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# TMS in adolescent depression: A milestone FDA clearance

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## INTRODUCTION

Adolescent depression remains a pressing public health challenge, with current treatments often yielding inconsistent and suboptimal outcomes. The recent U.S. Food & Drug Administration (FDA) clearance of transcranial magnetic stimulation (TMS) as an adjunctive treatment for major depressive disorder (MDD) in adolescents aged 15–21 years represents a significant step in expanding therapeutic options for this vulnerable population [1]. This milestone introduces a non-pharmacological intervention with the potential to enhance treatment outcomes, accelerate remission of major depressive episodes (MDEs), and mitigate the progression to treatment-resistant depression (TRD). Given the prevalence of adolescent depression, this clearance warrants a critical examination of its implications within the existing therapeutic landscape.

## CURRENT TREATMENT LANDSCAPE AND LIMITATIONS

Despite the availability of FDA-approved antidepressants and evidence-based psychotherapies, significant gaps persist in the treatment of adolescent depression. Among selective serotonin reuptake inhibitors (SSRIs), fluoxetine (approved for ages 8+) demonstrates response rates of 52–61% and remission rates of 31–55% in randomized controlled trials (RCTs) [2]. Similarly, escitalopram (approved for ages 12 +) shows response rates of 53–64% and remission rates of 35.7–41.6% across trials [2]. Other SSRIs, such as sertraline and citalopram, and non-SSRI antidepressants, including venlafaxine, duloxetine, and bupropion, have demonstrated limited or inconsistent efficacy [2].

In addition to modest efficacy, antidepressants are associated with side effects, including nausea, headache, insomnia, and fatigue, which can complicate adherence. Moreover, the FDA's 2004 boxed warning highlights the purported increased risk of suicidal thoughts and behaviors in adolescents, necessitating close monitoring [3]. The delayed onset of antidepressant effects, often requiring 4–6 weeks for initial improvement and up to 12 weeks for full efficacy, further hinders treatment outcomes.

Psychotherapy, while effective for some adolescents, also presents challenges. Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) are the most studied modalities, with response rates ranging from 23% in community settings to 67.6% in collaborative care models [4]. However, long-term efficacy remains uncertain, as high relapse rates and limited access to skilled providers constrain its impact [4]. The limitations of current adolescent depression treatments highlight the need for faster-acting, more durable interventions. TMS offers a promising neuromodulatory approach, directly targeting brain circuits involved in mood regulation. With its recent FDA clearance, TMS stands out as a non-pharmacological option that may fill critical gaps in adolescent mental health care.

## MECHANISM AND EFFICACY OF TMS

TMS is a non-invasive neuromodulatory treatment that delivers magnetic pulses to the left dorsolateral prefrontal cortex, targeting neural circuits involved in mood regulation. Standard repetitive TMS (rTMS) protocols involve daily sessions, five days per week, lasting 20–40 min over six to eight weeks. Since the FDA's 2008 clearance of TMS for TRD in adults, advancements such as intermittent theta-burst stimulation (iTBS) have shortened treatment durations without compromising efficacy. More recently, accelerated TMS protocols, which involve multiple sessions per day over a condensed timeframe, have been developed to further reduce time to response. TMS has a strong safety profile, with transient scalp discomfort and mild headache being the most commonly reported side effects. Severe adverse events, such as seizures, remain exceedingly rare, even in high-risk populations [5].

Current evidence supports the efficacy of TMS in adolescent depression, particularly as an adjunct to antidepressants. RCTs consistently demonstrate higher response rates for active TMS vs. sham when combined with antidepressant medications. For example, Liu et al. (2022; $n = 90$) reported an 89% response rate vs. 69% for sham, Fu et al. (2022; $n = 104$) found 90% vs. 75%, and Jiao et al. (2024; $n = 135$) observed response rates of 96–98% in active rTMS groups vs. 80% for sham [6–8].

Although multiple studies demonstrate superior response rates for adjunctive TMS, sham-controlled trials of TMS monotherapy for adolescent depression remain limited and yield mixed results. The largest trial used standard rTMS monotherapy in treatment-resistant adolescents (Croarkin et al., 2021; $n = 103$) and found no significant difference versus sham (42% vs 36%, $p = 0.6$). This finding suggests that while rTMS remains a promising adjunct intervention, its effectiveness in adolescents may be influenced by concurrent pharmacotherapy or patient-specific factors such as illness chronicity, symptom severity, or neurobiological variability [9].

More recently, two sham-controlled trials of accelerated intermittent theta burst stimulation (a-iTBS) have reported more favorable outcomes. In a smaller RCT (Liu et al., 2025; $n = 40$), adolescents receiving five iTBS sessions per day for two days demonstrated significantly greater symptom improvement than

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sham at 48 h (MADRS reduction: 9.5 vs 5.1 points; 33% vs 19%), with continued within-group improvement during a four-week maintenance phase. A larger a-iTBS trial (Liu et al., 2025; n = 74) reported significantly higher response rates at day 11 (87% vs 41%) and one month (65% vs 27%). At three months, group differences persisted numerically (32% vs 16%) but were no longer statistically significant. Across trials, adverse events were mild, with no serious safety signals reported [10, 11].

While TMS presents a promising intervention for adolescent depression, existing studies remain limited by small sample sizes and protocol heterogeneity. Differences in stimulation type, frequency, and duration further limit cross-trial comparisons, and most trials assess only short-term outcomes. Future research should validate existing findings through larger, standardized trials with longer follow-up, refine stimulation protocols, and clarify how TMS can be most effectively integrated into broader, multimodal treatment strategies for youth.

## SIGNIFICANCE OF THE FDA CLEARANCE

The recent FDA clearance for TMS in adolescents was based in part on real-world outcomes from a manufacturer-maintained registry (Neuronetics), alongside published evidence and a demonstration of substantial equivalence to the adult-cleared device.[1] A peer-reviewed analysis of the registry data has since been published [12]. Among 1,169 adolescents (ages 12–21) who completed treatment with TMS alongside antidepressants in the registry study, 59.4% met Patient Health Questionnaire-9 (PHQ-9) response criteria (≥50% symptom reduction), 30.0% achieved remission (PHQ-9 < 5), and approximately 74% experienced substantial symptom improvement (≥6-point PHQ-9 reduction). Fewer than 1% reported worsening. Notably, the greatest symptom improvements occurred within the first ten sessions, with continued benefit over the treatment course [12].

While promising, real-world response rates were lower than those observed in controlled RCTs, likely due to broader variability in clinical settings, patient selection, and adjunctive treatments. Although real-world data offer valuable insights into TMS's potential for adolescents, the absence of a sham-controlled comparison in registry findings limits causal conclusions.

Importantly, this clearance was granted through the FDA's 510(k) device pathway, which permits market entry based on substantial equivalence to previously cleared devices rather than requiring independent demonstration of efficacy in the target population. While this regulatory pathway facilitates access and reimbursement, it underscores the need for rigorous, ongoing research to confirm therapeutic benefit in adolescents.

Additional sham-controlled trials are needed to validate effectiveness and inform clinical guidelines. Expanding data collection across TMS manufacturers could strengthen the evidence base and support standardization of clinical practice. Collaboration among device manufacturers, academic institutions, and regulatory agencies is essential for ensuring robust data collection and ethical oversight. Integrating standardized self-report measures into electronic health records at baseline and follow-up could improve data validity while minimizing administrative burden.

Advancing these efforts could help solidify TMS as an evidence-based intervention for adolescent depression, increasing confidence among clinicians, families, and payers. Addressing key issues such as data ownership, clinical guidelines, and ethical data-sharing will be critical for fully integrating TMS into adolescent mental health care.

## BARRIERS TO ACCESSIBILITY AND INTEGRATION

Despite its promise, the widespread adoption of TMS in adolescent populations has faced challenges, particularly in insurance coverage. However, following FDA clearance, several major insurers have expanded their policies to include TMS for adolescents (ages 15-21). Humana was the first to approve adolescent TMS coverage in May 2024, followed by others including Aetna, HCSC (BCBS in multiple states), BCBS North Carolina, and Medi-Cal, with some now allowing TMS as a first-line treatment without requiring multiple failed medication trials [13].

While coverage is improving, access remains inconsistent as some private insurers impose strict prior authorization requirements. This reflects the complexity of TMS's evidence base. Policymakers must balance stringent trial data requirements with the urgent need for effective interventions in treatment-resistant adolescent depression.

Clinicians play a key role in bridging this gap by providing balanced, evidence-based guidance to adolescent patients and their families. Transparent discussions should frame TMS as an emerging but promising treatment, emphasizing its established efficacy in adults while addressing variability in adolescent response rates.

Logistical barriers also limit TMS accessibility, particularly the burden of daily sessions over multiple weeks. Accelerated theta-burst TMS protocols could help reduce these demands. Access is also constrained by a shortage of TMS devices and trained clinicians, particularly those specializing in child and adolescent psychiatry.

Addressing these barriers requires collaboration among healthcare providers, policymakers, and advocacy groups. Expanding TMS training in child and adolescent psychiatry, alongside ongoing professional development, will be crucial as demand grows. Standardizing clinical guidelines and reimbursement policies will further enhance accessibility, ensuring equitable treatment availability across regions.

## FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

While TMS is FDA-cleared for several adult conditions, including MDD with comorbid anxiety and obsessive-compulsive disorder, expanding its indications for adolescents requires stronger evidence. The limited number of RCTs in adolescents currently restricts the likelihood of FDA clearance for conditions beyond depression.

Future research should prioritize optimizing TMS protocols for adolescents, considering developmental factors such as neural network maturation and cortical excitability differences [14]. Long-term studies are needed to assess the durability of TMS effects and monitor potential delayed impacts on the developing brain [14]. Identifying which adolescent subgroups benefit most from TMS could improve clinical utility, highlighting the need for response predictors and refined patient selection criteria.

Given ongoing neurodevelopment in adolescents, their response to neuromodulation may differ significantly from adults, emphasizing the need for age-specific research. Investigating response biomarkers, including neuroimaging markers and genetic predispositions, could provide valuable insights for tailoring treatment [14]. Additionally, exploring whether TMS is particularly effective in early-stage depression, leveraging heightened neuroplasticity in younger populations, could be valuable [14].

Further research should examine TMS's role in relapse prevention and clarify whether accelerated protocols offer unique advantages over standard once-daily regimens in adolescents. Accelerated TMS has shown promise for more rapid symptom relief without added safety concerns. Theoretically, delivering multiple spaced sessions in a condensed timeframe may engage neuroplastic mechanisms more efficiently, particularly in younger brains with heightened synaptic responsiveness [15]. However, the long-term durability of benefit remains unclear, and no studies to date have directly compared accelerated and standard protocols in this population. Mixed findings from small,

methodologically heterogeneous trials underscore the need for larger, well-controlled studies to determine whether accelerated regimens provide meaningful clinical or practical advantages [15].

Finally, the current FDA clearance for adolescent TMS is notably broad, specifying no stimulation parameters, treatment duration, or defined adjunctive treatment. While this regulatory flexibility allows for innovation and individualized care, it also introduces clinical variability. Systematic research is needed to guide safe, effective, and standardized implementation in youth.

## CONCLUSION

The FDA clearance of TMS as an adjunctive treatment for adolescent MDD marks a significant milestone in psychiatric care, expanding treatment options for this challenging condition. To fully realize TMS's potential, addressing accessibility barriers, expanding training, and integrating TMS into routine clinical practice will be essential. Addressing these barriers, alongside ongoing research to refine protocols and patient selection, will be critical in transforming TMS into a widely accessible, evidence-based intervention for adolescent depression. By advancing TMS and addressing existing challenges, clinicians, researchers, and policymakers can collectively improve adolescent mental health outcomes, offering renewed hope to patients and their families.

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## AUTHOR CONTRIBUTIONS

AVS, SJO, and CBN contributed to conceptualization of the article. AVS conducted the literature review and drafted the manuscript. SJO contributed to refinement of the conceptual framework and interpretation of the literature. CBN provided senior supervision, critical intellectual input, and substantive revisions to the manuscript. All authors contributed to critical revision of the text and approved the final version.

## COMPETING INTERESTS

Dr. Arjun Srivastava has no conflicts of interest to declare. Dr. Sean O'Sullivan has no conflicts of interest to declare. Dr. Charles Nemeroff is supported by the National Institutes of Health, the National Institute of Mental Health, and the National Institute of Alcohol Abuse and Alcoholism. Charles Nemeroff is a consultant for ANeuroTech (division Anima BV), Janssen Research and Development, BioXcel Therapeutics, Engrail Therapeutics, Clexio Biosciences LTD, EmbarkNeuro, Galen Mental Health LLC, Goodcap Pharmaceuticals, ITI Inc, LUCY Scientific Discovery, Relmada Therapeutics, Sage Therapeutics, Senseye Inc, Precisement Health, Autobahn Therapeutics Inc, EMA Wellness, Skyland Trails, Denovo Biopharma, Alvogen, Acadia Pharmaceuticals, Inc., and the Brain & Behavior Research Foundation. Charles Nemeroff owns the following patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2), Compounds, Compositions, Methods of Synthesis, and Methods of Treatment (CRF Receptor Binding Ligand) (US 8,551, 996 B2). Charles Nemeroff owns stock in Corcept Therapeutics Company, EMA Wellness, Precisement Health, Relmada Therapeutics, Signant Health, Galen Mental Health LLC, and Senseye Inc.

## ADDITIONAL INFORMATION

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