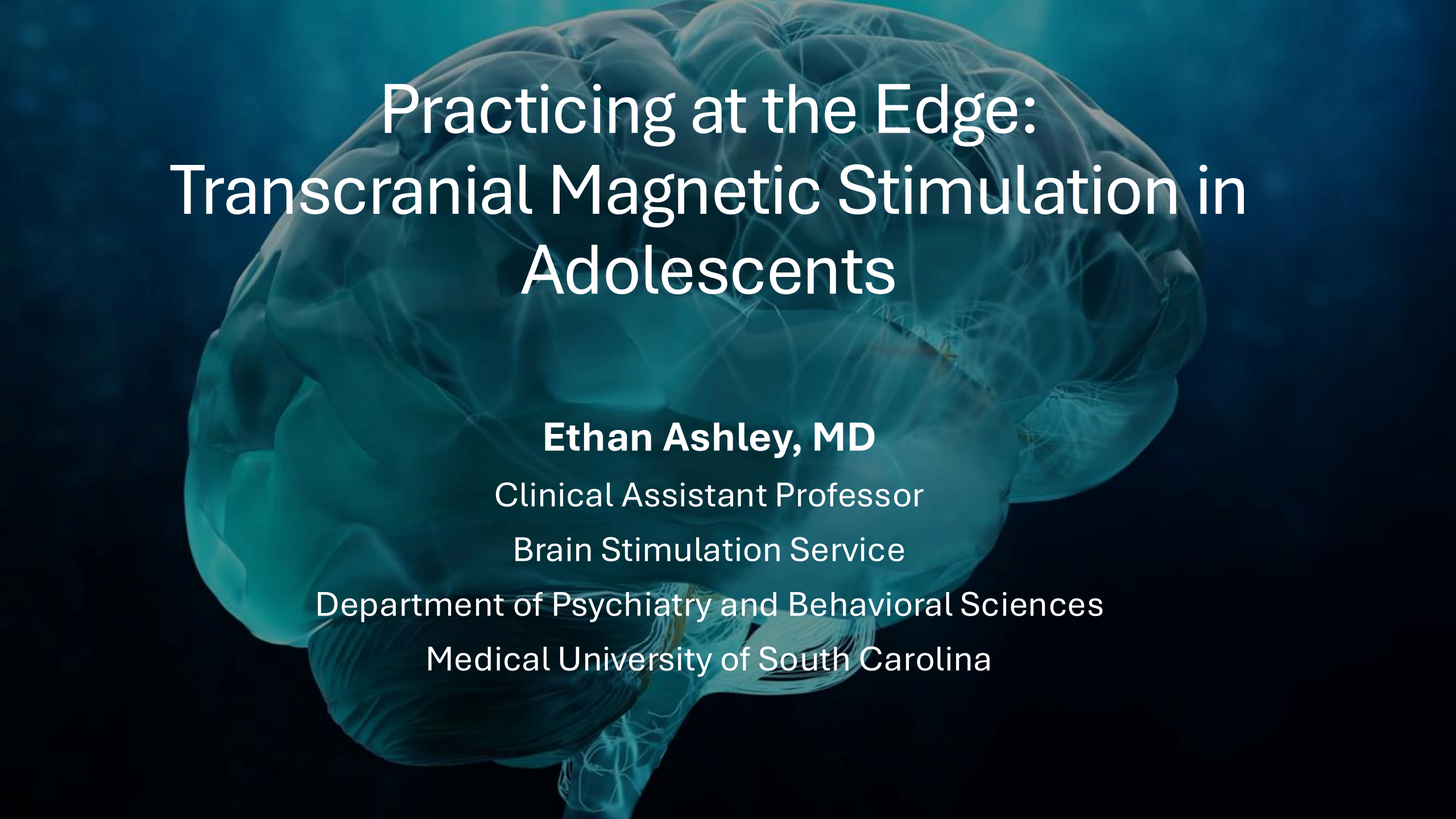

Practicing at the Edge: Transcranial Magnetic Stimulation in Adolescents

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Disclosures

Financial- None

BC Adult Psychiatrist, not BC/BE CAP

Lecture Objectives

1. Review prevalence and criteria for Treatment-Resistant Depression
2. Describe the mechanism of action for transcranial magnetic stimulation in the treatment of depression.
3. Evaluate established/emerging evidence for the use of TMS in pediatric populations.
4. Identify appropriate indications and safety considerations for TMS in children and adolescents.
5. Apply TMS protocols in pediatric care while monitoring treatment response and adverse effects.
6. Review MUSC clinical cases of adolescent TMS treatment

MUSC Patient- GL (17 yo F in 2025)

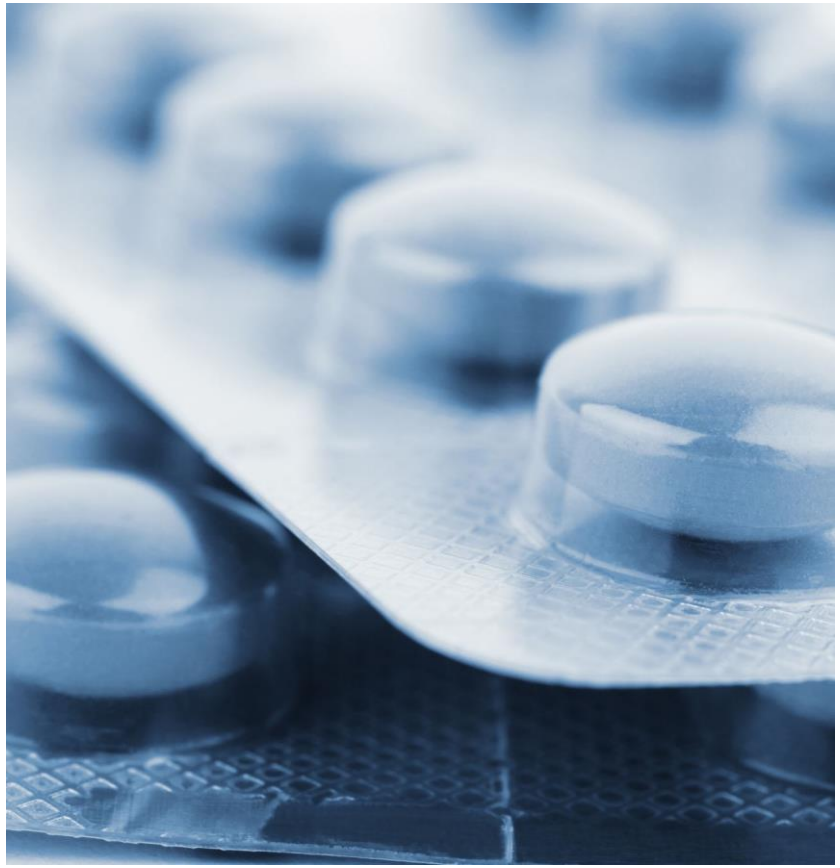
“I struggled with depression for six years. Everything felt hopeless, and I was plagued with constant thoughts of suicide. Numerous methods were used to help me: different medicines, continuous prayers, and more therapists. It didn’t get better. I stopped thinking it would. By my junior year, I was barely a human, just a shell. I couldn’t move, eat, or even will myself to live. At the time, the only logical solution was to kill myself. So I tried. And I failed. My parents knew they needed to try something different, so they researched TMS, contacted MUSC and got me scheduled. I was open to treatment, but I doubted much would change. At some point over the previous six years, depression became my baseline.”

Depression in the Adolescent population

- Global prevalence of depressive symptoms in adolescents has risen significantly, increasing from 24 % (2001–2010) to 37 % (2011–2020) (Daly 2022; Shorey et al., 2022).
- U.S. rates of adolescent MDD climbed from 8.1 % to 15.8 % between 2009–2019 (Daly 2022; Shorey et al., 2022).
- In that time, 40% increase in adolescent suicide rates, with 50–79% of suicide attempts linked to depressive symptoms (CDC; LeFevre 2014)
- 26% mean increase in depression symptoms in child/adolescent patients during the COVID-19 pandemic (Madigan et al., 2023)
- Prevalence ratio for depression was 2.54 (95% CI: 2.48, 2.60) in post COVID-19 period when compared with pre-pandemic (Wang et al., 2022)
- 2021: 20.1% of adolescents (12-17) had at least 1 depressive episode. 74% with severe impairment. (NIMH 2023)

Treatment-Resistant Depression (TRD)

- Failure to respond to at least **2** medications (2 different classes)
  - Adequate **dose** and **duration**
- Lack or response or medication intolerance
- Adolescents: ~40% fail to respond to initial medication or psychotherapy (Strawn et al., 2020)
- Once someone fails a medication, should they try a second? third? fourth?



STAR*D (adults)- Antidepressants have diminishing returns

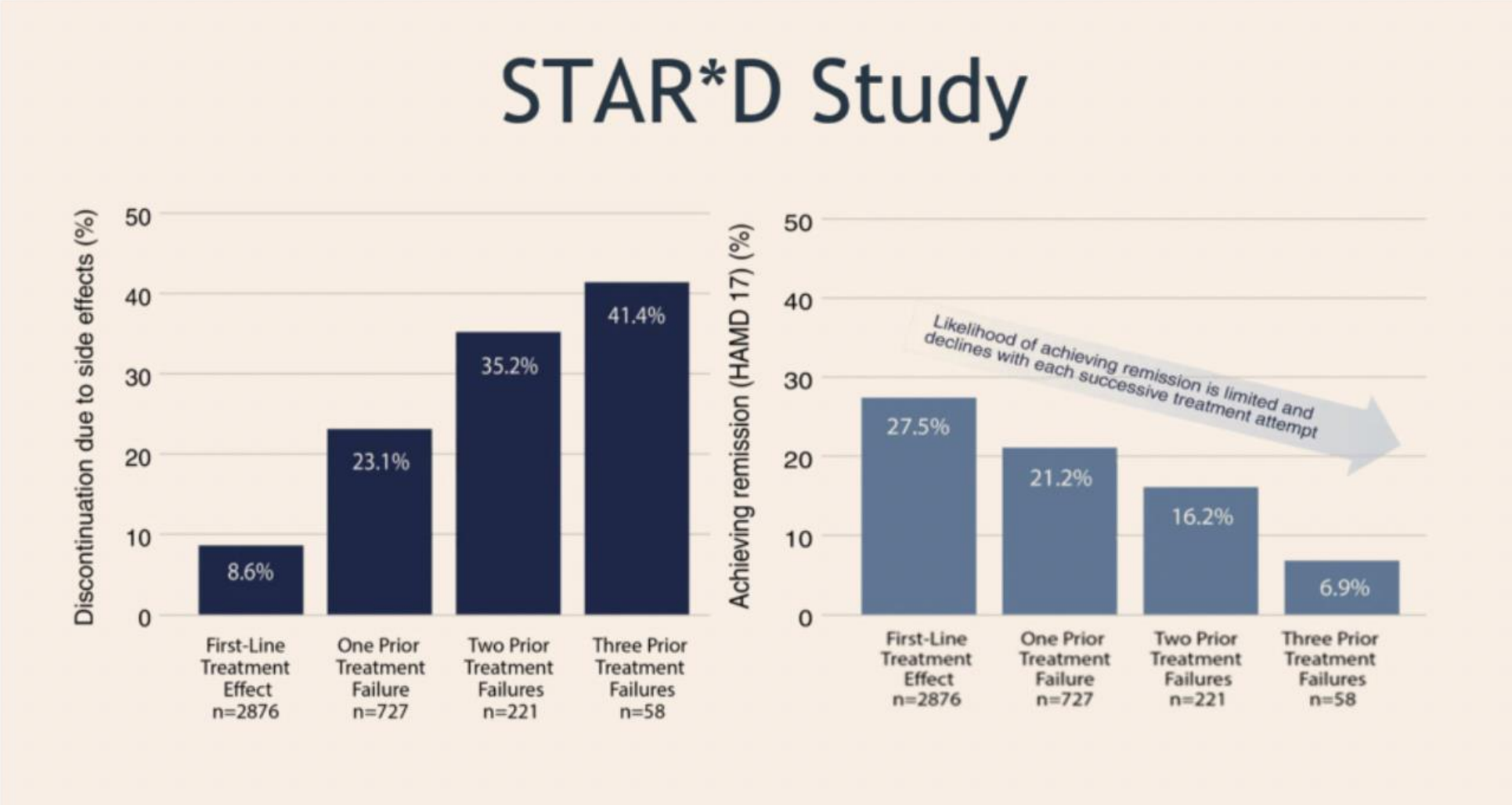


Image: Brink, Clear Path Psychiatry, 2024

TORDIA Study (Brent et al., 2008)

- 6-site RCT, 2000-2006
- Ages 12-18, 334 participants randomized, 231 completers
- Non-responders to initial SSRI Treatment for 2 months
- Clinically significant depression
  - (Children's Depression Rating Scale-Revised [CDRS-R]) total score of at least 40
- Goal: look at response rate at 12 weeks with switch to another SSRI vs Venlafaxine vs med+CBT

The headline result: equal efficacy, more side effects

SSRI switch — wk 12 response

47.0%

95% CI: 40–55%

Venlafaxine — wk 12 response

48.2%

95% CI: 41–56%

Difference (p = .83)

+1.2%

Not significant

Switching to a second SSRI was equally efficacious as switching to venlafaxine (48.2% vs 47.0%, p = .83), but venlafaxine produced significantly more cardiovascular side effects and skin problems.

12-week response rate with combination (**Med + therapy**) group: **54.8%**

<u>Important point:</u>

Almost half of the initial non-responders are still not having response after 2nd medication (+/- psychotherapy)

Brent et al., JAMA 2008 · n=334 · SSRI-resistant adolescent MDD

Do we have other options to help these patients?

“Time is Brain”

- Longer time to treatment correlates with poorer response/remission rate
  - Bukh et al., 2013
  - Ghio et al., 2015

- TADS Trial Secondary Analysis: Shorter depressive episodes predicted better outcomes. (Scott et al., 2019)

- more failed trials = more resistance to treatment

What if we could intervene earlier and more effectively?

Transcranial Magnetic Stimulation (TMS)

Higgins & George, Brain Stimulation Therapies, 2008 *Fig 6-1, Page 98*

The Mechanism of TMS: The Physics Chain

Capacitor discharge

~2,000 V → 5,000 A

→

Changing Magnetic field

dB/dt ~1–2 T pulse

→

Induced Electrical field

Faraday's law

→

Action potential

Neuron fires

Ampère's law

Current in a wire generates a magnetic field that circulates around it. More current → stronger B.

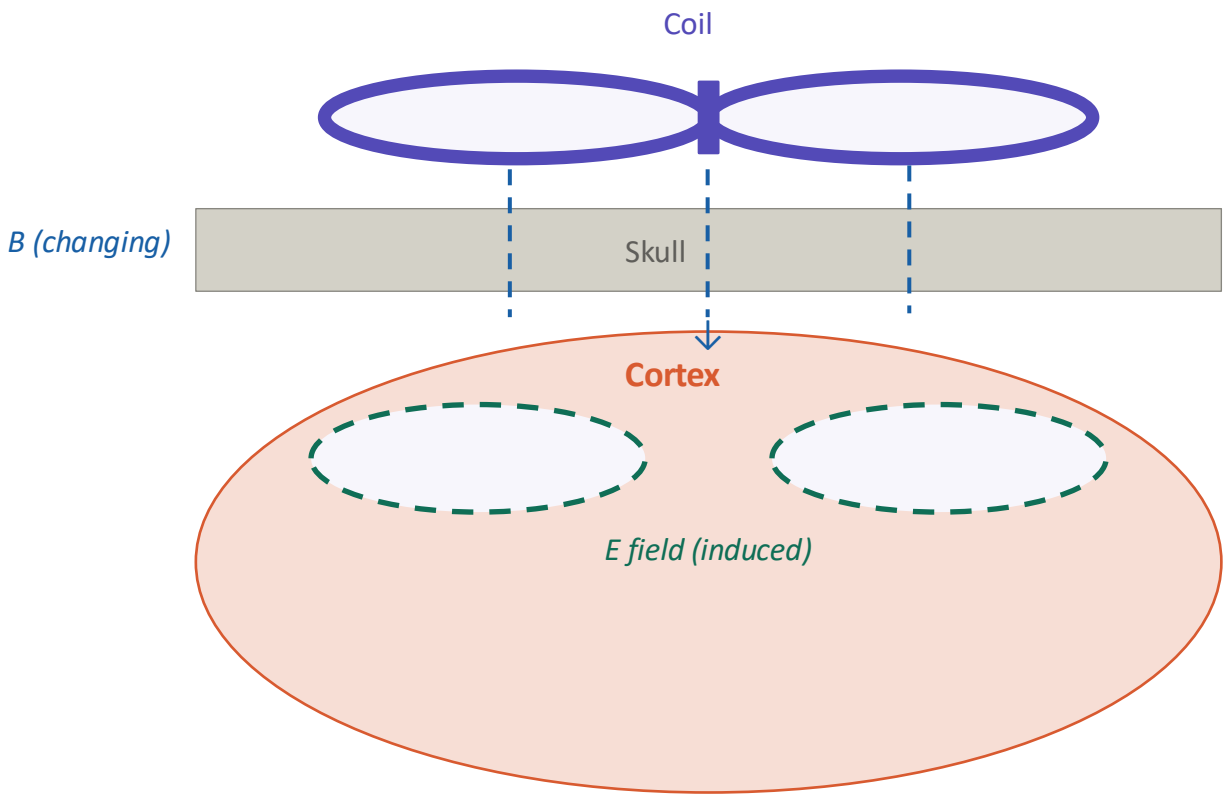
Faraday's law

A changing magnetic flux induces an electric field in conductors. Faster change → stronger E field.

Why it's safe & non-invasive

Bone and scalp are electrically resistive but magnetically transparent — the B field passes through unimpeded. Only electrically conductive tissue (ex. neurons) responds to the induced E field. The pulse is so brief (~200 µs) that no significant heating occurs.

Field induction — Faraday's law at work



What changes?

The magnetic flux (Φ_B) through the cortex changes as the coil current rapidly rises then falls.

What does it create?

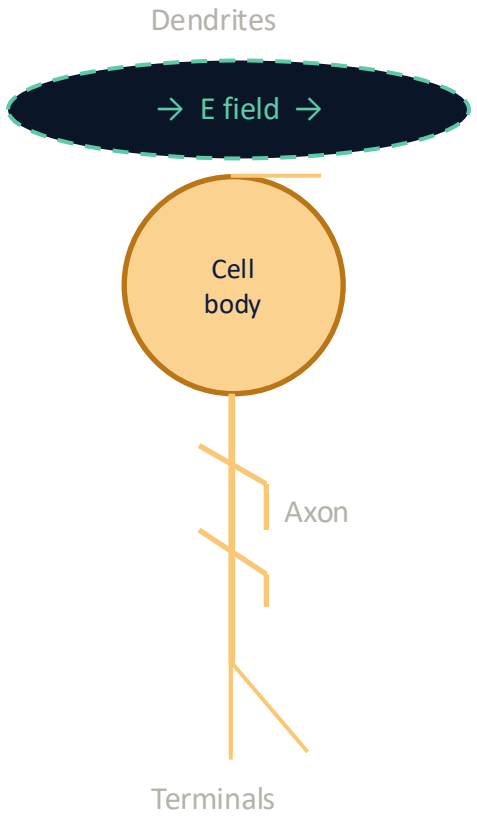
A changing flux induces a closed-loop electric field (E) in the conductive tissue, perpendicular to magnetic field.

Why figure-8?

Fields from both loops add at the center, cancel at the edges — focusing E to a ~1–2 cm target area.

The skull and scalp offer no resistance to the magnetic field — it passes straight through to the cortex.

Neuron firing — from E field to action potential



1

E field reaches membrane

The induced electric field (~100–150 V/m) reaches the neuronal cell membrane

2

Membrane depolarization

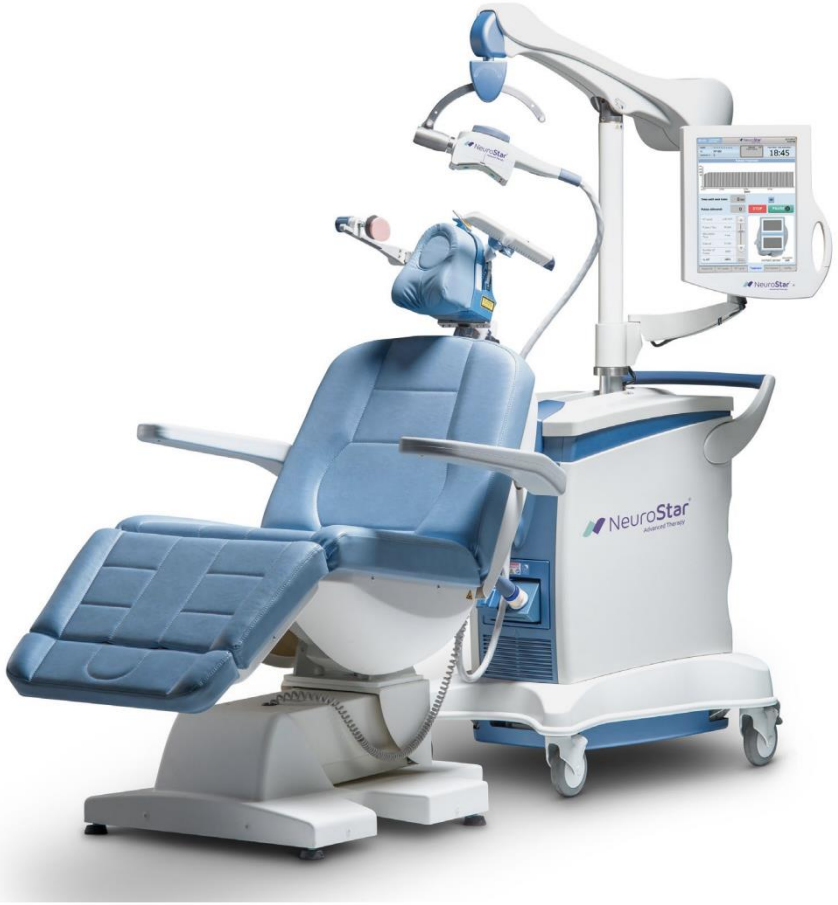
When the local potential crosses the threshold (~−55 mV), voltage-gated Na^+ channels open rapidly.

3

Action potential propagates

The depolarization wave travels down the axon, releasing neurotransmitters at synapses and recruiting neural circuits.

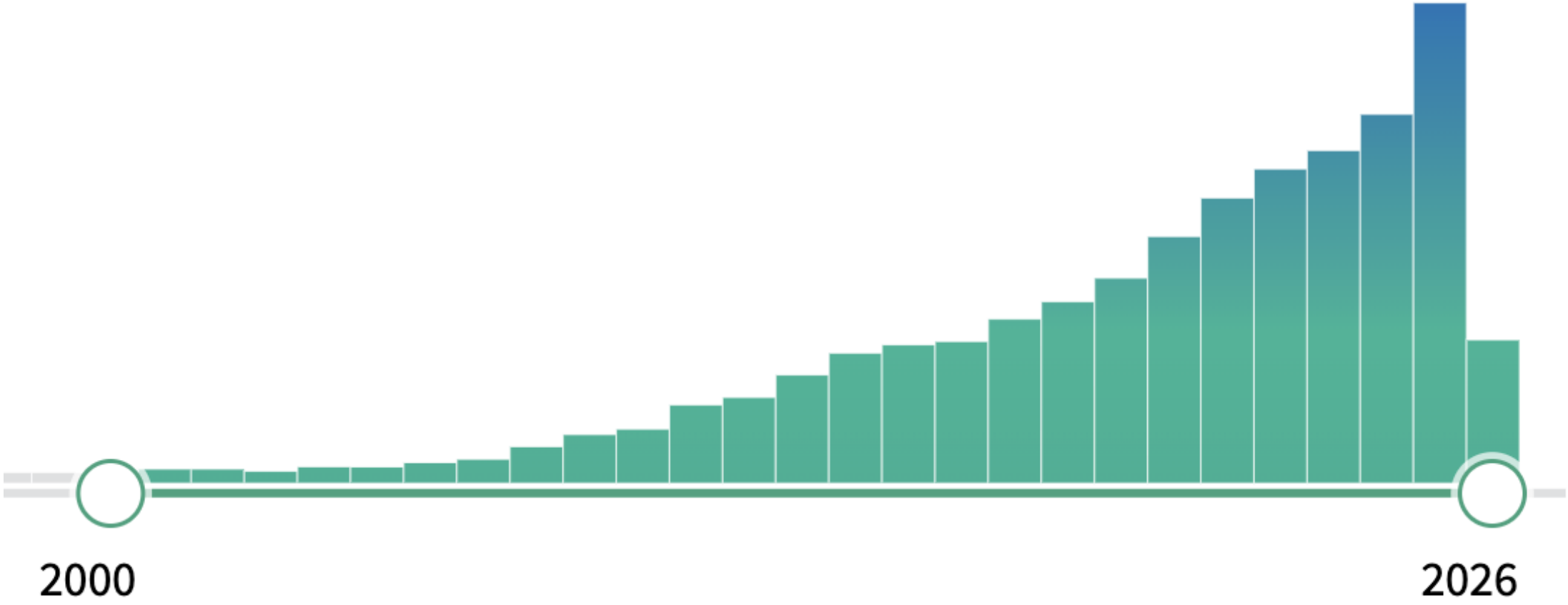
TMS Devices



Images: Neuromodec.org, 2024

TMS Research in Adolescents

Adolescent TMS-related Publications (PubMed)



cTBS: continuous theta burst, Hz: hertz, iTBS: intermittent theta burst, LDLPFC: Left Dorsolateral Prefrontal Cortex, RDLPFC: Right Dorsolateral Prefrontal Cortex, SMA: Supplementary Motor Area

Evidence for TMS in Adolescents (Croarkin et al., 2019)

References	N	Mean Age (yrs)	Frequency	Intensity	Location	Clinical Outcome
Walter et al. 2001	4	16	1–10 Hz (variable)	90–110%	LDLPFC	2 responders (one non-responder had bipolar depression)
Loo et al. 2006	2	16	10 Hz	110%	LDLPFC	2 responders
Bloch et al. 2008	9	17	10 Hz	80%	LDLPFC	3 responders 1 partial responder
Wall et al. 2011	8	16	10 Hz	120%	LDLPFC	6 responders
Mayer et al. 2012 (3 year follow-up from Bloch et al. 2008 study)	8	17	10 Hz	80%	LDLPFC	Improvement in depressive symptoms was durable at follow-up
Le et al. 2013	25	11	1 Hz	110%	SMA	Group level improvement in depressive symptoms
Yang et al. 2014	6	18	10 Hz	120%	LDLPFC	4 responders
Wall et al. 2016	10	15	10 Hz	120%	LDLPFC	6 responders
Farzan et al. 2017	16	21	iTBS and cTBS	80%	LDLPFC (iTBS) RDLPFC (cTBS)	4 responders 9 partial responders
MacMaster et al. 2018	32	17	10 Hz	120%	LDLPFC	18 responders

A few years later… (Roth et al., 2025)

2 studies- no benefit over sham treatment

- Croarkin et al., 2021 (largest sham-control study to date for TRD monotherapy)
- Zhang et al., 2024 (adjunctive)

5 studies demonstrating positive outcomes

- Pan et al., 2020
- Zhao et al., 2023
- Zhang et al., 2017
- Han et al., 2019
- Jiao et al., 2024

TMS FDA approval timeline

- 2008- original TMS approval for MDD in adults
- March 2024- Neuronetics (Neurostar) received indication for adjunctive treatment in adolescents (ages 15-21)
- March 2025- Magstim approval
- August 2025- MagVenture approval
- Nov 2025- Brainsway Deep TMS approval
- Both TMS and deep TMS approvals based on large RWE

Neurostar- TrakStar® platform data

- Croarkin et al 2025, abstract data presented at 2024 annual AACAP conference, later published June 2025
- Retrospective analysis of 1,283 adolescents (ages 12-21)
- 70% achieved clinically meaningful improvement in depression severity
- 59% response rate, 30% remission rate (PHQ-9)
  - No significant difference between adolescents and young adults (mean age of 18.1 and 20.5)

- What lead to FDA approval: This data + 14 published studies = 1,812 adolescents

Some of the other RCT studies considered

- **Ren & Pu (2022)** — RCT, n=107, ages 8–18. Active TMS + sertraline vs. sertraline alone. Primary measure: HAMD-24. The active group showed a 21.27-point greater reduction at week 4 ($p<0.005$). No sham control for device placebo effect.
- **Chen et al. (2022)** — Prospective RCT, n=97, ages 12–18, first-episode MDD. Active rTMS + sertraline vs. sertraline alone (2 weeks TMS + 4 weeks sertraline). HAM-D reduction −10.54 vs. −6.27 ($p<0.001$); CDRS-R reduction −27.73 vs. −4.23 ($p<0.001$). No sham device
- **Lu et al. (2020)** — RCT with sham, n=116, ages 12–18, first-episode. Active TMS + sertraline vs. sham TMS + sertraline. HAMD-24 reduction −14.10 vs. −7.10 ($p<0.0001$).
- **Qiu et al. (2021)** — RCT, n=100, ages 13–19, severe first-onset MDD (HAMD-24 ≥35). Active TMS + sertraline/aripiprazole vs. medication alone, 6 weeks. HAMD-24 reduction −35.14 vs. −31.10. No sham device.
- **Pan et al. (2020)** — Double-blind RCT with sham, n=42, treatment-naïve MDD patients with suicidal ideation, ages ~18 (active group mean 18.14 ± 3.94). Active rTMS + escitalopram vs. sham + escitalopram, 7 continuous days. Significant improvements on HAMD-24, MADRS, and Beck Suicide Ideation scale (all $p<0.0001$).

What about deep TMS?

Thai et al., 2024

- Open-label safety/efficacy study- data from 2015-2021
- 15 adolescents with TRD, mean age of 16.4
- BrainsWay deep TMS, 30 sessions, 10 Hz, 1980 pulses per session
- Out of the 14 participants who completed all dTMS sessions, 6 (42.86 %) achieved clinical response by the end of treatment.
- 1 participant withdrew- convulsive syncope
- No seizures
- Common SEs: headache, dizziness, dizziness when standing

More Evidence for deep TMS in Adolescents

"Safety and efficacy of **Deep TMS** for adolescent depression based on large real-world data analysis" (Roth et al 2025)

- Post-marketing surveillance study, ages <22, N=1,257
- Mean med trials: 4.5
- Mean age- 19.3 (range of 11-21), largest naturalistic study for this age group to date
- 62% female
- Limitations: does not account for non-specific/placebo effect, not specific to age <18

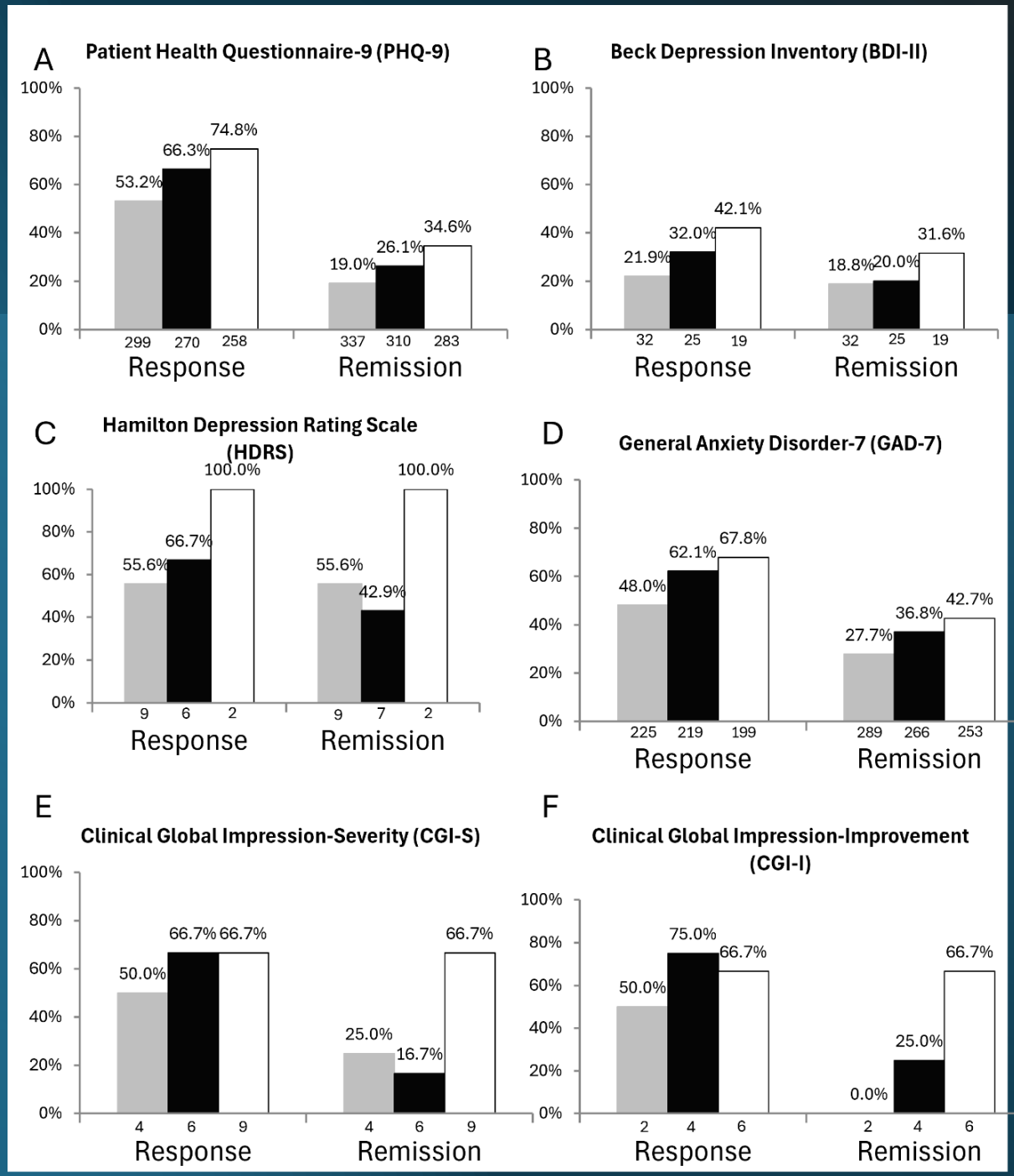


Fig. S3. Remission and response rates for adolescents (aged 11-18) based on individuals that received 20 sessions (gray), 30 sessions (black) and 36 sessions (white) of Deep TMS with the H1 coil. Subsets of data for the PHQ-9 (A), BDI-II (B), HDRS (C), GAD-7 (D), CGI-S (E) and CGI-I (F) are shown. Numbers of patients with available data are shown below the bars.

Study Safety/Side Effects

- 1 seizure (0.08%)
- No other serious adverse events
- Other side effects:

  headache (0.32 %),

  slight headache (0.08 %),

  tooth pain (0.16%),

  fatigue (0.24 %)

  left side mouth pain (0.08 %).

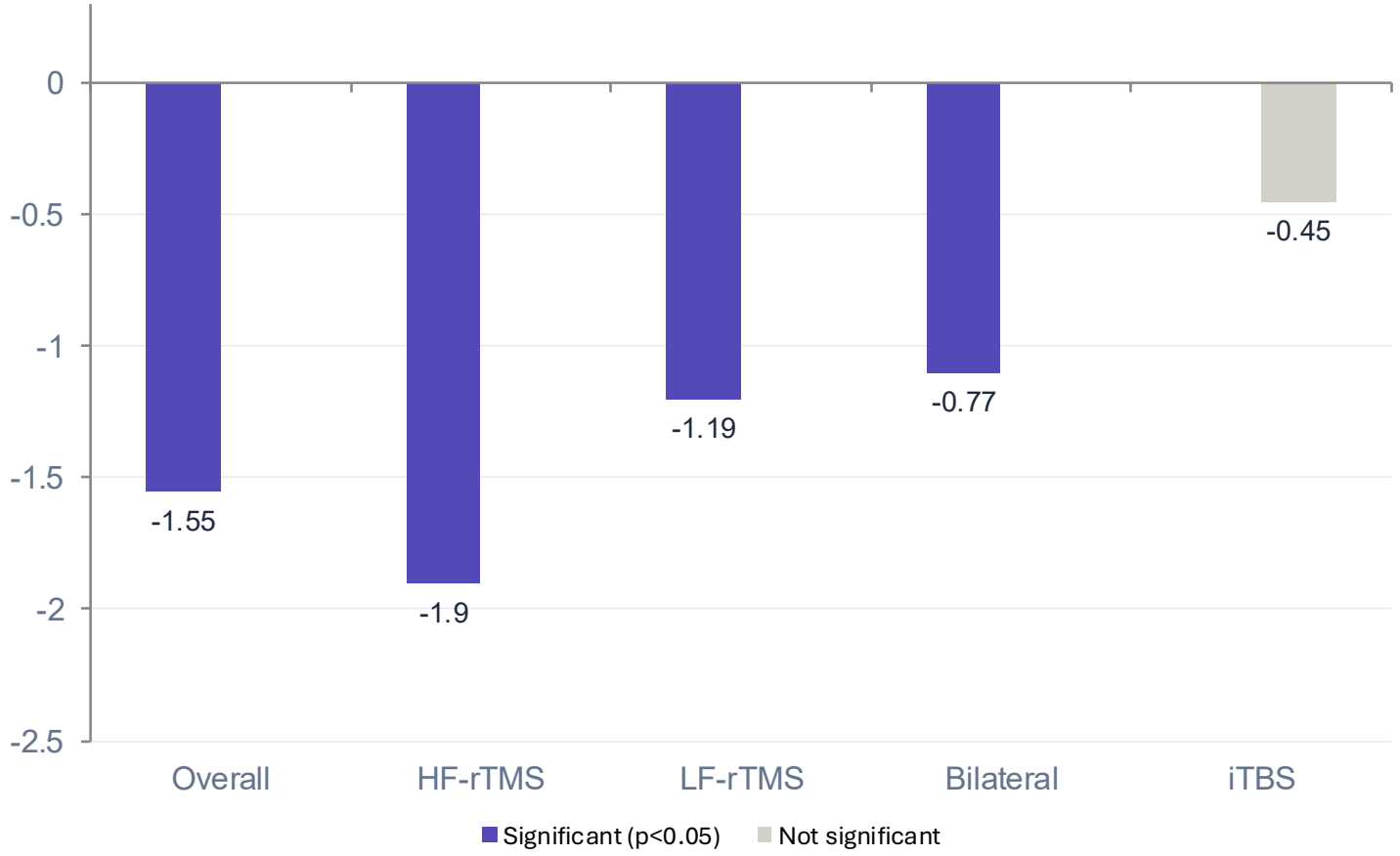
TMS in youth depression — meta-analysis (Wang et al., 2026)

RCTs included
34
searched to Feb 2025

Total patients
2,705
ages ~8–24 years

Overall SMD
−1.55
95% CI −1.88 to −1.23 p<0.001

Heterogeneity (I^2)
93%
very high — interpret with caution



HF-rTMS = strongest

SMD −1.90 (CI −2.42 to −1.37)
Largest effect of any modality

iTBS = inconclusive

SMD −0.45, CI includes zero
More RCTs needed

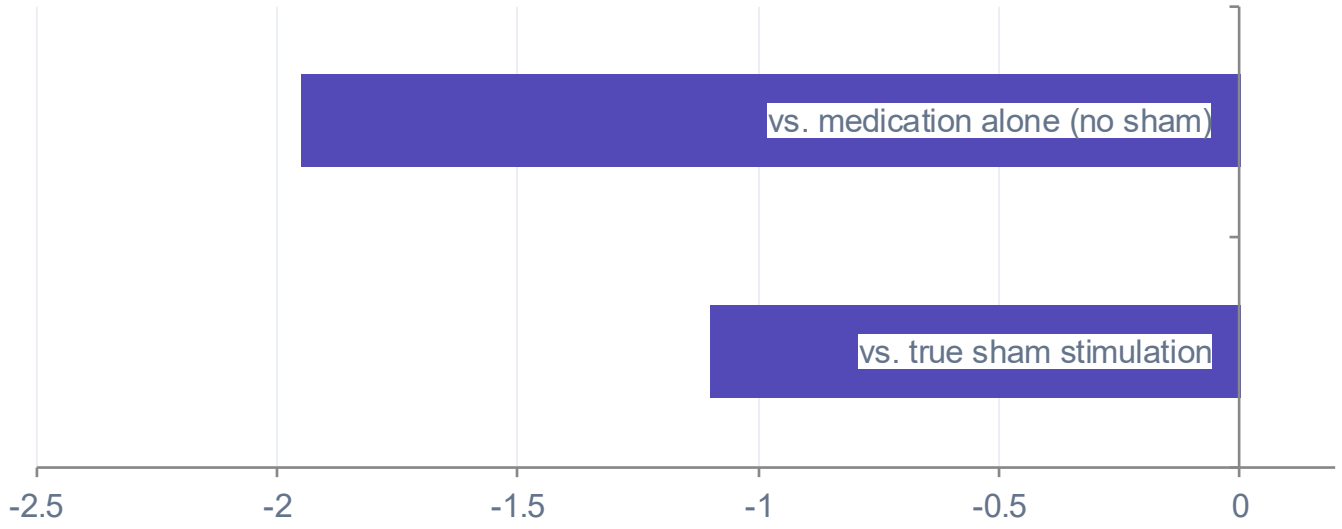
Adverse events OR 1.71

More AEs with TMS but mild:
headache, discomfort, dizziness

Dashed reference line at 0 = no effect | Negative = better than control

Subgroup: control type & key caveats

Effect size varies substantially depending on what TMS was compared against



Why this matters: studies without a sham device overestimate TMS's specific benefit because placebo effects are uncontrolled.

! Very high heterogeneity (I^2 = 93%)

Studies differ widely in population, protocol, and outcome scale. Pooled SMD is a rough average.

! Mostly first-episode Chinese patients

The majority of trials enrolled drug-naïve, first-episode adolescents in China — not the SSRI-resistant Western population seen in US clinics.

! iTBS not yet proven in youth

Despite growing real-world use and FDA clearance, RCT evidence for iTBS specifically in adolescents remains insufficient.

! Optimal protocol undefined

No consensus on dose, frequency, number of sessions, or target for youth. Developmental differences likely affect dose-response.

Bottom line

TMS is safe and effective in youth depression, particularly HF-rTMS. But high heterogeneity and a predominantly first-episode Chinese evidence base mean these effect sizes likely overestimate benefit for the treatment-resistant Western adolescent population seen in US clinical practice.

Wang X, Zhang Z, Li Y, Gao Y, Cao Q. J Affect Disord. 2026 Jan 1;392:120132. Epub 2025 Aug 25. doi: 10.1016/j.jad.2025.120132

TMS Risks/ Side Effects

- Very mild risk of inducing seizure (0.003% in adults per APA) – usually with underlying risk already
  - similar risk in adolescents compared to adults
  - Higher risk with CNS disorders (0.14% risk) (Stutz et al., 2020)
  - Higher risk- Seizure Hx, Seizure threshold-lowering meds, ETOH consumption
- No mortality risk noted in the literature
- Common Side Effects:
  - Headache
  - Eye Pain
  - Skin irritation (“wood pecker tapping”)

Prevalence of SEs in Child/Adolescents- *Krishnan et al.*, 2015

35 studies involving 322 children/adolescents (2.5-17.8 years of age)

- Seizures (2)(0.62%)
- Syncope (2)(0.62%)
- headache (11.5%),
- scalp discomfort (2.5%)
- twitching (1.2%)
- mood changes (1.2%)
- fatigue (0.9%)
- tinnitus (0.6%)

rTMS logistics

- Full course- 36 sessions, daily, Mon-Fri (about 8 weeks)
- 20 min sessions (rTMS)
- No anesthesia
- Talk, listen to music, watch content on phone/tablet, silence
- Able to drive yourself to sessions

“Accelerated” TMS for Adolescents?

- Nakano et al., 2023
  - Small case series of 6 patients (ages 16-18) receiving accelerated iTBS
  - 3 achieved remission, 2 achieved response (via PHQ-9)
  - No serious adverse events, 2 reported mild headache
- Liu et al., 2025
  - Chinese RCT with sham control, 2 days of iTBS (10 sessions total)
  - 22 in active group, 19 sham (average age of 15.5)
  - iTBS showed separation from sham in MADRS reduction (mean of 9.48 after 2 days compared to 5 in sham)
  - No serious adverse events, 12 reported headaches
- Ongoing Trial: SAINT-KID
  - Open-label trial, SAINT protocol for treatment-naïve patients ages 14-19
  - 2 arms- 5 or 10 sessions per day for 5 days

Who is a TMS candidate?

- **UNIPOLAR Depression** -> **MDD** in Adults and Adolescents (**15 years** and older)
- OCD, Smoking Cessation (FDA approved in adults only)

- **Not FDA approved:**
  - Bipolar Disorder
  - Acute/Chronic Psychotic Disorders
- **Needs Considerations/Possible Contraindications**
  - cochlear implant, implanted cardiac defibrillator (ICD), pacemaker, vagus nerve stimulator (VNS), implanted metal- aneurysm clips/coils, staples, or stents
  - Seizure Disorder
  - Acute Suicidality or need for inpatient treatment

Are these treatments covered by insurance?

- **YES:**
  - Humana
  - Aetna
  - Cigna/Evernorth
  - Optum
  - BCBS Federal
  - HCSC (BCBS IL, MT, NM, OK, TX)
  - Premera Blue Cross (AK, WA)
  - Highmark BCBS (DE, NY, PA, WV)
  - **BCBS North Carolina**
  - BCBS MI, LA, MS, SC
  - Med-Cal (California Medicaid)
- **NO**
  - Medicaid

General Insurance Criteria

- Moderate-Severe MDD (verified by a scale- PHQ9, HAMD, MADRS, BDI, etc.)
- Has failed at least **2** medications in **2 classes** (dose/duration)
  - Some require more med trials +/- augmenting medication
- Trial of psychotherapy sometimes required
- No contraindications
- No active substance use disorder

NeuroStar
Advanced Therapy for Mental Health

TMS Coverage For **MDD** Key Medical Necessity Criteria

June 2026

This resource is for informational purposes only on various plans. They are not to be interpreted in the strictest sense, based on this disclaimer. Practitioners may make medical decisions based on this information; therefore, it is incumbent on them to read the payers' Medical Policy in its entirety.

AcronymGlossary
UDS = Under Direct Supervision
DSE = Distinct Side Effects
BC = Board Certified
PCM = Primary Care Manager
BCLS = Basic Cardiac Life Support

NATIONAL PAYERS

Insurance	State	Age	Dx	Provider Type		Medications Trials		Psycho-therapy	iTBS [a]	Utilization
				Order	Treatment	Resistance	OR Intolerance			
UHC/UBH Optum	National	15	Severe MDD	Psychiatrist (MD, DO, NP[b])	Psychiatrist Supervision (MD, DO, NP[b])	2	2 with DSE	Not Required	No	30+taper
		18				2 (different classes)	2 (different classes) with DSE			
Aetna	National	15	Severe MDD	Psychiatrist (MD, DO, NP)	UDS of Psychiatrist (MD, DO, NP)	2 (different classes) + 1 augment, 8 weeks, within the last 5 years		Not Required	Not Specified	30+taper
Cigna/Evernorth	National	15	Moderate-Severe MDD	Not Specified	Not Specified	2, 4 weeks	2 with DSE	Failed Trial Required	No	36
		18				2 (different classes), 4 weeks	2 (different classes) with DSE			
BCBS Federal Employee Plan	National	15	Severe MDD	Not Specified	Healthcare Professional trained in BCLS	2 (different classes), 6 weeks	1 with DSE	Failed Trial Required	Yes	30
BCBS N Carolina	NC	15	Severe MDD	Not Specified	Not Specified	2 (different classes)	2 with DSE	Failed Trial Required	Not Specified	36

Some Clinical Cases

MUSC CASE PRESENTATION | TRD— 14 yo Female, 2022

PATIENT INFO

Age	14
Sex	Female
Diagnoses	MDD; Unspecified Eating Disorder
Onset	Middle school

TREATMENT

- Current Therapist
- MD psychiatrist for medications
- 2 prior psychiatric admissions

SAFETY HISTORY

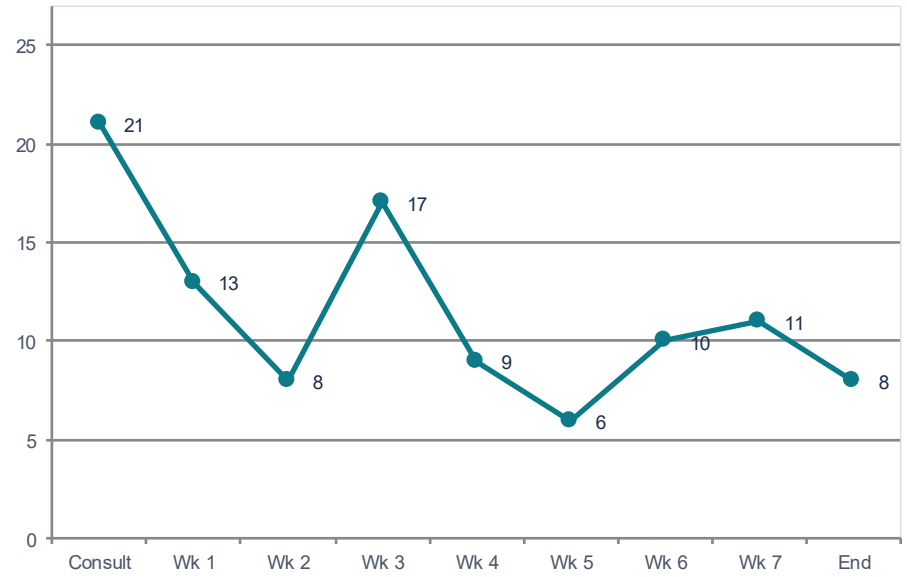
SA #1: Unspecified OD (July 2021)

SA #2: OD — isopropyl alcohol (June 2022; 2 mos prior to presentation)

REPORTED SYMPTOMS

- Depressed Mood
- Decreased Appetite
- Low Energy
- Poor Concentration
- Poor Sleep
- Anhedonia
- Hopelessness
- Chronic Suicidal Ideation

PHQ-9 Over Treatment Course



MEDICATION TRIALS

CURRENT

SNRI	Mood Stabilizer
Venlafaxine	Lithium

PRIOR TRIALS

SSRI	SSRI	SSRI
Fluoxetine	Sertraline	Escitalopram
No response	Intolerance	Intolerance

Med Summary:

3 SSRI/1 SNRI/1 Augmenting agent — intolerance/lack of response

MUSC CASE PRESENTATION | TRD— 16 yo Female, 2026

PATIENT INFO

Age	16
Sex	Female
Diagnosis	MDD
Onset	4th grade (age 9–10)
Duration	6–7 years

TREATMENT

- Therapy — every other week (past 3–4 years)
- No prior hospitalizations
- CAP Psychiatrist (medication management)

SEVERITY (Feb 2026 Consultation)

PHQ-9: 26 (Severe)
BDI-II: 51 (Severe)

REPORTED SYMPTOMS

- Hypersomnia
- Anhedonia
- Hopelessness
- Low Energy / Anergia
- Poor Concentration
- Appetite Decrease
- Frequent Crying Spells
- Self-Harm (cutting; last episode 2 wks prior to presentation)
- Suicidal Ideation (plan; no intent)

MEDICATION TRIALS

1st · SNRI	2nd · SSRI
Duloxetine	Sertraline

3rd · SSRI	4th · SSRI+NDRI
Fluoxetine	Fluoxetine + Bupropion XL

⚠ 4 trials, 3 classes — inadequate response

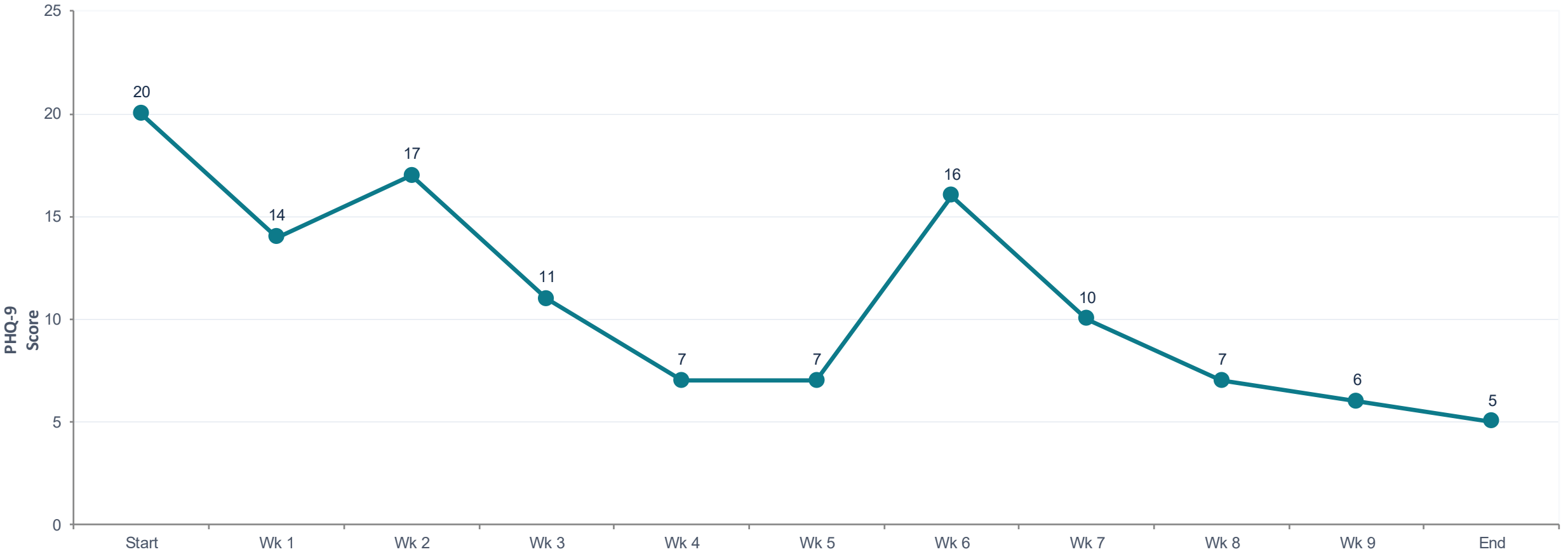
MUSC CASE PRESENTATION | PHQ-9 Scores Over Treatment Course

START OF TX
20 *Severe*

END OF TX
5 *Mild*

REDUCTION
75% *Improvement*

Severe (≥20)
Mod-Severe (15–19)
Moderate (10–14)
Mild (5–9)
Minimal (<5)



Evidence for extension (in adults)

Razafsha et al., 2022

- 28 non-responders after 36 sessions kept going for avg of 70 sessions
- 53.57% response rate and a 32.14% remission rate

Hutton et al., 2025

- “37–41 Sessions” group, following the 30th session, response rate increased from 45.9 to 61.6% and the remission rate increased from 14.7 to 29.7%
- In the “>41 Sessions” group the response rate increased from 34.0 to 53.6% and the remission rate increased from 8.5 to 20.9%
- No evidence of improvement plateau

TMS in other CAP Diagnoses

- El-Shahawy et al., 2025- Review of research in other diagnoses
- Limited, but safe/promising results in some other CAP illnesses
  - Tourette's Syndrome- high, 3 RCTs (~100 patients) with promising data
  - OCD- moderate,1 RCT, 3 pilot studies, ongoing trial: NExT
  - ASD- low, promising open label studies, RCTs mixed results
  - ADHD- low, 3 open label studies with potential but inconsistent

Important Take Home Points….

- TMS is a safe and effective treatment for adolescent TRD
- Earlier intervention = higher probability of response/better outcomes
- Data supports pursuing TMS in Adolescent TRD (and even treatment-naïve patients)
- There is a need for more sham RCTs in the adolescent TRD population (and other CAP diagnoses) and more standardized protocols to decrease literature heterogeneity
- TMS is indicated for adolescents age 15 and older after at least 2 medication trials (2 classes) for unipolar, severe depression
- There is now expanded insurance coverage and device approval for TMS use in adolescents

Gracyn’s Story

Following up: patient GL after TMS course

“After treatment was complete, I experienced a gradual change and felt as if I was slowly waking up. Everyone around me could tell there had been a change, and eventually, I realized it too. I was happy. I realized for the first time in six years, I was truly content and ready to live. Before healing, all I wanted was a way out. Everyone said it would get better. I got so sick of hearing it and criticized them for their naive hope. But they weren’t naive. In reality, they were right. It does get better. With TMS, I was given a way to escape without sabotaging myself, something I never thought possible. Not only did I escape, but I grew and adapted. The haze which clouded my entire world for the past six years was replaced with clarity and a sense of freedom. I was given happiness I hadn’t felt in years and energy to dream. My recovery gave me hope. It fostered my interest in medical technology, empowering me to choose biomedical engineering as a major. It allowed me to pursue this interest by being accepted into [college]. But most of all, it allowed me to keep living. I want other teenagers to know that there is help, that TMS treatment can work, and that it can save your life. I didn’t think I would live to see senior year, let alone be in a place where I could think about my future. However, thanks to TMS, I am here; I got better; and I am shaping the future I thought I’d never see.”

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Questions?