Repetitive transcranial magnetic stimulation for the treatment of depression

The use of repetitive transcranial magnetic stimulation (rTMS) as a therapeutic tool in neuropsychiatry is increasing, and careful assessment of the supporting scientific evidence is needed. Most studies to date investigating the efficacy of rTMS in medication-resistant depression have had small sample sizes and have used different methods and controls. Therefore, meta-analyses are valuable. Couturier,[1] in a meta-analysis of randomized controlled trials investigating the efficacy of rTMS for the treatment of a major depressive episode, concluded that rapid-rate rTMS is no different from sham treatment in major depression. However, her conclusions are based on only 6 studies. She conducted a thorough analysis of 19 randomized controlled trials, but the eventual exclusion of 13 of them (to obtain a homogeneous sample) decreased the external validity of this meta-analysis. More important, as Couturier acknowledges, an analysis of 6 studies with a total of only 68 patients is insufficient to allow conclusions to be drawn about the efficacy of rTMS in depression.

We believe that quantitative analysis of these data, with such a low number of patients and studies, should have been avoided, to prevent bias and misleading results. For instance, the author compared post-treatment scores on the Hamilton Rating Scale for Depression (HAM-D) for the sham and active groups rather than the difference between pre-treatment and post-treatment scores for these groups. Given the small sample sizes in the trials analyzed, the baseline values might be different between the active and placebo groups, and thus analysis of only the post-treatment scores could ignore significant weighted differences. For example, in one of the studies that was included in the meta-analysis (by George et al[2]) the post-treatment HAM-D scores were 22.2 for the active group and 19.0 for the sham group, whereas the pre-treatment (baseline) scores were 30.0 for the active group and 23.8 for the sham group. Comparing the post-treatment scores only, Couturier reported that this study favoured sham rTMS, when in fact patients in the active rTMS group had a larger improvement. The same flaw applies to the interpretation of the study by Padberg et al,[3] in which the baseline HAM-D scores were 30.2 for the active rTMS group and 22.2 for the sham group. In this case, after treatment, the score for the sham group worsened but that for the active rTMS group improved. Although the difference was not significant, the weighted mean difference should have been in favour of active rather than sham rTMS. Finally, for the study by Eschweiler et al,[4] Couturier reported the weighted mean difference as 0; however, the active rTMS group improved by 4.2 points and the sham rTMS group worsened by 3.0 points in terms of HAM-D results.

We also find the exclusion criteria questionable. The author excluded 2 studies because they used the 25-item HAM-D[5] or the 17-item HAM-D.[6] However, Couturier could have calculated the effect size (instead of the mean difference) to allow these studies to be included, which would have increased the information and therefore the power of her meta-analysis. Indeed, the technique of meta-analysis was developed as a way to combine data from studies with different methods, a strength that seems to have been underutilized by the author.

For these reasons we fear that this meta-analysis might mislead readers. There is no question that "randomized controlled trials with sufficient power to detect a clinically meaningful difference are required." However, the questionable conclusions of Couturier's meta-analysis might discourage, rather than encourage, further prospective, well-designed clinical trials investigating the effects of rTMS on depression.

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The author responds:

Repetitive transcranial magnetic stimulation (rTMS) has been growing in popularity as a treatment for depression, but its efficacy is still uncertain. Fregni and Pascual-Leone have expressed concern that my meta-analysis of rTMS for depression[1] is biased because of the small number of studies

included. However, the objective was not to pool many studies with different methods, but rather to pool several well-designed studies with similar methods to arrive at a conservative estimate of treatment effect for rTMS. As described in the *Users' Guides to the Medical Literature*,[2] it is essential that the sample of studies in a meta-analysis be homogeneous; otherwise, differences in results could be confounded by differences in methods, rendering the results of the meta-analysis invalid. Thus, to maintain homogeneity of the sample, it was necessary to include only studies that involved the same treatment (in terms of location, frequency, duration and intensity of rTMS) and the same types of patients with the same illness, while maintaining high scientific rigour according to criteria outlined in the *Cochrane Reviewers' Handbook*.[3]

Fregni and Pascual-Leone suggest that it would have been preferable to compare pre- and post-treatment scores on the Hamilton Rating Scale for Depression (HAM-D), rather than comparing post-treatment scores between treatment and sham groups. However, comparing only post-treatment scores is the most conservative and correct way of performing a meta-analysis. In fact, the RevMan software accepts only post-treatment outcome data. There is no option for entering pre-treatment scores with this software, which is the preferred software of the Cochrane Collaboration[3] (available through the Cochrane Collaboration Web site, www.cochrane.org). Furthermore, if patients are randomly assigned at the beginning of the study, there should be no pre-treatment differences between groups, as this would defeat the purpose of randomization.

Another concern presented by Fregni and Pascual-Leone is the exclusion of studies that used the 25-item[4] and 17-item[5] HAM-D. These studies were not included in the published paper for reasons of consistency. A sensitivity analysis, completed before publication of the article, included these 2 studies and used the standardized mean difference rather than the weighted mean difference. Because of space limitations, the sensitivity analysis was not included in the final publication. However, when these studies were included (for a total of 8 studies in the analysis), there was no significant difference between rTMS and sham treatment (overall effect $z = 1.42$, $p = 0.15$). Heterogeneity was not significant ($p = 0.24$). In addition, in this sensitivity analysis, a fixed-effects model was compared with a random-effects model for the 6 studies that were included in the final meta-analysis. The 2 models produced almost identical results, which indicates that heterogeneity was not present and there was no evidence of a difference in treatment effect. Furthermore, when data from both phases of the crossover trials were used, the overall weighted mean difference was –2.05 (95% confidence interval –5.00 to 0.89). The test for overall effect was also nonsignificant (z value = 1.37, p = 0.17), and the test for heterogeneity was not significant ($p = 0.36$). Therefore, including all of the data from the crossover trials did not change the results.

When inclusion criteria were relaxed, such that an intention-to-treat analysis was not required and a psychotic subtype of depression was not excluded, 2 more studies were eligible.[6,7] The study by Garcia-Toro et al[8] remained excluded because rTMS had been used as an add-on treatment to sertraline, which would have confounded the efficacy of rTMS. When a random-effects model was used with these inclusion criteria, the overall effect became significant, with a z value of 1.98 favouring treatment ($p = 0.05$). However, significant heterogeneity was present in the meta-analysis ($p = 0.013$), which indicates that combining these studies in a meta-analysis was inappropriate and invalid.

The consistent conclusion throughout this meta-analysis and the associated sensitivity analysis was that rTMS was not superior to sham treatment. This does not mean that rTMS does not require further study; instead, it means that we should be cautious in prescribing this treatment until adequate, well-designed studies showing the superiority of rTMS have been completed. This article was not meant to discourage the study of rTMS, but rather to encourage further clinical trials with appropriate sample size and high scientific rigour.

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