LETTERS TO THE EDITOR

Repetitive Transcranial Magnetic Stimulation for Tinnitus

I am writing to comment on the recent article by Piccirillo et al.1 The authors reported that daily low-frequency (1-Hz) repetitive transcranial magnetic stimulation (rTMS) delivered to the left temporoparietal region of the patient’s head was no more effective than placebo stimulation for chronic tinnitus. Numerous published studies have concluded otherwise: that rTMS is effective for reducing the severity or loudness of tinnitus for many patients.2,3 The following factors might have contributed to the negative findings reported by Piccirillo and colleagues:

1. Small sample size. Only 14 patients were included in the report. Because there is a great deal of variability among patients with tinnitus and their symptoms, 14 is an insufficiently small number on which to base conclusions regarding the efficacy of rTMS. The study should have continued and collected more data for analysis.

2. The authors’ choice of the left temporoparietal junction for the location of stimulation. Two problems with this location are the nonspecific description of this “target” and the fact that rTMS delivered to the left hemisphere is not usually effective for tinnitus perceived on the patient’s right side.2

3. The authors’ choice to use a TMS system made by Neuronetics, Inc (Malvern, Pennsylvania), which was designed to deliver stimulation to the frontal cortex as a treatment for depression. Most studies of TMS for tinnitus used Magstim Company Ltd (Carmarthenshire, Wales) brand stimulators; a few used Medtronic, Inc (Minneapolis, Minnesota), equipment.

4. Use of a crossover design for a TMS study. This type of design is problematic for 2 reasons: first, if rTMS causes reorganization of neural activity or networks (as it is purported to do), patients in the initial treatment group cannot return to a pre-TMS state for the placebo arm of the trial; and second, most patients can distinguish between active TMS and placebo TMS if they have received both forms of the procedure, because active TMS usually causes more intense sensations on the scalp, increased muscle activity, or jaw movements.

I am providing this information so that readers of the article by Piccirillo and colleagues do not conclude that TMS is an ineffective treatment for tinnitus. The authors stated, “We believe that rTMS is a very promising tool for the treatment of tinnitus, but more basic, clinical, and translational research is needed to identify the correct treatment settings.” I agree that more carefully designed studies need to be conducted with larger numbers of patients before definitive conclusions can be drawn regarding the efficacy of this procedure.

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In reply

We are writing in response to Folmer’s questions and concerns regarding our published results of daily low-frequency rTMS to the left temporoparietal region in patients with chronic bothersome tinnitus. First, Folmer claims that because there is a great deal of variability among patients with tinnitus, our inclusion of “only 14 patients” was inadequate to base conclusions regarding the efficacy of rTMS. The inclusion and exclusion criteria ensured that the patients enrolled in our study formed a homogeneous group of severely bothered patients with tinnitus without overt signs and symptoms of depression or other significant medical comorbidities. A homogeneous group of patients with tinnitus was not always created in previous studies. For instance, in the article by Frank et al4 that was cited by Folmer, roughly 30% of the participants had a Beck Depression Inventory score in the depression range (≥14). A smaller, yet still significant, number of patients in the study by Khedr et al5 were depressed. The positive response to rTMS reported in

these studies may have been a result of the treatment of depression. Furthermore, the use of a crossover design increased the power of our study to detect a clinically significant difference and, in this respect, partially compensated for the small size. Our decision to terminate the study was not made without careful consideration. The biostatistician who performed the interim analysis demonstrated that if a treatment effect was present, the effect would be no greater than a change of 14 points on the Tinnitus Handicap Inventory, a value well below our a priori selected minimal clinical difference of 20. The inclusion of additional patients would have, at best, allowed us to identify small and clinically nonsignificant effects, while exposing patients with tinnitus to the risk and discomfort (albeit slight) of rTMS. Furthermore, working with the limited budget afforded to us by the National Institutes of Health, we did not feel justified in continuing the enrollment of patients under this research protocol. The results of the interim analysis and the decision to terminate the study were approved by the Washington University Human Research Protection Office, St Louis, Missouri.

Second, Folmer states that the selection of the left temporo-parietal junction for rTMS stimulation was another factor that contributed to our negative study results. Stimulation of the left temporo-parietal junction is a standard target site for rTMS and has been used in numerous studies. The stimulation site was approved without comment by the members of the National Institutes of Health Study Section who reviewed the original grant application. Folmer criticizes our “nonspecific description of the target.” We described the location for the first 5 patients using the international 10-20 system of electroencephalographic coordinates and used a standard imaging software program for the remaining 9 patients. For these 9 patients, we even provided panels of pictures (Figure 1) showing the exact target (red cross) in each individual brain. We believe that this validates the specificity of the site of stimulation on the cortex, and we are at a loss to imagine how much more specific we could be with our target description. Folmer takes issue with our selection of the left side of the cortex and cites 1 previous study that demonstrated that rTMS delivered to the left hemisphere was not effective for tinnitus perceived on the patient’s right side. However, Khedr et al found that among patients with unilateral tinnitus, contralateral stimulation had a greater effect than ipsilateral stimulation. Regardless of the true relationship between perceived sidedness of tinnitus and efficacy of ipsilateral vs contralateral stimulation, 9 of our patients complained of bilateral tinnitus, rendering Folmer’s comments regarding sidedness irrelevant.

Third, Folmer states, without citing any research, that the Neuronetics Model 2100 device used in our study contributed to our negative findings as this device was designed to deliver stimulation to the frontal cortex as a treatment for depression. While it is true that the Neuronetics device was approved by the Food and Drug Administration for stimulation of the frontal cortex for depression, it does not mean that the Neuronetics magnet is not appropriate for stimulation of other cortical areas or for other clinical indications. The shape of the Neuronetics magnet conformed to the scalp stimulation site, and we were easily able to obtain motor thresholds. The use of magnets with differing designs, such as the Neuronetics and Magstim models, at 110% of motor threshold would likely compensate for any theoretical variations in the magnetic intensity of the field at the auditory cortical surface. Also, for our study, Neuronetics created a special articulating arm to hold the magnet in proper alignment. Furthermore, as a result of using the Neuronetics Model 2100, we were able to use a magnet that had a validated sham magnet partner. This same sham magnet device was approved by the Food and Drug Administration as an adequate sham for the pivotal studies of rTMS effectiveness in depression. We believe that the key features of rTMS effectiveness are based on stimulation parameters, especially the stimulation intensity relative to the motor threshold, and not the proprietary features or shape of the magnet.

Fourth, Folmer claims that the use of the crossover design contributed to our negative findings. We disagree. One of the main requirements for the use of a crossover design trial is that patients return to baseline or pre–arm 1 status before starting arm 2. In situations in which there may be a carryover effect and this requirement may not be fulfilled, a crossover design is inappropriate. Folmer claims that owing to the nature of rTMS stimulation and resultant brain reorganization, it is impossible for patients who received active stimulation in arm 1 to return to a baseline or pre–arm 1 state before starting arm 2. Our research protocol stipulated that before patients could enter the second arm of the study, their Tinnitus Handicap Inventory score needed to return to within 20 points of their baseline value. Furthermore, Folmer claims that patients can distinguish between active and sham TMS... because [off] more intense sensations on the scalp, increased muscle activity, or jaw movements with active rTMS. For 2 reasons, we believe that the sham magnet provided an adequate blind against the placebo effect. We assessed the validity of the blind by asking patients to guess what treatment arm—active TMS or sham—they believed they had just received. As stated in the article, there was no evidence that patients could correctly identify the magnet beyond chance alone. Furthermore, we believe that the failure to detect a statistical or clinical difference in Tinnitus Handicap Inventory scores between the 2 groups is further evidence of the integrity of our blind as it is counterintuitive to think that negative study findings resulted from unblinding.

In conclusion, we believe that the results of this study are internally valid and contribute to the growing literature on the assessment of the effectiveness of rTMS for tinnitus. Transcranial magnetic stimulation is costly and time-consuming, with an acute course of treatment potentially costing $3000 to $7500. Certainly, there are patients whose tinnitus gets better during the course of TMS, but it is important to discriminate this improvement from a nonspecific response to a novel, highly technical, patient-contact intensive treatment, the kind of treatment that typically will show a high placebo response. Regardless of what other studies show, we found that in the hands of an experienced TMS treatment team, the effects of TMS are not robust or generalizable, and, in our opinion, this treatment is not ready for clinical implementation in nonacademic settings for patients with tinnitus. It is important that we do not give patients a false hope that will result in their...
needlessly pursuing a costly and time-consuming treatment option.

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