The Case for a Definitive Multisite, Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation for Tinnitus

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The American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF) published clinical practice guidelines for tinnitus in 2014 and stated that clinicians should not recommend repetitive transcranial magnetic stimulation (rTMS) for the routine treatment of patients with persistent bothersome tinnitus. This recommendation was based on a review of single-site experimental studies and small randomized clinical trials (RCTs) that often represented initial attempts to demonstrate safety and efficacy or to explore new treatment variables. Mixed results in these studies may be attributable to heterogeneity in study designs, patient samples, and outcome measures.

In this Viewpoint, we discuss new evidence since the publication of the AAO-HNSF’s clinical practice guideline. New evidence from a large RCT and from the first meta-analysis of rTMS for tinnitus indicate that the time has come for a large definitive multisite RCT in the United States to test this potential treatment. To demonstrate why a multisite RCT is needed, we draw a parallel between the once uncertain efficacy of rTMS for treatment-resistant depression (TRD) and the aforementioned mixed results of rTMS for tinnitus.

At the time that funding from the National Institutes of Health was being sought for the first large-scale, multisite RCT of rTMS for TRD, the results of early clinical trials of rTMS for depression, which were not standardized and were underdosed in several ways (days of treatment, intensity of stimulation, and number of pulses per day), were weak and mixed. Reviews and meta-analyses at that time, like those for tinnitus, averaged the results of treatment responders and nonresponders from small patient samples and found no strong evidence of a benefit of rTMS in TRD. The changes that occurred during the years spanning the period before and after approval by the US Food and Drug Administration of rTMS for the treatment of TRD were incremental improvements in stimulation variables (more treatments at higher intensity), patient selection (patients who were nonpsychotic, moderately but not severely affected TRD), and improvements in RCT design that enhanced the results of meta-analytic studies by making effect sizes (ie, the mean difference between active and sham treatments) less heterogeneous across studies.

In fact, treatment effect sizes decreased with each subsequent year of study publication, but improvements in the design of RCTs (eg, better sham methods and double-blinding, larger sample sizes, and greater methodologic rigor in studies with randomization protocols and intention-to-treat analyses) led to more robust and consistent results. Efficacy of rTMS for TRD is now documented in more than 10 meta-analytic studies and several qualitative reviews, including more than 30 RCTs and more than 2000 patients. Few can doubt in hindsight that investing in rTMS studies for the treatment of TRD was worthwhile. With US Food and Drug Administration approval of 4 devices (manufactured by Neuronetics, Brainsway, Magstim Company Ltd, and MagVenture), rTMS now provides a beneficial treatment option for 30% to 40% of patients with TRD.

The methodologic rigor of efficacy studies of rTMS for tinnitus is improving. International standards for RCTs in tinnitus were published in 2012. With improvement in methodologic rigor, recent evidence indicates that the beneficial effect of rTMS on tinnitus is clinically significant and durable. However, just as in the studies of rTMS for TRD, early trials of rTMS for tinnitus produced mixed results that cast doubt on treatment efficacy.

A major problem for rTMS studies of tinnitus is heterogeneity in study design and patient selection. The heterogeneity was so pronounced that early attempts at meta-analyses were not possible. A review of 20 placebo-controlled studies for tinnitus involving a total of 601 patients concluded that a course of rTMS could reduce tinnitus in 50% of patients, but the effects were described as “transient” (10 days of stimulation may produce longer lasting effects) and the approach was rated as “possible efficacy” owing to methodologic problems in these studies.

The first meta-analysis of RCTs of rTMS for tinnitus appeared in May 2016. Stimulation was delivered at 1 Hz over the temporal cortex for 10 days in most of the studies reviewed. Results from 7 RCTs were analyzed quantitatively, but not all had comparable end points—4 studies could be analyzed for 1-month posttreatment effects and 3 studies could be analyzed for 6-month posttreatment effects. The mean difference between active and sham rTMS was clinically and statistically significant (a 6.7-point difference on the Tinnitus Handicap Inventory at 1 month after treatment and a 12.9-point difference at 6 months after treatment). Comparisons revealed medium to large effect sizes, and the pooled odds ratio of 3 studies with 1-month follow-up data indicated that active rTMS was 15 times more likely than sham rTMS to be associated with improvement in the Tinnitus Handicap Inventory.

A placebo-controlled, double-blind RCT of 64 patients with tinnitus who were treated for 10 days with 1-Hz rTMS over the temporal cortex was published in 2015 but was not part of the meta-analysis. Change in the Tinnitus Functional Index was assessed at multiple end points to 26 weeks after treatment. Although the
Tinnitus Functional Index decreased by 30% from baseline in the active treatment group by week 26, the Tinnitus Functional Index decreased only 7% in the placebo group. Effect sizes were large for active rTMS. Moreover, 56% of patients who received active rTMS met the criteria for a clinical response (a change of >7 points in the Tinnitus Functional Index), whereas 22% of patients who received placebo treatment met the same criteria.²

Experience designing RCTs for rTMS and vagal nerve stimulation treatments of depression indicate that a multisite RCT requires the following elements: (1) valid estimates of the effect size for power analyses to determine sample size; (2) standardized, controlled treatment designs and study end points with outcome measures whose sources of variance can be reduced or controlled; (3) eligibility criteria that target the most appropriate patient population for study; and (4) information about effective treatment doses to prevent undertreatment. Recent rTMS studies for tinnitus shed some light on several of these elements.

Medium to large effect sizes have now been documented across studies, as has evidence that 10 days of rTMS over the auditory areas in the temporal cortex can produce clinically meaningful and durable effects. Choosing the best outcome measure is more challenging. Teams are working toward consensus on what may be the most effective outcome measures and patient selection criteria³; although which measure is best remains unclear, a reasonable suggestion is that all RCTs include at least 1 common measure, such as the internationally used Tinnitus Handicap Inventory, to serve as a basis for comparison.

Multiple baseline assessments can be used to measure and statistically control sources of variance related to spontaneous fluctuations in tinnitus. In addition, use of a common core set of measures is recommended to reflect the multifaceted nature of tinnitus. Furthermore, with the advent of digital mobile technology, repeated measurements of the patient’s physical, functional, and emotional problems in the patient’s natural setting are possible. This approach, termed the ecological momentary assessment, offers an improvement over retrospective self-assessments that cannot measure the dynamic and context-specific nature of symptoms. Finally, study designs that include double-blinding, valid placebo stimulation, randomization, and intention-to-treat analysis will improve the rigor and replication of RCTs.

We should reiterate that the RCTs of rTMS for TRD improved significantly after the first multisite RCT was completed and US Food and Drug Administration approval was granted. Therefore, each RCT can be expected to represent an incremental improvement over the previous RCT, which is why the first multisite RCT of rTMS for tinnitus in the United States is necessary.

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