The Emerging Role for Repetitive Transcranial Magnetic Stimulation in Optimizing the Treatment of Adolescent Depression

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Abstract: Major depressive disorder (MDD) in adolescents is a common illness and significant public health problem. Treatment is challenging because of recurrences and limited modalities. Selective serotonin reuptake inhibitors and cognitive behavioral therapy are considered the standard of care in severe or treatment-resistant MDD in this age group. However, responses to these interventions are often suboptimal. A growing body of research supports the efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of MDD in adults. Induced seizures are a primary safety concern, although this is rare with appropriate precautions. There is, however, limited experience with rTMS as a therapeutic intervention for adolescent psychiatric disturbances. This review will summarize the rTMS efficacy and safety data in adults and describe all published experience with adolescent MDD. Applications in other adolescent psychiatric illnesses such as schizophrenia and attention-deficit/hyperactivity disorder are reviewed. Safety and ethical issues are paramount with investigational treatments in adolescent psychiatric illnesses. However, further research with rTMS in adolescent MDD is imperative to establish standards for optimal stimulation site, treatment parameters, and its role in treatment algorithms. These may diverge from adult data. Early intervention with neuromodulation could also hold the promise of addressing the developmental course of dysfunctional neurocircuitry.

Key Words: transcranial magnetic stimulation, adolescents, major depressive disorder

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Treatment options for adolescents with major depressive disorder (MDD) remain relatively limited. Thus far, standard of care for the treatment of adolescent depression as defined by the American Academy of Child and Adolescent Psychiatry uses pharmacotherapies and psychotherapies,[1] with combination therapy generally deemed most effective.[2] A third treatment option is electroconvulsive therapy (ECT). However, ECT is used sparingly because of its potential significant adverse effects and limited availability owing to geographic and legal constraints.[3] Unfortunately, many depressed adolescents remain suboptimally treated, with significant resultant morbidity that includes ineffective polypharmacy, inpatient psychiatric hospitalization, psychosocial maldevelopment, and suicide. Thus, newer therapeutic modalities for the treatment of adolescent depression are essential. Repetitive transcranial magnetic stimulation (rTMS) is a well-tolerated, safe, and potentially effective treatment approach for depression. Currently, its role as a treatment option in adolescent depression is under investigation.[4,5]

Transcranial magnetic stimulation is a noninvasive tool that uses brief magnetic pulses for cortical stimulation. The magnetic field penetrates the scalp and skull with virtually no impedance, thereby producing electrical currents in the underlying cortical tissue. Repetitive transcranial magnetic stimulation involves trains of magnetic pulses for neuromodulation, which can be applied as a therapeutic treatment. Thus far, most data supporting a therapeutic effect of rTMS have been demonstrated in adults with depression.[6–9] Researchers have also used this modality for pediatric populations.[4,5,10] The objective of this article was to review the existing literature related to the use of rTMS in adults with depression as well as in child and adolescent psychiatry. Given that there are limited options for adolescents with depression who do not respond to traditional treatments,[11] future research in this area is critical. Additional published therapeutic trials for other psychiatric disorders in

adolescents will be discussed. Safety and ethical issues related to the use of rTMS in adolescent populations will also be addressed.

THERAPEUTIC USE OF rTMS IN ADULTS WITH MDD

There are more than 30 controlled trials of rTMS[12] and 7 meta-analysis studies that support the use of prefrontal rTMS for the treatment of MDD in adult patients.[6–9,13–15] It is important to note that only 1 of these meta-analysis studies[15] included the largest rTMS trial for MDD to date.[16] However, 1 recent meta-analysis did not support its efficacy.[14] Most of these studies used high-frequency rTMS (>1 Hz) over the left dorsolateral prefrontal cortex (LDLPFC) with the assumption that high-frequency rTMS would enhance cortical excitability in that region. Other trials have targeted the right DLPFC (RDLPFC) with the idea that it is overactive in depressed patients and may be normalized with low-frequency stimulation (<1 Hz).[17–19] Yet, another novel approach involves sequential bilateral low-frequency and high-frequency stimulations.[20,21] Collectively, studies involving rTMS applied to the LDLPFC and RDLPFC are promising but also pose limitations. This includes heterogeneous subjects and rTMS dosing parameters. The interpretation of results is also often challenging because of inadequate study masking, short treatment duration, and small sample sizes. It does seem that patients with minimum treatment resistance and shorter courses of illness may reap the most benefit from rTMS.[22] Other analyses have suggested that increasing age may also be a negative predictor of response to rTMS owing to the increased cortical atrophy with age and increased coil-to-cortex distance.[23] Prospective investigations will assist in characterizing the optimal treatment parameters including stimulation site, TMS stimulus intensity, and treatment duration.[24]

A recent, multicenter, double-blind, sham-controlled trial involving 301 subjects provided additional data that rTMS is an efficacious treatment of adult MDD. Active treatment was administered to the LDLPFC, 5 times per week, with 10 pulses per second (3000 pulses per session) at 120% motor threshold for 4 to 6 weeks. Response rates were significantly higher for patients receiving active treatment at weeks 4 and 6, with a number needed to treat of 11 and 9, respectively. At 4 weeks, patients receiving active rTMS had a response rate of 20.6% (compared with 11.6% with sham treatment) and a remission rate of 7.1% compared with 6.2% with sham treatment. After 6 weeks, the response rate was 24.5% and 13.7% with sham treatment. At this point, the remission rate was 15.5% with rTMS and 8.9% with sham treatment.[16] In October 2008, data from this trial led to the US Food and Drug Administration (FDA) clearance for rTMS treatment of adults with MDD who have failed 1 previous medication trial at an adequate dose and duration.

Given that the safety of any new antidepressant treatment in adolescents is a paramount concern, it is encouraging that adult studies with rTMS indicate that it is a safe and well-tolerated procedure. Major adverse effects and safety concerns included the risk for possible cognitive or structural changes, pain, headaches, hormonal changes, and hearing loss. Although seizures have occurred in healthy participants during TMS and rTMS, there have been no known lasting sequelae.[25,26] Seizures are much more likely to occur in patients with significant neurological morbidity (ie, a history of stroke, cortical structural lesions, epilepsy) or when existing safety guidelines for stimulation parameters are exceeded.[27–29] The incidence of seizures with rTMS in depressed patients who are healthy otherwise has been estimated to be no higher than 0.1% to 0.6%.[30] Studies of cognitive functioning before and after rTMS have found no clinically significant impairment in exposed patients.[31,32] Most commonly, patients experience mild headaches, neck pain, and scalp pain that respond well to analgesics. There is no evidence that rTMS exposure induces temporary or permanent hearing loss in adults when earplugs are worn.[33,34] Ear plugs are provided for comfort and added safety uniformly in rTMS studies. Experts agree that patients with metal hardware near the area of the rTMS coil (eg, cochlear implants, pulse generators, or medication pumps) should not be exposed to rTMS because there is the risk that these devices will malfunction.[28] Patients with baclofen pumps and deep brain stimulation implants have been safely exposed to TMS, but this is still considered a relative contraindication.[35,36] A recent large multicenter trial also supports the argument that rTMS is safe because it was administered to subjects in more than 10,000 sessions with no seizures or deaths and a dropout rate of 4.5% for adverse events. In this trial, adverse effects were mild to moderate and most commonly involved transient headaches and scalp pain.[37] Patient preference and comfort are paramount in treatment planning. It is noteworthy that systematic studies regarding the attitudes of patients who have received rTMS demonstrate that most recipients characterize it as helpful and preferable to treatment with ECT.[38]

TREATMENT OF MDD IN ADOLESCENTS

Major depression is a common and recurrent illness in adolescents, frequently resulting in negative psychosocial consequences and increased risk of suicide and substance abuse.[1,3] The prevalence of MDD is estimated to be 4% to 8% in adolescence, with a male-to-female ratio[39,40] of 1:2. By age 18 years, the cumulative incidence of MDD is approximately 20% in community samples.[1] Several studies have suggested that successive generations since 1940 are at greater risk for developing MDD, and this disorder is now being recognized at younger ages.[41] Suicide is the third leading cause of death in adolescents, and depressive disorders are strongly correlated with suicide attempts. Although adolescents must meet the diagnostic criteria for MDD of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, the clinical picture of depression in adolescents varies considerably across developmental stages and diverse ethnic groups, making them unique and different from an adult population when implementing successful treatment interventions.[42]

The treatment of MDD in this age group is challenging owing to the difficulty in diagnosis, limited therapeutic modalities, paucity of evidence-based clinical practice, and research with discordant conclusions. Psychosocial interventions are generally considered first for uncomplicated, mild to moderate MDD. One meta-analysis of 35 randomized controlled trials of psychotherapy for the immediate treatment of MDD in children indicated that, although some studies have large effects, overall results are meager.[43] Of the psychotherapies, cognitive behavioral therapy (CBT) and interpersonal psychotherapy have received significant investigation. Meta-analysis studies[44,45] support the efficacy of CBT for the treatment of MDD in teenagers, but a recent, large-scale, randomized, controlled trial found it to be no different than placebo.[46] Relative to pharmacotherapy, long-term effectiveness data indicated that after 36 weeks of treatment with CBT alone, fluoxetine alone, or combined treatment with fluoxetine and CBT, response rates among all 3 modalities were similar. However, CBT was found to

protect against suicidal events in the course of treatment with fluoxetine.[2] Interpersonal psychotherapy is another evidence-based psychotherapy for adolescent MDD, which has been found to be superior to other supportive psychotherapeutic interventions[47,48] and equal in efficacy to CBT.[49] Family therapy and psychodynamic psychotherapy are 2 other options for clinicians but both have a paucity of data on efficacy.

On the basis of the available data, selective serotonin reuptake inhibitors (SSRIs) continue to be an effective treatment of moderate to severe MDD in adolescents and are considered the first-line medication approach for this population.[50] Tricyclic antidepressants are no longer considered to be an effective treatment option in this age group.[51,52] Fluoxetine and escitalopram are the only FDA-approved medications for this indication. One recent meta-analysis of 15 separate trials of antidepressants in patients younger than 18 years revealed a number needed to treat of 10 and a number needed to harm of 125. These authors concluded that SSRIs are safe and efficacious in the treatment of MDD in this population.[50] Since 2004, when the FDA issued a black box warning for patients younger than 18 years treated with antidepressants relating an increased risk for clinical worsening and suicidality, there has been ongoing controversy regarding the efficacy and safety of antidepressant medications. In adolescent trials of SSRIs for the treatment of MDD, remission rates range from 30% to 40%, and even with optimal treatment involving combined psychotherapy and pharmacotherapy, at least 40% of patients treated do not show a significant clinical response.[11,53,54] This information substantiates the necessity for novel, safe, and efficacious somatic treatment alternatives or adjuncts in this population.

The American Academy of Child and Adolescent Psychiatry Practice Parameter officially endorses the use of ECT in adolescents for severe, major depression, mania, schizoaffective disorder, schizophrenia, catatonia, and neuroleptic malignant syndrome. Although limited, there have been reports of adolescents with treatment-resistant depression who responded to ECT.[55] In a study of 72 adolescents, aged 14 to 18 years, who underwent a total of 84 courses of ECT from 1990 to 1999, Walter and Rey[56] found the changes in ECT practice for adolescents to be consistent with the ECT practice in general during this survey period. These investigators concluded that overall safety and effectiveness support the use of ECT in children and adolescents. However, the study relied on retrospective data, which could have limited the systematic collection of ECT-associated adverse effects. The main negative effects of ECT revolve around neurocognitive sequelae. Possible ECT iatrogenically induced cognitive adverse effects include disorientation and anterograde and retrograde amnesia. As with adults, ECT techniques can be modified to mitigate these risks by the use of right unilateral electrode placement and ultrabrief pulse-width stimulation. Other safety concerns include tardive or prolonged seizures and the risks associated with receiving general anesthesia.[55] Although Cohen et al[57] showed no significant cognitive deficits in adolescents receiving ECT, this study had several limitations, including a small sample size and lack of sophisticated neurocognitive measures of retrograde amnesia. Adolescents are not believed to be at additional risk than adults from ECT- or anesthesia-related complications; however, hospitalization is usually recommended for adolescents receiving ECT to allow for comprehensive monitoring of recovery after anesthesia and treatment response. Adolescents may have lower seizure thresholds and more prolonged seizures with ECT than adults.[55] Previous research suggested that most adolescents who have been treated with ECT view the treatment as less aversive than the illness itself[58]; however, both adolescents and parents have expressed fear associated with ECT, and in 1 study, parents found it difficult to provide consent.[59] There are also no data to guide the practice of maintenance ECT for patients younger than 18 years.[55] Generally, ECT is still viewed as a treatment option only after multiple psychotropic and psychotherapeutic interventions have been exhausted.

rTMS FOR MDD IN CHILDREN AND ADOLESCENTS

Data regarding the treatment of adult MDD with rTMS are accruing, but there is relatively little information regarding the use of this modality in children and adolescents with MDD. Current literature includes a few case studies with varied results (Table 1).

Walter et al[10] described the antidepressant treatment of 4 teenagers with rTMS. For 2 weeks, one 17-year-old adolescent boy received daily sessions (for 10 days) of 10-Hz rTMS over the LDLPFC at more than 90% of the motor threshold. This patient's depression was recalcitrant to medication, and he had received maintenance ECT before this rTMS course. He improved with rTMS but did have a tension headache during 2 of the treatment sessions. Also, a 16-year-old adolescent boy with treatment-resistant MDD received a similar course of rTMS treatment. His previous treatment included 2 courses of ECT. This patient's depression improved with rTMS, and there were no reported adverse effects or complications. The third patient, a 17-year-old patient with refractory MDD, mild mental retardation, and attention-deficit/hyperactivity disorder (ADHD), received the same course of rTMS, except it was administered at more than 110% of the motor threshold. Unlike the other 2 adolescents, no clinical improvement was found. No adverse effects or complications were reported. Finally, another 18-year-old woman with bipolar depression was treated with 14 sessions of 1-Hz rTMS to the RDLPFC at 110% of the motor threshold. She had no improvement and no adverse effects.[10]

In another case series, Loo et al[4] reported on two 16-year-old adolescent girls with MDD who were enrolled in a double-blind sham-controlled study of 10-Hz rTMS at 110% of the motor threshold for depressed adolescents. Both of these patients were assigned to active treatment. The first female received 29 rTMS sessions during 6 weeks. She responded to this treatment with minimal depressive symptoms or functional impairment 4 months after the last session. The other patient with MDD missed 1 session per week during the treatment and then had almost a 2-week period with no rTMS sessions. She later returned for 20 sessions for 5 weeks on an open-label basis. During the rTMS course, the patient also took venlafaxine and methylphenidate. This patient had a slower response to rTMS, but 3 months after this treatment course, she maintained improvement. Neither of these patients had significant adverse effects from the treatment, and formal neuropsychological assessments failed to show any adverse effects in cognitive functioning.[4]

A recent open-label study of rTMS involved 9 teenagers (aged 16–18 years) with treatment-resistant depression who were treated with 20 sessions of 10-Hz rTMS applied to the LDLPFC at 80% motor threshold for 20 minutes over 2 weeks. A few of the patients had been treated with ECT previously and all were taking psychotropic medications concurrently with the rTMS treatments. Treatment parameters for rTMS were likely suboptimal in this pilot trial owing to safety concerns, although 3 of 9 patients showed a clinical response. Regarding adverse effects, 1 patient stopped treatment early because of anxiety and mood lability, 1 had hypomania, and 1 attempted suicide 3 weeks

TABLE 1. Published Case Reports and Case Series: rTMS for MDD in Adolescents[4,5,10]

Age	Treatment	No. Treatments	Response	Adverse Effects
16 F	10-Hz 40 trains 5 s/25 s at 110% MT	29	Clinically significant	None
16 F	10-Hz 40 trains 5 s/25 s at 110% MT	38	Clinically significant	None
16 M	LDLPFC 10-Hz 20 trains 8 s/25 s at 90% MT	10	Clinically significant	Headache
16 M	LDLPFC 10-Hz 20 trains 8 s/25 s at 90% MT	10	Clinically significant	None
17 M	LDLPFC 10-Hz 40 trains 2 s/58 s at 110% MT	10	No improvement	None
18 F	RDLPFC 1-Hz 1600 stimuli/26.6 min at 110% MT	10	No improvement	None
			Of 9 below: 3 patients had clinically significant response	Of 9 below: 5 had headaches, 1 had "fear and mood swings," 1 made a suicide attempt 3 wk after the treatment, and 1 had hypomania
18 M	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
18 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	10		
16 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
18 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
16 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
17 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
17 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
18 M	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		
17 F	LDLPFC 10-Hz 20 trains 2 s/58 s at 80% MT	14		

MT indicates motor threshold.

after rTMS. Also, aside from the 5 patients who reported a mild headache, no other adverse effects or adverse events were found.[5]

Collectively, this literature demonstrates that, at this time, there are no definitive guidelines for the application of rTMS to adolescent MDD. Although it is premature to make definitive recommendations, current information suggests that high-frequency stimulation applied to the LDLPFC for 6 or more weeks may be an optimal strategy for the treatment of adolescent MDD. Moreover, rTMS does seem to be safe and well tolerated in this population even in conjunction with psychotropic medications.

ADDITIONAL TRIALS AND APPLICATIONS OF rTMS IN ADOLESCENTS

Other studies with psychiatric patients younger than 18 years can inform clinicians and researchers of the safety and possible utility of rTMS. One such area where this treatment modality has been found promising is childhood and adolescent schizophrenia. Published cases include 3 teenagers with schizophrenia treated with 10 daily sessions for 2 weeks with 20-Hz rTMS applied to the right frontal cortex. Two of these patients were 18-year-old men who showed significant improvements in rating scales of positive and negative symptoms. The third patient reported subjective improvement in hallucinations, agitation, and global functioning. In all 3 cases, no adverse effects or adverse events were reported.[10]

A separate case described by Fitzgerald et al[18] involved an 18-year-old woman with longstanding schizophrenia (since age 9 years) with recalcitrant symptoms on multiple medications. Clozapine at 400 mg daily had improved her positive symptoms and disorganized thought processes. However, she continued to experience auditory hallucinations. This patient was ultimately treated with 10 sessions of rTMS on consecutive weekdays. A 1-Hz rTMS at 90% resting motor threshold was applied to the left temporoparietal cortex for 15 minutes. This resulted in a reduction of hallucinatory severity based on the Hallucinations Change Scale[60] and the Positive and Negative Syndrome Scale.[61] Her clozapine dosage was maintained during and after the treatment course. She did relatively well for 6 months, but then 10 identical rTMS sessions were repeated for a relapse in auditory hallucinations. Clinical improvement was temporary and required a third course or rTMS 3 months later. With the immediate and continuation courses combined, 30 rTMS sessions with the aforementioned treatment parameters were administered successfully.[62]

Researchers from France recently published a case that involved an 11-year-old boy with medication-resistant schizophrenia. This inpatient had struggled with aggression and psychotic symptoms (delusions and hallucinations) for 2 years. Neuroleptics were ineffective and led to a dystonia. A comprehensive evaluation included functional magnetic resonance imaging that displayed increased auditory cortex activity with concurrent auditory hallucinations. He received 10 sessions of 1-Hz functional magnetic resonance imaging–guided rTMS applied to the left temporoparietal cortex. This decreased the auditory hallucinations by 50% as rated on the Auditory Hallucinations Rating Scale.[62] This gain was maintained by repeating sessions every 5 weeks. This patient also had significant improvement in his adaptive functioning based on the Children's Global Assessment Scale.[63] The patient was discharged home and was able to attend school. No side effects or adverse events were reported.[64]

Weaver et al[65] recently reported preliminary results from a double-blind sham-controlled trial of 10-Hz rTMS at 100% of the motor threshold, 2000 pulses per session, applied to the RDLPFC for 10 sessions for 2 weeks in patients aged 17 to 21 years with ADHD. Seven subjects completed the study with no seizures, adverse cognitive effects, or shifts in auditory thresholds. There was also a mean improvement based

on the Clinical Global Impression–Improvement and ADHD-IV scales.[66]

Another work has examined the therapeutic effects of rTMS for status epilepticus in children. For example, rTMS was applied in 2 patients with intractable epilepsia partialis continua[67] and in another case of a child with intractable seizures due to Rasmussen encephalitis. The foundation of this approach relies on the ability of a low-frequency (1-Hz) stimulation to suppress neuronal activity and cortical excitability.[68]

SAFETY OF rTMS IN CHILDREN AND ADOLESCENTS

Single-pulse and paired-pulse TMSs have been used safely in children to assess brain maturation, neurophysiologic parameters, and motor development.[69,70] No adverse events were reported in 75 TMS studies including more than 2000 children.[71,72] Experts have argued that single-pulse and paired-pulse studies confer only minimal risk to children.[73] However, there is much less experience with rTMS in children and adolescents. As with adults, concerns for rTMS exposure include seizure risk, hearing damage, pain, and neurocognitive effects. Despite the concern that children have lower seizure thresholds, to date, there have been no reported seizures in children and adolescent exposed to TMS. However, caution is warranted because, although no seizures have occurred in this age range, the total number of subjects exposed to rTMS is far less than that in adult studies. Also, an evaluation of 18 children with numerous TMS exposures did not detect decreases in auditory functioning.[74] A theoretical concern is that TMS could cause structural changes when administered to developing brains. However, imaging[75–77] and histologic studies[78] failed to find significant changes in adults exposed to rTMS. Differences in brain size in developing patients could affect the extent and focality of stimulation in pediatric populations. As with medications, dose-finding studies for rTMS treatments in children and adolescents would be indispensable in guiding future clinical practice. Experts contend that safety guidelines for the use of TMS in pediatric patients should be developed.[79]

ETHICS

In considering the ethics involved with using rTMS in the pediatric population, a myriad of factors must be considered. One important factor includes the likelihood of efficacy in this population. In adult studies, rTMS has shown acceptable response rates and effect sizes.[80] These results are similar to other augmentation strategies for antidepressant treatment. A review of previous rTMS studies in depressed adolescent cases showed a total of 15 adolescents with major depression who were treated with a variety of rTMS treatment parameters (Table 1). These limited data are promising, and these will require further research using rTMS in this population. Support for ongoing pediatric-specific research comes from Rowell and Zlotkin[81] who argued that, ultimately, improved clinical care of children depends on their participation in pediatric research. For a physician to fulfill a responsibility to provide the best care possible, research is necessary. Furthermore, in the absence of relevant research, harm to children can result. For example, a reluctance to carry out studies to evaluate the uses of drugs in pediatric populations has resulted sometimes in children being deprived of optimal care and, in other cases, exposure to untested interventions resulting in severe toxic effects, including death. Their assertion logically extends to the research and use of rTMS in the treatment of pediatric and adolescent neuropsychiatric disturbances. Ongoing research of rTMS as a potentially safe, effective, and optimal treatment modality in depressed adolescents is imperative on the basis of the available literature.

FEASIBILITY

Several factors are important to consider when implementing rTMS in adolescents including the timing, frequency, and tolerability of the treatments. Typical rTMS treatment protocols require daily treatment during the early phase. The time intensity of this treatment approach can certainly interfere with school requirements, extracurricular activities, and other social functions. However, one must also consider the real impact and suffering endured by adolescents with suboptimally treated depression. Current standard models of care for depression in this population include weekly visits to therapists, psychotherapy groups, and visits with physicians for medication management. Furthermore, if these modalities result in suboptimal treatment, there is an increased risk of suicidality, psychiatric hospitalization, and further deterioration in developmental and biopsychosocial functioning. Antidepressant medication intolerance, adverse effects, and noncompliance in the pediatric population provide another real and important barrier to optimal treatment in the depressed adolescent population.

Importantly, children's perceptions of rTMS have been observed. Garvey et al[82] reported a study of 40 boys and girls—20 with ADHD and 20 healthy controls—who participated in a neurophysiologic TMS investigation. The children ranked TMS as more enjoyable than a long car ride, and 34 of the 40 subjects said they would participate in a TMS study again. Although this was not a therapeutic trial, it provides important insights into the tolerability of TMS procedures in children. Therefore, early indications from pediatric studies regarding treatment response data, minimal reported adverse effect profile, and generally favorable subjective review, position rTMS as a feasible treatment modality.

CONCLUSIONS

Depressive disorders in childhood and adolescence are a considerable source of mortality and morbidity. Currently, treatment options for depressive disorders in this population are limited. Adult data support the use of rTMS in depression as a safe, tolerable, and effective treatment. Currently, treatment of adolescent MDD with rTMS is limited to case reports and open trials. However, extensive experience with TMS in children as a neurophysiological probe suggests that it is safe and well tolerated. Safety, ethical, and feasibility concerns must be considered in applying this modality in the treatment of adolescent MDD and in constructing well-designed trials in the future. Ultimately, the optimal stimulation site, dosing parameters, and treatment choices with rTMS in adolescent depression may vary from those of adults. Brain stimulation techniques such as rTMS may one day play a significant role in shifting the developmental course of pathological neurocircuitry.

REFERENCES

1. Birmaher B, Brent D, et al, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry.* 2007;46:1503–1526.
2. March JS, Silva S, Petrycki S, et al. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry.* 2007;64:1132–1143.
3. Walter G, Rey JM. An epidemiological study of the use of ECT in adolescents. *J Am Acad Child Adolesc Psychiatry.* 1997;36:809–815.

4. Loo C, McFarquhar T, Walter G. Transcranial magnetic stimulation in adolescent depression. *Australas Psychiatry.* 2006;14:81–85.
5. Bloch Y, Grisarv N, Harel EV, et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. *J ECT.* 2008;24:156–159.
6. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002;5:73–103.
7. Holtzheimer PE 3rd, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. 2001;35:149–169.
8. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002;8:270–275.
9. McNamara B, Ray JL, Arthurso J, et al. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychol Med*. 2001;31:1141–1146.
10. Walter G, Tormos JM, Israel JA, et al. Transcranial magnetic stimulation in young persons: a review of known cases. *J Child Adolesc Psychopharmacol*. 2001;11:69–75.
11. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. 2008;299:901–913.
12. Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. *J Clin Psychiatry.* 2006;67:1870–1876.
13. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *J Psychiatry Neurosci*. 2005;30:83–90.
14. Gross M, Nakamura L, Pascual-Leone A, et al. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*. 2007;116:165–173.
15. Lam RW, Chan P, Wilkins-Ho M, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. *Can J Psychiatry.* 2008;53:621–631.
16. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry.* 2007;62:1208–1216.
17. Tormos JM, Catala, Pascual-Leone A. Transcranial magnetic stimulation. *Rev Neurol*. 1999;29:165–171.
18. Fitzgerald PB, Benitez J, Daskalakis ZJ, et al. The treatment of recurring auditory hallucinations in schizophrenia with rTMS. *World J Biol Psychiatry.* 2006;7:119–122.
19. Schutter DJ, van Honk J. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. *J Psychiatry Neurosci*. 2005;30:91–97.
20. Fitzgerald PB, Benitez J, deCastella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry.* 2006;163:88–94.
21. Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. *Can J Psychiatry.* 2008;53:555–566.
22. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology.* 2009;34:522–534.
23. Fregni F, Marcolin MA, Myczkowski M, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2006;9:641–654.
24. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry.* 2008;69:441–451.
25. Wassermann EM. Side effects of repetitive transcranial magnetic stimulation. *Depress Anxiety.* 2000;12:124–129.
26. Tharayil BS, Gangadhar BN, Thirthalli J, et al. Seizure with single-pulse transcranial magnetic stimulation in a 35-year-old otherwise-healthy patient with bipolar disorder. *J ECT.* 2005;21: 188–189.
27. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108:1–16.
28. Rossi S, Hallet M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120:2008–2039.
29. Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, et al. Seizure induction and transcranial magnetic stimulation. *Lancet*. 1992;339:997.
30. Loo C, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol*. 2008;11:131–147.
31. Weber M, Eisen AA. Magnetic stimulation of the central and peripheral nervous systems. *Muscle Nerve*. 2002;25:160–175.
32. Martis B, Alam D, Down SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin Neurophysiol*. 2003;114:1125–1132.
33. Pascual-Leone A, Cohen AG, Shotland LI, et al. No evidence of hearing loss in humans due to transcranial magnetic stimulation. *Neurology.* 1992;42:647–651.
34. Loo C, Sachdev P, Elsayed H, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry.* 2001;49:615–623.
35. Molnar GF, Sailer A, Gunraj CA, et al. Changes in cortical excitability with thalamic deep brain stimulation. *Neurology.* 2005;64:1913–1919.
36. Siebner HR, Dressnandt J, Auer C, et al. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve*. 1998;21:1209–1212.
37. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry.* 2008;69:222–232.
38. Walter G, Martin J, Kirkby K, et al. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Aust N Z J Psychiatry.* 2001;35:58–61.
39. Martin A, Cohen DJ. Adolescent depression: window of (missed?) opportunity. *Am J Psychiatry.* 2000;157:1549–1551.
40. Lewinsohn PM, Rohde P, Seeley JR, et al. Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. *Am J Psychiatry.* 2000;157: 1584–1591.
41. Ryan ND, Williamson DE, Iyengar S, et al. A secular increase in child and adolescent onset affective disorder. *J Am Acad Child Adolesc Psychiatry.* 1992;31:600–605.
42. Jeffery DA, Sava DB, Winters NC. Depressive disorders. In: Cheng K, Myers KM, eds. *Child and Adolescent Psychiatry.* Philadelphia, PA: Lippincott Williams and Wilkins; 2005:169–189.

43. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;132:132–149.
44. Harrington R, Campbell F, Shoebridge P, et al. Meta-analysis of CBT for depression in adolescents. *J Am Acad Child Adolesc Psychiatry.* 1998;37:1005–1007.
45. Compton SN, March JS, Brent D, et al. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry.* 2004;43:930–959.
46. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807–820.
47. Mufson L, Weissman MM, Moreau D, et al. Efficacy of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry.* 1999;56:573–579.
48. Mufson L, Dorta KP, Wickramaratne P, et al. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry.* 2004;61:577–584.
49. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin Psychol*. 1999;67:734–745.
50. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297:1683–1696.
51. Hughes CW, Emslie GJ, Crimson ML, et al. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46:667–686.
52. Cheung AH, Emslie GJ, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. *J Child Psychol Psychiatry.* 2005;46:735–754.
53. Kennard B, Silva S, Vitello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry.* 2006;45:1404–1411.
54. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry.* 1997;54:1031–1037.
55. Ghaziuddin N, Kutcher SP, Knapp P, et al. Practice parameter for use of electroconvulsive therapy with adolescents. *J Am Acad Child Adolesc Psychiatry.* 2004;43:1521–1539.
56. Walter G, Rey WM. Has the practice and outcome of ECT in adolescents changed? Findings from a whole-population study. *J ECT.* 2003;19:84–87.
57. Cohen D, Taieb O, Flament M, et al. Absence of cognitive impairment at long-term follow-up in adolescents treated with ECT for severe mood disorder. *Am J Psychiatry.* 2000;157:460–462.
58. Walter G, Koster K, Rey JM. Electroconvulsive therapy in adolescents: experience, knowledge, and attitudes of recipients. *J Am Acad Child Adolesc Psychiatry.* 1999;38:594–599.
59. Taieb O, Cohen D, Mazet P, et al. Adolescents' experiences with ECT. *J Am Acad Child Adolesc Psychiatry.* 2000;39:943–944.
60. Doane JA, Falloon IR, Goldstein MJ, et al. Parental affective style and the treatment of schizophrenia. Predicting course of illness and social functioning. *Arch Gen Psychiatry.* 1985;42:34–42.
61. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
62. Hoffman RE, Hawkins KA, Gueorguieva R, et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry.* 2003;60:49–56.
63. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry.* 1983;40:1228–1231.
64. Jardri R, Lucas B, Delevoye-Turell Y, et al. An 11-year-old boy with drug-resistant schizophrenia treated with temporo-parietal rTMS. *Mol Psychiatry.* 2007;12:320.
65. Weaver L, Mace W, Akhtar, et al. Safety and efficacy of rTMS in treatment of ADHD in adolescents and young persons. *J ECT.* 2008;24:105–106.
66. McGoey KE, DuPaul GJ, Haley E, et al. Parent and teacher ratings of attention-deficit/hyperactivity disorder in preschool: the ADHD Rating Scale-IV Preschool Version. *J Psychopathol Behav Assess*. 2007;29:269–276.
67. Morales OG, Henry ME, Nobler MS, et al. Electroconvulsive therapy and repetitive transcranial magnetic stimulation in children and adolescents: a review and report of two cases of epilepsia partialis continua. *Child Adolesc Psychiatr Clin N Am*. 2005;14(1):193–210.
68. Rotenberg A, Depositario-Cabacar D, Bae EH, et al. Transient suppression of seizures by repetitive transcranial magnetic stimulation in a case of Rasmussen's encephalitis. *Epilepsy Behav.* 2008;13(1):260–262.
69. Lin KL, Pascual-Leone A. Transcranial magnetic stimulation and its applications in children. *Chang Gung Med J*. 2002;25:424–436.
70. Garvey MA, Ziemann U, Bartko JJ, et al. Cortical correlates of neuromotor development in healthy children. *Clin Neurophysiol*. 2003;114:1662–1670.
71. Quintana H. Transcranial magnetic stimulation in persons younger than the age of 18. *J ECT.* 2005;21:88–95.
72. Garvey MA. Transcranial magnetic stimulation studies in children. In: Hallet M, Chokroverty S, eds. *Magnetic Stimulation in Clinical Neurophysiology.* Philadelphia, PA: Elsevier Inc; 2005:429–433.
73. Gilbert DL, Garvey MA, Bansal AS, et al. Should transcranial magnetic stimulation research in children be considered minimal risk? *Clin Neurophysiol*. 2004;115:1730–1739.
74. Collado-Corona MA, Mora-Magana I, Cordero GL, et al. Transcranial magnetic stimulation and acoustic trauma or hearing loss in children. *Neurol Res*. 2001;23:343–346.
75. Nahas Z, DeBrux C, Chandler V, et al. Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *J ECT.* 2000;16:380–390.
76. Niehaus L, Hoffman KT, Grosse P, et al. MRI study of human brain exposed to high-dose repetitive magnetic stimulation of visual cortex. *Neurology.* 2000;54:256–258.
77. Li X, Nahas Z, Lomareu M, et al. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: a magnetic resonance imaging study in patients with depression. *Cogn Behav Neurol*. 2003;16:128–135.
78. Gates JR, Dhuna A, Pascual-Leone A. Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. *Epilepsia*. 1992;33:504–508.
79. Frye RE, Rotenberg A, Ousley M, et al. Transcranial magnetic stimulation in child neurology current and future directions. *J Child Neurol*. 2008;23(1):79–96.
80. Ebmeier KP, Herrmann LL. TMS—the beginning of the end or the end of the beginning? *Psychol Med*. 2008;38:319–321.
81. Rowell M, Zlotkin S. The ethical boundaries of drug research in pediatrics. *Pediatr Clin North Am*. 1997;44:27–40.
82. Garvey MA, Kaczynski KJ, Becker DA, et al. Subjective reactions of children to single-pulse transcranial magnetic stimulation. *J Child Neurol*. 2001;16:891–894.