurotherapeutic Devices Branch

Washington State Health Care Authority

Costs/Cost-effectiveness

- Two studies based on U.S. data on MDD and one study based on U.S. data on OCD.
- All three studies were funded by TMS companies.
- **Very limited data** with low to insufficient strength of evidence (SOE).

Other Payers' Policies

Table 25. Select Overview of Payer Coverage Policies for TMS

Condition	Medicare[153]	Cigna[154]	Kaiser Permanente[155.1 56]	Premera Blue Cross[157]	Regence BlueShield[158]	UnitedHealth[159]
Depression	LCD only	✓	✓	✓	✓	✓
OCD	X	✓	X	✓	X	X
Smoking cessation	X	X	X	X	X	X
PTSD	X	X	X	X	X	X
GAD	X	X	X	X	X	X
Substance abuse	X	X	X	X	X	X

Notes: ✓ = covered; X = not covered; — = no policy identified.

Abbreviations: GAD = generalized anxiety disorder; LCD = local coverage determinations through Medicare contractors; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; TMS = transcranial magnetic stimulation

Guidelines on the Use of TMS

- Five clinical practice guidelines on use of TMS for depression ranged from general to specific about when and how to use TMS for treatment.
  - 2/5 guidelines specifically recommends **Not** using TMS as a first-line treatment for initial major depressive episodes without adequate pharmacotherapy trials.
- Three clinical practice guidelines on use of TMS for OCD made similar general statements.
  - NICE 2020: Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Few guidelines on use of TMS were found for GAD, PTSD, and SUD.
- No guidelines were found for smoking cessation.

Agency Medical Directors Recommendations

- TMS for the treatment of confirmed Major Depression Disorder (MDD) in adult patients (age 18 or older) is a covered benefit with conditions:
  - Initial treatment (up to 30 treatment sessions) is covered when ALL of the following criteria are met:
    - Failure of at least 2 different antidepressant medications from at least 2 separate classes at maximum tolerated dose for 4-12 weeks in separate trials; and
    - Failure of an adequate trial of evidence-based psychotherapy in the treatment of MDD; and
    - TMS is administered according to an FDA-cleared protocol.

Agency Medical Directors Recommendations (cont.)

- TMS for the treatment of confirmed Major Depression Disorder (MDD) in adult patients (age 18 or older) is a covered benefit with conditions:
  - Repeat TMS treatment (up to 30 treatment sessions) for a recurrence or an acute relapse of MDD is covered when ALL of the following criteria are met:
    - Patient had significant improvement in depressive symptoms after initial course of TMS (> a 50% improvement substantiated with one or more standardized rating scales for depression); and
    - The improvement by the initial course has been maintained for at least 3 months.

No evidence or precedent for number of courses.

Agency Medical Directors Recommendations (cont.)

- TMS is not covered for the treatment of other behavioral health disorders, including:
  - Obsessive-compulsive disorder (OCD);
  - Generalized anxiety disorder (GAD);
  - Post-traumatic stress disorder (PTSD);
  - Tobacco use disorder; and
  - Substance use disorder (SUD)

Questions?

More Information:

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Washington State Health Care Authority

Washington State Health Care Authority

Transcranial magnetic stimulation for selected conditions

Order of scheduled presentations:

No scheduled comments

Day of comments:

	Name
1	
2	
3	
4	
5	
6	

Transcranial Magnetic Stimulation for Selected Behavioral Health Conditions

Health Technology Assessment

Washington State Health Care Authority

Contributors:

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Clinical Advisor: Bradley Gaynes, MD, MPH
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Presented by:

Shivani Reddy, MD, MSc

March 17, 2023
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Overview of Presentation

- Background and policy context
- Methods and search results
- Summary findings and conclusions
- Questions

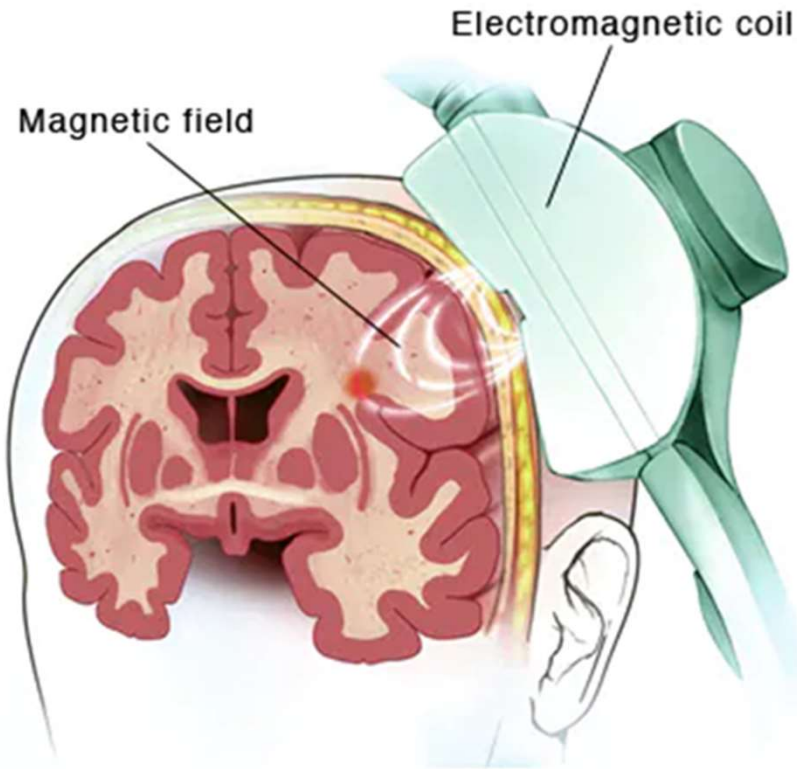
Background

Background: Transcranial Magnetic Stimulation

- Neuromodulation therapy
  - Generally not a first-line therapy
- Administered as an outpatient, does not require sedation
- Sessions last 20 to 40 minutes
- A typical course for depression may include 5 sessions per week for 4 to 6 weeks
- Patients may experience a tapping sensation and clicking sounds
- Common side effects: headache, scalp pain

Source: https://mycloudtms.com/tms-machine/

Background: TMS Technology



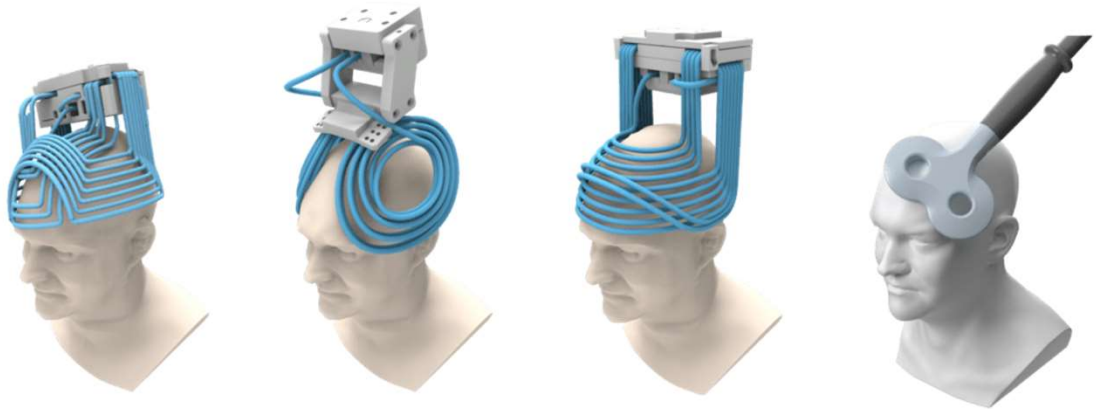
- TMS wand consisting of coiled wire; electric current placed through the wire creates a focal magnetic field that is delivered as ‘pulses’
- Magnetic field penetrates the skull and induces electrical activity in neurons and neural networks.

Background: TMS Technology

Treatment parameters include:

- Wand/coil type
- Stimulation site
- Frequency (magnetic pulses/second, Hz)
- Intensity (% resting motor threshold)
- Number pulses per session
- Treatments per week
- Total duration of treatment

Protocols for optimal efficacy are unknown and under ongoing study



H1-Coil for Major Depressive Disorder (MDD)

H7-Coil for Obsessive-Compulsive Disorder (OCD)

H4-Coil for Smoking Cessation

Traditional TMS Coil for Major Depressive Disorder (MDD)

Background: TMS Technology

- Types of TMS most typically found in this review and in clinical practice
  - Repetitive TMS (rTMS)
  - Deep TMS (dTMS)
  - Theta-burst Stimulation (TBS)

Background: Regulatory approvals

- TMS first cleared by FDA in 2008 for treatment resistant depression
- Currently 8 manufacturers with 510K clearance for one or more of the following conditions:
  - Depression
  - Obsessive-compulsive disorder
  - Smoking cessation
  - Migraine with aura (not within the scope of HTA)
- Indications include individuals who
  - have failed at least one prior medication (Depression)
  - require adjunctive treatment (Obsessive-compulsive disorder)
  - short-term aid (Smoking cessation)

Clinical Practice Guidelines (CPGs)

Among considered conditions, TMS is most often included in CPGs for Depression

National Network of Depression Centers and the American Psychiatric Association Consensus Recommendations (2018)

- The expert opinion is that rTMS is appropriate as a treatment in patients with MDD even the patient is medication-resistant or has significant comorbid anxiety.

Canadian Network for Mood and Anxiety Treatments (2016)

- rTMS is a first-line recommendation for patients with MDD who have failed at least 1 antidepressant.

National Institute of Health and Care Excellence (2015)

- rTMS shows no major safety concerns; evidence on its efficacy in the short term is adequate, although the clinical response is variable.
- Clinicians should make sure that patients understand the possibility the procedure may not give them benefit.

Clinical Practice Guidelines

Guidelines for Obsessive-compulsive disorder, Generalized anxiety disorder, and Posttraumatic stress disorder – infrequent mention of TMS

- ***NICE (2020):*** Evidence on the safety of TMS for OCD raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- ***Canadian Clinical Practice Guideline for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders (2014)***: Biologic therapies, including rTMS, may be useful for some patients; however, more data are needed.

There was no mention of TMS in specialty-specific professional organizations for:

- Smoking cessation
- Substance Abuse

Policy Context

- The State of Washington Health Care Authority chose TMS for selected behavioral health conditions for an HTA because of medium concerns of safety and high concerns for efficacy and cost.
- Selected behavioral health conditions include:
  - Generalized Anxiety Disorder (GAD)
  - Obsessive-compulsive disorder (OCD)
  - Major depressive disorder (MDD)
  - Posttraumatic stress disorder (PTSD)
  - Smoking cessation
  - Substance use disorder (SUD)

Methods

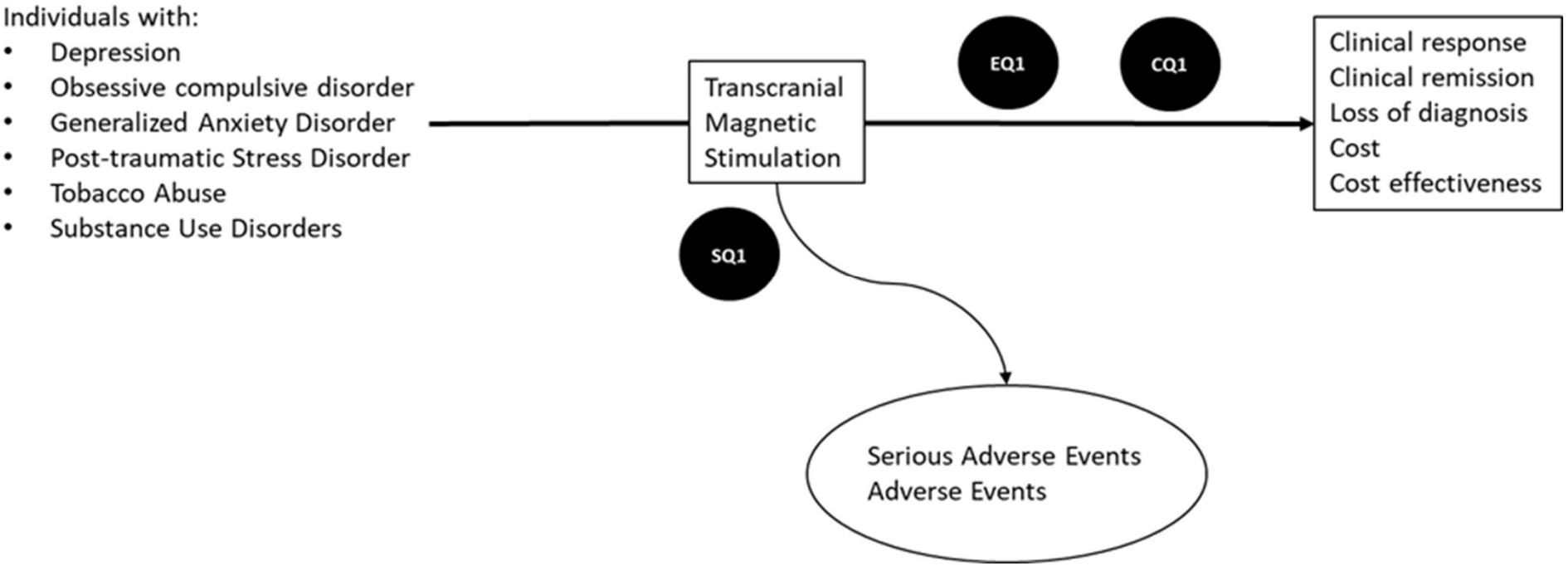
Key Questions

- **Efficacy Question (EQ 1).** What is the efficacy of transcranial magnetic stimulation for the treatment of selected behavioral disorders?

- **Safety Question (SQ 1).** What are the harms associated with transcranial magnetic stimulation for the treatment of selected behavioral disorders?

- **Cost Question (CQ 1).** What are the costs and cost-effectiveness of transcranial magnetic stimulation for the treatment of selected behavioral disorders?

Analytic Framework



Abbreviations: CQ = cost question; EQ = efficacy question; SQ = safety question

PICOTS

	Include	Exclude
Population	Adults and children; diagnosis of MDD, OCD, GAD, PTSD, Tobacco Use or Substance Use Disorder	• Animals • Other mental health or neurologic conditions; populations including a mix of eligible and ineligible conditions without results stratified by population of interest
Intervention	• Repetitive TMS • Deep TMS • Theta Burst Stimulation (TBS) • With or without concurrent pharmaco- and/or psychotherapy	• Other non-invasive or invasive neuromodulation therapies • Protocols containing only one delivery session
Comparator	Sham TMS with or without concurrent pharmaco- and/or psychotherapy	• No comparator • Active comparisons to usual care, or wait-list control • Active comparisons between TMS protocols

Abbreviations: GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; TMS = transcranial magnetic stimulation

PICOTS, cont.

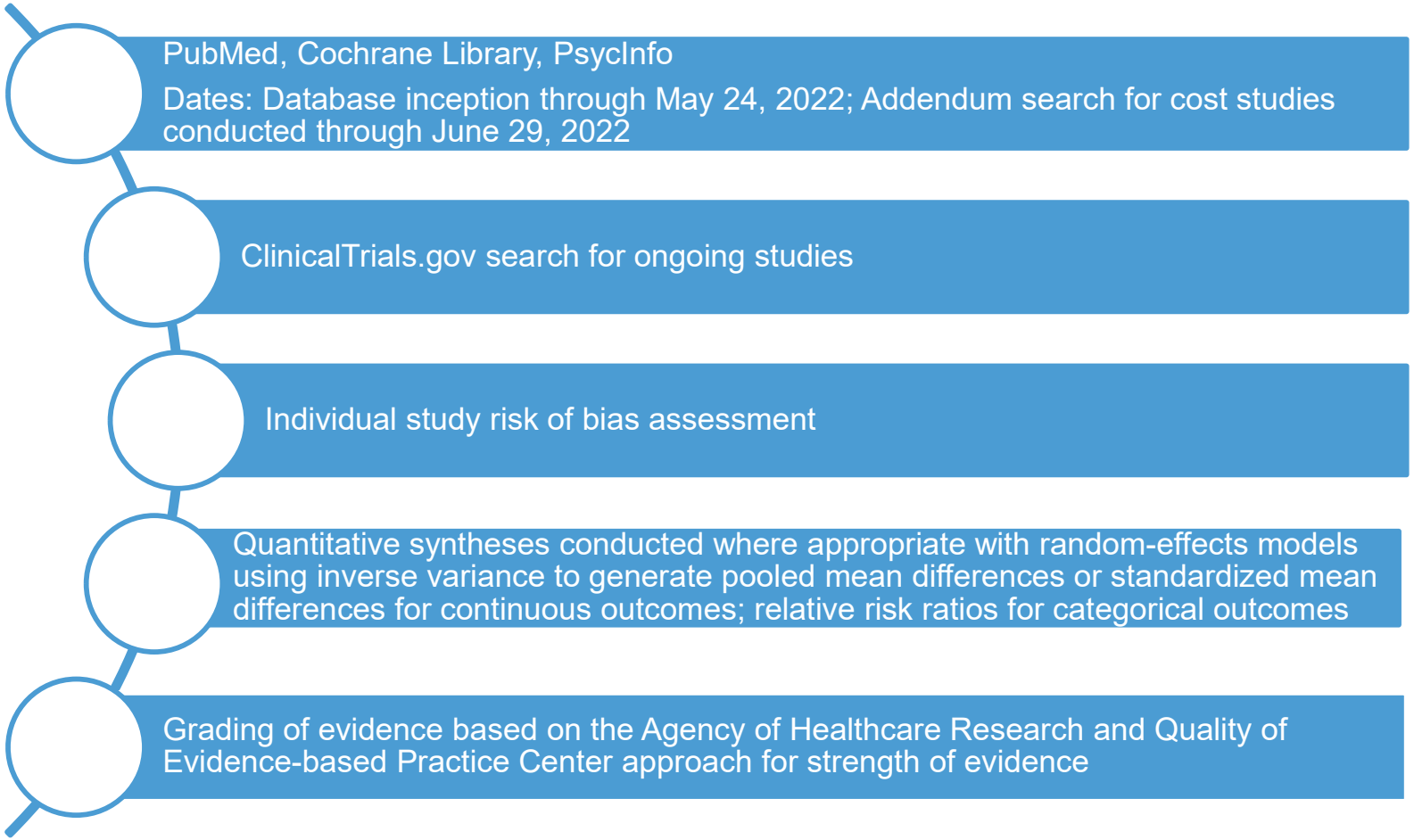
	Include	Exclude
Outcomes	Clinical response, remission, loss of diagnosis, AE, SAE, specific AEs (e.g., seizures), costs, cost-effectiveness	Non-validated measures of clinical response, remission, loss of diagnosis; imaging outcomes
Study Design	*EQ and SQ:* RCTs, non-randomized controlled trials, crossover trials *CQ:* cost-effectiveness, cost-utility, cost-benefit analyses performed from the societal or payor perspective	Other study designs, editorials, narrative reviews; systematic reviews were used to identify primary research studies
Setting	Very high development on UN Human Development Index	Other than very high development
Other	Studies published in English	Studies < 10 participants; studies published in non- English languages

Abbreviations: AE = adverse events; CQ = cost question; EQ = efficacy question; SAE = serious adverse events; SQ = safety question

Validated Measures Reported by Included Studies

	Instrument Name	Abbreviation
Depression	Beck Depression Inventory	BDI
	Hamilton Rating Scale for Depression (17 to 24 items)	HAMD
	Montgomery–Åsberg Depression Rating Scale	MADRS
Non-Depression Conditions	Clinician Administered PTSD Scale	CAPS
	Fagerstrom Test For Nicotine Dependence	FTND
	Hamilton Anxiety Rating Scale	HARS
	Yale–Brown Obsessive-Compulsive Scale	Y-BOCS
Global Measures	Clinical Global Impression Scale-Improvement	CGI-I
	Clinical Global Impression Scale-Severity	CGI-S

Search and Assessment Methods

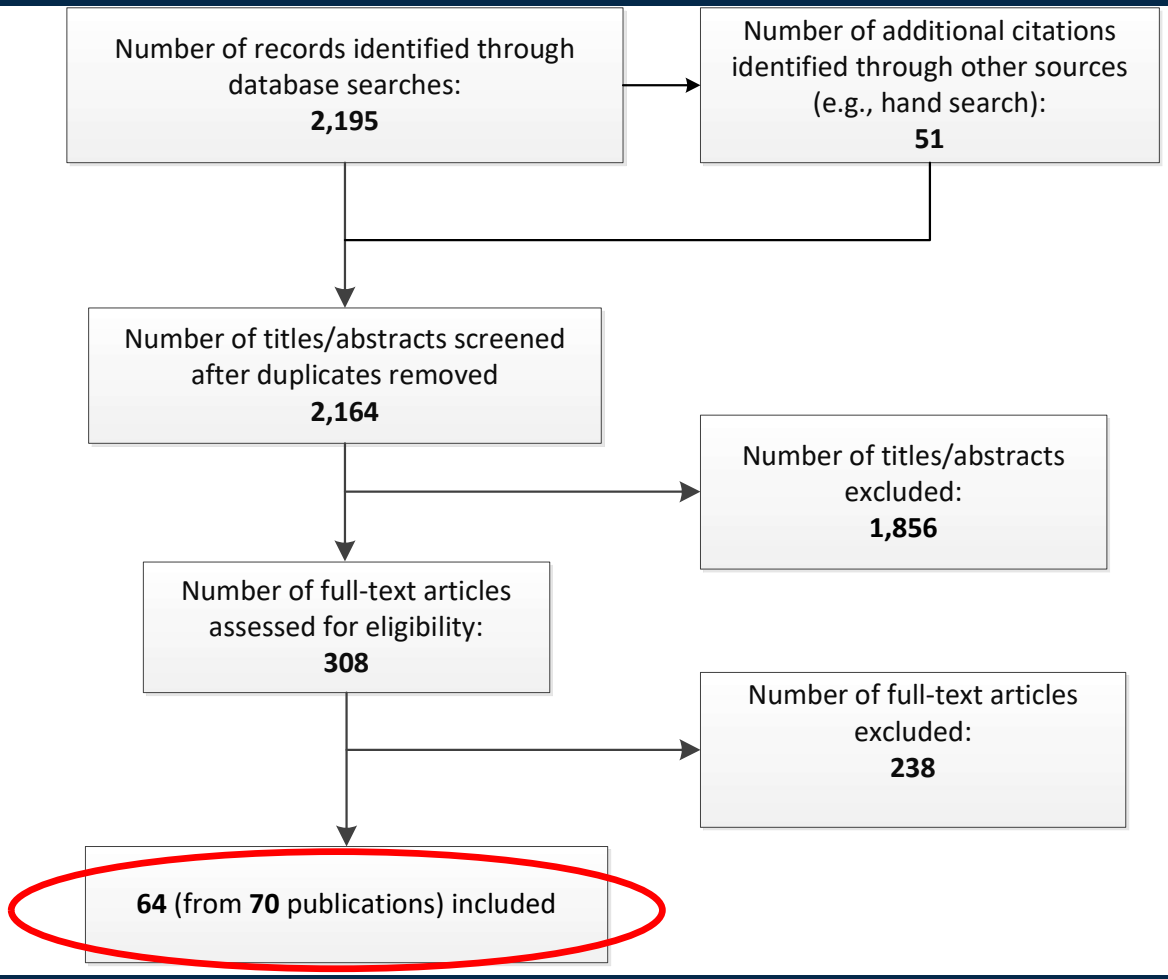


AHRQ Strength of Evidence

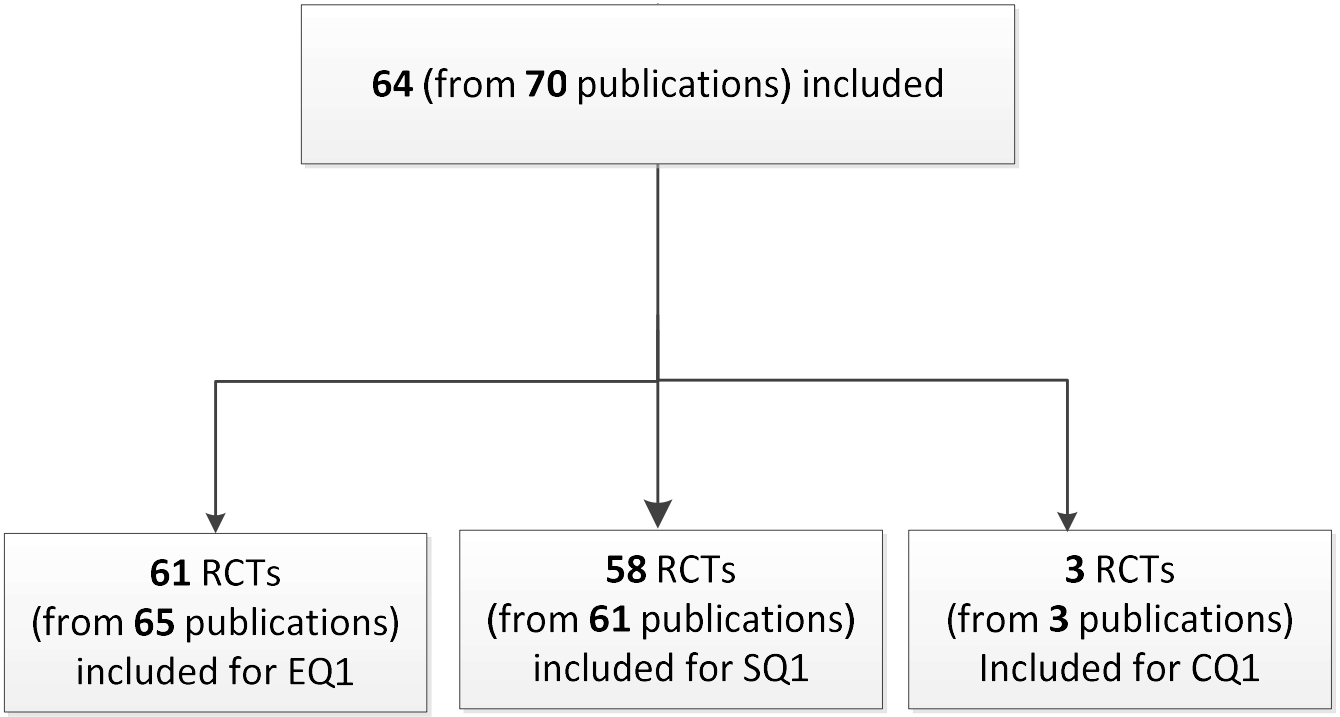
Strength of Evidence	**Outcomes assessed:** remission, response, disease-specific and non-disease-specific continuous outcomes, safety, and cost.
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.** No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Summary of Findings

Summary of Search Yield



Summary of Search Yield



Summary of Search Yield

Condition	EQ1	SQ1	CQ1
GAD	2	2	0
OCD	9	8	1
MDD	36	35	2
PTSD	4	3	0
Smoking	5	5	0
SUD	6	6	0

Topline Summary

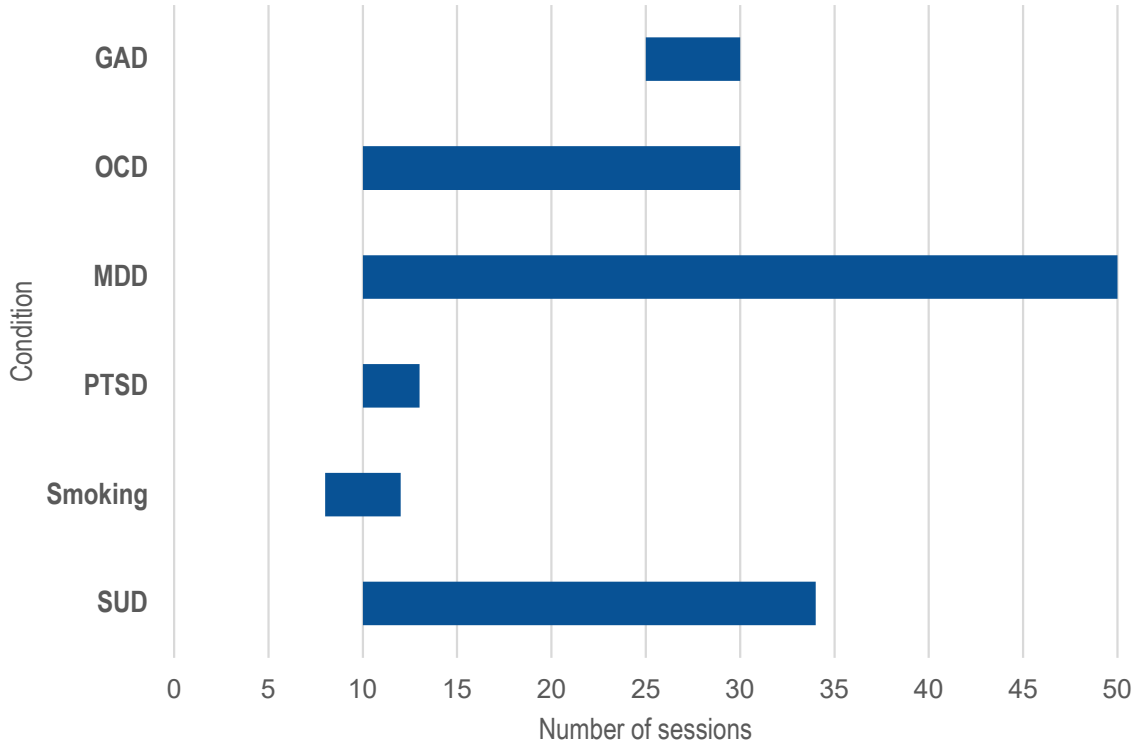
- TMS has moderate to high SOE for benefit in MDD at posttreatment
- TMS has low SOE for benefit in OCD at posttreatment
- Evidence for benefit for GAD, PTSD, smoking cessation, and SUD ranges from insufficient to low for benefit
- For safety outcomes, generally there were fewer AEs for sham TMS; few SAEs were reported for either active or sham TMS.
- Evidence is lacking with respect to
  - cost-effectiveness outcomes
  - efficacy of TMS at longer follow-up assessment timepoints

Populations

Condition	Disease Severity*	Treatment-resistant	Treatment-naive	Both TR and TN	TR not specified
GAD	Moderate-severe				2
OCD	Very severe	8			1
MDD	Severe	25	1	3	7
PTSD	Moderate-severe	1		1	2
Smoking	Variable reporting	1			4
SUD	Variable reporting			1	5

* Disease severity based on validated clinical severity score among majority of studies for that condition

TMS Intervention Protocols



- In general, 1 session/day during working week, 4-6 weeks of treatment
- 5 studies evaluated ≥ 1 session / day, 1-3 weeks of treatment

TMS Intervention Protocols

Study	Condition	Number sessions per day	Duration Treatment
Meek et al, 2021	OCD	2	2 week
Cole et al. 2022 (SAINT protocol)	MDD	10	1 week
Duprat et al, 2016	MDD	5	1 week
Theleritis et al, 2017	MDD	2	3 weeks
Martinotti et al, 2022	SUD	2	2 weeks

Findings: Generalized Anxiety Disorder

Study Characteristics: Generalized Anxiety Disorder

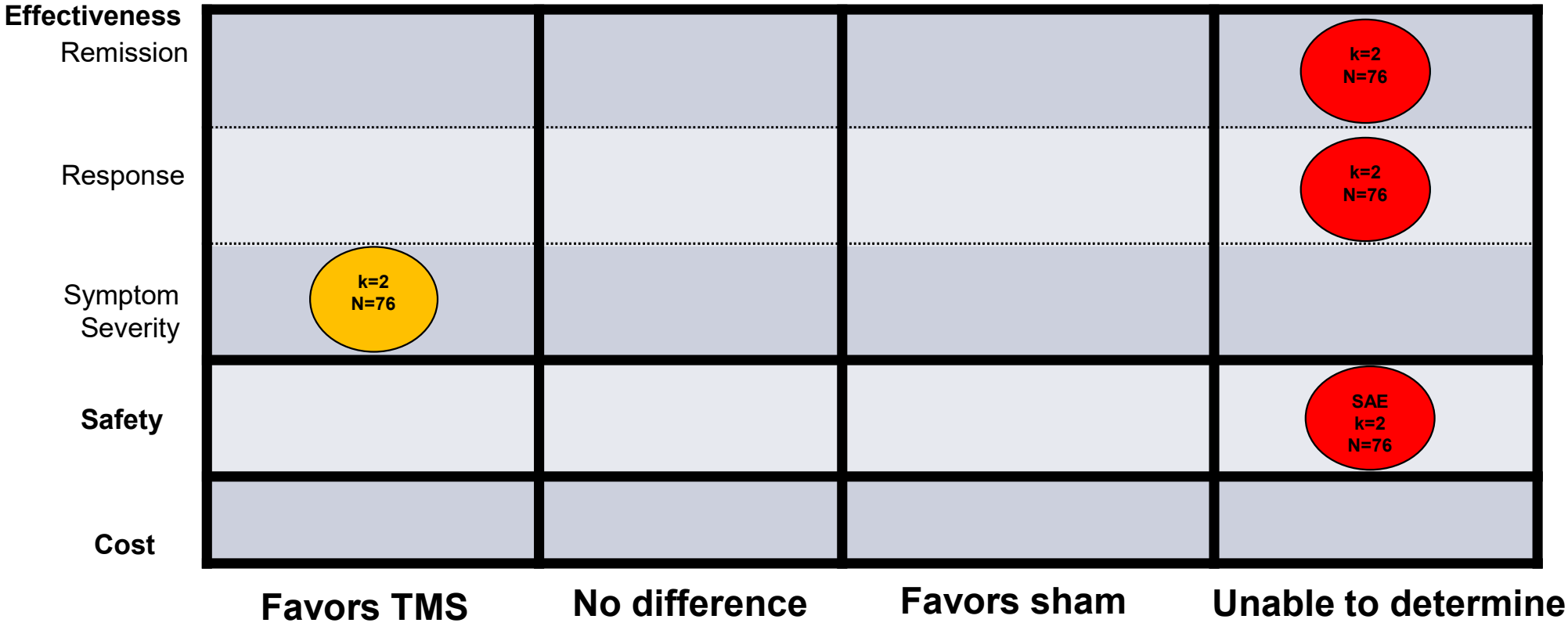
2 RCTs

◆ 2008 to 2014 ◆ N range 26-50 ◆ Treatment Duration: 6 weeks ◆ Follow-up: 12 weeks

1 U.S.	1 in other countries
1 some risk of bias	1 high risk of bias
1 partial industry support	1 NR
2 rTMS	
1 medication per usual treatment	1 medication and psychotherapy per usual treatment

Abbreviations: N = number of participants; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Evidence Map: GAD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

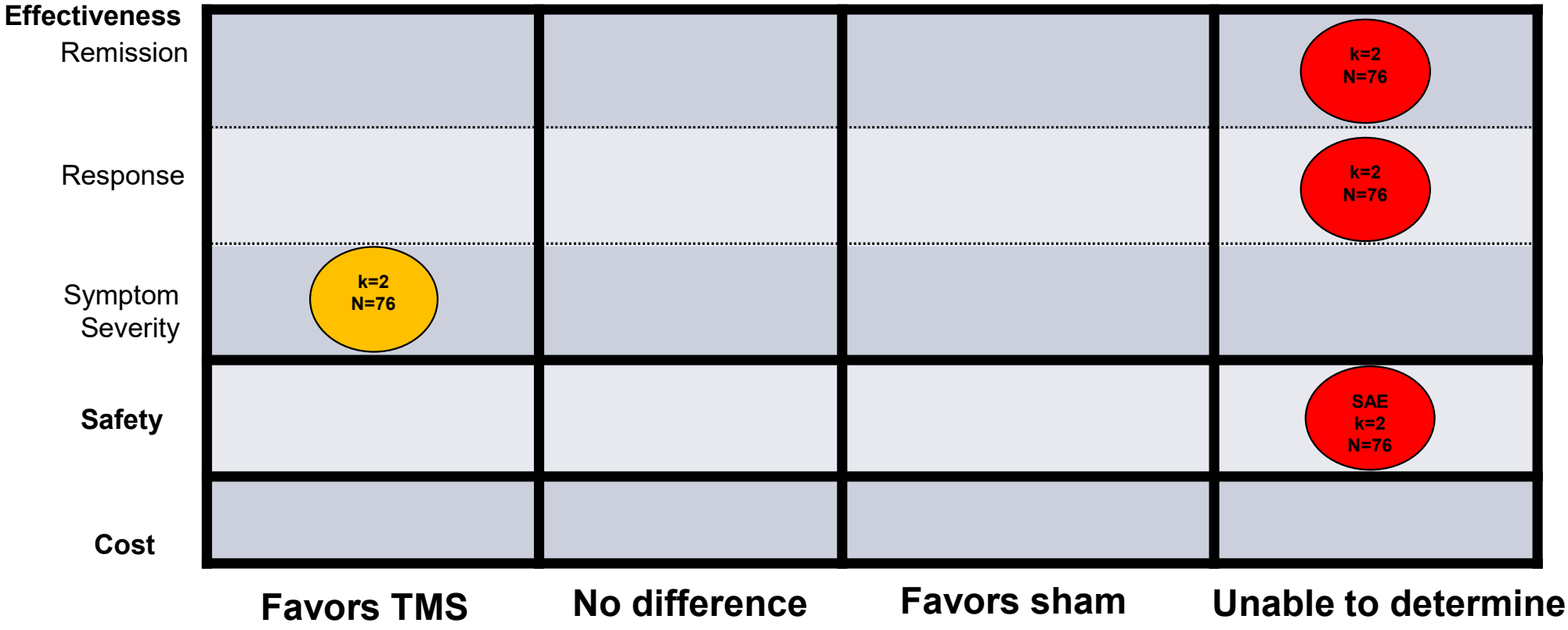
GAD Results: Benefits

- Remission and response
  - Studies favored TMS for remission and response for one of two timepoints, though results were not statistically significant.
  - SOE downgraded for imprecision (x2) and study limitations
- Symptoms severity
  - Both studies favored TMS for reduction in symptom severity using the Hamilton Anxiety Rating Scale at various timepoints
  - SOE downgraded for imprecision and study limitations

GAD Results: Harms

- Any Adverse Events
  - None reported
- Any Serious Adverse Events
  - Both studies reported 1 SAE in the TMS group only
  - 1 study reported generalized tonic-clonic seizure
  - 1 study reported chest pain, which was determined to be unrelated to the study intervention.
- Most common specific AE reported: facial twitching

Evidence Map: GAD



Legend

AHRQ Strength of Evidence

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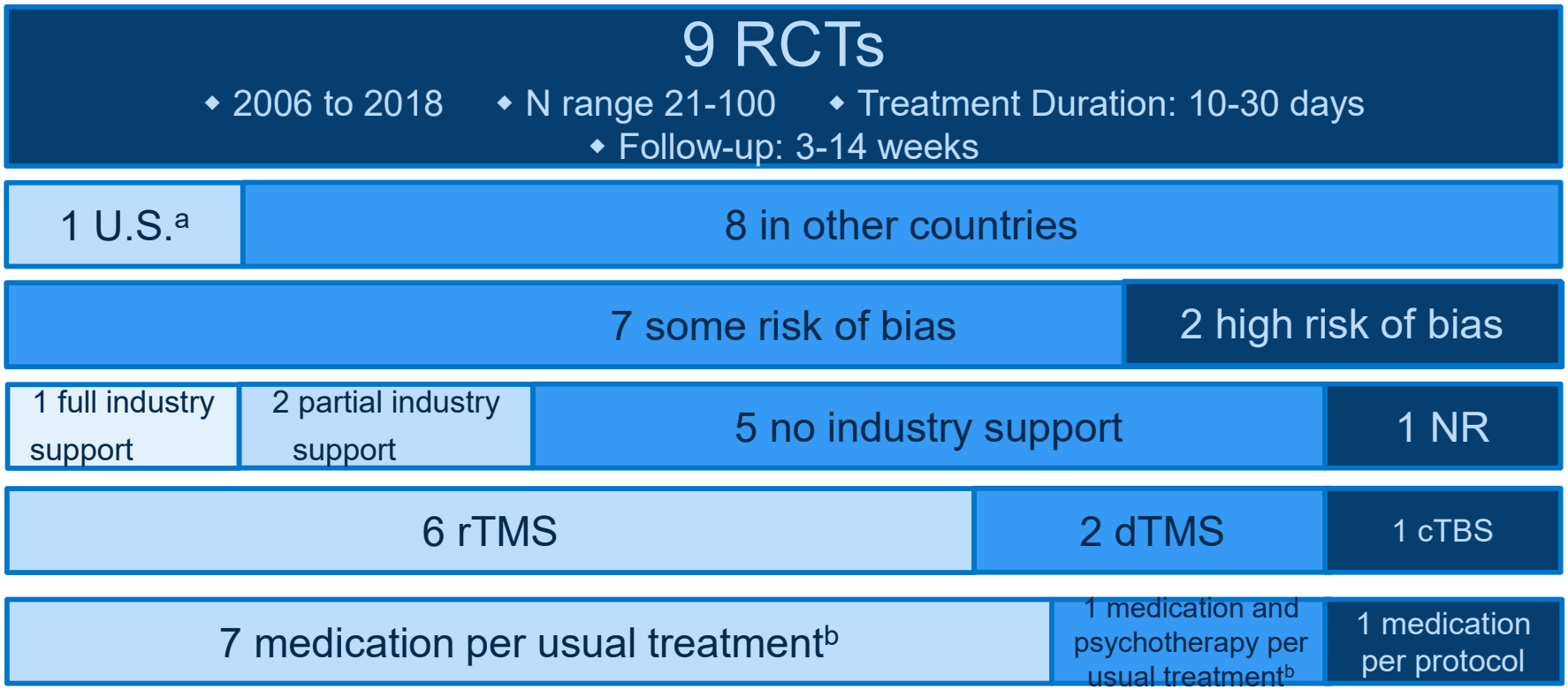
Findings: Obsessive-Compulsive Disorder

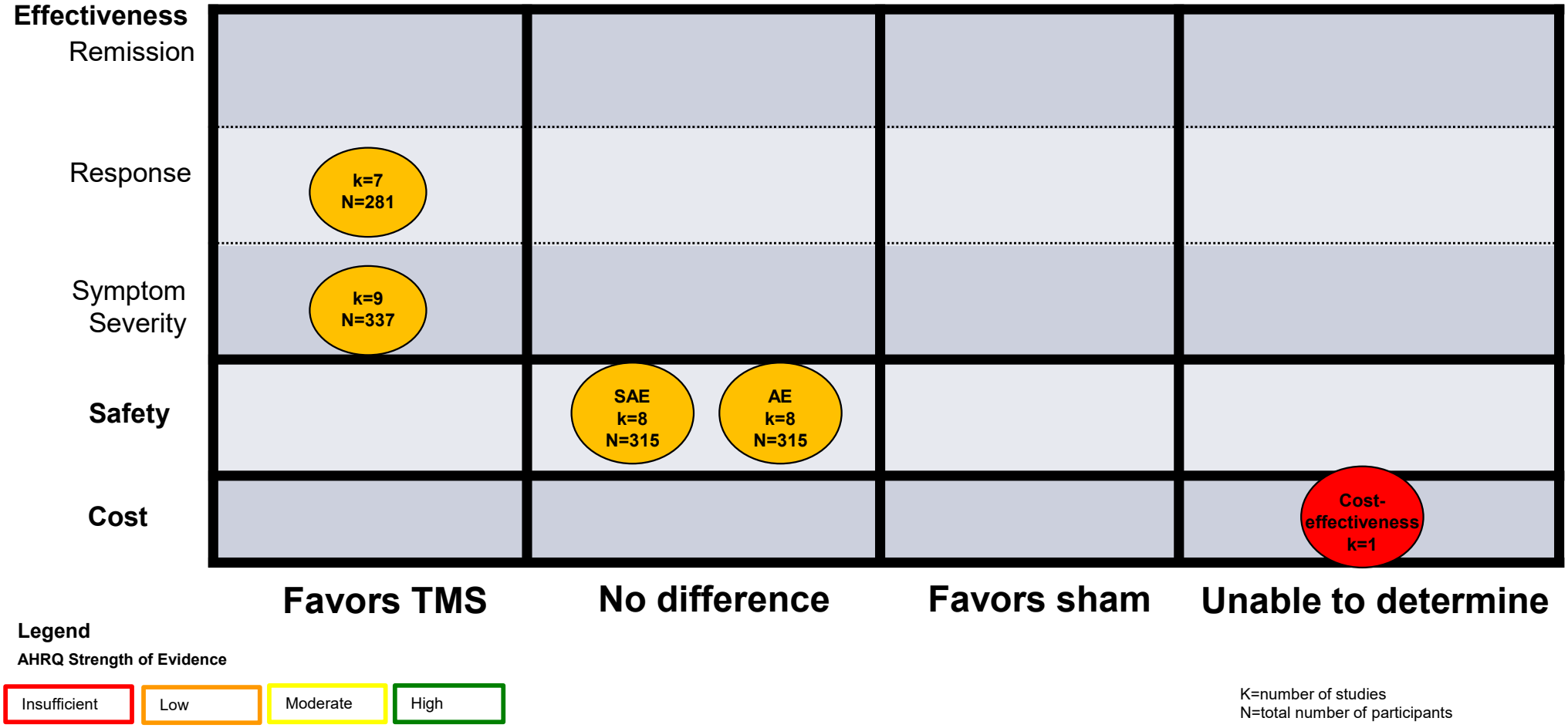
Study Characteristics: Obsessive-Compulsive Disorder



Abbreviations: cTBS = continuous theta burst stimulation**;** dTMS = deep transcranial magnetic stimulation; N = number of participants; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

[a]multi-country study; [b]one study in this group also included exposure therapy

Evidence Map: OCD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

OCD Results: Benefits

- Remission
  - No studies
- Response
  - Defined as decrease in YBOCS ≥ 25%
  - Pooled RR 1.96 (95% CI, 0.94 to 4.09)
  - SOE downgraded for imprecision and study limitations
- Symptom severity
  - 5 of 9 studies reported symptom severity improvements in TMS vs. sham (statistically significant in 4 of 5)
  - SOE downgraded for imprecision and study limitations

OCD Results: Response

Author, Year	TMS Treatment	Response Definition	Sessions (N)	Follow-up	Intervention Events (N)/Total N (%)	Sham Events (N)/Total N (%)	Risk Ratio (95% CI)
Carmi, 2018	dTMS	Reduction YBOCS ≥ 30%	25	5 weeks	7/16 (43.8)	1/14 (7.1)	6.13 (0.86, 43.86)
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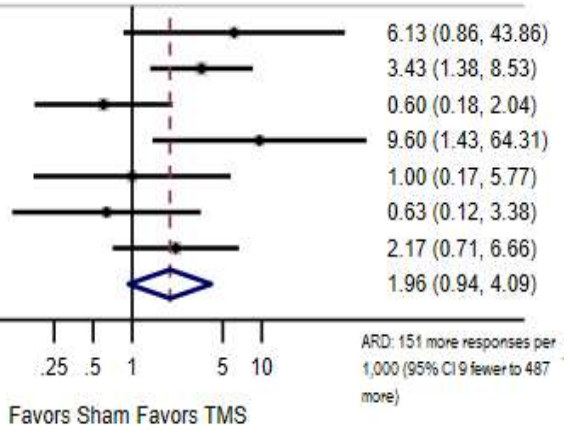
Seo, 2016	LF-rTMS	Reduction YBOCS ≥ 25%	15	3 weeks	7/14 (50.0)	3/13 (23.1)	2.17 (0.71, 6.66)
Overall, DL (I^2 = 47.1%, p = 0.078)							1.96 (0.94, 4.09)



Pooled Risk Ratio: 1.96 (95% CI 0.94 to 4.09)

ARR: 151 more responses to active treatment compared to sham per 1000 individuals treated (95% CI 9 fewer to 487 more)

OCD Results: Harms

- Any Adverse Events
  - Only 2 studies reported overall AEs between groups
  - 1 study: 73% (TMS) vs. 69% (sham); P=0.639
  - 1 study: 7% (TMS) vs. 14% (sham) in other study
- Serious Adverse Events
  - All but 1 study reported 0 events across both groups. Exception was 1 study with 1 participant with suicidal ideation before treatment.
- Specific Harms
  - frequently reported include headache and localized scalp discomfort
- SOE downgraded for imprecision and study limitations

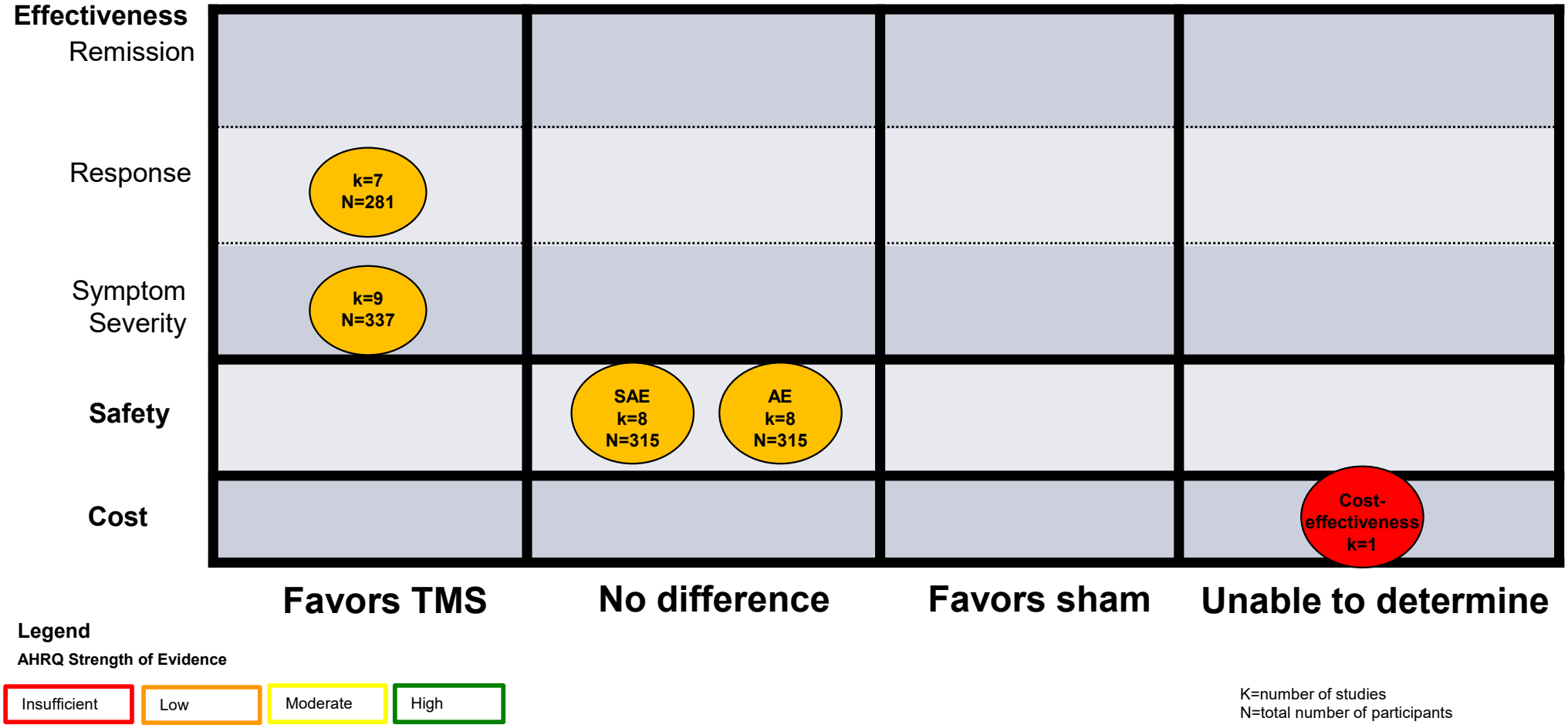
OCD Results: Special Populations

- Two studies reported results by subgroups of age or sex.
  - In 1 study there was no significant difference in treatment effect by age.
  - In 1 study, male individuals with OCD were more likely to be treatment responders than female individuals with OCD ($P<0.05$)

OCD Results: Cost-effectiveness

- One study based on U.S. data reported cost-effectiveness outcomes
- Compared to monotherapy with antidepressant medication, dTMS costs more (incremental cost $6,425) but was more effective (marginal reduction in Y-BOCS score of 3.9 points) for an incremental cost-effectiveness ratio (ICER) of $1,647 per unit reduction in Y-BOCS.
- A similar ratio was observed when compared to treatment with a combination of antidepressant and antipsychotic medication.

Evidence Map: OCD



Legend

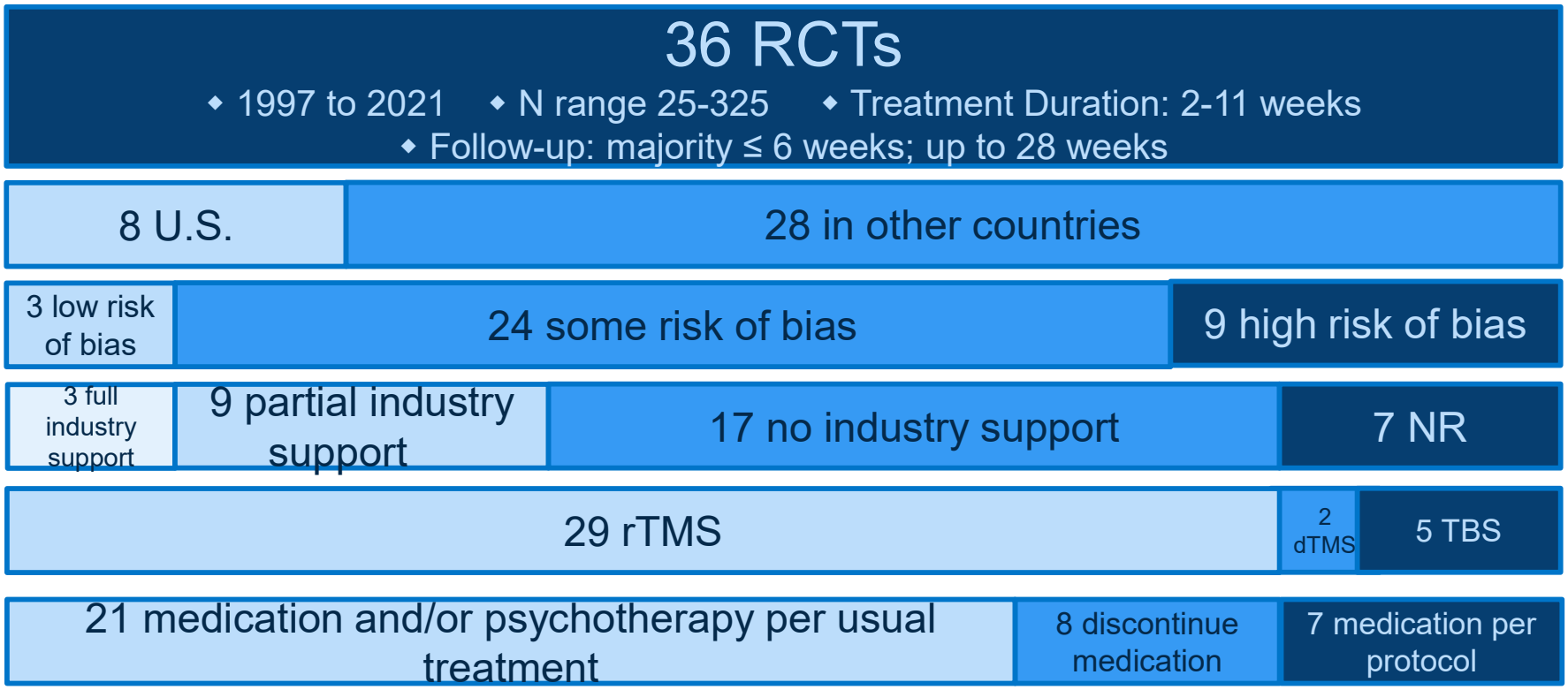
AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

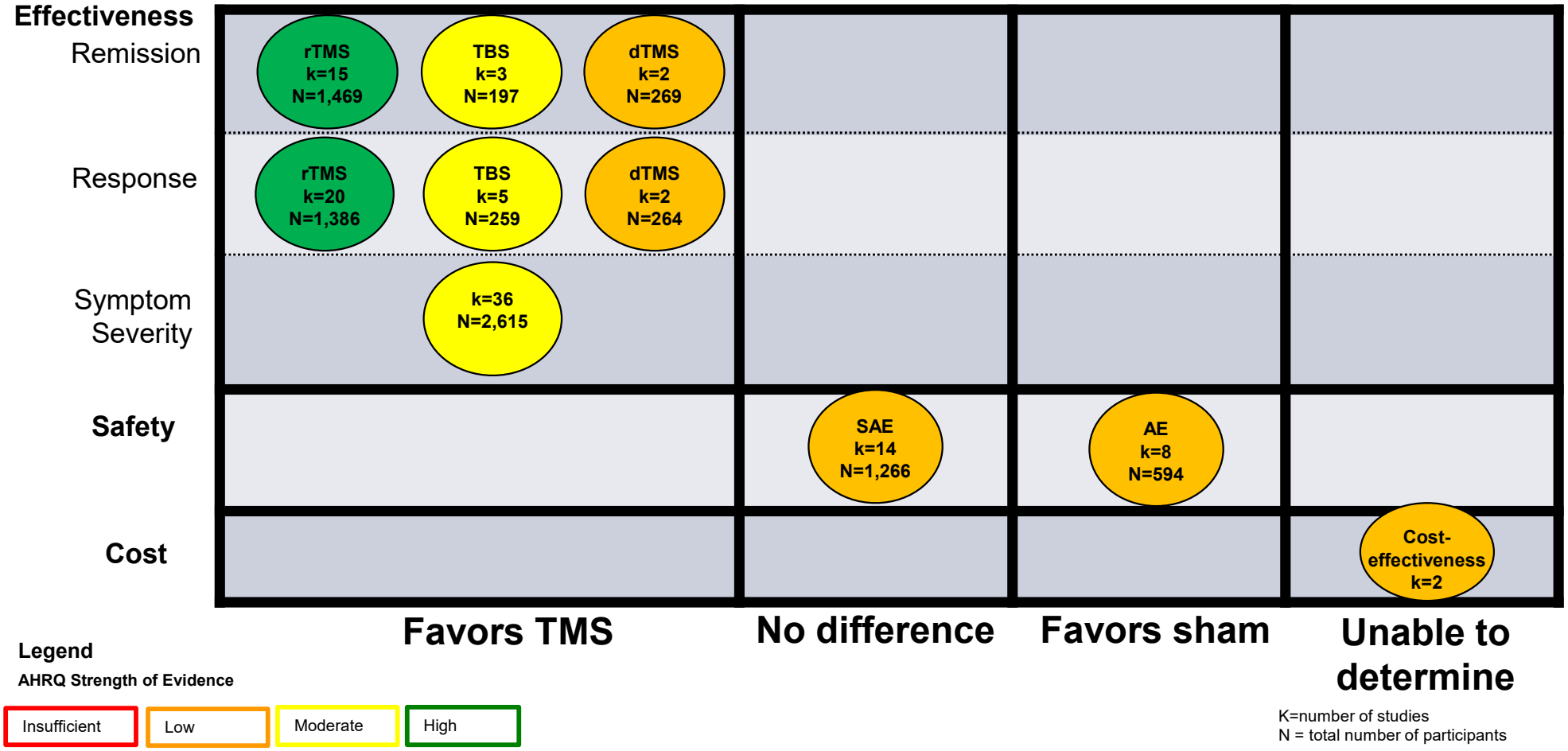
Findings: Major Depressive Disorder

Study Characteristics: Major Depressive Disorder



Abbreviations: dTMS = deep transcranial magnetic stimulation; N = number of participants; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; TBS = theta burst stimulation

Evidence Map: MDD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

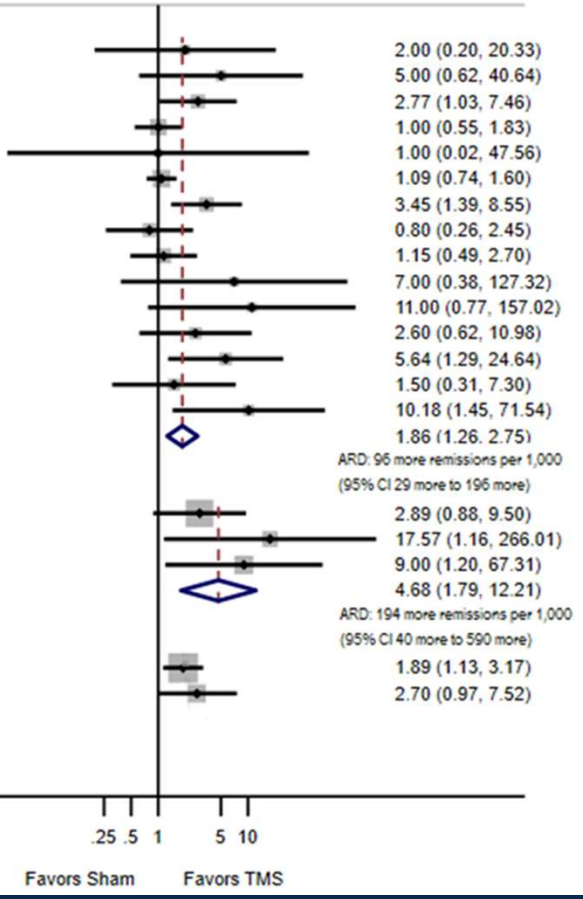
K=number of studies
N = total number of participants

MDD Results: Benefits

- Remission and Response
  - rTMS
    - Remission: pooled RR, 1.86 (95% CI, 1.26 to 2.75)
    - Response: pooled RR, 1.90 (95% CI, 1.45 to 2.49)
  - TBS
    - Remission: pooled RR, 4.68 (95% CI, 1.79 to 12.21)
    - Response: pooled RR, 3.92 (95% CI, 2.28 to 6.73)
    - SOE downgraded for imprecision
  - dTMS
    - Remission: RRs 1.89 (95% CI, 1.13 to 3.17) and 2.70 (95% CI, 0.97 to 7.52)
    - Response: RRs 1.31 (95% CI, 0.88 to 1.94) and 2.38 (95% CI, 0.96 to 5.88)
    - SOE downgraded for imprecision

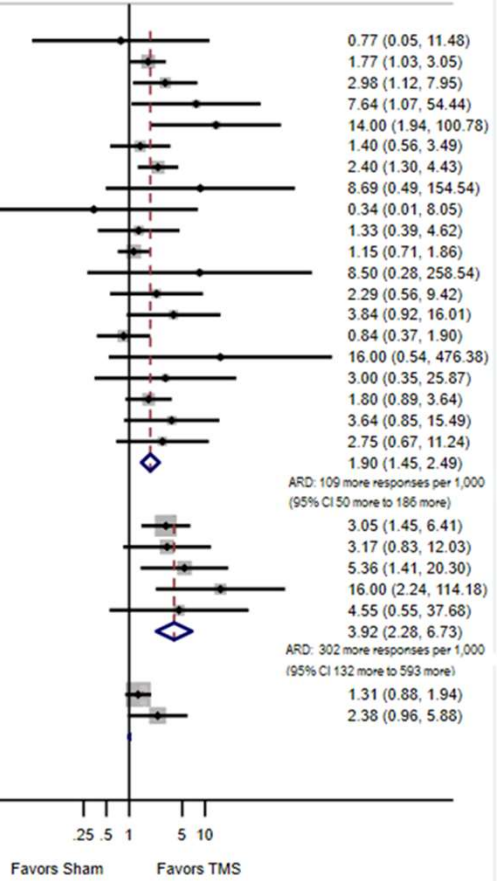
MDD Results: Remission

Type of TMS and Author, Year	TMS Treatment	Remission Definition	Sessions (N)	Follow-up	Intervention Events (N)/Total N (%)	Sham Events (N)/Total N (%)	Risk Ratio (95% CI)
rTMS							
Pallanti, 2010	Bilateral rTMS	HAMD28 ≤8	15	3 w	2/20 (10.0)	1/20 (5.0)	2.00 (0.20, 20.33)
Li, 2020	HF-rTMS	HAMD17 ≤ 7	10	2 w	5/35 (14.3)	1/35 (2.9)	5.00 (0.62, 40.64)
George, 2010	HF-rTMS	HAMD24 ≤ 3[a]	15	3 w	13/92 (14.1)	5/98 (5.1)	2.77 (1.03, 7.46)
Croarkin, 2020	HF-rTMS	NR	30	6 w	14/48 (29.2)	16/55 (29.1)	1.00 (0.55, 1.83)
van Eijndhoven, 2020	HF-rTMS	HAMD17 ≤ 7	20	5 w	0/15 (0)	0/16 (0)	1.00 (0.02, 47.56)
Yesavage, 2018	HF-rTMS	HAMD24 ≤ 10	30	4 to 11 w	33/81 (40.7)	31/83 (37.3)	1.09 (0.74, 1.60)
Rossini, 2005	HF-rTMS	HAMD21 ≤ 8	10	2 w	18/49 (36.7)	5/47 (10.6)	3.45 (1.39, 8.55)
Taylor, 2018	HF-rTMS	MADRS < 10	20	4 w	4/16 (25)	5/16 (31.3)	0.80 (0.26, 2.45)
O'Reardon, 2007	HF-rTMS	HAMD17 < 8	36	4 w	11/155 (7.1)	9/146 (6.2)	1.15 (0.49, 2.70)
Padberg, 2002	HF-rTMS[b]	HAMD < 9	10	2 w	3/20 (15.0)	0/20 (0)	7.00 (0.38, 127.32)
Stern, 2007	HF-rTMS, LF-rTMS[c]	HAMD21 ≤10	10	2 w	4/30 (13.3)	0/45 (0)	11.00 (0.77, 157.02)
Blumberger, 2012	HF-rTMS/Bilateral rTMS	HAMD17 ≤ 10	15 to 30	3 or 6 w	10/48 (20.8)	2/25 (8.0)	2.60 (0.62, 10.98)
Blumberger, 2016	HF-rTMS/Bilateral rTMS	HAMD17 ≤ 7	15 to 30	3 or 6 w	11/80 (13.8)	2/82 (2.4)	5.64 (1.29, 24.64)
Kim, 2019	LF-rTMS	HAMD17 < 8[d]	20	4 w	3/11 (27.3)	2/11 (18.2)	1.50 (0.31, 7.30)
Januel, 2006	LF-rTMS	HAMD17 < 9	16	4 w	7/11 (63.6)	1/16 (6.3)	10.18 (1.45, 71.54)
Subgroup, DL (I^2 = 38.1%, p = 0.067)							1.86 (1.26, 2.75)
							ARD: 96 more remissions per 1,000 (95% CI 29 more to 196 more)
TBS							
Chou, 2020	cTBS	HAMD21 < 8	10	4 w	9/27 (33.3)	3/26 (11.5)	2.89 (0.88, 9.50)
Cole, 2022	iTBS	MADRS ≤ 10	50	1 w	8/14 (57.1)	0/15 (0)	17.57 (1.16, 266.01)
Li, 2020	iTBS	HAMD17 ≤ 7	10	2 w	9/35 (25.7)	1/25 (2.9)	9.00 (1.20, 67.31)
Subgroup, DL (I^2 = 0.0%, p = 0.378)							4.68 (1.79, 12.21)
							ARD: 194 more remissions per 1,000 (95% CI 40 more to 590 more)
dTMS							
Levkovitz, 2015	dTMS	HAMD21 < 10	20	5 w	31/101 (30.7)	18/111 (16.2)	1.89 (1.13, 3.17)
Kaster, 2018	dTMS	HAMD24 ≤ 10[e]	20	4 w	10/25 (40.0)	4/27 (14.8)	2.70 (0.97, 7.52)



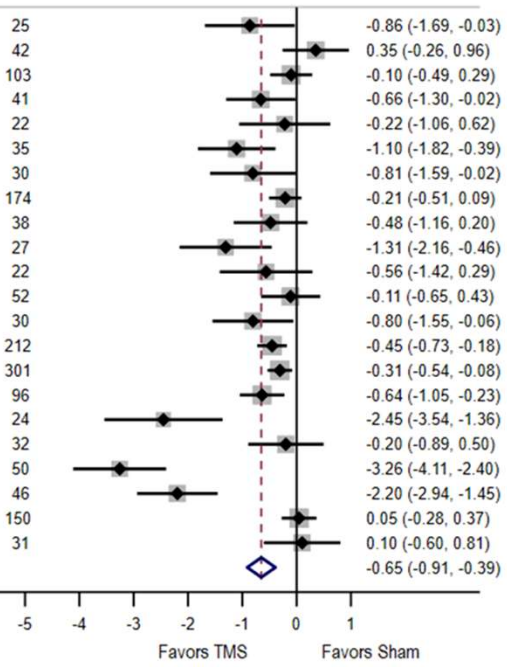
MDD Results: Response

TMS Type and Author, Year	TMS Treatment	Response Definition: ≥ 50% reduction	Sessions (N)	Follow-up	Intervention Events (N)/Total N (%)	Sham Events (N)/Total N (%)	Risk Ratio (95% CI)
rTMS							
Fitzgerald, 2012	Bilateral rTMS	HAMD17	15	3 w	1/22 (4.5)	1/17 (5.9)	0.77 (0.05, 11.48)
O'Reardon, 2007	HF-rTMS	HAMD17	36	4 w	32/155 (20.6)	17/146 (11.6)	1.77 (1.03, 3.05)
George, 2010	HF-rTMS	HAMD24	15	3 w	14/92 (15.2)	5/98 (5.1)	2.98 (1.12, 7.95)
Anderson, 2007	HF-rTMS	MADRS [a]	12 to 18	4 to 6 w	6/11 (54.5)	1/14 (7.1)	7.64 (1.07, 54.44)
Li, 2020	HF-rTMS	HAMD17	10	2 w	14/35 (40.0)	1/35 (2.9)	14.00 (1.94, 100.78)
Taylor, 2018	HF-rTMS	MADRS	20	4 w	7/16 (43.8)	5/16 (31.3)	1.40 (0.56, 3.49)
Rossini, 2005	HF-rTMS	HAMD21	10	2 w	25/49 (51.0)	10/47 (21.3)	2.40 (1.30, 4.43)
Herwig, 2003	HF-rTMS	HAMD21 [b]	10	2 w	4/13 (30.8)	0/12 (0.0)	8.69 (0.49, 154.54)
van Eijndhoven, 2020	HF-rTMS	HAMD17	20	5 w	0/15 (0.0)	1/16 (6.3)	0.34 (0.01, 8.05)
Garcia-Toro, 2001	HF-rTMS	HAMD21	10	2 w	4/11 (36.4)	3/11 (27.3)	1.33 (0.39, 4.62)
Croarkin, 2020	HF-rTMS	HAMD24	30	6 w	20/48 (41.7)	20/55 (36.4)	1.15 (0.71, 1.86)
Padberg, 2002	HF-rTMS [c]	HAMD21	10	2 w	5/20 (25.0)	0/10 (0.0)	8.50 (0.28, 258.54)
Blumberger, 2012	HF-rTMS/Bilateral rTMS	HAMD17	15 to 30	3 w	11/48 (22.9)	2/20 (10.0)	2.29 (0.56, 9.42)
Blumberger, 2016	HF-rTMS/Bilateral rTMS	HAMD17	15 to 30	4 to 6 w	15/80 (18.8)	2/41 (4.9)	3.84 (0.92, 16.01)
Hoppner, 2003	HF-rTMS/LF-rTMS	HAMD21	10	2 w	8/19 (42.1)	5/10 (50.0)	0.84 (0.37, 1.90)
Stern, 2007	HF-rTMS/LF-rTMS [d]	HAMD21	10	2 w	10/30 (33.3)	0/15 (0.0)	16.00 (0.54, 476.38)
Schutter, 2009	LF-rTMS	HAMD17	10	2 w	3/16 (18.8)	1/16 (6.3)	3.00 (0.35, 25.87)
Kim, 2019	LF-rTMS	HAMD17	20	4 w	9/11 (81.8)	5/11 (45.5)	1.80 (0.89, 3.64)
Januel, 2006	LF-rTMS	HAMD17	16	4 w	5/11 (45.5)	2/16 (12.5)	3.64 (0.85, 15.49)
Pallanti, 2010	LF-rTMS/Bilateral rTMS	HAMD28	15	3 w	11/40 (27.5)	2/20 (10.0)	2.75 (0.67, 11.24)
Subgroup, DL (I^2 = 17.2%, p = 0.240)							1.90 (1.45, 2.49)
							ARD: 109 more responses per 1,000 (95% CI 50 more to 186 more)
TBS							
Chou, 2020	cTBS	HAMD21	10	4 w	19/27 (70.4)	6/26 (23.1)	3.05 (1.45, 6.41)
Li, 2014	cTBS/iTBS/iTBS & cTBS	HAMD17	10	2 w	19/45 (42.2)	2/15 (13.3)	3.17 (0.83, 12.03)
Cole, 2022	iTBS	MADRS	50	4 w	10/14 (71.4)	2/15 (13.3)	5.36 (1.41, 20.30)
Li, 2020	iTBS	HAMD17	10	2 w	16/35 (45.7)	1/35 (2.9)	16.00 (2.24, 114.18)
Duprat, 2016	iTBS	HAMD17	20	1 w	4/22 (18.2)	1/25 (4.0)	4.55 (0.55, 37.68)
Subgroup, DL (I^2 = 0.0%, p = 0.603)							3.92 (2.28, 6.73)
							ARD: 302 more responses per 1,000 (95% CI 132 more to 593 more)
dTMS							
Levkovitz, 2015	dTMS	HAMD21	20	5 w	37/101 (36.6)	31/111 (27.9)	1.31 (0.88, 1.94)
Kaster, 2018	dTMS	HAMD24	20	4 w	11/25 (44.0)	5/27 (18.5)	2.38 (0.96, 5.88)



MDD Results: Symptom Severity

Author, Year	TMS Treatment	MDD severity measure	Sessions (N)	Follow-up	Sample Size	SMD (95% CI)
Anderson, 2007	HF-rTMS	MADRS	12 to 18	4 to 6 w	25	-0.86 (-1.69, -0.03)
Blumberger, 2012	HF-rTMS	HAMD17	15 to 30	3 w	42	0.35 (-0.26, 0.96)
Croarkin, 2020	HF-rTMS	HAMD24	30	6 w	103	-0.10 (-0.49, 0.29)
Fitzgerald, 2012	HF-rTMS	HAMD17	15	3 w	41	-0.66 (-1.30, -0.02)
Garcia-Toro, 2001	HF-rTMS	HAMD21	10	2 w	22	-0.22 (-1.06, 0.62)
Garcia-Toro, 2001	HF-rTMS	HAMD21	10	3 w	35	-1.10 (-1.82, -0.39)
Garcia-Toro, 2006	HF & LF-rTMS	HAMD21	10	2 w	30	-0.81 (-1.59, -0.02)
George, 2010	HF-rTMS	HAMD24	15	3 w	174	-0.21 (-0.51, 0.09)
Hausmann, 2004	HF & Bilateral rTMS	HAMD21	10	2 w	38	-0.48 (-1.16, 0.20)
Januel, 2006	LF-rTMS	HAMD17	16	4 w	27	-1.31 (-2.16, -0.46)
Kim, 2019	LF-rTMS	HAMD17	20	4 w	22	-0.56 (-1.42, 0.29)
Koerselman, 2004	HF-rTMS	HAMD17	10	2 w	52	-0.11 (-0.65, 0.43)
Lee, 2018	HF-rTMS	HAMD17	15	3 w	30	-0.80 (-1.55, -0.06)
Levkovitz, 2015	dTMS	HAMD21	20	2 w	212	-0.45 (-0.73, -0.18)
O Reardon, 2007	HF-rTMS	HAMD17	36	4 w	301	-0.31 (-0.54, -0.08)
Rossini, 2005	HF-rTMS	HAMD21	10	2 w	96	-0.64 (-1.05, -0.23)
Stern, 2007	HF-rTMS	HAMD21	10	2 w	24	-2.45 (-3.54, -1.36)
Taylor, 2018	HF-rTMS	HAMD17	20	4 w	32	-0.20 (-0.89, 0.50)
Theleritis, 2017	HF-rTMS (2/day)	HAMD17	15	3 w	50	-3.26 (-4.11, -2.40)
Theleritis, 2017	HF-rTMS (1/day)	HAMD17	15	3 w	46	-2.20 (-2.94, -1.45)
Yesavage, 2018	HF-rTMS	HAMD24	30	4 to 11 w	150	0.05 (-0.28, 0.37)
van Eijndhoven, 2020	HF-rTMS	HAMD17	20	5 w	31	0.10 (-0.60, 0.81)
Overall, DL (I^2 = 81.6%, p = 0.000)						-0.65 (-0.91, -0.39)



The pooled SMD (-0.65) is roughly equivalent to a HAMD17 difference of -3.8 points and is equal to the minimum clinically important change established for this measure.

MDD Results: Harms

- Any Adverse Events
  - 1 study reported a greater number of any AEs in the active TMS group compared to sham (41% vs. 29%, no significance testing reported)
  - 7 studies reported no difference between active TMS and sham groups
- Serious Adverse Events
  - 2 studies reported SAEs in the TMS group and no events in the sham
  - 2 studies reported no differences between any SAEs between groups.
  - Remaining 10 studies reported 0 SAEs across groups.
- Specific Harms
  - Most frequent headache and application site discomfort, higher or similar frequency in the active TMS group compared to sham

MDD Results: Special Populations

- Three studies reported outcomes for subgroups of age, sex, and comorbidity.
  - There was no difference in clinical response by age, or sex.
  - In a study of veterans with MDD, rates of remission were higher for individuals with MDD (without PTSD) for active TMS groups compared to sham condition, whereas there was little difference between groups for individuals with MDD and comorbid PTSD (P=0.03).
- One study each was identified for the following special populations: adolescents, pregnant individuals, and older adults
  - There was no difference between TMS and sham for these 3 studies.

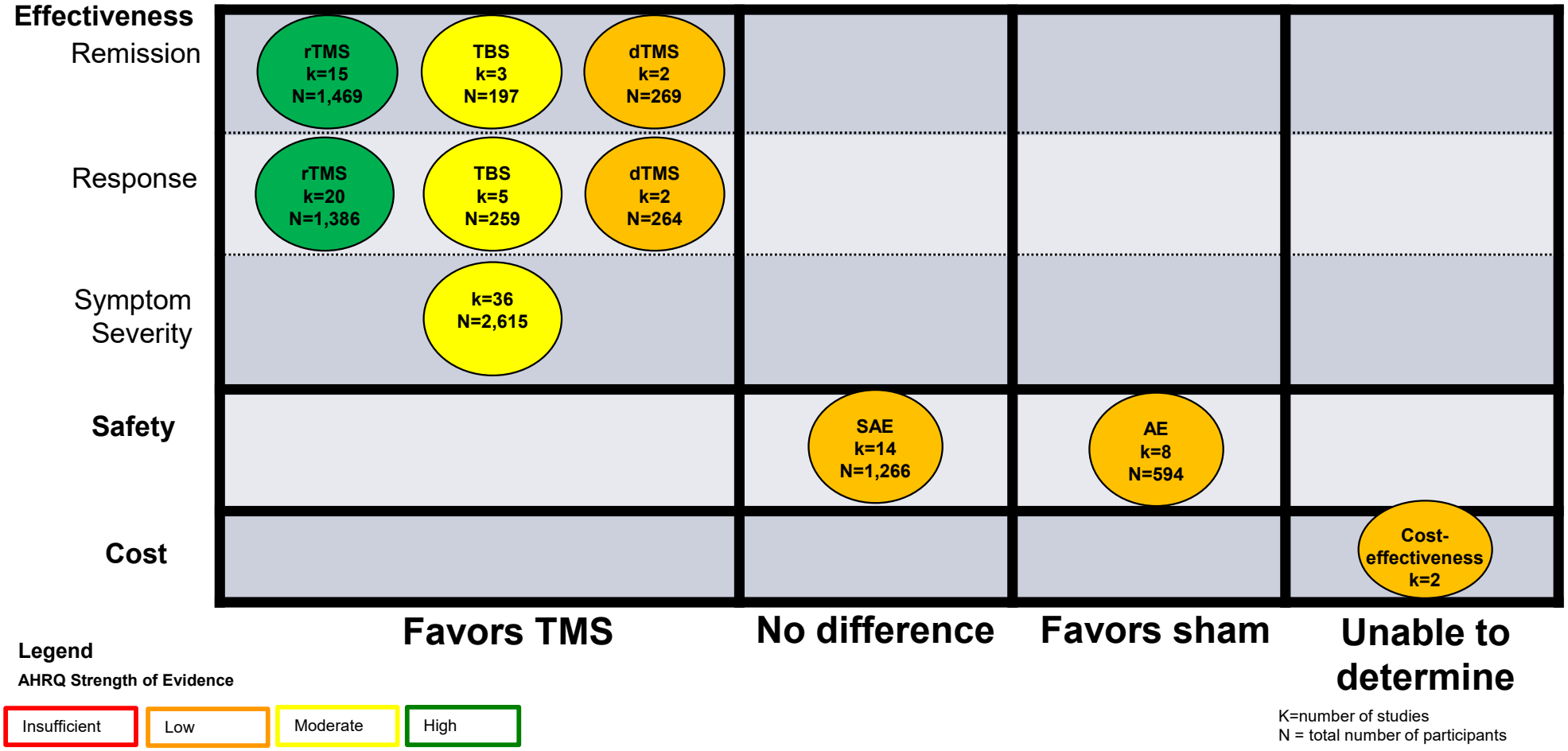
MDD Results: Accelerated protocols

Study	Sessions per day	Duration Treatment	Outcomes
Cole et al. 2022 (SAINT protocol)	10	1 week	Remission and response: greater RR than pooled estimate, wide confidence intervals
Duprat et al, 2016	5	1 week	Response: greater RR than pooled estimate, wide confidence intervals
Theleritis et al, 2017	2	3 weeks	Symptom reduction: Greatest RR symptom reduction among all studies in MA

MDD Results: Cost-effectiveness

- 2 studies reported on cost-effectiveness of TMS
  - In the base case for both studies, rTMS was the dominant strategy compared to pharmacotherapy, meaning that it cost less and was more effective.
  - In the study using a 1-year time horizon, the cost savings per QALY gained was $746 without productivity costs and was $7,243 when productivity costs were considered.
  - In the study using a lifetime horizon, the cost savings per QALY gained ranged from $9,225 to $25,907 depending on the age at diagnosis; more savings accumulated for younger age groups

Evidence Map: MDD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N = total number of participants

Findings: Posttraumatic Stress Disorder

Study Characteristics: Posttraumatic Stress Disorder

4 RCTs

- 2011 to 2020
- N range 20-134
- Treatment Duration: 2-12 weeks
- Follow-up: 2 weeks-6 months

4 U.S.[a]		
1 low risk of bias	2 some risk of bias	1 high risk of bias
1 full industry support	3 no industry support	
2 rTMS	1 dTMS	1 iTBS
3 medication and psychotherapy per usual treatment[b]		1 psychotherapy per protocol

Abbreviations: dTMS = deep transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation**;** N = number of participants; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

[a]1 study was a multi-country study in the U.S., Israel, Canada and Europe; [b]one study also included exposure therapy

Evidence Map: PTSD

Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

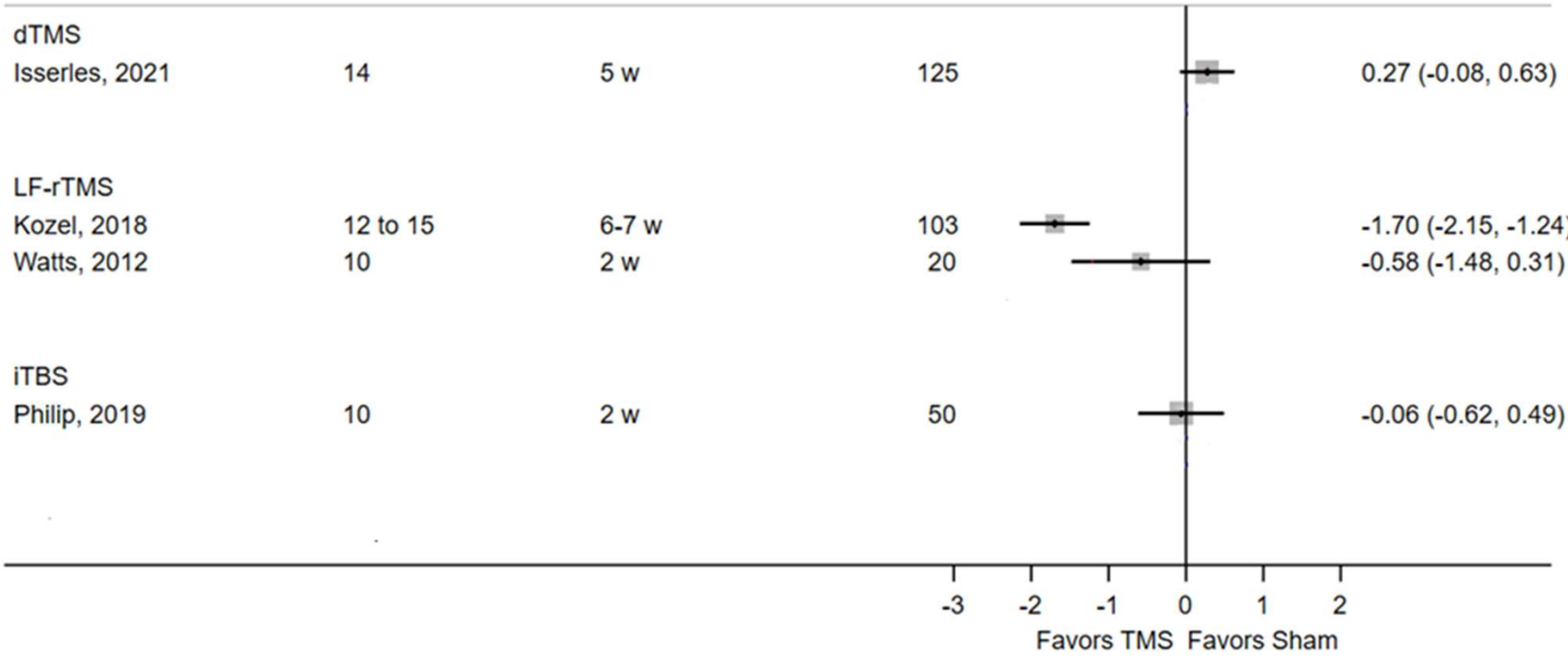
K=number of studies
N=total number of participants

PTSD Results: Benefits

- Remission
  - 1 study reported remission rates very low; no statistical difference between groups
- Response
  - 1 study: participants in sham group more likely to have a response to treatment at both time points, although not statistically significant
- SOE downgraded for consistency and imprecision (x2)

PTSD Results: Symptom Severity

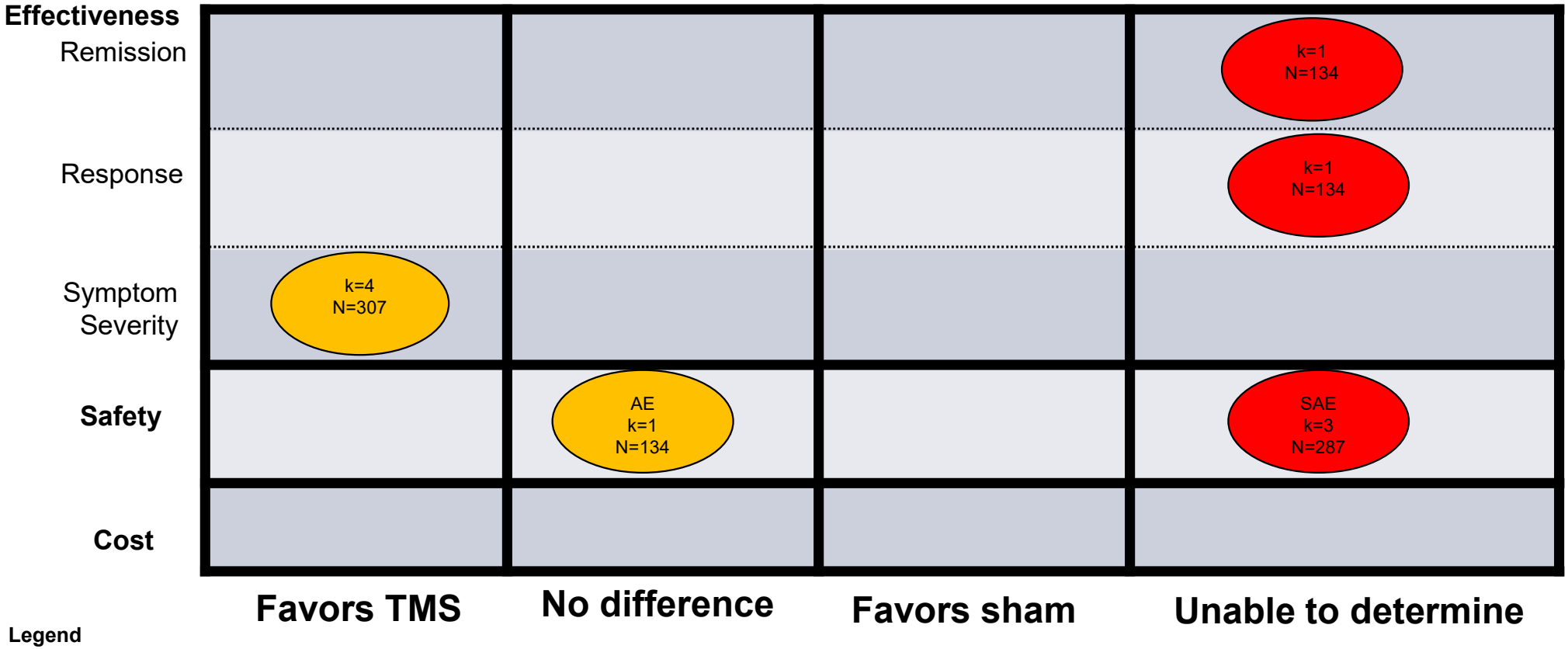
TMS Type and Author, Year	Sessions (N)	Follow-up	Sample Size (N)	SMD (95% CI)
dTMS				
Isserles, 2021	14	5 w	125	0.27 (-0.08, 0.63)
LF-rTMS				
Kozel, 2018	12 to 15	6-7 w	103	-1.70 (-2.15, -1.24)
Watts, 2012	10	2 w	20	-0.58 (-1.48, 0.31)
iTBS				
Philip, 2019	10	2 w	50	-0.06 (-0.62, 0.49)



PTSD Results: Harms

- Any Adverse Events
  - 1 study reported a similar number of any AEs in both dTMS and sham groups (77% vs. 63%, P=0.099)
  - SOE downgraded for consistency and imprecision
- Serious Adverse Events
  - 3 studies mixed findings
    - One study reported no SAEs; 1 study reported 2 SAE (1 emergent homicidal ideation; 1 hospitalization for suicidality) in the sham group only; 1 study reported on specific AEs, with similar moderate or severe anxiety across groups and 2 reports of suicidal ideation in the TMS group, none in the sham groups
  - SOE downgraded for consistency and imprecision (x2)

Evidence Map: PTSD



Legend

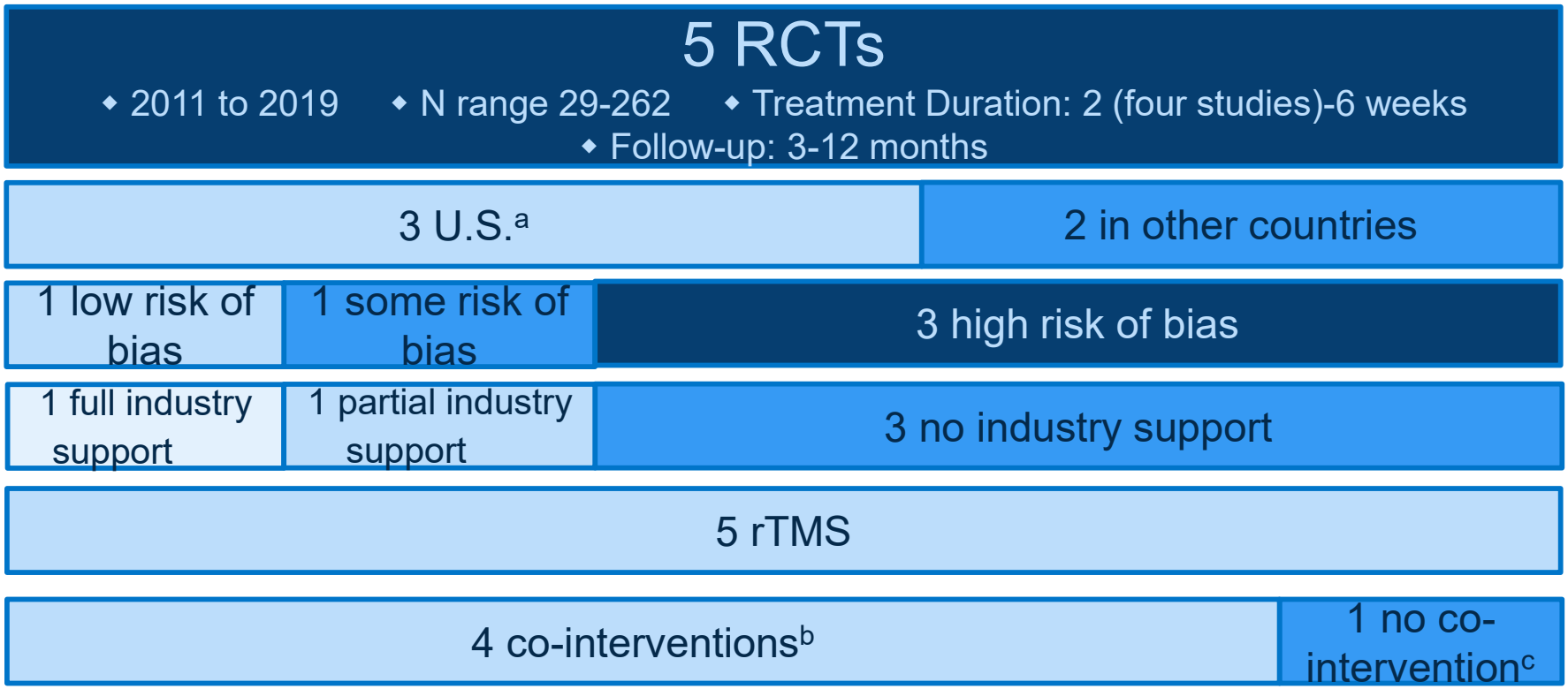
AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

Findings: Smoking Cessation

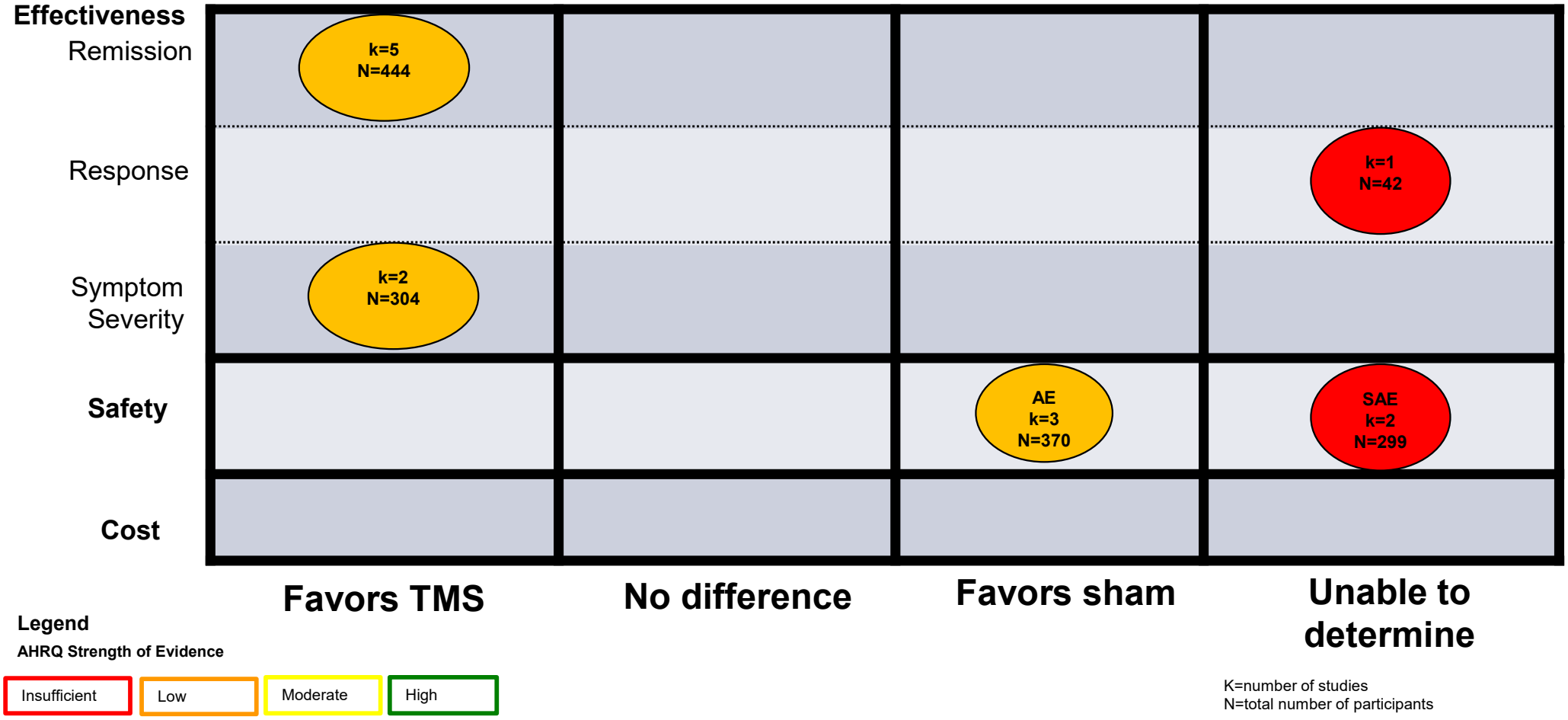
Study Characteristics: Smoking Cessation



Abbreviations: N = number of participants; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

[a] one study conducted in U.S. and Israel; [b]nicotine replacement therapy, psychotherapy, self-help materials, motivational talk; one study also included exposure therapy; [c]this study also included exposure therapy

Evidence Map: Smoking Cessation



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

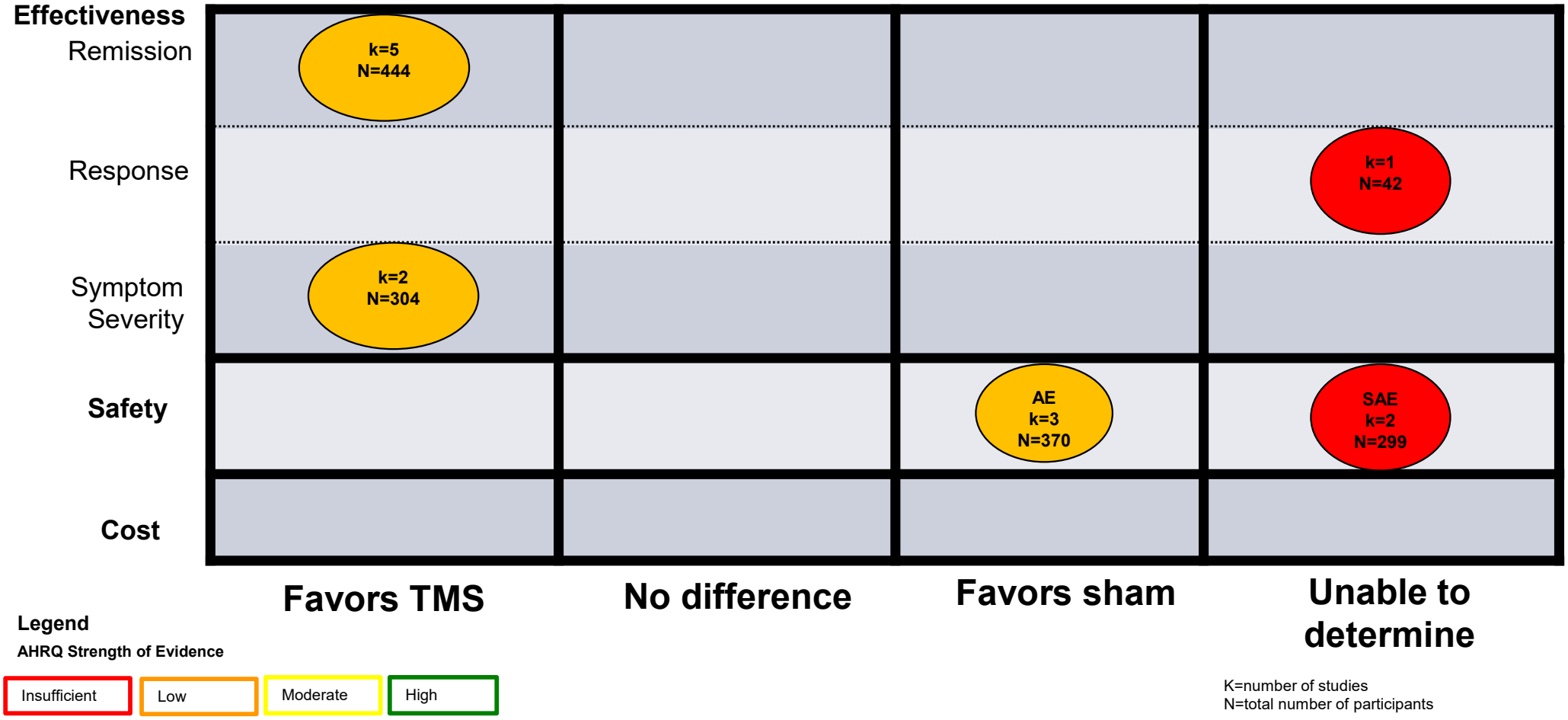
Smoking Cessation Results: Benefits

- Abstinence
  - Various measures of abstinence generally favored TMS over sham, although findings statistically significant in only 3 studies of 5 studies
- Nicotine Use
  - Various measures reported. Majority of participants from 1 RCT (n=262).
  - Studies reported lower number cigarettes smoked or lower CO and cotinine levels by participants in TMS group compared to sham.
- Nicotine Dependence (FTND)
  - 2 studies reported lower nicotine dependence in the TMS group at post-treatment, statistically significant in 1 study
- SOE downgraded for imprecision and study limitations

Smoking Cessation Results: Harms

- Any Adverse Event
  - 1 study reported no AEs in either group
  - 2 studies reported higher incidence of AEs in the active TMS group compared to sham, statistically significant for 1 study only
- Serious Adverse Events
  - One study reported no SAEs and 1 study reported only 1 SAE (tinnitus)
- Specific Harms
  - Most frequently reported was headache, application site discomfort

Evidence Map: Smoking Cessation



Legend

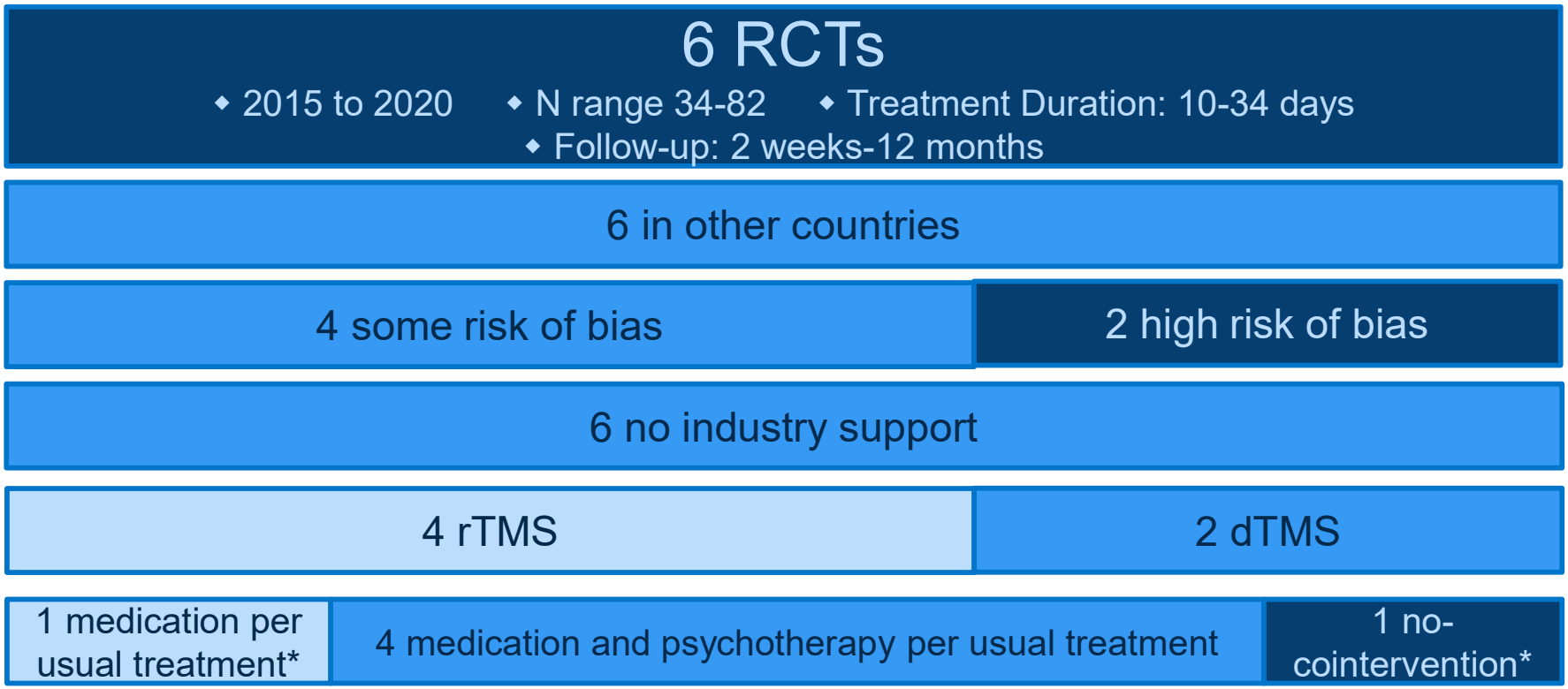
AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

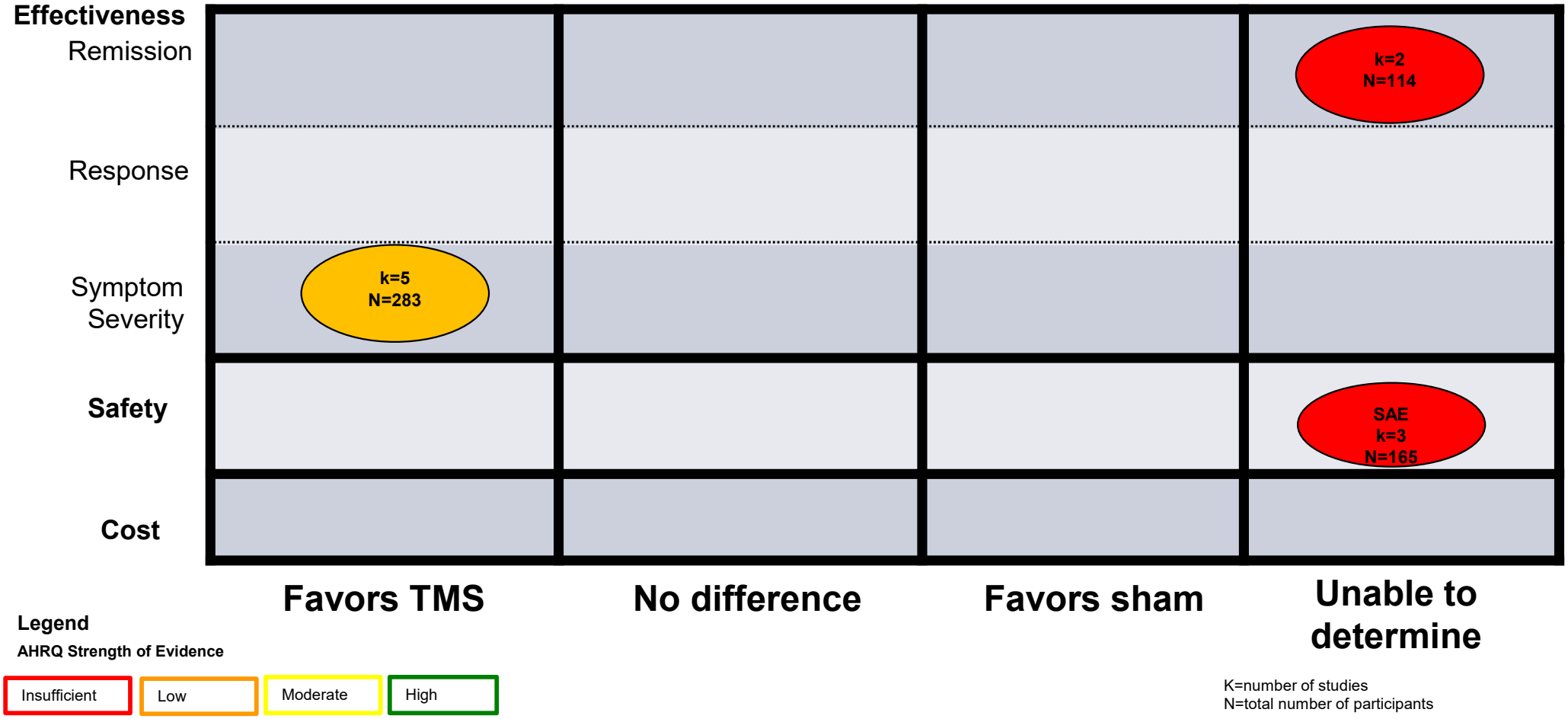
Findings: Substance Use Disorder

Study Characteristics: Substance Use Disorder



Abbreviations: cTBS = continuous theta burst stimulation**;** dTMS = deep transcranial magnetic stimulation; N = number of participants; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation
*these studies also included exposure therapy

Evidence Map: SUD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

SUD Results: Benefits

- Abstinence
  - One study of AUD and one study of cocaine use disorder favored TMS though results not significant
  - SOE downgraded for imprecision (x2) and study limitations
- Substance Use
  - Various measures reported (self-reported days of use and heavy drinking days, biomarkers in urine or blood).
  - 3 studies reported statistically significant differences in substance use favoring TMS at multiple timepoints. 2 studies reported no differences
  - SOE downgraded for imprecision and study limitations

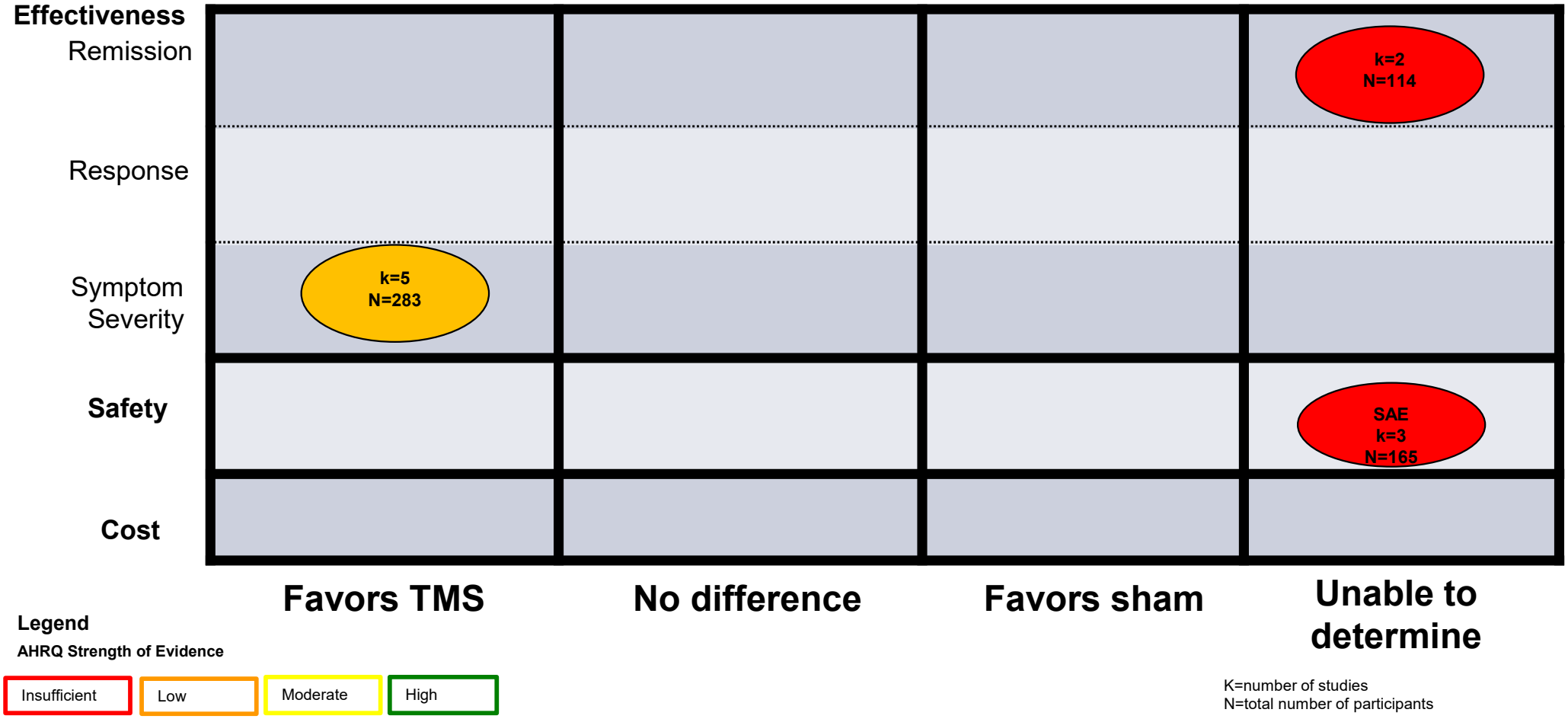
SUD Results: Harms

- Any Adverse Events
  - Studies did not report total AEs by group.
- Serious Adverse Events
  - No events reported across three studies
  - SOE downgraded for imprecision (X2) and study limitations
- Specific harms
  - Headache, discomfort at the stimulation site present in both groups

SUD Results: Subgroup Analyses

- One study on cocaine use disorder reported a statistically significant difference favoring TMS for days of cocaine use (P<0.05) among the subgroup of participants with higher depression levels (MADRS score >20).

Evidence Map: SUD



Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

K=number of studies
N=total number of participants

Summary of SOE

Condition	Remission	Response	Symptom Severity	AE	SAE	Cost
GAD			TMS			
OCD		TMS	TMS	ND	ND	
MDD	TMS	TMS	TMS	ND	SHAM	N/A
PTSD			TMS	ND		
Smoking cessation	TMS		TMS	SHAM		
SUD			TMS			

Legend

AHRQ Strength of Evidence

Insufficient | Low | Moderate | High

Text in cell indicates direction of effect (N/A=not applicable, ND=No difference)

Discussion

Limitations of the Evidence

- Many RCTs with high ROB and studies with small sample sizes, resulting in imprecise effect estimates
- Infrequently reported on race or ethnicity
- Limited number of studies reported outcomes at follow-up time point beyond a few weeks after the end of treatment
  - For each condition, only 1 to 2 studies with follow-up of 3 months or longer
  - In general, results were durable at 3 months with respect to remission, response, or reduction in symptom severity for GAD, OCD, MDD, and SUD
  - Only 2 studies evaluated outcomes at 20 weeks and 24 weeks (MDD)
    - Changes in symptom severity: durable for 1 study and statistical testing was not reported for the other

Limitations of the HTA

- Did not include comparative effectiveness studies (between various TMS types or between TMS and other treatment options)
- For practical reasons, abstracted only symptom severity scores for the primary indication for TMS (eg. depression scores only for MDD)
- Reviewed harms by condition, though no biologic reason to believe harms of TMS are condition-specific.
- Did not use data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database to assess safety
  - Passive surveillance systems include incomplete, inaccurate, untimely, and unverified data
- Did not include non-English studies, or studies conducted in non-very high HDI countries

Payor Coverage Policies

Discussion: Payor Coverage Policies

Condition	Medicare	Cigna	Kaiser Permanente	Premera Blue Cross	Regence BlueShield	UnitedHealth
Depression	LCD only (no NCD)	✓	✓	✓	✓	✓
OCD	X	✓	X	✓	X	X
Smoking cessation	X	X	X	X	X	X
PTSD	X	X	X	X	X	X
Generalized Anxiety Disorder	X	X	X	X	X	X
Substance Abuse	X	X	X	X	X	X
Migraine	X	X	X	X	X	X

Notes: ✓ = covered; X = not covered
Abbreviations: GAD = generalized anxiety disorder; LCD = local coverage determinations through Medicare contractors; OCD = obsessive-compulsive disorder PTSD = posttraumatic stress disorder

Discussion: Payor Coverage Policies

Company	Condition	TMS Type	Sessions	Prior medications	Prior Psychotherapy
Cigna	MDD OCD	Not specified	30-36	At least 2 medications from 2 difference classes	Yes
Medicare (LCD only)	MDD	rTMS	Not specified	At least 1 medication	Yes
Premera	MDD OCD	rTMS dTMS TBS*	30-36	At least 3 medications from 2 different classes	Not specified
Regence	MDD	Not specified	36	At least 3 medications	Yes
United	MDD	rTMS	30-36	At least 4 medications from 2 difference classes	Not specified

*No accelerated protocols

Discussion Ongoing Studies

Condition	Not yet recruiting	Active or recruiting[a]	Completed	Stopped or unknown[b]	Total by Condition
Depression	26	104	137	92	359
OCD	2	12	20	10	44
Smoking cessation	6	29	48	32	115
PTSD	3	11	21	8	43
GAD	0	1	4	2	7
Substance abuse	16	57	56	47	176
Total by Status	**53**	**214**	**286**	**191**	**744**

Summary

- TMS has moderate to high SOE for benefit in MDD at posttreatment
- TMS has low SOE for benefit in OCD at posttreatment
- Evidence for benefit for GAD, PTSD, smoking cessation, and SUD ranges from insufficient to low for benefit
- For safety outcomes, there generally reported fewer AEs for sham TMS; few SAEs were reported for either active or sham TMS.
- Evidence is lacking with respect to
  - Cost and cost-effectiveness outcomes
  - Efficacy of TMS at longer follow-up assessment timepoints

Future Research Considerations

- Research on non-depression conditions may require additional work to determine the optimal TMS treatment parameters to be evaluated in larger, sham-controlled effectiveness trials
- All trials should include measures of disease severity and treatment resistance to support clinical decision making on when to use TMS compared to another treatment
- Trials should include longer term outcomes to evaluate the durability of treatment effect and to identify harms that may only emerge later

Questions?

HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

Based on Legislative mandate: RCW 70.14.100(2).

The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the

task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Adverse events		
Serious adverse events		
Specific harms		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Remission		
Response		
Symptom Severity		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost-effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Sex		
Comorbidity		
Adolescents		
Pregnant individuals		
Older adults		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is:

Not covered	Covered unconditionally	Covered with conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Washington State Health Care Authority

Final Key Questions and Background

Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Health Disorders

August 23, 2022

Background

Mental health conditions affect a large proportion of the American population, according to several nationally representative surveys.[1-4] Individuals suffering these conditions often experience decreased quality of life and impaired function across physical, emotional, and social domains. Over 14 million adults (5.6%) are estimated to have serious mental illness (SMI), in which the mental illness causes serious functional impairment interfering with one or more major life activities.[1,5]

Current treatment approaches for behavioral health disorders often begin with psychotherapy, pharmacotherapy, or both. However, many people do not achieve adequate clinical responses after the initial treatment attempt, and second and third-line medications or procedures (e.g., electroconvulsive therapy (ECT)) carry risk of adverse side effects that many individuals do not tolerate. Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that has been FDA approved for some behavioral health and neurologic conditions. There is a growing evidence base that TMS may be efficacious, with fewer or more tolerable side effects, and has led to growing interest in applying TMS to a broader set of conditions, most often those deemed treatment resistant.

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of TMS to assist the State of Washington's Health Technology Clinical Committee (HTCC) in determining coverage of TMS for the following selected behavioral health disorders: depression; anxiety disorders including generalized anxiety disorder (GAD); obsessive-compulsive disorder (OCD); post-traumatic stress disorder (PTSD); and addiction disorders including tobacco use disorder and substance use disorder (SUD).

Policy context

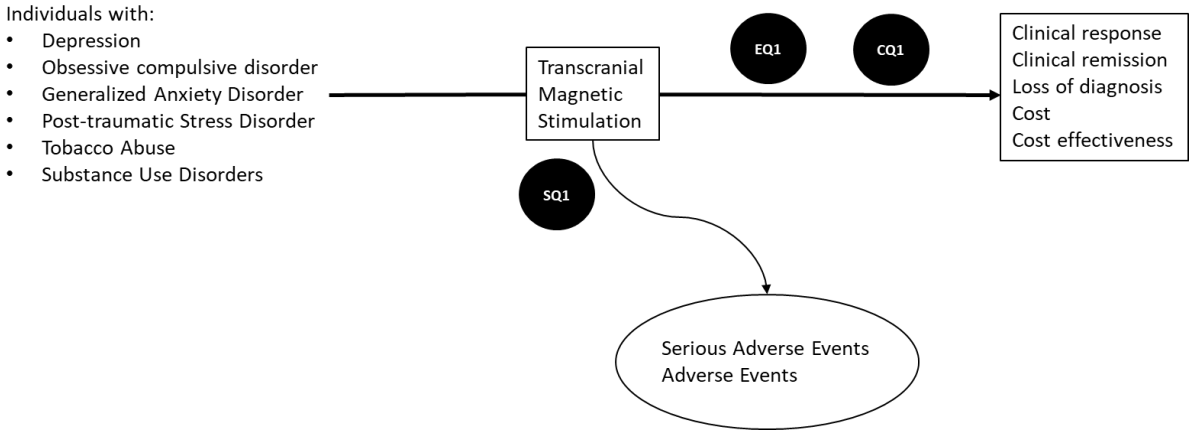
The State of Washington Health Care Authority selected TMS for selected behavioral health conditions for a health technology assessment (HTA) because of low/medium concerns of safety and medium/high concerns for efficacy and cost.

Washington State Health Care Authority

Scope of this HTA

The analytic framework (**Figure 1**), research questions, and key study selection criteria (**Table 1**) are listed in this section.

Figure 1. Analytic Framework Depicting Scope of this Health Technology Assessment



Abbreviations: SQ = safety question, CQ = cost question; EQ = efficacy question

Research Questions

Efficacy Question 1 (EQ 1). What is the efficacy of transcranial magnetic stimulation for the treatment of selected behavioral disorders?

Safety Question 1 (SQ 1). What are the harms associated with transcranial magnetic stimulation for the treatment of selected behavioral disorders?

Cost Question 1 (CQ 1). What are the costs and cost-effectiveness of transcranial magnetic stimulation for the treatment of selected behavioral disorders?

Study Selection Criteria

Table 1 provides the study selection criteria we will use to include studies in the HTA and are organized by population, intervention, comparator, outcomes, timing, setting, and study design (PICOTS) criteria.

Washington State Health Care Authority

Table 1. Proposed Population, Intervention, Comparator, Outcome, Timing, and Setting for Health Technology Assessment

PICOTS	Include	Exclude

Population	• Individuals of all ages with eligible clinical diagnosis:
	  • Depression, major depressive disorder (MDD)
	  • Obsessive compulsive disorder (OCD)
	  • Generalized Anxiety Disorder (GAD)
	  • Post-traumatic stress disorder (PTSD)
	  • Tobacco Use Disorder, or regular smoker
	  • Substance Abuse Disorder (SUD)
	• Subgroups: Individuals who are peri- or post-partum, elderly, age < 18 years
		• Individuals with ineligible mental health diagnosis
		• Individuals with no mental health diagnosis (e.g. healthy controls)
		• Individuals with a primary medical (i.e., non-psychiatric) diagnoses
		• Studies conducted in animals, *in vitro*, or *in silico*

Intervention	• Repetitive TMS (rTMS) with or without concurrent pharmaco- and/or psychotherapy delivered over more than 1 session • Deep TMS (dTMS) with or without concurrent pharmaco- and/or psychotherapy	• Single session TMS (TMS) • Other non-invasive neuromodulation procedures (e.g. transcranial direct current stimulation, neurofeedback; transcutaneous vagus nerve stimulation) • Invasive neuromodulation therapies (e.g. implanted vagus nerve stimulation, deep brain stimulation, brain surface implants)
Comparator	• Sham TMS with or without concurrent pharmaco- and/or psychotherapy	• Head-to-head comparisons between alternative TMS protocols, with medications, psychotherapy, other neuromodulation procedures (e.g. ECT), o complementary or alternative therapies • Waitlist control • No comparator
Outcomes	• EQ: Primary study outcome or outcome used for determining power or sample size is a clinical outcome: response (e.g. symptom scales or indices), remission, or loss of diagnosis as measured by validated instruments or clinical evaluation. Clinical outcomes from studies where the primary outcome is an intermediate or biomarker but that also report a validated clinical outcome will only be included if the study was also adequately powered for the clinical outcome. • SQ: Serious adverse events (e.g., seizure), adverse events (e.g., headache), side effects including device-related complications (e.g., scalp pain) • CQ: Cost; cost-effectiveness	• Non-validated measures of clinical response or remission • Individual symptom response outside of a validated scale (e.g. guilt, hopelessness) • Intermediate or biomarker outcomes, such as electrophysiologic or functional imaging outcomes, lab measures, craving measures
Timing & Language	• No timing restrictions • English language articles	• No timing exclusions • Non-English language articles
Study Design	• EQ: RCTs, non-randomized controlled trials, crossover trials • SQ: same as EQ plus we will consider prospective controlled cohort studies if evidence from trials is insufficient • CQ: CEA, CUA, or CBA performed from the	• Editorial, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series; retrospective controlled cohort studies; case-control studies; other observational study designs without a comparator group not already specified

	societal or payor perspective	• Relevant systematic reviews will be excluded but will be hand searched to identify potentially eligible primary studies • Studies with fewer than 10 individuals in each arm will be excluded.
Setting	• Countries categorized as "very high human development" on the United Nations Development Programme's HDI Report6[a] • Inpatient settings • Outpatient settings, community and residential (e.g. group homes, long-term care facilities) • For Cost Outcomes, primarily rely on US studies	• Countries not categorized as "very high human development" according to the United Nations Development Programme's 2018 Human Development Report6 • No exclusions based on care setting

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; PICOTS = population, intervention, comparator, outcome, timing, and setting; RCT = randomized controlled trial; SQ = safety question

[a] Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Costa Rica, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Palau, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay.

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