Adjunctive rTMS in Adolescent Depression

Repetitive transcranial magnetic stimulation (rTMS), dosed according to the current adult protocol, was a safe and feasible adjunct to antidepressant medication in adolescents, according to results of a preliminary study.

Background: Previous research on rTMS in adolescents appears to be limited to 3 studies in a total of 10 patients treated with varying devices and doses. Recent rTMS guidelines in adults allow for increased levels of stimulation. The present study used the highest feasible doses consistent with present safety guidelines in adults.

Methods: Participants in this prospective, open-label, pilot study were 8 adolescents, aged 14–17 years, with major depression that had been unresponsive to ≥2 adequately dosed antidepressant drugs. All patients continued to receive SSRI therapy during rTMS. Each patient received a total of 30 rTMS treatments, and sessions were flexibly scheduled 5 days per week over 6–8 weeks. Each treatment consisted of 10 Hz, 4-second stimuli at 120% of the calculated motor threshold, delivered every 30 seconds, for a total of 3000 stimuli per session. Safety and feasibility of rTMS were the primary outcomes evaluated, using neurocognitive testing and elicited reporting of safety and patient comfort. Efficacy, a secondary study outcome, was assessed with the Children's Depression Rating Scale, Revised (CDRS-R); the Quick Inventory of Depressive Symptomatology, adolescent version (QIDS-A17); and the Clinical Global Impressions (CGI)* Severity and Improvement scales. Suicidality was measured with the Suicide Status Rating Scale-short form.

Results: One patient discontinued rTMS treatment during the first session because of scalp discomfort. The remaining 7 patients completed treatment as specified by the protocol. Scalp discomfort occurred in an additional 2 patients. No significant adverse events were reported. No patient reported worsening of headache, and, unexpectedly, headache frequency and severity decreased with continued rTMS exposure. Repeat neuropsychological testing did not demonstrate any decline in cognitive function or auditory thresholds.
The mean duration of depression before rTMS was 20 months, and scores on the clinical rating instruments indicated symptoms were moderate to severe. Depression was significantly ameliorated as early as the 10th treatment and continued to show improvement throughout the delivery of rTMS and at the 6-month follow-up. (See table.) At the completion of treatment, CGI severity ratings were normal in 3 patients, borderline ill in 1, and mildly ill in 2. At 6 months, CGI severity ratings were mild or better in all patients. CGI improvement ratings were much improved or very much improved in 5 patients.

<table>
<thead>
<tr>
<th>Depression Rating Measure</th>
<th>Baseline</th>
<th>After 10 Sessions</th>
<th>End of Treatment</th>
<th>6-Month Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRS-R</td>
<td>65.9</td>
<td>50.9</td>
<td>32.6</td>
<td>32.7</td>
</tr>
<tr>
<td>QIDS-A17</td>
<td>14.7</td>
<td>12.1</td>
<td>8.3</td>
<td>7.1</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.4</td>
<td>4.0</td>
<td>2.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

A total of 3 adolescents reported suicidal ideation at baseline. Expressions of suicidal ideation decreased with treatment, although 1 patient continued to have passive suicidal thoughts. Of the 7 patients who completed treatment, all said that they would use rTMS again to treat their depression if prescribed. Nearly all patients and families said that they preferred rTMS to medication or psychotherapy.


*See Reference Guide.*

**Age and Differences in Adverse Drug Events**

There have been few long-term medication safety studies in young patients, and adverse events in children appear to be under-reported. According to a systematic literature review, preschool children are more vulnerable than older children and adolescents to psychotropic medication adverse effects. They are particularly at risk from stimulants, antipsychotics, SSRIs, and anticonvulsants.

This review of reported adverse events was based primarily on published clinical trials, most of which were large, industry sponsored, and short term. Reports from case series, open trials, reviews, and meta-analyses were also included. Patterns of adverse effects grouped by age are presented for common psychotropic classes.

**Stimulants and other ADHD medications.** Stimulants and atomoxetine can reduce growth velocity, particularly in younger children. Preschoolers also experience more stimulant-associated emotional symptoms, including irritability and anxiety, than older children. Younger children may also be prone to tearfulness. Stimulant-induced tics are more frequent in younger than older children, as are atomoxetine-related somatic symptoms such as vomiting and somnolence.

**Antidepressants.** Behavioral disinhibition has been reported in 11% of children in SSRI trials, a higher proportion than in adolescents and adults. SSRI-related activation is particularly common in preschoolers. Risk of suicidal ideation and behavior is increased with SSRIs and
other antidepressants throughout youth and up to the age of 25 years, after which risk declines steeply. Antidepressant-related suicidality in youth is associated particularly with venlafaxine and paroxetine. Antidepressant-related sexual dysfunction was reported by one-fourth of a small sample of adolescent boys; this rate may be lower than that in adults. Venlafaxine is associated with reduced gains in weight and height in preadolescents.

**Antipsychotics.** Sedation associated with antipsychotic treatment affects more youths than adults. Tardive dyskinesia is less common in youths than adults. Antipsychotic-induced weight gain is particularly prominent in young children but also affects higher proportions of adolescents than adults. Other effects that occur more frequently in youths than adults are increased lipid levels with olanzapine, elevations in prolactin and liver enzymes with olanzapine and risperidone, increases in heart rate and blood pressure with quetiapine, and QTc prolongation with ziprasidone.

**Anticonvulsants.** Valproic acid is associated with liver toxicity particularly in infancy but also in children aged <10 years, compared with adolescents and adults. Valproic acid is also more likely to induce pancreatitis in children than in adults, and a polycystic ovarian syndrome is more likely to occur in teenage girls than in adults. Phenobarbital is more likely to induce agitation in young children, and long-term use in infants and toddlers can impair intellectual development.

Safer D. Age-grouped differences in adverse drug events from psychotropic medication. *Journal of Child and Adolescent Psychopharmacology* 2011;21:299–309. From the Johns Hopkins Institutions, Baltimore, Md. **This review was conducted without funding. The author disclosed no competing interests.**

**Drug Trade Names:** atomoxetine—Strattera; olanzapine—Zyprexa; paroxetine—Paxil; quetiapine—Seroquel; risperidone—Risperdal; valproic acid—Depakene; venlafaxine—Effexor; ziprasidone—Geodon

### Adjunctive CBT in OCD

Augmentation of SRIs with cognitive-behavioral therapy was effective in children and adolescents with treatment-resistant obsessive-compulsive disorder, but adjunctive treatment with a lower-intensity modification of CBT was not superior to medication alone.

**Methods:** Study subjects (n=124) were outpatients, aged 7–17 years, with residual OCD symptoms despite adequate treatment with an SRI. Patients were randomized to 1 of 3 treatment conditions, each lasting 12 weeks. All participants received medication management in 7 in-person visits (35-min each), in which a child/adolescent psychiatrist monitored maintenance drug therapy and provided encouragement. In addition, the CBT group received a manualized program consisting of 14 visits (1 hour each), administered by a psychologist, which featured exposure and response prevention. The third intervention, called "instructions in CBT," was designed to test the feasibility of a less intensive form of therapy that could be administered in routine clinical practice. CBT instruction consisted of 7 expanded medication management visits (45 min each) provided by the medication management psychiatrist. In this intervention, patients were taught how to apply exposure and response prevention, but the clinician did not directly assist in the exposure. Treatment efficacy was measured using the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS), administered by an independent, blinded rater, with response defined as a ≥30% reduction in score.

**Results:** The mean duration of SRI treatment before trial enrollment was 75 weeks (range, 9–402 weeks). A total of 101 patients completed all treatment sessions. Notable among the treatment discontinuations were 7 patients assigned to medication management alone, whose participation ended prematurely because they sought out-of-protocol CBT.

All randomized patients were included in the efficacy assessments. Medication plus CBT was significantly superior to both CBT instruction and medication management alone. Response
rates were 69% for the CBT group, 34% for the CBT-instruction group, and 30% for the medication-management group. Treatment effect sizes* were 0.85 for CBT vs medication management and 0.16 for CBT instruction vs medication management.

**Discussion:** In OCD incomplete responses to medication alone are the norm, but many patients do not have access to a clinician with expertise in pediatric CBT. Results of this trial support the growing evidence that exposure and response prevention is effective in OCD as an initial or augmentative treatment. Other evidence suggests CBT can be administered in community settings by supervised therapists who are not experts in the technique. The present study supports increasing the availability of the full CBT protocol in the community, rather than attempting to create less intensive versions.

Franklin M, Sapyta J, Freeman J, Khanna M, et al: Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder. The Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. JAMA 2011;306 (September 21):1224–1232. From the University of Pennsylvania School of Medicine; and other institutions. Funded by the NIMH. One study author disclosed financial relationships with commercial sources.

*CSee Reference Guide.*

### Caffeine and Depressive Symptoms Linked

Results of a cross-sectional study suggest that caffeine consumption may be associated with depression in children.

**Background:** Consumption of caffeine-containing drinks by children and adolescents has been steadily increasing. A large majority of youths consume at least 1 can of caffeinated soda daily, and use of “energy drinks” is also increasing. Some research has also shown a link between early caffeine consumption and later substance abuse.

**Methods:** The present investigation was carried out as part of a longitudinal study of Brazilian children with suspected learning, mood, attention, or hyperactivity problems. Children in grades 1–5 (aged 9–12 years) had been referred for study by their teachers. Because boys tend to be clinically referred for behavior problems more often than girls, the sample was primarily male (84%). Depressive symptoms were assessed with the Children’s Depression Inventory (CDI), with a score of ≥15 indicating significant depression. Food/beverage consumption and its relationship to psychological symptoms of behavior were assessed with the Nutrition-Behavior Inventory (NBI).

**Results:** A total of 34 of the 51 study participants (67%) met criteria for significant depression. These children had significantly higher NBI scores than children without depression (52 vs 26; p<0.0001), indicating an association between psychological symptoms and eating habits. Among eating habits analyzed individually, only consumption of caffeine-containing drinks was associated with depression. All of the children who said that they "often" or "always" consumed >3 cups of coffee, cola, or tea per day had significant depressive symptoms.

**Discussion:** It is not clear whether the association shown in this study represents a cause-and-effect relationship. High consumption of caffeine may represent an attempt to relieve some symptoms of depression or a common genetic predisposition with depression. Caffeine acts on different neural receptors and may have conflicting effects at different concentrations. In adults, low levels of caffeine consumption appear to protect against depression and suicide, while higher levels of consumption may increase risks. Further studies of caffeine consumption by children, particularly those already at risk for depression, appear to be warranted.

Benko C, Farias A, Farias L, Pereira E, et al: Potential link between caffeine consumption and pediatric depression: a case-control study. BMC Pediatrics 2011; doi 10.1186/1471-2431-11-73. From the Pele Pequeno Principe Research Institute, Curitiba, Brazil; and other institutions. Funded by the State of Parana Department of Science and Technology; and the State of Parana Health Department. The authors did not include disclosure of potential conflicts of interest.
Stimulant Use Patterns Continue to Change

Use of stimulants in children and adolescents increased rapidly from the mid-1980s to the mid-1990s. According to national survey data, stimulant use continues to increase every year, although not as rapidly. Despite the increase, ADHD prevalence has remained stable and a majority of youths with ADHD are not treated with stimulants.

Data on stimulant use was collected from the 1996–2008 Medical Expenditure Panel Surveys (MEPS), a representative household survey conducted by the Agency for Healthcare Research and Quality, and was then compared with data from the 1987 National Medical Expenditure Survey, the predecessor to the MEPS.

In 2008, an estimated 2.8 million U.S. children and adolescents aged ≤18 years received stimulant medication, 3.5% of all persons in this age group. Stimulant use increased by 3.4% per year between 1996 and 2008, a much slower rate than the 17% annual growth rate seen in 1987–1996.

Stimulant use was highest in children aged 6–12 years across the years, but by 2008 the rate of use in adolescents aged 13–18 years had increased to the same level, about 5%. The increase in adolescents is likely to reflect recent data suggesting that ADHD persists into puberty and continues to cause significant impairment. Stimulant use in children aged <6 years significantly decreased and remained low, only 0.1% from 2004 onward.


Long-Term Cardiac Safety of Stimulants

Ten years of stimulant treatment was not associated with increased risk of hypertension or prehypertension in young people with ADHD. However, continued heart-rate elevations at 10 years suggest that patients do not become completely tolerant of the adrenergic stimulation produced by these agents.

Methods: The study was a naturalistic follow-up of patients originally enrolled in the Multimodal Treatment Study of Children with ADHD (MTA). The 579 study participants, children aged 7–9 years with combined-type ADHD and no evidence of cardiovascular disease, were randomly assigned to 14 months of treatment with stimulant medication (usually methylphenidate [Ritalin, and others]), behavioral therapy, both treatments, or a control condition. Results of acute and follow-up treatment effects have been previously published, and a collection of Child & Adolescent Psychiatry Alerts articles on the MTA study is available at www.alertpubs.com. After the 14 months of randomized treatment, 289 age- and gender-matched children without ADHD were added as a comparison group. Study participants were examined at 2, 3, 6, 8, and 10 years.

Results: Heart rate, blood pressure, and medication data was available at year 10 for nearly 60% of participants. The number of patients who continued taking stimulants declined over time to 316 at 14 months, 257 at 3 years, 91 at 8 years, and 18 at 10 years. During the randomized study and the extended follow-up period, there were no cardiovascular adverse events leading to stimulant discontinuation or dosage reduction. No association was found at any time point between current or past stimulant use and blood pressure or rates of hypertension or prehypertension.

Heart rates were higher on average in persons exposed to stimulants. At the conclusion of the clinical trial (14 months), the average heart rate was about 5 bpm higher in the groups who
received methylphenidate than in the unexposed groups. Although there was no difference in the percentage of patients meeting criteria for tachycardia (i.e., heart rate >95th percentile of age and gender norms) during the follow-up years, statistically significant effects of exposure on heart rate were observed at 14 months and at 3 and 8 years, but not at other time points. The effect of stimulants on heart rate was largely driven by current stimulant use rather than past exposure.

**Discussion:** The clinical implications of these findings are unclear. However, because adrenergic stimulation contributes to cardiac arrhythmia, stimulant-induced sympathomimetic activity may be a concern for those with underlying cardiac abnormalities, and further evaluation of the long-term safety of stimulants is warranted.


**Reference Guide**

**Clinical Global Impression Improvement (CGI-I) Scale:** A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

**Clinical Global Impression Severity (CGI-S) Scale:** A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.