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Editorial

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Neuromodulation treatments in clinical practice: should TMS be used for the treatment of major depressive disorder?

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Editorial

In the past decade, advances in science have produced several novel neuromodulation therapies. As novel neuromodulation therapies are introduced, it is imperative that clinicians in the field of Psychology and Psychiatry carefully weigh the evidence base, risks and benefits before applying these new treatments to our patients Neuromodulation therapies that have emerged include: (1) Transcranial Magnetic Stimulation (rTMS or TMS); Vagal Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), and; Transcranial Direct Current Stimulation (tCDS).[1] These four neuromodulation therapies have been proposed as treatments for several neuropsychiatric disorders, specifically: (1) TMS for recurrent major depressive disorder (MDD)[2,3] and refractory auditory hallucinations/persistent negative symptoms in schizophrenia;[4–6] (2) VNS for refractory MDD;[7] (3) DBS for treatment-refractory obsessive-compulsive disorder (OCD)[8] and treatment-refractory unipolar and bipolar depression,[9,10] as well as; tCDS for MDD[11,12] and schizophrenia.[13] The evidence to support the use of these neuromodulation modalities for these indications varies in strength. It is well beyond the scope of this editorial to summarize, analyze and critique the data supporting every potential neuromodulation treatment for every possible neuropsychiatric disorder. Yet, the current evidence, combined with clinical experience, is now adequate to comment on the use of TMS for MDD.

The US Food and Drug Administration (FDA) announced in 2008 approval of a proprietary TMS system manufactured by Neuronetics Inc.[14] for the treatment of major depressive episodes that have not responded to an adequate trial of one antidepressant medication. Prior to the 2008 FDA approval of TMS for the MDD indication, there was ample evidence in the peer-reviewed scientific literature to show that high-frequency (fast) TMS targeted over the left dorsolateral prefrontal cortex (DLPFC) was more effective than sham in the treatment of depression. One meta-analysis published in 2008 [15] examined thirty double-blind sham-controlled parallel studies comprising 1164 patients. Each study allowed comparison of the percentage change in depression scores from baseline to endpoint of active versus sham treatment. The results of the metanalysis showed a significant overall weighted mean effect size of nearly 0.40 (d=0.39 95% confidence interval (CI) 0.25–0.54) for active treatment which reached statistical significance at a very high level (z=6.52, p<0.0001). These results suggested that the effect size was significant and robust as well as being comparable to at least a subset of commercially available antidepressant drugs.

The industry sponsored study[16] that lead to the aforementioned 2008 FDA approval: had a randomized double-blind, multisite design; examined 301 medication-free patients with MDD who had previously failed an adequate trial of one antidepressant; randomized 155 patients to active TMS (with the proprietary Neuronetics system) and 146 patients to sham TMS; showed in the results that active TMS was significantly superior to sham TMS, and; concluded that transcranial magnetic stimulation was effective in treating major depression. A non-industry sponsored replication study [3] using a non-proprietary system: had a prospective, multisite, randomized, active sham-controlled design; 190 antidepressant drug–free patients with unipolar MDD were randomized to active TMS or sham TMS (with a non-proprietary system); showed an overall retention rate of 88% (90% sham and 86% active); demonstrated a significant effect of active TMS treatment on the proportion of remitters (14.1% active rTMS and 5.1% sham) (P=.02); the odds of attaining remission was 4.2times greater with active TMS than with sham; concluded that left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham with minimal side effects. Subsequently, another metanalysis that included the two aforementioned studies and any other trials,[17] a metanalysis of all the metalysise yet conducted,[18] and an independent review commissioned by the U.S. Department of Health and Human Services,[19] supported the safety and efficacy of TMS for MDD.

Despite the overwhelming evidence supporting TMS as an effective treatment for MDD, several outstanding questions remaining lead to continuing concern. First, there is currently evidence about the duration of the antidepressant effect[20] once TMS is stopped. However, since 80-90% patients with recurrent MDD will relapse without maintenance treatment, the absence of knowledge about the persistence of effect from TMS does not imply that TMS is not an effective antidepressant, rather, it suggests that more research should be conducted examining maintenance TMS schedules. Second, clinical TMS studies generally show low response and remission rates (25% and 17% for active TMS compared to 9% and 6% for sham, respectively). Of note, the response rate of MDD for any single antidepressant class is also quite low.[21] For this reason, TMS should be considered as a first-line monotherapy for MDD.

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Conflicts of interest

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