Repetitive transcranial magnetic stimulation for the treatment of depression: To stimulate or not to stimulate?

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Major depressive disorder (MDD) is one of the most prevalent mental illnesses in North America, affecting about 4% of Canadians annually.[1] Although a number of effective treatments are available, as many as 30% of patients fail to respond to treatment[2] and about 60% experience a relapse.[3] These statistics emphasize the need for alternative treatment strategies to optimize outcomes, but few alternatives are available to treat refractory depressive symptoms. One alternative is electroconvulsive therapy (ECT); however, ECT is associated with significant side effects, most notably memory impairment. ECT requires the use of a general anesthetic and the induction of a seizure, thereby making it an invasive procedure with an increased risk of complications. In addition, the stigma that is associated with ECT often limits its widespread acceptance as a treatment for depressive symptoms. Repetitive transcranial magnetic stimulation (rTMS) has been shown to be an effective therapeutic tool for the treatment of several neuropsychiatric disorders, including MDD and schizophrenia;[4-6] however, some studies that have evaluated this treatment technique have demonstrated equivocal efficacy.[7,8]

In this issue of the *Journal of Psychiatry and Neuroscience*, Couturier[9] provides a systematic review and meta-analysis of the efficacy of rTMS treatment in MDD. In a second article, Schutter and van Honk[10] provide a compelling review of rTMS in MDD, while suggesting alternative methodological approaches that may further enhance therapeutic outcomes. As these 2 studies nicely complement one another (i.e., one being a review of the therapeutic efficacy of conventional rTMS therapeutic approaches and the other, a review suggesting novel treatment approaches), I will discuss the findings of these studies in this order, comment on some of their limitations and conclude by offering suggestions regarding possible future directions to pursue vis-à-vis the optimization of rTMS treatment.

Couturier[9] begins by introducing the historical aspects of rTMS and discusses early studies that utilized rTMS for the treatment of MDD, while outlining some of their limitations. This author then conducts a meta-analysis of rTMS treatment articles that met a priori inclusion and exclusion criteria. A total of 6 studies were included in the meta-analysis, and 13 were excluded. Reasons for excluding rTMS depression articles included the following: (1) not using the 21-item Hamilton Rating Scale for Depression (HAM-D) to evaluate treatment efficacy; (2) stimulation over areas other than the left dorsolateral prefrontal cortex (DLPFC); (3) lack of an intent-to-treat analysis; (4) a treatment duration that was not 5–10 days; (5) concurrent treatment with antidepressant medications; (6) elderly subjects; and (7) inclusion of subjects with psychotic depression. On the basis of the 6 studies chosen for analysis, Couturier concluded that rTMS is not significantly better than placebo for treatment-refractory MDD. However, several key issues must be considered before these findings are interpreted as definitive evidence for a lack of efficacy of rTMS for treatment-refractory MDD. First, and perhaps most importantly, there is burgeoning evidence that 2 weeks (i.e., 10 rTMS treatments) may be insufficient to obtain substantive clinical improvement. For example, Fitzgerald et al[6] reported a 20%–25% reduction in depressive symptoms after 10 rTMS treatments, whereas after 20 treatments most subjects experienced a 50%–60% reduction in depressive symptoms. As such, the findings of this meta-analysis may simply imply that 10 treatments, or 2 weeks of rTMS, are ineffective for the treatment of refractory MDD. Such findings are certainly not surprising when considering that 2 weeks of ECT are often insufficient in treatment-refractory MDD and that treatments are often extended to 4 weeks. Second-generation studies have been completed or are currently underway using 20 or more treatments to optimize clinical efficacy. To my knowledge, however, no meta-analyses have been performed on these studies. Second, excluding studies that used different

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versions of the HAM-D or for the concomitant use of medications, while reasonable, greatly reduced the number of studies included in this meta-analysis. As such, a total of 91 subjects in 6 studies were included, which may have limited the power of this meta-analysis to find a significant difference between active-treatment and sham-treatment groups. By contrast, in a recent meta-analysis by Kozel and George[11] a total of 12 studies with 230 subjects were included. All treatments were between 5 and 10 days over the left DLPFC. From these studies, a moderate effect size of 0.53 was reported with a mean HAM-D change after rTMS of 7.24 in the active-treatment group and 3.58 in the sham-treatment group.[11] The meta-analysis by Couturier,[9] however, raises important caveats regarding most treatment studies including (1) the lack of a consistent means of defining and quantifying treatment resistance, (2) inconsistency regarding the maintenance versus the discontinuation of medications and (3) diagnostic heterogeneity. Couturier also raises an important limitation of most treatment studies: the unreliable method of localizing the DLPFC — the so-called "5-cm method." Herwig et al[12] reported that this method resulted in the coil being located more dorsally (i.e., over the premotor cortex) in 15 of 22 subjects. Clearly, better methods to more precisely target the DLPFC with rTMS are required to optimize treatment response in MDD.[13] Another concern that should also be raised is the link between the severity of MDD symptoms and placebo response. For example, there is evidence to suggest that, when comparing treatments for MDD, studies that include subjects with more severe depressive symptoms have lower placebo response rates (e.g., a score of ≥ 25 on a 17-item HAM-D has been reported to minimize placebo response in previous medication trials[14]). Therefore, in studies that include subjects experiencing mild-to-moderate depressive symptoms, placebo response rates are anticipated to be as high as 50%, potentially undermining the benefits of active rTMS treatment.

The article by Schutter and van Honk[10] begins with a review of the principles of rTMS in the treatment of MDD, followed by a critique of several treatment studies. The authors then pursue a discussion of alternative treatment approaches that may optimize the efficacy of rTMS as treatment for MDD. One overriding theme of this article relates to the reliance of current treatment studies on the DLPFC as an rTMS therapeutic target. The authors raise several compelling lines of evidence suggesting that alternative treatment sites including the right parietal cortex (RPC) and cerebellum may prove as efficacious as treatment targets for rTMS in MDD, or perhaps more efficacious. For example, they address evidence that RPC hypoactivity may be related to depression. Thus, high-frequency rTMS (i.e., rTMS > 1 Hz), which has been shown to result in increased cortical activation,[15] may ameliorate depressive symptoms, which is akin to the rationale for high-frequency stimulation over the left DLPFC. Moreover, the authors cite evidence for cerebellar involvement in MDD and posit neurophysiologic mechanisms through which rTMS targeting of the cerebellum may have antidepressant effects (e.g., increased dopaminergic tone in the DLPFC after cerebellar rTMS). In fact, neurophysiologic evidence for dysfunctional cerebellocortical connectivity in schizophrenia has been recently provided through paired-pulse TMS.[16] Similar investigations in MDD can be used to evaluate cerebellocortical connectivity and, if such connectivity is shown to be dysfunctional, then cerebellar rTMS can potentially be used to treat these patients.

In summary, these 2 papers combined provide compelling evidence that the convention of high-frequency rTMS over the left DLPFC for 2 weeks may be insufficient to treat refractory MDD. Furthermore, they highlight the need for a better understanding of the neuroanatomy and neurophysiology of illnesses such as MDD, which may one day help identify a greater array of future treatment targets.

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References

1. Stephens T, Joubert N. The economic burden of mental health problems in Canada. *Chronic Dis Can* 2001;22:18-23.
2. Pincus HA, Pettit AR. The societal costs of chronic major depression. *J Clin Psychiatry* 2001;62(Suppl 6):5-9.
3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington: the Association; 1994.
4. Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M. Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. *Biol Psychiatry* 1999;46:1451-4.
5. Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K, et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry* 2003;60:49-56.
6. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003;60:1002-8.
7. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry* 2000;47:332-7.
8. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 1999;156:946-8.
9. 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(2):83-90.
10. Schutter DJLG, 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(2):91-7.
11. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract* 2002;8:270-275.
12. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biol Psychiatry* 2001;50:58-61.
13. Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* 2000;12:191-200.
14. Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol* 2002;22:40-5.
15. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol Psychiatry* 2000;48:1133-41.
16. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Fountain SI, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. *Am J Psychiatry*. In press.