Transcranial Magnetic Stimulation for Chronic Tinnitus

Jay F. Piccirillo, MD

JAMA OTOLARYNGOLOGY–HEAD & NECK SURG

Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial

Robert L. Folmer, PhD; Sarah M. Theodoroff, PhD; Linda Casiana, MS, CCRP; Yongbing Shi, MD, PhD; Susan Griest, MPH; Jay Vachhani, AuD

IMPORTANCE Chronic tinnitus negatively affects the quality of life for millions of people. This clinical trial assesses a potential treatment for tinnitus.

OBJECTIVES To determine if repetitive transcranial magnetic stimulation (rTMS) can reduce the perception or severity of tinnitus and to test the hypothesis that rTMS will result in a statistically significantly greater percentage of responders to treatment in an active rTMS group compared with a placebo rTMS group.

DESIGN, SETTING, AND PARTICIPANTS A randomized, participant and clinician or observer–blinded, placebo-controlled clinical trial of rTMS involving individuals who experience chronic tinnitus. Follow-up assessments were conducted at 1, 2, 4, 13, and 26 weeks after the last treatment session. The trial was conducted between April 2011 and December 2014 at Portland Veterans Affairs Medical Center among 348 individuals with chronic tinnitus who were initially screened for participation. Of those, 92 provided informed consent and underwent more detailed assessments. Seventy individuals met criteria for inclusion and were randomized to receive active or placebo rTMS. Sixty-four participants (51 men and 13 women, with a mean [SD] age of 60.6 [8.9] years) were included in the data analyses. No participants withdrew because of adverse effects of rTMS.

INTERVENTIONS Participants received 2000 pulses per session of active or placebo rTMS at a rate of 1-Hz rTMS daily on 10 consecutive workdays.

MAIN OUTCOMES AND MEASURES The Tinnitus Functional Index (TFI) was the main study outcome. Our hypothesis was tested by comparing baseline and posttreatment TFIs for each participant and group.

RESULTS Overall, 18 of 32 participants (56%) in the active rTMS group and 7 of 32 participants (22%) in the placebo rTMS group were responders to rTMS treatment. The difference in the percentage of responders to treatment in each group was statistically significant ($\chi^2_1 = 7.94$, $P < .005$).

CONCLUSIONS AND RELEVANCE Application of 1-Hz rTMS daily for 10 consecutive workdays resulted in a statistically significantly greater percentage of responders to treatment in the active rTMS group compared with the placebo rTMS group. Improvements in tinnitus severity experienced by responders were sustained during the 26-week follow-up period. Before this procedure can be implemented clinically, larger studies should be conducted to refine treatment protocols.

JAMA Otolaryngol Head Neck Surg. 2015;141(8):716-722. doi:10.1001/jamaoto.2015.1219.

Tinnitus is the experience of noise without external stimulation and is thought to represent a phantom sensation. It is estimated that as many as 60 million individuals in the United States experience tinnitus.[1] Tinnitus is related to loud noise exposure and other forms of acoustic trauma, hearing loss, and aging. Tinnitus and hearing loss are the 2 most common disabilities among recently discharged military personnel. A significant number of people with tinnitus experience the phantom noise but are not bothered enough to seek treatment. On the other hand, distressed patients experience myriad bothersome symptoms that may include disruptions in attention, concentration, perception, and emotions, each of which can significantly decrease functional status and quality of life. Recent neuroimaging research findings[2] suggest that the maintenance of tinnitus and its effects on various important functions are related to the degree of dysfunction in one or more cortical neural networks.

A variety of treatment options exist, although there is no cure for the phantom noise perception. The most commonly used treatments involve behavioral, audiological, and pharmacologic therapies and include education and counseling, sound-based therapies, such as hearing aids and sound maskers, cognitive behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), medications, dietary changes and supplements, and acupuncture.

Brain stimulation in the form of repetitive transcranial magnetic stimulation (rTMS) is a particularly intriguing form of therapy for tinnitus. rTMS creates a magnetic field beneath the stimulating coil, which passes through the scalp and skull and induces an electrical current in the brain that can, depending on the frequency of stimulation, stimulate or depress neuronal activity. rTMS was first used in humans in 1985 and the effect of rTMS in tinnitus was first described in 2003.[3] Since then, numerous clinical trials have been completed and the effect of rTMS in tinnitus has been the subject of a Cochrane Review[4] and included in an AHRQ Comparative Effectiveness Review[5] and a specialty society clinical practice guideline.[6] All of the reviews concluded that short-term, but not long-term, reduction in tinnitus was observed in some of the trials but that the lack of a significant response and multiple methodological problems prevented rTMS from being recommended

as standard therapy. Methodological problems identified in the reported trials included enrollment of patients with varying duration and severity of tinnitus, short follow-up time, failure to identify and control for comorbid conditions, such as depression, the use of a variety of different outcome measures, different rTMS stimulus parameters, and inadequate use of placebo, making valid conclusions difficult. As a result of these methodological challenges and the generally modest clinical response, enthusiasm for the role of rTMS in tinnitus has seemed to wane over the past few years. For these reasons the recent report[7] in *JAMA Otolaryngology–Head & Neck Surgery* by Folmer and colleagues is so important and interesting.

In this randomized, placebo-controlled, double-blind clinical trial, 64 patients with tinnitus from the Portland (Oregon) Veterans Affairs Medical Center were randomly assigned to receive 2000 pulses per day of either active 1-Hz low-frequency rTMS or placebo over the temporal region of the head for 10 consecutive workdays. Based on assessment immediately after completion of the 10 rTMS sessions, 18 of the 32 patients (56%) who received active rTMS compared with only 7 of the 32 (22%) who received placebo were rated as responders based on change from baseline on the patient-reported outcome measure Tinnitus Functional Index (TFI). Even more remarkable than the observed results at the end of the intervention were the results at the end of follow-up. At that time, 21 (66%) of the active rTMS group and 12 (38%) of the placebo group were classified as responders. Response to rTMS did not seem to be related to side of head stimulation or perception of tinnitus. However, similar positive effects of rTMS relative to placebo were not observed on the secondary outcome measures: visual numerical scale for self-rated tinnitus loudness, Tinnitus Handicap Index, Beck Depression Inventory II, and State Trait Anxiety Inventory.

This article adds to the growing literature on the effect of rTMS for tinnitus. This literature contains a spectrum of treatment response with only some studies reporting improvement. In particular, several aspects of the study by Folmer et al[7] are unique. First, this article describes long-term (26 weeks) follow-up and demonstrates that the positive effects at 10 days of rTMS can be maintained for longer than suggested by earlier studies and perhaps the positive effects can be strengthened. However, the mechanism behind this surprising "build-up" of the effects of rTMS over time remains undefined. Second, the article demonstrates that the patient-reported TFI is sensitive to clinical change within a treatment efficacy study. Third, the use of parallel groups, rather than a crossover design, avoids the problem of blinding study participants.

Several methodological issues continue to challenge the conduct and interpretation of the clinical research related to rTMS for tinnitus. These issues include the identification of patients who are more or less likely to respond to rTMS to optimize the conduct of efficacy or effectiveness studies. Can responders be identified by clinical features of their tinnitus, such as its duration, severity, laterality of tinnitus, or by the presence of comorbid conditions, such as depression or anxiety? Do other factors like the degree to which patients are bothered by their tinnitus or by resultant disturbances in concentration, attention, and emotion help explain the treatment response? Could alternative methods of assessing tinnitus improve both the understanding of how rTMS influences tinnitus perception and how it should be assessed before and after treatment? For example, would incorporation of ecological momentary assessment, a method of repeatedly assessing a symptom or behavior in real time in the patient's natural environment, reduce the inherent bias associated with retrospective self-report tinnitus questionnaires and improve the identification of study participants who are likely to respond to rTMS?[8] What influence does the age of the patient have on the response to rTMS? What stimulation sites, temporal or dorsolateral prefrontal, and stimulation parameters, low-frequency or high-frequency, are most effective? Are certain sites and parameter frequencies more effective for certain patients than other sites and parameters? Would use of concomitant interventions, such as CBT or MBSR, augment the effect of rTMS? Finally, given the long-term response reported by Folmer et al, how can rTMS be used as a maintenance therapy for those patients who respond positively to acute therapy?

In conclusion, the results from the clinical trial by Folmer et al[7] suggest that rTMS might be an effective treatment for tinnitus and should reignite enthusiasm for research into the role of rTMS for tinnitus. No one study can definitely answer questions regarding treatment efficacy. Instead, medical knowledge is advanced through the steady accumulation of trial results and the interpretation of results in the context of past trials. The recommendation of the authors for multisite clinical trials in an attempt to replicate these findings seems warranted. If the long and arduous experience of the investigators who conducted the numerous trials of rTMS for medication-resistant depression is a guide, then continued research in the use of rTMS for tinnitus is warranted. The results from the depression clinical trials, which were sometimes mixed, ultimately led to approval for the use of rTMS for depression.[9] Perhaps with additional rigorous evidence, rTMS will achieve a similar level of support for treatment of tinnitus.

ARTICLE INFORMATION

Author Affiliation: Department of Otolaryngology–Head & Neck Surgery, Washington University School of Medicine, St Louis, Missouri; and Editor, *JAMA Otolaryngology–Head & Neck Surgery*.

Corresponding Author: Jay F. Piccirillo, MD, Washington University School of Medicine, Department of Otolaryngology-Head & Neck Surgery, 660 Euclid Ave, CB 8115, St Louis, MO 63110 (piccirilloj@ent.wustl.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. *Am J Med*. 2010;123(8):711-718.

2. Husain FT, Schmidt SA. Using resting state functional connectivity to unravel networks of tinnitus. *Hear Res*. 2014;307:153-162.

3. Plewnia C, Bartels M, Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. *Ann Neurol*. 2003;53(2):263-266.

4. Meng Z, Liu S, Zheng Y, Phillips JS. Repetitive transcranial magnetic stimulation for tinnitus. *Cochrane Database Syst Rev*. 2011;CD007946(10):CD007946.

5. Pichora-Fuller MK, Santaguida P, Hammill A et al. *Evaluation and Treatment of Tinnitus: Comparative Effectiveness*. Comparative Effectiveness Review No. 122. Rockville, MD: AHRQ; 2013.

6. Tunkel DE, Bauer CA, Sun GH, et al. Clinical practice guideline: tinnitus. *Otolaryngol Head Neck Surg*. 2014;151(2)(suppl):S1-S40.

7. Folmer RL, Theodoroff SM, Casiana L, et al. Repetitive transcranial magnetic stimulation treatment for chronic tinnitus: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2015;141(8):716-722.

8. Wilson MB, Kallogjeri D, Joplin CN, et al. Ecological momentary assessment of tinnitus using smartphone technology. *Otolaryngol Head Neck Surg*. 2015;152(5):897-903.

9. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression. *Biol Psychiatry*. 2007;62(11):1208-1216.