DISCLOSURES

| Source | Employment | Educational Institution | Research | Speaking | Consultation | Travel | Other
|--------|------------|-------------------------|----------|----------|--------------|-------|--------
| American Academy of Child and Adolescent Psychiatry (AACAP) | X | (Sponsorship & CAGP) | | | | |
| Brain and Behavior Research Foundation (NARSAD) | X | | | | | |
| Clinical TMS Society | X | | | | | |
| Engrail Therapeutics, Inc. | X | | | | | |
| MagVenture, Inc. | X | | | | | |
| Magyn Ehr | X | | | | | |
| MedStar, Inc. | X | | | | | |
| MedTech | X | | | | | |
| Pfizer | X | | | | | |
| Providence & Saint Joseph's Company | X | | | | | |
| Myriad Neuroscience | X | (Sponsorship & CAGP) | | | | |
| TMS Health Solutions | X | | | | | |
| Salience TMS Neuro Solutions | X | (Sponsorship & CAGP) | | | | |
| Salient | X | | | | | |

LEARNING OBJECTIVES

• To review recent research focused on the application of TMS to adolescents and young adults.
• To discuss challenges and future related innovations and direction to address this unmet need.
THE CHALLENGE…


DEFICITS AND OPPORTUNITIES

Repetitive Transcranial Magnetic Stimulation for Adolescent Major Depressive Disorder: A Focus on Neurodevelopment

Lindsey M. O'Brien, Megan Heed, blair M. Watson, Kenneth E. Twining, Karen M. Leer, and Margot McFarland

National Institute of Mental Health, Bethesda, MD, United States

Meet protocol-defined treatment benefit?

Phase I
Randomized, sham-controlled
1:1 active/sham
30 treatments, 6 weeks

If symptoms worsen, acute course of known active TMS offered for up to 6 weeks until symptoms return to level recorded at entry into Phase III, followed by taper phase.

Yes

3-week taper, 6 treatments

No

Meeting criteria, onward to Phase II

3-week taper, 6 treatments exit trial

Phase II
Non-randomized, open-label
30 treatments, 6 weeks

Yes

3-week taper, 6 treatments

No

Phase III
Non-randomized, open-label,
6-month follow-up

3-week taper, 6 treatments

PHASE III

Entering Phase III, n=65
Completed Phase III, n=41
Discontinued prior to end of month 6, n=24

Patients entering retreatment, n=28

PHASE III

Reasons for Discontinuation (n=24)

Satisfactory Response (efficacy) n=1
Unsatisfactory Response (efficacy) n=5
Adverse Event n=2
Failed to Return n=7
Subject Request n=4
Symptoms Worsened n=1
Other n=4

PHASE III OUTCOMES HAMD24

<table>
<thead>
<tr>
<th></th>
<th>Baseline Score (SD)</th>
<th>Month 3 Score (SD)</th>
<th>Month 3 Change</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I Active</td>
<td>17 27.3 (5.86)</td>
<td>16 7.7 (7.43)</td>
<td>-19.1 (7.99)</td>
<td>5.9 (6.13)</td>
</tr>
<tr>
<td>Phase I Active to Phase II Active</td>
<td>8 27.3 (3.54)</td>
<td>8 12.1 (8.13)</td>
<td>-15.1 (10.20)</td>
<td>7.4 (6.66)</td>
</tr>
<tr>
<td>Phase I Sham to Phase II Active</td>
<td>13 26.2 (3.31)</td>
<td>13 8.1 (7.48)</td>
<td>-18.1 (7.32)</td>
<td>4.3 (3.82)</td>
</tr>
<tr>
<td>Phase I Sham</td>
<td>17 28.2 (6.62)</td>
<td>16 8.7 (7.13)</td>
<td>-19.9 (7.96)</td>
<td>4.4 (4.92)</td>
</tr>
</tbody>
</table>
### PHASE III PATIENTS WITH RETREATMENT

**HAMD24**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy</th>
<th>MDD</th>
<th>TRD</th>
<th>Active rTMS</th>
<th>Sham rTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>19</td>
<td>34</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>70%</td>
<td>57.9%</td>
<td>58.8%</td>
<td>66.7%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>15.60 (2.25)</td>
<td>15.2 (1.8)</td>
<td>16.4 (1.8)</td>
<td>16.3 (2.0)</td>
<td>17.5 (1.2)</td>
</tr>
<tr>
<td>CDRS-R (SD)</td>
<td>19.1 (2.8)</td>
<td>54.1 (8.2)</td>
<td>59.6 (11.4)</td>
<td>50.2 (15.1)</td>
<td>61.4 (8.4)</td>
</tr>
</tbody>
</table>

### NEUROSTRUCTURAL IMPACT OF TRD IN ADOLESCENTS AND POTENTIAL TREATMENT EFFECTS OF TMS

- **Characteristic**
  - Healthy
  - MDD
  - TRD
  - Active rTMS
  - Sham rTMS

- **n**
  - 30
  - 19
  - 34
  - 34
  - 18

- **Female**
  - 70%
  - 57.9%
  - 58.8%
  - 66.7%
  - 71.4%

- **Age (SD)**
  - 15.60 (2.25)
  - 15.2 (1.8)
  - 16.4 (1.8)
  - 16.3 (2.0)
  - 17.5 (1.2)

- **CDRS-R (SD)**
  - 19.1 (2.8)
  - 54.1 (8.2)
  - 59.6 (11.4)
  - 50.2 (15.1)
  - 61.4 (8.4)
Clinical Effectiveness of 1 Hz/20 Hz Bilateral rTMS Treatment in Adolescents with Major Depressive Disorder

- Multisite, naturalistic treatment
- N=201
- Ages 12-22
- 1 Hz delivered to the right dorsolateral prefrontal cortex for 360 pulses, followed by 20 Hz delivered to the left dorsolateral prefrontal cortex for 1200 pulses
- 30-36 sessions
Inhibitory

1 Hz – 20 Hz Excitatory

1 Hz Inhibitory

1 Hz vs 10 Hz TMS

Intracortical Facilitation


GLUTAMATERGIC AND GABAERGIC BIOMARKERS FOR TMS TREATMENT OF DEPRESSION IN ADOLESCENTS
SUICIDE PREVENTION IN 2021 AND BEYOND

Utku Kucukerd, MD

A Systematic Review of Neuromodulation Treatment on Suicidality

Introduction: Neuromodulation is an important part of therapeutic modality for neurovascular abnormalities. Here, studies have been done to differ with diverse interventions with neuromodulation. Since it seems regarding control of emotional and treatment of suicidal behavior, this systematic review sought to evaluate the effects of various neuromodulation techniques on suicidality. Methods: A systematic review of the literature was done to identify relevant studies published for 2021. Results: Sixteen studies were included, and overall, there is evidence that neuromodulation can be effective in reducing suicidality. Conclusion: Overall, findings of neuromodulation on suicidality are positive, and further research is needed.
LICI DEFICITS AS A MARKER OF TREATMENT RESISTANCE IN ADOLESCENTS’ MAJOR DEPRESSIVE DISORDER


Charles P, Lewis, M.D.

Biomarkers of Suicidality in Adolescents with Major Depressive Disorder


A Systematic Review of the Safety and Tolerability of Theta Burst Stimulation in Children and Adolescents

Rana Elmaghraby, MD; Qi Sun, MD; Can Ozkar, BS; Julia Shekunov, MD; Magdalena Romanowicz, MD; Paul E. Croarkin, DO, MS

Methods: Theta burst stimulation (TBS) is often used in clinical practice and research protocols for adults with neuropsychiatric disorders. Given its potential for inducing changes in neural excitability, there are safety concerns when applied in the population of TBS in children and adolescents. This meta-analysis reviewed the safety and tolerability of TBS in children and adolescents, focusing on adverse events (AEs) and tolerability issues. The review included studies that used TBS protocols and reported safety and tolerability outcomes. A total of 47 studies were included, and 596 patients were analyzed. The primary outcome measures were tolerability and safety issues, including adverse events, treatment-emergent symptoms, and sustainability of treatment response.

Results: Twenty-six adverse events met the criteria for inclusion. The reported adverse events were mild and transient, and similar to what is noted in adult studies. The most common symptoms were headache, dizziness, nausea, and anxiety. The most reported side effect was depression (14%). Tolerability was assessed as good to excellent in most studies. The trial data showed a positive correlation between treatment response and tolerability.

Conclusion: TBS interventions in children and adolescents should be approached with caution, as further research is needed to fully understand their safety and tolerability.

Conflict of Interest: Paul E. Croarkin has received research grant support from Neuravive, Inc., and Medtronic, Inc. He has received travel support from Neuravive, Inc., and Magellan Neuroscience, Inc. He has served as a consultant for Myriad Neuroscience and Positivera, Inc. The other authors have no other financial disclosures or conflicts of interest.

Keywords: Theta burst stimulation, electrophysiological stimulation, safety, tolerability, children, adolescents, systematic review.
THETA BURST STIMULATION (TBS) IN YOUTH WITH MAJOR DEPRESSIVE DISORDER

- N=20
- Ages 16-24
- 10 treatment sessions over 2 weeks
- Sequential Bilateral TBS (1800 pulses of continuous TBS to the Right DLPFC and 1800 pulses of intermittent to the Left DLPFC at 80% active motor threshold)
- 18 completers with a significant reduction in Hamilton Rating Scale for Depression 17 scores (p < 0.001)
- Tolerable treatment


TMS-EEG Biomarkers


ACCELERATED TMS

A Preclinical Model of Accelerated TMS


**Session** | **Participants** | **Topic**
--- | --- | ---
1 | Adolescent and Parent | Chain analysis and safety plan
2 | Adolescent and Parent | Review adherence, psychosocial, and safety plan
3 | Adolescent | Reasons for living module
4 | Adolescent | Mindfulness module
5 | Adolescent | Distress tolerance module
6 | Adolescent and Parent | Review sessions 3-5 with parent
7 | Adolescent | Problem-solving module
8 | Adolescent | Socialization and support module
9 | Adolescent | Wellness and relapse prevention module
10 | Adolescent and Parent | Review work with parent
AUTISM SPECTRUM DISORDER: ASSOCIATED SYMPTOMS

- Hyperactivity
- Short Attention Span
- Impulsivity
- Irritability
- Aggressiveness
- Severe Tantrums
- Hypersensitivity to sensory stimuli
- Abnormal eating
- Affective/Mood Lability
- Abnormal emotional reactions
- Anxiety
- Self-Injurious Behaviors

Intability and Aggression

Repetitive Behaviors

Hyperactivity, Inattention, Neurocognitive Deficits

PREDICTORS OF OUTCOME IN ASD

LANGUAGE OUTCOME

IQ

EXECUTIVE FUNCTIONING

TMS for Executive Function Deficits in Autism Spectrum Disorder

Screened

Assessed for eligibility (n=64)

Randomized (n=48)

Eligible (n=74)

Not interested/ineligible to consent (n=22)

Did not meet inclusion criteria (n=5)

Lost to follow-up (n=17)

Eligible (n=18)

Not interested/conversion criteria (n=8)

Discontinued participation (n=4)

Eligible (n=20)

Allocation

Allocated to receive TMS (n=20)

Allocated to sham TMS (n=20)

Assessment/Analysis

Completed one month follow-up (n=17)

Completed one month follow-up (n=17)

Completed one month follow-up (n=17)

Preliminary efficacy analysis (n=17)
TMS FOR EXECUTIVE FUNCTION DEFICITS IN AUTISM SPECTRUM DISORDER

• N=40 16-35 years old
• Double-blind, randomized, sham controlled trial
• 20 sessions, 4-week course of 20 Hz rTMS delivered to bilateral DLPFC (750 pulses per session at each hemisphere) at 90% resting motor threshold
• 95% of randomized patients completed the protocol
• No significant difference between active and sham
• Patients with lower baseline functioning experiences significant improvement with active TMS


BILATERAL TRANSCRANIAL MAGNETIC STIMULATION OF THE SUPPLEMENTARY MOTOR AREA IN CHILDREN WITH TOURETTE SYNDROME

• Ten children with Tourette syndrome (8 males) aged 9-15 years
• Eight of the subjects had comorbid ADHD
• Other comorbidities: OCD, epilepsy, anxiety, social phobia
• Medications continued (guanfacine, clonidine, ethosuximide, methylphenidate, fluoxetine, aripiprazole, risperidone, clomipramine, citalopram, amitriptyline, and fluphenazine)
• 15 sessions of neuronavigated, robotic 1 Hz rTMS at 100% motor threshold with 1800 pulses
• The Yale Global Tic Severity Scale decreased from baseline (p < 0.001, Cohen’s d=2.9)
• Dominant motor cortex cortical silent period measures increased with treatment.

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