



# Clinical Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder, Generalized Anxiety Disorder, and Bipolar Disorder

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## KEYWORDS

- Transcranial magnetic stimulation • TMS • Posttraumatic stress disorder • PTSD
- Generalized anxiety disorder • GAD • Bipolar disorder

## KEY POINTS

- A growing body of literature is demonstrating the possibility of using repetitive transcranial magnetic stimulation (rTMS) to treat posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and bipolar disorder.
- These findings are still preliminary and require well-designed and adequately powered studies before rTMS can be recommended for use clinically in PTSD, GAD, or bipolar disorder.
- More studies are required to determine optimal treatment parameters with the caveat that the results may suggest that choice of certain parameters are not critical to efficacy.
- A better understanding of the neuropathology of these disorders as well as how the mechanism of action of rTMS interacts with that pathology could help with optimizing treatment parameters.

## INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technology that has been investigated as both a clinical and neurophysiology research tool. When the stimulation is given repetitively, it is commonly referred to as repetitive transcranial

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magnetic stimulation (rTMS).<sup>1</sup> An acute course of rTMS for major depressive disorder (MDD) generally consists of daily visits (Monday through Friday) for about 6 weeks.<sup>2</sup> The treatment dose is individualized for each patient and reported as a percentage of the motor threshold (MT). The MT is typically defined as the intensity of stimulation that moves the contralateral abductor pollicis brevis 50% of the time determined by either visual observation or electromyography measures. Several large trials and meta-analyses have demonstrated its antidepressant effect in MDD.<sup>3-6</sup> In 2008, the Food and Drug Administration (FDA) in the United States cleared the first rTMS device for the treatment of MDD targeting the left dorsolateral prefrontal cortex (DLPFC) using 10 Hz stimulation at 120% MT. Subsequently, the FDA has cleared 5 additional rTMS devices as well as expanded the initial rTMS device's indication to a broader range of treatment resistance in patients with MDD. Beyond efficacy studies for MDD, other studies have supported the effectiveness of rTMS across a variety of settings outside randomized trials.<sup>7-11</sup> Given its effectiveness in MDD and excellent safety profile, rTMS is being investigated in several other neuropsychiatric disorders, including posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and both phases of bipolar disorder.<sup>12</sup>

### REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND POSTTRAUMATIC STRESS DISORDER

PTSD is a significant public health problem. The National Co-morbidity Survey (NCS) reported a lifetime prevalence rate of 7.8% for PTSD in a national sample,<sup>13,14</sup> whereas the data from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions found the lifetime prevalence of PTSD to be 6.4%.<sup>15</sup> Current clinical guidelines support evidence-based psychotherapies such as prolonged exposure and cognitive processing therapy as first-line treatments for PTSD.<sup>16</sup> However, a recent review of randomized clinical trials for military-related PTSD demonstrated that although these therapies do result in meaningful improvement in patients with PTSD, approximately two-thirds of patients continued to meet full criteria for PTSD.<sup>17</sup> Thus, new treatment approaches are critically needed to improve treatment outcomes.

Early in clinical development, rTMS was considered for PTSD, and the research has progressed through increasing levels of evidence for its clinical utility. In 1998, Grisaru and colleagues<sup>18</sup> ( $n = 10$ ) were among the first to report some benefit for treating PTSD using 1-Hz rTMS stimulation to the right and left motor cortex. They, however, used only 15 pulses on each side and the improvement lasted only a short time. McCann and colleagues,<sup>19</sup> also in 1998, administered 1 Hz rTMS at 80% MT over the right DLPFC to 2 patients with PTSD and demonstrated temporary reduction in several core symptoms in both patients. Rosenberg and colleagues<sup>20</sup> in 2002 found ( $n = 12$ ) that 1 Hz and 5 Hz over the left DLPFC for 10 days demonstrated improvement in depressive symptoms but did not lead to a significant change in PTSD symptoms, although the treatment dose was small, with only 6000 pulses over the 10 days. Taghva and colleagues<sup>21</sup> in 2015 studied ( $n = 16$ ) whether rTMS frequencies determined by electroencephalography (EEG) and electrocardiography at 80% MT for 30 trains of 6 second stimulation and 30 second intertrain intervals were effective for PTSD symptoms. The location of stimulation was determined by the area in the prefrontal cortex with the highest EEG irregularity. After 5 times a week for 2 weeks, the participants who completed the treatment demonstrated positive clinical as well as EEG changes.

Several studies have investigated rTMS for PTSD in patients specifically with comorbid conditions. Nakama and colleagues<sup>22</sup> in 2014 reported on the successful

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