A review of repetitive transcranial magnetic stimulation for adolescents with treatment-resistant depression

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ABSTRACT
This review examines the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) as a treatment for treatment-resistant depression in adolescents. A systematic review of six databases was conducted. Ten multi-subject trials, all uncontrolled, and five case reports met inclusion criteria. Twelve studies focused on treatment efficacy, whereas three studies focused exclusively on adverse events. All efficacy studies focused on adolescents only; 10 of these studies indicated that rTMS may demonstrate some benefit. Improvement within 2–8 weeks was reported in most studies, with a few studies indicating potential long-term benefits. A variety of adverse events occurred including scalp pain, which was the most common, as well as seizures. Controlled studies of rTMS are warranted to further examine whether this treatment is a potential option for adolescents with treatment-resistant depression.

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Introduction
Paediatric depression is a debilitating disorder that adversely affects educational achievement, peer relationships, and family functioning (Knapp, McCrone, Fombonne, Beecham, & Wostear, 2002). This disorder affects 2% of pre-pubertal children and 4% of adolescents (Birmaher et al., 1996). Approximately 30% of youth with depression suffer from significant suicidal ideation (Kennard et al., 2006). Evidence shows that currently available treatments for depression are sub-optimal. Acute treatment with pharmacotherapy and cognitive behavioural therapy results in a 73% response rate, although many remain symptomatic post-treatment (Kennard et al., 2006; March et al., 2004). Only 40% of adolescents who fail to respond to initial treatments (i.e. treatment-resistant) respond to additional combined therapies (Emslie et al., 2010). Developing new treatments for paediatric depression is, therefore, a critical priority to improve short- and long-term outcomes.

Electroconvulsive therapy (ECT) is one available option for youth with treatment-resistant depression or for those who cannot tolerate antidepressants (Ghaziuddin et al., 2004). The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters recommend ECT for adolescents with a diagnosis of major depressive disorder, severe symptoms (i.e. life-threatening and severe suicidal intent), and lack of response to at least two medications that were delivered together with psychosocial treatments (Ghaziuddin et al., 2004). Several studies report that ~60–77% of adolescents with paediatric depression respond to ECT (Calev, 1994; Puffer, Wall, Huxsahl, & Frye, 2016; Shoirah & Hamoda, 2011; Strober et al., 1998). ECT, however, has major adverse effects, including cognitive impairment, confusion, tardive seizures, as well as risks of anaesthesia. These drawbacks may deter families from considering ECT as an acceptable treatment option (Ghaziuddin et al., 2004).

Repetitive transcranial magnetic stimulation (rTMS) may be an advantageous treatment for some adolescents suffering from depression. rTMS is a non-invasive procedure that has been approved by the Food and Drug Administration for the treatment of major depressive disorder in adults who have failed to receive satisfactory improvement with antidepressant medications (Janicak & Dokucu, 2015). The procedure involves placing an electromagnetic coil over the left dorsolateral prefrontal cortex (DLPFC). Magnetic pulses are delivered to this area, which modulate cerebral activity via electrical currents, and are hypothesized to result in long-lasting alteration in neural pathways implicated in major depressive disorder (Hulvershorn, Cullen, & Anand, 2011; Janicak & Dokucu, 2015; Liston, Chen, & Zebley, 2014).
In adults, research indicates that rTMS may be efficacious for treatment-resistant depression. Results of a recent meta-analysis of 29 randomized, controlled clinical trials of high-frequency rTMS indicated a statistically and clinically significant pooled odds ratio for response and remission (Berlim, Van den Eynde, Tovar-Perdomo, & Daskalakis, 2014). A systematic review and meta-analysis of 16 randomized controlled trials of high-frequency rTMS relative to inactive sham rTMS found a statistically significant effect size for antidepressant efficacy (Kedzior, Reitz, Azorina, & Loo, 2015).

Over the past decade, treatment studies of rTMS for paediatric depression have been emerging. This review systemically examines the efficacy of rTMS as a treatment for paediatric depression. Although several prior reviews have been written on this topic (Croarkin et al., 2010; Donaldson, Gordon, Melvin, Barton, & Fitzgerald, 2014; Hu et al., 2011; Krishnan, Santos, Peterson, & Ehinger, 2015), an updated review on both the efficacy and safety of rTMS for paediatric depression is needed to provide clinicians and researchers with current knowledge in the field. The current review differs from prior reviews because it organizes the data according to three key questions. These are as follows:

1. Is rTMS an efficacious treatment for adolescent depression?
2. What types of adverse events occur in children and adolescents receiving rTMS?
3. How do age, co-morbid conditions, and rTMS treatment parameters impact rTMS treatment response?

**Method**

A systematic search of six databases was conducted: PubMed, Embase, PsycINFO, CINAHL, Scopus, and Web of Science. A Johns Hopkins medical informationist worked with the authors to develop and execute a search strategy within the designated databases. The search strategy included terms related to three concepts: condition (clinically diagnosed depression), population (paediatric), and treatment (repetitive transcranial magnetic stimulation [rTMS]). There were no limits for dates of publication, and the search was conducted through August 2016. Inclusion criteria consisted of individuals below 18 years. Studies including participants below 18 years but focusing primarily on adults were omitted. To capture all of the available data, studies conducted both within and outside the US were included for review. Studies reporting on single-pulse TMS were excluded, as it is not a treatment modality for major depressive disorder.

Figure 1 illustrates the results of the search. A total of 470 articles were subjected to title and abstract review. The first author (LM), in consultation with the co-authors, winnowed this initial list of articles to include only those pertaining to paediatric depression. Of the initial 470 articles, a total of 15 studies met inclusion criteria during the full-text review phase. The reference lists of these 15 studies were hand-searched for additional potentially missed studies, but none were found to meet inclusion criteria.

Table 1 presents the sample characteristics, rTMS parameters, and outcomes of the 15 included studies. Sample sizes across studies ranged from 1–18, and sample age ranged from 10–22 years. Twelve studies...
focused on treatment efficacy and safety (nine multi-subject studies and three case reports), and three focused exclusively on adverse events (one multi-subject study and two case reports).

Results

Question 1: Is rTMS an efficacious treatment for adolescent depression?

All efficacy studies focused on adolescents only. Five of these studies established the diagnosis of depression by clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders (Croarkin et al., 2012, 2016; Segev, Spellun, & Bloch, 2014; Wall et al., 2013; Yang et al., 2014), and six studies used the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (Bloch et al., 2008; Cristancho, Akkineni, Constantino, Carter, & O’Reardon, 2014; Loo, McFarquhar, & Walter, 2006; Mayer, Aviram, Walter, Levkowitz, & Bloch, 2012; Wall et al., 2016; Wall et al., 2011). One study did not specify diagnostic assessment procedures (Cullen et al. 2016). Criteria for inclusion in 11 studies were the lack of response to one antidepressant medication; in one study, the participant did not respond to 6 months of psychotherapy (Loo et al., 2006). In all but four studies, adolescents continued taking antidepressant medications during rTMS treatment (Cullen et al., 2016; Loo et al., 2006; Segev et al., 2014; Yang et al., 2014).

Ten out of 12 studies (nine multi-subject trials, one case report) reported that rTMS may have a benefit for adolescent depression (Bloch et al., 2008; Cristancho, Akkineni, Constantino, Carter, & O’Reardon, 2014; Loo, McFarquhar, & Walter, 2006; Mayer, Aviram, Walter, Levkowitz, & Bloch, 2012; Wall et al., 2016; Wall et al., 2011). One study did not mention scalp pain, headache, dizziness, eye twitch, nausea, or scalp pain (n = 1). Other studies did not specify the number of subjects with adverse events.

Table 1. Studies on safety and efficacy of rTMS in adolescents with treatment-resistant depression.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age range (mean)</th>
<th>rTMS location^a</th>
<th>Number of rTMS sessions^b</th>
<th>Session duration (sec per train, sec per interval)</th>
<th>Frequency of stimulation (Hz)</th>
<th>Intensity %MT (n)</th>
<th>Results^c</th>
<th>Adverse events^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cullen et al. (2016)</td>
<td>1</td>
<td>17</td>
<td>L-DLPFC</td>
<td>8</td>
<td>(2, 20)</td>
<td>18</td>
<td>85–120</td>
<td>Neutral</td>
<td>Seizure, scalp pain</td>
</tr>
<tr>
<td>Segev et al. (2014)</td>
<td>1</td>
<td>17</td>
<td>L-DLPFC</td>
<td>20</td>
<td>(4, 30)</td>
<td>10</td>
<td>100</td>
<td>Neutral</td>
<td>Headache, scalp pain, burning</td>
</tr>
<tr>
<td>Hu et al. (2011)</td>
<td>1</td>
<td>15</td>
<td>L-PFC</td>
<td>&lt;1</td>
<td>10 min (4, 26)</td>
<td>10</td>
<td>80</td>
<td>Neutral</td>
<td>N/A</td>
</tr>
<tr>
<td>Cristancho et al. (2014)</td>
<td>1</td>
<td>15</td>
<td>R-DLPFC</td>
<td>10</td>
<td>(10, 10–30)</td>
<td>1</td>
<td>89</td>
<td>Positive</td>
<td>Seizure, transient jaw twitch, dizziness</td>
</tr>
<tr>
<td>Chiramberro et al. (2013)</td>
<td>1</td>
<td>16</td>
<td>L-DLPFC</td>
<td>12</td>
<td>20 min (5, 25)</td>
<td>10</td>
<td>Unspecified</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Multi-subject trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croarkin et al. (2016)</td>
<td>10</td>
<td>13–17 (15.4)</td>
<td>L-DLPFC</td>
<td>30</td>
<td>(4, 26)</td>
<td>10</td>
<td>120</td>
<td>Positive</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Wall et al. (2016)</td>
<td>10</td>
<td>13.9–17.4 (15.9)</td>
<td>L-DLPFC</td>
<td>30</td>
<td>(4, 26)</td>
<td>10</td>
<td>80–120</td>
<td>Positive</td>
<td>Scalp pain, headache, dizziness, eye twitch, nausea</td>
</tr>
<tr>
<td>Yang et al. (2014)</td>
<td>6</td>
<td>15–21 (18.7)</td>
<td>L-DLPFC</td>
<td>15</td>
<td>37.5 min (4, 26)</td>
<td>10</td>
<td>120</td>
<td>Positive</td>
<td>Scalp pain, headache</td>
</tr>
<tr>
<td>Wall et al. (2013)</td>
<td>18</td>
<td>13.9–17.8 (16.2)</td>
<td>L-DLPFC</td>
<td>30</td>
<td>(4, 26)</td>
<td>10</td>
<td>120</td>
<td>Positive</td>
<td>Scalp pain, headache (n = 1)</td>
</tr>
<tr>
<td>Croarkin et al. (2012)</td>
<td>8</td>
<td>14–17 (16.5)</td>
<td>L-DLPFC</td>
<td>30</td>
<td>(4, 26)</td>
<td>10</td>
<td>120</td>
<td>Positive</td>
<td>Scalp pain (n = 3)</td>
</tr>
<tr>
<td>Mayer et al. (2012)</td>
<td>8</td>
<td>19–22 (20.4)</td>
<td>L-DLPFC</td>
<td>14</td>
<td>20 min (2, 58)</td>
<td>10</td>
<td>80</td>
<td>Positive</td>
<td>Scalp pain (n = 3)</td>
</tr>
<tr>
<td>Cristancho et al. (2011)</td>
<td>3</td>
<td>10–17 (12.33)</td>
<td>L-DLPFC</td>
<td>&lt;1</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>40–56</td>
<td>N/A</td>
<td>Scalp pain (n = 3)</td>
</tr>
<tr>
<td>Wall et al. (2011)</td>
<td>8</td>
<td>14.6–17.8 (16.5)</td>
<td>L-DLPFC</td>
<td>30</td>
<td>(4, 26)</td>
<td>10</td>
<td>120</td>
<td>Positive</td>
<td>Scalp pain (n = 3)</td>
</tr>
<tr>
<td>Bloch et al. (2008)</td>
<td>9</td>
<td>16–18 (17.3)</td>
<td>L-DLPFC</td>
<td>14</td>
<td>20 min (2, 58)</td>
<td>10</td>
<td>80</td>
<td>Positive</td>
<td>Scalp pain (n = 3)</td>
</tr>
<tr>
<td>Loo et al. (2006)</td>
<td>2</td>
<td>16 (16)</td>
<td>L-DLPFC</td>
<td>27–29</td>
<td>(5, 25)</td>
<td>10</td>
<td>110</td>
<td>Positive</td>
<td>Headache (n = 5)</td>
</tr>
</tbody>
</table>

CORS-R: Children’s Depression Rating Scale-Revised; L-DLPFC: Left Dorsolateral Prefrontal Cortex; R-DLPFC: Right Dorsolateral Prefrontal Cortex; MT: Motor Threshold.

^aAll studies used the figure-of-eight coil except for Cullen et al. (2016), which used the H-coil.

^bThe participant in Cullen et al. (2016) prematurely withdrew from treatment due to a seizure.

^cPositive refers to improvement in depressive symptoms. Neutral refers to no improvement in depressive symptoms. N/A indicates that the study only focused on adverse events.

^dSome studies did not specify the number of subjects with adverse events.
O’reardon, 2014; Croarkin et al., 2012, 2016; Loo et al., 2006; Mayer et al., 2012; Wall et al., 2011, 2013, 2016; Yang et al., 2014). In nine of these 10 studies, 39 out of 62 (63%) adolescents were reported to respond to rTMS. Objective criteria for response, however, were not clearly specified in some studies. In Wall et al. (2013), which is the largest multi-trial study ($n=18$), a substantial decrease in depression severity was reported, although CDRS-R data for the group and individual participants were not reported. Two case reports indicated no improvement (Cullen et al., 2016; Segev et al., 2014). In one case report, the participant withdrew from treatment prematurely due to a seizure (Cullen et al., 2016).

In terms of timing of response, nine of the 10 studies reported improvement within 2–8 weeks of initiating treatment; the tenth study only focused on long-term benefits (Mayer et al., 2012). Six of the 10 studies indicated sustained treatment benefits for up to 6 months (Croarkin et al., 2016; Wall et al., 2011, 2013, 2016), 12 months (Bloch et al., 2008), and 3 years (Mayer et al., 2012).

When reviewing the outcome data, many studies indicated that, although treatment shows benefit, residual depressive symptoms were present after treatment. Seven of nine studies captured improvement using the Children’s Depression Rating Scale-Revised (CDRS-R), a clinician-rated measure that integrates parent and participant report. Four of these studies were multi-subject trials and specified both pre- and post-treatment CDRS-R scores, and, therefore, the magnitude of the change in depressive symptoms could be appreciated. Across these four multi-trial studies, the pre-treatment CDRS-R score ranged from 53–75 (moderate-to-severe depression), and the post-treatment score fell in the mild depression range (31.9–39.9) (Croarkin et al., 2012, 2016; Wall et al., 2011, 2016). The remaining two studies reported lack of response.

In one study, the participant prematurely withdrew after experiencing a seizure during the eighth session of rTMS. The CDRS-R score was 60 (severe depression) at baseline, and remained persistently elevated at 60 after phase one (Cullen et al., 2016). In the other study, the participant completed 20 sessions of treatment, but the CDRS-R score showed no statistically significant improvement and remained above 80 from baseline to treatment end (Segev et al., 2014).

Data from the Beck Depression Inventory (BDI), an adolescent self-report measure, also indicated varied post-treatment outcomes including persistent symptoms. Only three studies reported pre- and post-treatment scores (Loo et al., 2006; Segev et al., 2014; Yang et al., 2014). In one study, pre-treatment scores were 25 (moderate) to 38 (severe), and dropped to 10–15 (normal and mild mood disturbance, respectively) (Loo et al., 2006). Four participants improved in another study, in which average scores decreased from 37.3 to 3.0, but two were non-responders, and their average scores increased from 37.5 to 44.5 (Yang et al., 2014). One case study reported no change in the Beck Depression Inventory-2nd Edition score, which remained in the 40s (extreme depression) (Segev et al., 2014).

Suicidality was assessed in some studies, but not others. Studies that included general depression scales, which included a question about suicidality, did not indicate whether suicidality improved or not. Four studies included a separate measure to assess suicidality (Bloch et al., 2008; Segev et al., 2014; Wall et al., 2011, 2016). Two studies included the Suicidal Ideation Questionnaire (SIQ). One reported no change in suicidality, although pre- and post-rTMS SIQ scores were not reported (Bloch et al., 2008); the other study reported a mild increase in suicidal ideation at 1 week, which improved and plateaued after week 3 (Segev et al., 2014). Two studies used the Columbia Suicide Severity Rating Scale (C-SSRS). One reported a decline in suicidal ideation in all but one participant, who endorsed passive death wishes at the end of treatment and then engaged in self-mutilatory behaviour at 6 months (Wall et al., 2011). The other study showed that 80% of adolescents reported some baseline suicidal ideation; one participant experienced...
transient suicidal ideation after a life stressor, and another engaged in self-injurious behaviour at the 6-month follow-up (Wall et al., 2016).

Question 2: What are the types of adverse events that occur with rTMS?

Adverse events were assessed in all 12 efficacy studies except for one (Croarkin et al., 2016), which did not mention any information on adverse events. Additionally, there were three studies that exclusively focused on adverse events, one multi-subject study (Croarkin, Wall, King, Kozel, & Daskalakis, 2011), which included children as young as 10 years old, and two case reports (Chiramberro, Lindberg, Isometsä, Kähkönen, & Appelberg, 2013; Hu et al., 2011).

The most common adverse outcome reported in many studies was scalp pain (Croarkin et al., 2011, 2012; Cullen et al., 2016; Segev et al., 2014; Wall et al., 2011, 2016; Yang et al., 2014), which was generally tolerated. In one study, however, two participants discontinued rTMS treatment due to scalp discomfort, despite pain resolution within 30 min of stopping treatment (Croarkin et al., 2011). In the same study, another participant’s pain started after six trains, had an intensity of 7/10, and was described as a migraine between her eyes, which led to study withdrawal.

Three studies reported seizures and, in all cases, treatment was discontinued. In a case study, the participant experienced a 1-min generalized tonic-clonic seizure 3 min after the first rTMS session, which resolved with intravenous diazepam; this participant also experienced transient hypomanic symptoms that evening (Hu et al., 2011). In another study, one participant’s pain started after six trains, had an intensity of 7/10, and was described as a migraine between her eyes, which led to study withdrawal.

In three studies, improvements in co-morbid anxiety were noted simultaneously with improvements in depression (Bloch et al., 2008; Cristancho et al., 2014; Yang et al., 2014). In one of these studies, participants with depression also had co-occurring conditions, including a history of childhood sexual trauma, post-traumatic stress disorder, obsessive compulsive disorder, attention deficit hyperactivity disorder, history of substance abuse, history of eating disorder, and borderline personality disorder (Bloch et al., 2008). In two studies, anxiety, as measured by the Screen for Child Anxiety Related Disorders (SCARED), was noted to improve (Segev et al., 2014; Yang et al., 2014).

Treatment parameters

In terms of treatment duration, in eight studies, a range of 20–30 treatments were administered with a figure-of-eight coil over the course of 1–8 weeks (Croarkin et al., 2012, 2016; Loo et al., 2006; Mayer et al., 2012; Segev et al., 2014; Wall et al., 2011, 2013).
and improvements in depression were seen in all but one study (Segev et al., 2014). When assessing stimulus parameters, six studies indicated that 10-Hz rTMS at 120% motor threshold applied to the left DLPFC reduced depression severity (Croarkin et al., 2012, 2016; Wall et al., 2011, 2013, 2016; Yang et al., 2014). 1-Hz rTMS at 90% motor threshold was delivered over the right DLPFC in one study, and improvement in depression was observed (Cristancho et al., 2014).

Discussion

Since the last review on rTMS for adolescent depression (Donaldson et al., 2014), eight additional studies have been published, none of which are randomized controlled trials. All studies to date are still either case reports or open label trials. Collective limitations of existing studies include small sample sizes, and inconsistent reporting of pre- and post-treatment scores on measures of depression symptoms, severity, and improvement. Responses to key questions explored in this review are discussed below.

Question 1: Is rTMS an efficacious treatment for adolescent depression?

Despite study limitations, results suggest that rTMS might have some benefit for adolescent depression. Many studies report a reduction in depressive symptoms and severity using both clinician-rated and self-report measures. When using clinician-rated measures, residual symptoms were often present at the end of treatment. Some studies using the CGI-S reported participants as being moderately ill post-treatment. The BDI data, which reflect adolescent self-report, are inconsistent, with some indicating a reduction in depressive symptoms and even remission, and others reporting no improvement.

Overall, when comparing the efficacy data for rTMS to other treatments for treatment-resistant depression, available evidence indicates that the outcomes appear to be somewhat comparable. In nine of the included rTMS studies on efficacy, participants had a response rate of 63% within 8 weeks. Similarly, results from the Treatment of Resistant Depression in Adolescents (TORDIA) study indicated that 54.8% of adolescents who received cognitive behavioural therapy plus medication responded by 12 weeks (Emslie et al., 2010). Likewise, in a randomized controlled trial, 64% of adolescents were categorized as responders after ~4 weeks of ECT treatment (Ghazziuddin et al., 1996). It is important to note that these comparisons are very preliminary, as there are significant methodological differences across studies. The pharmacological studies are the most rigorous, with detailed information about enrollment criteria (e.g., participant characteristics, depression severity, past treatment, comorbidities) as well as definitions of response and remission. Methods in the rTMS and ECT studies, however, are quite variable with respect to how the depression diagnosis was made, definitions of response, and inclusion of all pre- and post-treatment data on outcomes. In future studies of rTMS, it will be important to characterize the types of symptoms that do not improve, and investigate whether pharmacological and/or psychosocial treatments during the course of rTMS and post-treatment continuation phase could improve outcomes.

Only a few studies tracked suicidality throughout the course of treatment, and, therefore, there is a shortage of data that enable conclusions about the course of suicidality. Studies that did track this symptom reported different results, i.e. no change, mild improvement. There were a couple of participants who reported suicidality after treatment; however, it appears that this may have been secondary to life stressors or possibly psychosocial adjustments related to improvement (Wall et al., 2011, 2016). In adults, rTMS may decrease suicidality. Several studies have reported that adults with major depressive disorder demonstrate a reduction in suicidal thinking within 3–10 days after accelerated, intermittent, or daily high-dose left prefrontal rTMS, and this was considered safe and feasible (Desmyter, Duprat, Baeken, Bijttebier, & van Heeringen, 2014; George et al., 2014; Hadley et al., 2011). Given that both standard rTMS protocols and antidepressants may take weeks to take effect, this high-dose treatment deserves investigation in acutely suicidal adolescents, given their impulsivity and poor coping skills, which necessitates constant supervision to maintain safety during the illness period. Monitoring of suicidality at specific time points is warranted in future studies to determine both the timing as well as treatment parameters associated with optimal outcomes.

In summary, preliminary data from uncontrolled trials indicate that rTMS might decrease depressive symptoms. Many adolescents, however, continue to have symptoms after short-term treatment.

Question 2: What are the types of adverse events that occur with rTMS?

Overall, rTMS appears to be reasonably well-tolerated. Scalp pain was the most common adverse event, which appeared to be self-limited in some cases, but,
nevertheless, caused significant discomfort for some participants and led to discontinuation (Croarkin et al., 2011, 2012; Wall et al., 2011, 2016; Yang et al., 2014). This discomfort most likely occurs secondary to contraction of facial muscles, stimulation of the facial or trigeminal nerves, or activation of nociceptors in the scalp or bone (Borckardt et al., 2007). Constitutional symptoms also emerged, but these were tolerated. The available evidence also suggests that rTMS does not seem to cause any major cognitive sequela, making this treatment significantly more advantageous than ECT.

One serious adverse event was the occurrence of tonic-clonic seizures, which led to treatment termination in all cases. Seizures may result from increased cortical excitability with rTMS treatment (Cullen et al., 2016). Given that some antidepressants may cause seizures, it is unclear whether combined antidepressant and rTMS treatment may pose a risk (Finkelstein, Hutson, Freedman, Wax, & Brent, 2013). In the adult literature, rTMS does induce seizures; however, their occurrence is rare and estimated as less than 0.1% (Wassermann, 1998). The developing brain, however, may be more vulnerable and, therefore, seizure risk will need to be evaluated carefully in the adolescent population.

Although not formally assessed, one challenge of rTMS is the time commitment involved, which can result in negative outcomes. Current evidence shows that rTMS is usually delivered daily over the course of 4–8 weeks, with each visit taking ~30–40 min. Typically, children attend sessions after school to minimize absences. Likewise, there is the parental burden of missed time from work. These demands may lead to a different set of adverse outcomes including academic lags, decreased socialization, withdrawal from recreational activities, as well as reduced productivity for parents. One study that assessed treatment satisfaction showed that seven of eight adolescents were not frightened by rTMS and would choose rTMS again if given the choice, preferably over antidepressant medications or psychotherapy (Wall et al., 2011).

In summary, rTMS is linked to adverse events, namely scalp discomfort and isolated cases of seizures. Further controlled studies examining the safety profile of rTMS are needed.

**Question 3: How do age, co-morbid conditions, and rTMS treatment parameters impact antidepressant treatment response?**

Attempts to examine the impact of age and co-morbidities were constrained by the lack of data. Similar to the ECT data, there are limited data on rTMS efficacy in younger children. Comparisons within the adolescent group were not possible due to small sample sizes. Most studies did not track how co-morbidities may moderate treatment outcomes, which is critical since depression is associated with high rates of co-morbid disorders, particularly anxiety and ADHD, which could potentially maintain symptoms (Arnold et al., 1997). Trauma, losses, and the nature of psychosocial support are also other factors that may affect rTMS outcome and require investigation.

Most studies used 20–30 treatments of 10-Hz rTMS at 120% motor threshold delivered to the left DLPFC over 1–8 weeks. However, more frequent use of this treatment parameter is not an indication that it is the most efficacious. Comparisons between disparate parameters were not made in the included studies. It would, therefore, be erroneous to identify this parameter as most effective due to the paucity of studies.

In summary, the impact of age, co-morbidities, and treatment parameters on outcome continues to be limited.

**Future research directions**

Research on the use of rTMS for adolescent depression has been progressing at a slow pace. This may in part be secondary to cost. Randomized, double-blind controlled trials of neuromodulation devices are quite expensive to conduct, due to the necessity of several consecutive treatments. There are also ethical issues pertaining to randomizing severely ill children to sham treatments. Methods to decrease the need for daily treatment and consequently decrease cost require investigation. For example, the development of different coils, which could target deeper regions of the brain, may possibly expedite treatment response and decrease frequency of treatment. Additionally, since studies included in this review reported possible benefit with short-term treatment, researchers could address ethical issues by continuing pharmacotherapy in both treatment arms and delivering rTMS for a short duration of time to the selected treatment group. Currently, Neuronetics, Inc. is conducting the first randomized, controlled trial examining rTMS for the treatment of resistant depression in adolescents residing in America and Canada, which may inform the direction of future studies in the field (Neuronetics Inc., 2015).

Another area of future research pertains to suitability of the H-coil for children and adolescents. The H-coil was recently approved for treatment-resistant depression in adults (Levkovitz et al., 2015), but its efficacy for
childhood depression is unknown. It was developed to stimulate deeper and larger brain volumes in the dorsal-lateral and ventrolateral prefrontal areas than can be obtained with the figure-of-eight coil. These anatomical targets have been suggested to be particularly relevant for therapeutic effects of non-invasive brain stimulation in major depression (Roth & Zangen, 2013). However, there are no head-to-head studies comparing the H-coil with the figure-of-eight coil. Paediatric trials of the H-coil will need to be particularly attuned to the risk of seizure (Cullen et al., 2016), which may be higher with the H-coil than with the figure-of-eight coil (Deng, Lisanby, & Peterchev, 2014). Finally, rTMS may help advance our understanding of the neurobiology of paediatric depression. Converging lines of evidence implicate both glutamatergic and GABAergic neurotransmitter systems in the pathophysiology of depression. For example, Croarkin et al. (2013) and Croarkin et al. (2014) found that depressed youth had significantly increased intracortical facilitation, a measure of cortical excitability, compared with healthy controls, implicating excessive glutamatergic activity. Consistent with these findings, Lewis et al. (2016) found a correlation between the degree of depressive symptomatology and GABAergic dysfunction monitored by the cortical silent period, which is a TMS paradigm that measures cortical inhibition. Such TMS measures are showing promise as biomarkers of cortical excitability and inhibition, which could help guide the treatment of paediatric depression in the future by solidifying evidence for the use of pharmacologic agents that directly target GABA and glutamate receptors.

Clinical implications

From a clinical standpoint, results of this review indicate that there are insufficient data supporting the use of rTMS as a treatment for paediatric depression. Although the existing evidence appears to be encouraging, there are still no data demonstrating that rTMS fares better than sham treatment. Furthermore, clear indications for rTMS have not been established, and optimal treatment parameters have not been delineated. Until further data are available, clinicians are faced with the dilemma of continuing to prescribe medication and psychotherapy or considering ECT for adolescents with treatment-resistant depression.

Limitations

There are two limitations of this review. First, only one person conducted the literature review, which could introduce potential bias regarding articles selected. Despite this limitation, the review itself was conducted with the utmost fidelity, with frequent checking of all articles to ensure accuracy, and discussion with co-authors on a regular basis. Another limitation is that some of the studies had overlapping subjects; however, each of these studies was focused on a different sub-set of results. These studies were not omitted, as a small number of datasets were available on the use of rTMS in adolescents.

Summary

There are no controlled trials of rTMS for adolescent depression. Further research on its efficacy and safety are needed.

Disclosure statement

Drs Magavi and Vasa report no conflicts of interest. Dr Reti has received supplies at no cost from Neuronetics, Inc. Dr Reti was and is site principal investigator on multisite TMS trials sponsored by Brainsway, Inc. and the US Department of Defense.

References


