Letter to the Editor

Reply to Tass et al. on "Counteracting tinnitus by acoustic coordinated reset neuromodulation" Restorative Neurology and Neuroscience Vol. 30 (2), 2012

Gerta Rücker* and Gerd Antes
German Cochrane Centre, Institute of Medical Biometry and Medical Informatics,
University Medical Center Freiburg, Germany

Dear Sir,

In a published study, Tass et al. brought up the scientific question whether a special treatment is associated with relief of symptoms of tinnitus over time (Tass et al., 2012). The study design was a prospective, randomized, single blind, placebo-controlled trial in 63 patients, allocated to five treatment arms. For the statistical analysis of this design we would expect a direct comparison, such as an analysis of covariance (ANCOVA), with the visual analogue scale (VAS) and a tinnitus questionnaire (TQ) as outcomes of interest (Senn, 2006). The baseline values could serve as a covariate, especially since it seems necessary to adjust for baseline differences given the small sample size, apart from the large number of arms.

However, throughout the more than 20 pages of the article, we did not find such an analysis. We did find pre-post comparisons within each treatment arm, which, on their own, do not allow a valid comparison between groups. Moreover, a concise definition of groups and treatments is missing. Such a definition should have been included in paragraph 2.1 (Study subjects) or paragraph 2.3 (Study design).

Instead, we found a number of shortcomings and surprising analyses.

1. The overall number of participants is far below the minimum of participants needed for a valid investigation of treatment effects, in particular because there are five treatment groups. In addition, the distribution of participants across groups is violating basic statistical principles. Groups should be equal in size or, if they are unequal, more participants should be allocated to the group that is used as comparator for the other groups, e.g., the placebo group. The placebo group having only 5 participants makes the statements about effectiveness of the treatment meaningless.

2. In paragraph 2.4, an unnecessarily complex distance measure is defined, which would be completely obsolete if the authors used an ANCOVA approach.

3. In paragraph 3.1.2, 'equally sized, matched subgroups' are formed, which is also completely unnecessary, given that the groups were randomized before. And what is gained by defining

*Corresponding author: Gerta Rücker, German Cochrane Centre, Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Germany. Tel.: +49 761 2036673; Fax: +49 761 2036680; E-mail: ruecker@imbi.uni-freiburg.de.

subgroups, when the groups have sample sizes around ten?

4. In paragraph 3.1.3 and Table 4, a pooled comparison between 'effective' and 'ineffective' stimulation groups is presented. We understand this as a *post-hoc* comparison between treatment arms that have been suitably recomposed. However, even here we found only pre-post differences, but no direct comparison between randomized arms.

5. A sentence from paragraph 4.1, which is also included in the abstract, states: 'Response ... was obtained in 75% of patients with a mean TQ reduction of 50% among responders.' The problem with the second part of this sentence is that the authors do not refer to the mean TQ reduction of all patients treated, but only to that of responders, however they are defined. Unfortunately, it is always possible to find a definition of response such that responders show an impressive treatment effect, without mentioning non-responders. For this reason, an analysis based merely on responders is likely to be biased (Senn and Julious, 2009).

Given this is currently the only RCT trying to provide evidence of efficacy of acoustic CR neuro-modulation, these are severe concerns which lead us to argue that there is still insufficient evidence for recommendation of this technique in clinical practice.

Yours faithfully,
Gerta Rücker, PhD
Gerd Antes, Professor, PhD
German Cochrane Centre
Institute of Medical Biometry and Medical Informatics
University Medical Center Freiburg
Stefan-Meier-Strasse 26
Freiburg, 79104, Germany

Conflict of interest

None.

References

Senn, S. (2006). Change from baseline and analysis of covariance revisited. *Statistics in Medicine*, *25*(24), 4334-4344.

Senn, S. & Julious, S. (2009). Measurement in clinical trials: A neglected issue for statisticians? *Statistics in Medicine*, *26*, 3189-3209.

Tass, P.A., Adamchic, I., Freund, H.J., von Stackelberg, T. & Hauptmann, C. (2012). Counteracting tinnitus by acoustic coordinated reset neuromodulation. *Restorative Neurology and Neuroscience*, *30*, 137-159. DOI 10.3233/RNN-2012-110218.