ASHA American Speech-Language-Hearing Association

JSLHR

Research Article

# Contributions of Counseling and Sound Generator Use in Tinnitus Retraining Therapy: Treatment Response Dynamics Assessed in a Secondary Analysis of a Randomized Trial

**Craig Formby,[a] Xin Yang,[b] Roberta W. Scherer,[c]**
**and The Tinnitus Retraining Therapy Trial (TRTT) Research Group**

[a] Emeritus, Department of Communicative Disorders, University of Alabama, Tuscaloosa [b] The Culverhouse College of Business, University of Alabama, Tuscaloosa [c] Retired from Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

ARTICLE INFO

Article History:
Received April 13, 2021
Revision received August 20, 2021
Accepted October 19, 2021

Editor-in-Chief: Peggy B. Nelson
Editor: Richard Tyler

https://doi.org/10.1044/2021_JSLHR-21-00210

ABSTRACT

**Purpose:** Tinnitus retraining therapy (TRT) has been widely used for 30 years, but its efficacy and the component contributions from counseling and sound therapy remain controversial. The purpose of this secondary analysis from the Tinnitus Retraining Therapy Trial (TRTT) was to compare treatment response dynamics for TRT (counseling and conventional sound generators) with partial TRT (pTRT; counseling and placebo sound generators) and standard of care (SOC; a patient-centered counseling control).

**Method:** The TRTT randomized 151 participants with primary tinnitus (*no significant hearing or sound tolerance problems*) to TRT, pTRT, or SOC, each of which encouraged use of enriched environmental sound. The primary outcome, mean change in Tinnitus Questionnaire score assessed at baseline and follow-up across 18 months, was normalized for a common baseline and fitted with an exponential model. Time constants were estimated to quantify and compare the treatment response dynamics, which were evaluated for statistical significance using bootstrap analyses.

**Results:** The change in response to TRT took less time to achieve than that for either pTRT or SOC, as demonstrated by time for normalized Tinnitus Questionnaire scores to decline to 63% and 99% of baseline TRT values: 1.2 months (95% CI [0.2, 1.9]) and 5.7 months (95% CI [0.9, 9.0]), respectively. Corresponding SOC values were 2.7 months (95% CI [1.5, 4.1]) and 12.4 months (95% CI [6.9, 19.0]), while those for pTRT were 2.2 months (95% CI [1.2, 3.4]) and 10.1 months (95% CI [5.7, 15.9]). The differences were significant for TRT versus SOC ($p$ = .020), borderline significant for TRT versus pTRT ($p$ = .057), but nonsignificant for pTRT versus SOC ($p$ = .285). The magnitude of the asymptotic treatment response did not differ significantly among groups.

**Conclusion:** Sound generator use in TRT increases treatment efficiency (beyond any advantage from enriched environmental sound) without affecting treatment efficacy (determined by counseling).

Since its origin in the early 1990s, tinnitus retraining therapy (TRT) has been a widely used, but controversial, intervention at the forefront of clinical approaches for treating subjective tinnitus (Jastreboff, 2015). This influential nonmedical intervention has at its core the neurophysiological model of tinnitus proposed by Jastreboff

---

Correspondence to Craig Formby: cformby@as.ua.edu. **Disclosure:** *The authors have declared that no competing financial or nonfinancial interests existed at the time of publication.*

(Jastreboff, 1990). The neurophysiological model assumes that maladaptive interactions between the auditory system and conscious and subconscious processes within the brain result in negatively learned responses to the tinnitus. It is these negative reactions that give rise to clinically significant tinnitus. The primary objective of TRT is habituation of negatively learned responses (i.e., conditioned reflexes) between the auditory system and the limbic and autonomic nervous systems. These latter processes are conjectured to contribute to the primary tinnitus-related distress and inordinate negative physiological responses that exacerbate the tinnitus condition. Subsequent to habituation of the negative reactions to the tinnitus, TRT theory posits that habituation of the awareness of the tinnitus will follow in due course.

The TRT protocol begins with audiological and medical evaluations to categorize the patient's problems and rule out a medical or surgical cure (Gold et al., 2021). Armed with this information, the clinician can then offer the habituation-based TRT intervention to address the patient's tinnitus problem (while also managing associated hearing and sound tolerance problems if these coexist with the tinnitus) through prescribed counseling and sound therapy principles within the context of Jastreboff's neurophysiological model (Jastreboff & Hazell, 2004). A fundamental purpose of the counseling is to reduce fears of and misconceptions about the tinnitus condition, along with apprehension associated with the underlying mechanisms that may give rise to the tinnitus problem; this initiating step sets in motion the process of habituation of the negatively learned reactions to the tinnitus, leading to reclassification of the tinnitus as a neutral stimulus. The second component of the TRT intervention, namely, the use of therapeutic sound, is intended to decrease the strength of the tinnitus-related neuronal activity (Jastreboff, 2015). In TRT, this objective is achieved by reducing the contrast between the tinnitus signal and the increased therapeutic sound background. Ostensibly, an ancillary effect of the therapeutic sound is downregulation of elevated tinnitus-related neuronal activity associated with maladaptive increases in central auditory gain. This latter effect may also contribute to a decrease in the tinnitus strength. In TRT, sound therapy is thought to facilitate habituation of the perception (awareness) and, ultimately, the impact of the tinnitus (Jastreboff & Hazell, 2004).

Critics of TRT have for more than 2 decades called for a definitive trial to assess the efficacy of TRT and, secondarily, to delineate the mechanistic contributions from the counseling and sound therapy components in the TRT treatment (Formby & Scherer, 2013; McKenna & Irwin, 2008; Tyler et al., 2012; Wilson et al., 1998). In the absence of such a trial, the Tinnitus Retraining Therapy Trial (TRTT) was undertaken to address these long-standing issues and concerns (Scherer & Formby, 2019). Briefly, the TRTT was a National Institutes of Health–sponsored, Phase III, multisite, double-blind, placebo-controlled, randomized trial that was designed to evaluate the definitive efficacy of TRT and the contributions to TRT from counseling and sound therapy achieved with sound generators (Scherer & Formby, 2019). We have previously described the TRTT in detail in a series of linked reports, including a summary presentation of the findings (Scherer & Formby, 2019). These past reports have documented the rationale (Formby & Scherer, 2013); design protocol (Scherer et al., 2014); the study participants, their recruitment, description, qualifications, enrollment, and randomization (Scherer & Formby, 2019; Scherer et al., 2014); the study treatments and their selection and implementation (Erdman et al., 2019; Gold et al., 2021; Scherer & Formby, 2019; Scherer et al., 2014); the study organization and participating study sites (Formby & Scherer, 2013; Scherer & Formby, 2019); the outcome measures and collection schedule (Formby & Scherer, 2013; Scherer & Formby, 2019; Scherer et al., 2014); the statistical plans for powering the trial and analyzing the outcomes (Scherer & Formby, 2019; Scherer et al., 2014); efforts to ensure study protocol fidelity and adherence (Scherer et al., 2014, 2020); and study challenges and limitations in conducting the TRTT (Formby & Scherer, 2019; Scherer & Formby, 2019; Scherer et al., 2018).

This report follows up on a potentially significant observation, not previously considered in the primary analyses of the TRTT, namely, evidence of clinically meaningful differences in the rates of response to treatment among the three interventions studied in the TRTT. This is an obviously important practical clinical issue in the treatment of debilitating subjective tinnitus inasmuch as most of us if given the option to recommend or chose among two or more treatments for debilitating tinnitus, each of which yields similar long-term positive outcomes, would likely select the treatment option that achieves this ultimate result the fastest. Here, we formally evaluate this observation in secondary analyses of the primary outcome measure used in the TRTT. These new analyses are focused on quantifying, describing, and comparing the treatment response dynamics for TRT and the comparison interventions implemented in the TRTT. These analyses reveal and highlight the contributions to TRT from counseling and sound generator use in the TRTT.

## METHOD

As noted above, the study protocol, description of the participants and treatments, and all methodological aspects of the TRTT have been documented fully in multiple publications linked to the TRTT. Thus, we provide here an abbreviated overview of the previously described methods, with primary focus in this report on the analyses implemented to assess differences in the treatment response dynamics among the interventions in the TRTT.

## Subjects

The adult study participants ($n$ = 151; $M_{\text{age}}$ = 50.6 years) included active duty, retired members of the military, and dependents who qualified for care at participating military medical centers. Approximately 70% of the participants were males. Each participant suffered chronic (> 1 year) moderate-to-severe tinnitus (a score ≥ 40 on the Tinnitus Questionnaire [TQ]; Hallam, 1996) that could not be managed medically or surgically. The participants, who presented with functionally adequate unaided hearing sensitivity (i.e., median hearing thresholds ≤ 10 dB HL at 250–2000 Hz; ≤ 20 dB HL at 4000 Hz; and ≤ 30 dB HL at 6000 and 8000 Hz), denied significant sound tolerance problems (i.e., primary hyperacusis, misophonia, or phonophobia) and exhibited primary tinnitus generally consistent with Jastreboff Type 1 categorization (Jastreboff & Hazell, 2004; Scherer & Formby, 2019). This category of individuals with primary tinnitus was targeted because they were most likely to adjust to sound generator use and enriched sound therapy with minimal difficulty. Moreover, their sound generator use was unlikely to be confounded by elevated hearing thresholds. By contrast, individuals presenting with significant hearing loss (requiring amplification) and/or sound intolerance represented a more formidable challenge for implementing therapeutic sound enrichment in a successful intervention for tinnitus and, thus, they were excluded from the TRTT. All participants were screened for specified inclusion/exclusion criteria and provided approved informed consents per their respective institutional review board guidelines (Scherer & Formby, 2019; Scherer et al., 2014).

## Interventions

The participants were randomized with equal likelihood to one of three intervention groups:

(a) The TRT group ($n$ = 51) received tinnitus (directive) counseling and sound therapy from wearable sound generators as described by Jastreboff and Hazell (2004). The tinnitus counseling followed a scripted protocol that included a checklist of topics beginning with an introduction to the overarching goal of habituation of the tinnitus by TRT (Gold et al., 2021). The counseling then reviewed the participant's audiometric results, including any evidence of hearing loss or sound intolerance (as measured by loudness discomfort levels), and documentation of the participant's tinnitus pitch and loudness matches. This review was followed by a brief description of the peripheral and central auditory system anatomy and physiology. The counseling then transitioned to a presentation of the critical concepts and principles of TRT that are necessary for understanding tinnitus, its associated distress, and annoyance within the context of Jastreboff's neurophysiological model of tinnitus. This counseling included the presentation of the TRT objectives of habituation of the negative reactions to the tinnitus, followed by habituation of the awareness and, ultimately, the tinnitus impact. These counseling concepts were reinforced at scheduled follow-up visits across the 18-month TRT intervention period.

The conventional sound therapy was implemented with ear-worn sound generators, supplied by General Hearing Instruments, Inc. These instruments, which were based on the digital platform used in their *Tranquil* model, were fitted bilaterally to produce continuous low-level broadband noise. The noise output was matched for loudness between the ears within an acceptable range of levels for each participant. The volume setting of each sound generator was initially adjusted to locate the "mixing point" (i.e., the level at which the therapeutic noise blended with the tinnitus) and then was reduced to avoid output levels inducing annoyance or communication difficulties. After acceptable upper level volume settings were selected and matched for loudness between the ears, the participant had a range of 4 dB (in steps of 2 dB) over which to reduce the output volume of the therapeutic noise from each sound generator. Volume settings near detection threshold that potentially might elicit an amplifying effect from stochastic resonance were avoided by restricting the output levels near the low end of the volume range. These therapeutic conditions were generally consistent with those proposed by Tyler and Bentler (1987) and, subsequently, promoted by Jastreboff and Hazell (2004) and Jastreboff (2016). Over the course of their interventions, the sound generator output settings were monitored and adjusted as needed to accommodate each participant's treatment at follow-up visits.

(b) The partial TRT (pTRT) group ($n$ = 51) received the same tinnitus counseling as that provided to the TRT group (Gold et al., 2021), but the bilateral therapeutic noise was produced by short-acting, double-blind placebo sound generators (Scherer & Formby, 2019). These sound generators were similar in appearance to the conventional sound generators described above, and they were fitted similarly. However, following initial activation, the placebo sound generators produced a constant low-level broadband noise (set at acceptable levels below the mixing point) for the first 40 min of operation, after which the placebo output began a gradual decay process (over the next 30 min of use) to silence (Scherer & Formby, 2019). This output decay process took advantage of the natural perceptual adaptation that routinely occurred in response to ongoing exposure to the low-level therapeutic noise; this perceptual decay was an important process and concept in the success of the double-blind placebo sound generators. Accordingly, the expectation that the therapeutic noise output would perceptually decay over time was reinforced in the counseling and fitting process for all sound generators. The placebo sound generator output also was designed to reset to its original volume setting within 3 s of removal from the ear, which further facilitated double-blinding of the participant and clinician when either attempted to check the operation of the placebo devices outside of the ear. Follow-up for the pTRT group was the same as that described for Group 1.

(c) The standard of care (SOC) group ($n$ = 49) received a patient-centered counseling intervention that aligned with American Speech-Language-Hearing Association tinnitus treatment guidelines (American Speech-Language-Hearing Association, 2006) and with care for tinnitus in the participating medical centers (Erdman et al., 2019). The emphasis of SOC was on the participant's tinnitus symptoms, with the goal of reducing the negative cognitive, affective, physical, and behavioral reactions to the tinnitus. The SOC counseling concepts were reinforced at follow-up visits across the period of intervention. Each of the three interventions encouraged participant exposure to enriched environmental sound at all times (Scherer & Formby, 2019), but wearable sound generators were not issued nor allowed for use by the SOC group.

## Primary Outcome

The primary outcome for the TRTT was change in the TQ assessed at baseline and across 18 months of follow-up at 3, 6, 12, and 18 months (Scherer & Formby, 2019). The TQ is a 52-item self-report questionnaire for quantifying tinnitus symptoms across five subscales (Psychological Distress, Intrusiveness, Hearing Difficulties, Sleep Disturbances, and Somatic Symptoms; Hallam, 1996). Higher TQ scores (maximum score 102) indicate a greater tinnitus problem. The efficacy of TRT was evaluated by comparing TQ scores for TRT versus SOC; the contribution of counseling was assessed by comparing TQ scores for pTRT versus SOC; and the contribution of the sound generators was determined by comparing TQ scores for TRT versus pTRT (Scherer & Formby, 2019; Scherer et al., 2014). The primary analysis was based on intention to treat, including all available TQ scores except those from participants with no follow-up visits (Scherer & Formby, 2019).

## Quantitative and Statistical Analyses

In the summary report of the TRTT outcomes (Scherer & Formby, 2019), we concluded in our primary analysis that all three intervention groups, TRT, pTRT, and SOC, achieved significant treatment effects, but we found no significant differences in the magnitudes of the TQ scores among the groups at the end of treatment. There was, however, an apparent trend in the TQ scores suggesting that the TRT group achieved a positive response to their intervention earlier than that for either of the other groups. The primary TRTT analysis was not designed to evaluate group differences in treatment response dynamics and, therefore, would not necessarily have detected such differences. Accordingly, in this secondary analysis, we have reanalyzed the TQ scores with focus on time constants derived from exponential models fitted to TQ change scores across visits. The resulting time constants enabled us to quantify and assess differences in the treatment response dynamics between and across groups.

The change scores for each group were normalized by subtracting each participant's TQ score at each study visit from his/her baseline score to determine the group mean change in TQ score at each study visit. Best-fitting exponential functions were then fit to the respective sets of mean TQ change scores for each group (Billingsley, 1986; Hoffman, 2015; Littell et al., 2006; SAS, 2015). Time constants were derived from coefficients fitted for each exponential model. The resulting time constants quantified the time points (in months from baseline) at which the change scores declined (improved) by 63% ($TQ_{63}$) and 99% ($TQ_{99}$) relative to baseline and where 100% is represented by the asymptote. These time constants, which are designated $\tau_{63}$ and $\tau_{99}$, respectively, are consistent with those commonly used in scientific and engineering applications to characterize response dynamics; the latter time constant effectively quantifies the time point at which the response becomes asymptotic. The derivation of the $TQ_{63}$ and $TQ_{99}$ values and the corresponding time constants are illustrated in the Appendix to this report. The Appendix also includes a presentation of the general equation, the coefficients for fitting the exponential model, and a description of its implementation in our analyses of the treatment response dynamics.

Parametric statistical analyses to evaluate differences in the time constants between individual participants or between the groups were not applicable in this study. In the former case, the problem with parametric statistics arose because the individual participants differed widely in the number of follow-up visits (i.e., 1, 2, 3, or 4) for which TQ scores were available to fit the exponential model (across the 18-month period of their interventions). Consequently, it was impractical to fit the exponential model and derive sensible time constants when, in some cases, participants had TQ scores at only one or two follow-up visits (which was consistent with the TRTT intention-to-treat analysis plan). In the case of the group data, it was obviously not possible to conduct parametric tests to compare group mean time constants for statistical differences when only a single exponential model was available per group. We therefore turned to bootstrap resampling, which is an established nonparametric statistical approach that has been widely used to calculate *p* values and 95% confidence intervals (CIs) by resampling and comparing group data from original data sets (Efron & Tibshirani, 1993; Konietschke & Pauly, 2014). Indeed, the bootstrap approach has been advocated for use in communication disorders research (Rietveld & van Hout, 2015) and has recently been described and implemented in audiological research (Chesnaye et al., 2021).

For our bootstrap analyses, we resampled (with random replacement) each of the original sets of TQ change scores for each treatment group. We repeated this resampling process 10,000 times to create 10,000 bootstrap samples, each containing 10,000 exponential models for each group. Each of these models provided estimates of the corresponding $\tau_{63}$ and $\tau_{99}$ values. To compare the respective model time constants between treatment pairs, we then calculated *p* values as the proportion of those 10,000 time constants that were inconsistent with the corresponding time constants estimated from the original set of TQ change scores for paired treatments (Wicklin, 2009). That is, to compare groups, we took the group having a smaller original $\tau_{63}$ (or $\tau_{99}$) value than that for either of the other groups and, for that group (with the smaller original time constants), calculated the total number of exponential models with time constant values exceeding those of either of the other groups with the larger original $\tau_{63}$ or $\tau_{99}$ values. We then divided the resulting value for either $\tau_{63}$ or $\tau_{99}$ by 10,000 to derive the *p* value for the respective paired treatment comparison. So, for example, for the original set of fitted TQ change scores, both the $\tau_{63}$ and $\tau_{99}$ values estimated for the TRT group were smaller than the corresponding values for either pTRT or SOC, so we calculated the *p* value based on the total number of exponential models for TRT with time constants greater than the corresponding original time constant values for either pTRT or SOC. The same process then was repeated to calculate the *p* value for pTRT versus SOC, with the respective time constants for pTRT expected to be somewhat smaller than those for SOC per the original data sets.

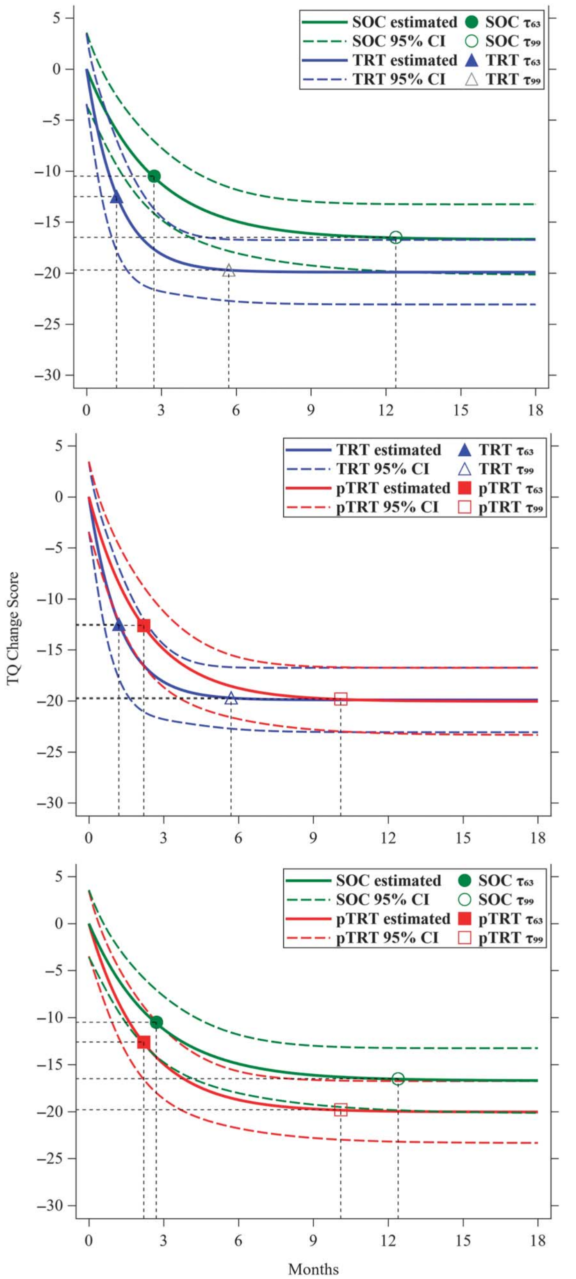
To assess the practical significance of mean differences in the bootstrap time constants for TRT versus SOC, TRT versus pTRT, and pTRT versus SOC, we evaluated effect sizes by calculating Cohen's *d* values for each mean pair (Cohen, 1988). These effect sizes represent the standardized difference between the mean pairs. Cohen's *d* was calculated by dividing the mean difference between each pair of group time constants by the pooled standard deviation. The Cohen's *d* calculation is independent of sample size, making it well suited for evaluation of mean differences between pairs of group time constants from our bootstrap analyses. In addition to the bootstrap analyses of the time constants, we conducted an independent post hoc analysis using approximate *F* tests (Hoffman, 2015) to assess significant differences in the exponential (whole-curve) models between groups.

## RESULTS

The fitted TQ change scores are shown in Figure 1 for the treatment groups we paired to evaluate TRT efficacy and to assess the contributions from counseling and sound generator use. It is evident in Figure 1 that TRT affects a more rapid early improvement in the tinnitus condition than that achieved by either pTRT or SOC. Moreover, asymptotic improvement is achieved before treatment end by all three treatments and is achieved much earlier for TRT than for either pTRT or SOC. These treatment response dynamics are quantified in Table 1 in which the time constants and corresponding $TQ_{63}$ and $TQ_{99}$ change scores are shown for each intervention. The time constants for TRT ($\tau_{63}$ = 1.2, 95% CI [0.2, 1.9]; $\tau_{99}$ = 5.7, 95% CI [0.9, 9.0]) are about half the values estimated for either pTRT ($\tau_{63}$ = 2.2, 95% CI [1.2, 3.4]; $\tau_{99}$ = 10.1, 95% CI [5.7, 15.9]) or SOC ($\tau_{63}$ = 2.7, 95% CI [1.5, 4.1]; $\tau_{99}$ = 12.4, 95% CI [6.9, 19.0]), which are similar. These results suggest that TRT with sound generator use appreciably accelerated the tinnitus treatment response time when compared with that for either pTRT or SOC. This outcome was observed notwithstanding that all three groups achieved similar asymptotic $TQ_{99}$ values (TRT = −19.7; pTRT = −19.8; SOC = −16.5). This latter result is consistent with an independent analysis that yielded insignificant differences among the exponential models fitted to the TQ change scores for the three treatment groups (*F* = 1.33; *p* = .248; df (numerator) = 6; df (denominator) = 150; Billingsley, 1986; Littell et al., 2006). This statistically insignificant finding is not a surprising result inasmuch as the TQ change scores were essentially asymptotic and equivalent across the three groups at the 12- and 18-month visits. This finding indicates that additional time in their respective interventions beyond about 12 months afforded no further treatment benefit for any of the groups. Accordingly, because of this plateauing effect, the analysis of whole-curve differences among the exponentials was insensitive to the group differences in the treatment response dynamics that were indexed by the time constants. That is, these latter differences in the treatment response dynamics, quantified by the time constants, were primarily occurring by or before 12 months into each intervention.

Consequently, to test whether the time constants for the TRT group were meaningfully smaller than those for either of the other groups, we followed up with the bootstrap analysis. The results from this analysis are shown in Table 2 in which group mean bootstrap time constants,

**Figure 1.** Fitted exponential models to TQ change scores. TQ change scores as a function of treatment visit for paired comparisons of the treatment groups indicated in the inset legend of each panel. Best-fitting exponential models and associated confidence limits are superimposed on each pair of change scores. Larger negative TQ change scores represent greater improvement over the course of an intervention. Time constants and corresponding TQ change scores also are denoted for each treatment group. SOC = standard of care (patient-centered counseling control); $\tau_{63}$ and $\tau_{99}$ = time constants derived from the exponential model quantify the time points (in months from baseline) at which the TQ change scores improved by 63% and 99%, respectively; TRT = tinnitus retraining therapy (TRT counseling and sound generator use); CI = confidence interval; pTRT = partial tinnitus retraining therapy (TRT counseling and placebo sound generator use); TQ = Tinnitus Questionnaire.



averaged for 10,000 exponential models, and the *p* values for statistical comparisons of the paired groups are presented for $\tau_{63}$ and $\tau_{99}$. The bootstrap means for $\tau_{63}$ and $\tau_{99}$, 1.2 and 5.5 months, respectively, for TRT are less than half of the respective values, 2.7 and 12.5 months, for SOC. Likewise, the TRT bootstrap time constants are similarly smaller than the corresponding $\tau_{63}$ and $\tau_{99}$ values, 2.2 and 10.3 months, for pTRT. It is reassuring that the bootstrap time constants in Table 2 are in excellent agreement with the corresponding values in Table 1 derived from fitting the original set of TQ change scores.

The *p* values for the paired groups, estimated relative to the original group time constants, are significantly different ($p$ = .020) for TRT versus SOC for both $\tau_{63}$ and $\tau_{99}$ and are borderline significant ($p$ = .057) for both time constants for TRT versus pTRT. By contrast, there are only small insignificant differences ($p$ = .285) between the respective time constants for SOC versus pTRT.

A direct comparison of the group mean bootstrap time constants shown in Table 2, assessed by calculating Cohen's *d* values, yielded effect sizes of 2.73 (95% CI [2.68, 2.78]), 2.08 (95% CI [2.04, 2.12]), and 0.76 (95% CI [0.73, 0.79]) for the comparisons of TRT versus SOC, TRT versus pTRT, and pTRT versus SOC, respectively. (The $\tau_{63}$ and $\tau_{99}$ time constants were derived from the same exponential models within the same group; therefore, the effect size for both time constants was the same for each paired comparison of the group mean differences. Thus, only a single common Cohen's *d* value is reported above for $\tau_{63}$ and $\tau_{99}$.) Cohen's *d* values larger than 2.0 represent a difference between a pair of means that is larger than 2 *SD*s, which is considered a "huge" effect size (Sawilowsky, 2009). Thus, the effect sizes for TRT versus SOC and for TRT versus pTRT are highly significant, and even that for pTRT versus SOC represents a medium effect size. Accordingly, the mean bootstrap time constants for TRT, pTRT, and SOC differ meaningfully among themselves and these differences represent effect sizes that are potentially of real clinical importance, especially those for TRT versus SOC or pTRT.

# DISCUSSION

## The Contribution of Sound Generator Use in TRT

The obvious and parsimonious conclusion from the analyses reported here is that the ongoing exposure to controlled low-level broadband noise from sound generators in the TRT assignment accelerated the treatment response in comparison with that for either pTRT or SOC. Sizable early treatment effects, representing 63% improvement and an almost twofold minimal clinically

**Table 1.** TQ$_{63}$ and TQ$_{99}$ change scores and corresponding time constants for each TRTT treatment group.

| | TQ change scores | | Time constants (in months) | |
|---|---|---|---|---|
| | TQ$_{63}$ | TQ$_{99}$ | $\tau_{63}$ | $\tau_{99}$ |
| Group | *M* (95% CI) | *M* (95% CI) | *N* (95% CI) | *N* (95% CI) |
| TRT | −12.5 [−15.3, −9.9] | −19.7 [−24.0, −15.6] | 1.2 [0.2, 1.9] | 5.7 [0.9, 9.0] |
| pTRT | −12.6 [−15.5, −9.8] | −19.8 [−24.3, −15.5] | 2.2 [1.2, 3.4] | 10.1 [5.7, 15.9] |
| SOC | −10.5 [−13.4, −7.7] | −16.5 [−21.1, −12.1] | 2.7 [1.5, 4.1] | 12.4 [6.9, 19.0] |

*Note.* TQ$_{63}$ and TQ$_{99}$ = Tinnitus Questionnaire (TQ) change scores corresponding to 63% and 99% improvement in the tinnitus condition relative to baseline and where 100% is represented by the asymptote (i.e., plateauing of the treatment response); TRTT = Tinnitus Retraining Therapy Trial; $\tau_{63}$ and $\tau_{99}$ = time constants derived from the exponential model quantify the time points (in months from baseline) at which the TQ change scores improved by 63% and 99%, respectively; *M* = mean change in TQ change score; CI = confidence interval; *N* = number of months from baseline; TRT = tinnitus retraining therapy (TRT counseling and sound generator use); pTRT = partial tinnitus retraining therapy (TRT counseling and placebo sound generator use); SOC = standard of care (patient-centered counseling control).

significant reduction in the TQ-assessed tinnitus symptoms (relative to baseline; Scherer & Formby, 2019), occurred shortly after the first month of TRT with sound generator use. By contrast, comparable early treatment effects for pTRT and SOC were relatively prolonged by approximately a factor of two. Similarly, participants assigned to these latter treatments required approximately twice the time of treatment to reach an asymptotic outcome compared to those designated to TRT using sound generators. Thus, because only TRT afforded the benefit of a constant uniform therapeutic sound source over the course of the TRTT, the most sensible explanation for the sizable differences in the treatment dynamics for TRT compared with either pTRT or SOC is the use of sound generators in TRT. This is a clinically meaningful finding inasmuch as the benefit from sound generator use in TRT can now be explained to the tinnitus patient in terms of a tool for enhancing the efficiency of the intervention by several months. It is tempting to conjecture here that sound generator use also would be expected to accelerate other counseling interventions for tinnitus. This conjecture assumes that non-TRT interventions also would be advantaged by sound-induced reduction in the awareness of tinnitus, which, in turn, would diminish activation of those processes that give rise to the negative reactions to the tinnitus.

It is important here to place the contribution of sound generator use in context with our previous findings and conclusions from the TRTT. The primary conclusion from the TRTT was that, after 18 months of intervention, TRT, SOC, and pTRT all produced statistically and clinically meaningful treatment effects as shown by comparable changes (improvements) in the magnitude of the TQ scores from baseline to end of treatment (Scherer & Formby, 2019). There were no statistical differences among the interventions in the primary analysis of the TRTT, which is consistent with the finding in this report that there were no statistically significant group differences among the fitted full-curve exponential models. Thus, the summary conclusions from the primary analyses of the TRTT outcomes remain unchanged with respect to the analyses in this report.

What is new and important in this secondary analysis of the time constants, derived from the same data set used in conducting the primary analysis for the TRTT, is the finding of a clinically meaningful advantage in terms of the treatment response dynamics achieved with sound generator use; this advantage translates into an

**Table 2.** Bootstrap model time constant estimates and corresponding *p* values from statistical tests of the time constants for paired treatment group comparisons.

| | Model time constant estimates (months) | | | *p* value* | | |
|---|---|---|---|---|---|---|
| Group | TRT | pTRT | SOC | TRT vs. SOC | TRT vs. pTRT | pTRT vs. SOC |
| $\tau_{63}$ | 1.2 | 2.2 | 2.7 | .020 | .057 | .285 |
| $\tau_{99}$ | 5.5 | 10.3 | 12.5 | .020 | .057 | .285 |

*Note.* TRT = tinnitus retraining therapy; pTRT = partial tinnitus retraining therapy; SOC = standard of care; *p* = probability; $\tau_{63}$ and $\tau_{99}$ = time constants derived from the exponential model quantify the time points (in months from baseline) at which the TQ change scores improved by 63% and 99%, respectively, relative to baseline and where 100% is defined by the asymptote (i.e., plateauing of the intervention response).

**p* value determined using bootstrap methods.

accelerating treatment benefit for the full TRT intervention. Furthermore, we now know that because each of the three interventions in the TRTT encouraged participant exposure to enriched environmental sound at all times, the accelerated TRT treatment effect from sound generator use provided a clinically meaningful therapeutic advantage beyond that achieved with enriched environmental sound. Thus, these are previously undocumented advantages for sound generator use in TRT. The accelerating advantage for sound generators, early on in the TRT intervention, has not previously been recognized in guidelines for TRT or other tinnitus treatment options (Cima et al., 2019; Tunkel et al., 2014). Consequently, a recommendation for sound generator usage in TRT should be considered in terms of accelerating the therapeutic response to an asymptotic outcome rather than that of affecting the magnitude of the asymptotic treatment response. We have conjectured elsewhere that the counseling component of TRT is likely the primary determinant of the latter (Gold et al., 2021; Scherer & Formby, 2019).

This thinking is consistent with other evidence and analyses of TRT, and with the tinnitus treatment literature in general, most of which largely discount the contribution of sound generators in favor of a primary role for counseling in tinnitus treatment (Cima et al., 2019; Hoare et al., 2014; McKenna & Irwin, 2008; Tunkel et al., 2014). The question then becomes what is the mechanism by which sound generator use in the TRTT promoted acceleration of the TRT treatment response?

## Mechanisms Underlying the Expeditious Sound Generator Effect in TRT

Consider that most, if not all, forms of sound therapy used in tinnitus treatment, including sound generator use in TRT, assume a role in reducing the perception (or awareness) of the tinnitus (Hoare et al., 2014). This positive effect of sound generators in TRT is intended to reduce the tinnitus-related neural activity (Jastreboff, 2015). This fundamental concept was promoted in the counseling of both TRT and pTRT participants using a visual contrast analogy of a lighted candle viewed in darkness being perceived as much brighter than in sunlight. Likewise, the augmentation of the acoustic background in the TRTT, using therapeutic noise delivered by sound generators, was prescribed for both the TRT and pTRT groups to reduce the perceived strength of the tinnitus by diminishing the contrast between the levels of the tinnitus and the enhanced acoustic background (Gold et al., 2021). However, in the latter case, the therapeutic noise delivered by the short-acting placebo sound generators was purposely ineffectual.

To the extent that sound generator use in TRT reduced the participants' awareness of the tinnitus and their attention to it, one would also expect reduced tinnitus-induced activation of the reactionary nonauditory processes (i.e., limbic and autonomic nervous system structures) that mediate the debilitating impact of tinnitus (Hoare et al., 2014). For the TRT group, these faciliatory treatment effects began the moment that the sound generators were activated at onset of treatment with the counseling. In contrast, the habituation process for the pTRT group, who received counseling with use of a short-acting ineffectual sound generator, required a much longer time course to achieve reductions in the untoward emotional, cognitive/psychological, and physiological reactions to the tinnitus.

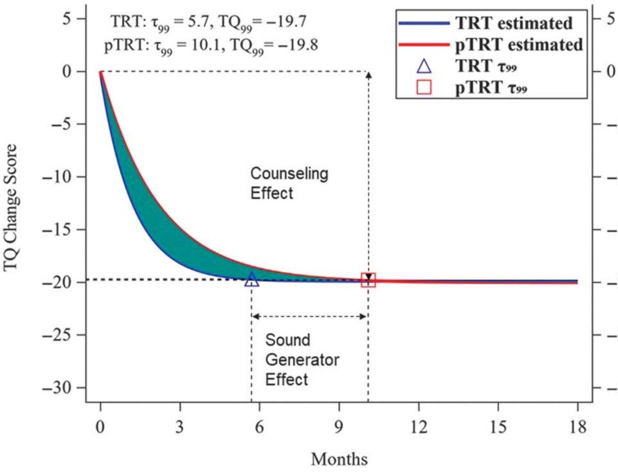
## The Contributions of Counseling and Sound Generator Use in the TRT Treatment Model and Their Courses of Action

Following the logic above, the contributions of counseling and sound generator use and their courses of action in TRT would seem to merit reconsideration in the Jastreboff treatment model (Jastreboff & Hazell, 2004). The TRT treatment model initially assumes habituation of the negative reactions to the tinnitus and, subsequently, passive habituation of the perception of the tinnitus. Our analyses suggest an alternative treatment model with sound generators accelerating the habituation response early on (beginning at the time of activation of the therapeutic sound) by reducing the awareness of the tinnitus and, in turn, the associated activation of those subconscious processes responsible for the negative reactions to the tinnitus. Without the tinnitus awareness–reducing benefits of sound generators, the habituation initiated and fostered by counseling alone will ultimately be achieved, but with a relatively delayed asymptotic response. This time course, therefore, is seemingly inconsistent with the passive habituation of the perception of the tinnitus following after habituation of the reactions.

The passive habituation of tinnitus perception in the treatment model supposedly occurs after a sufficient level of habituation of the negative reactions has been affected and these debilitating effects reduced or eliminated (Gold et al., 2021). This assumes the conditioned reflexes that mediate the tinnitus-associated negative reactions in the model have been severed (by the habituation) from connections with the tinnitus-related neural activity within the auditory pathways. This leaves the end-stage habituation of perception to block tinnitus-related neural activity within the central auditory pathways, effectively eliminating this activity from being transmitted to cortical centers responsible for awareness of the tinnitus and the cognitive processing of this activity. It is arguable whether this end-stage habituation is needed in the model if, in fact, the awareness of the tinnitus is simultaneously reduced as part of the process in the habituation of the negative reactions. If not needed, then the TRT treatment model would simplify and be consistent with counseling-induced habituation of the negative reactions to the tinnitus accelerated by tinnitus awareness–reducing effects of the sound generators. With the debilitating negative reactions to the tinnitus greatly reduced or eliminated, successfully treated individuals would then be encompassed within the vast majority of those individuals with tinnitus who are not inordinately distressed or annoyed by their condition. That is, their tinnitus would still be present, but not bothersome for them. Indeed, this is usually the case for a successfully treated TRT patient and is the ultimate goal of TRT (Gold et al., 2021). Thus, for the sake of economy, the habituation of the perception of the tinnitus, as a delayed final stage of the tinnitus habituation process, could potentially be eliminated from the TRT treatment model, seemingly with little consequence.

A summary illustration consistent with our analyses of the treatment response dynamics and this simplified treatment model is depicted in Figure 2 in which the TRT and pTRT exponential models from Figure 1 have been replotted together to highlight the respective contributions of counseling and sound generator use in TRT. The difference between the exponential curves shown by shading represents the overall contribution to TRT from sound generator use, a benefit not afforded pTRT participants; whereas, the almost identical magnitudes of the asymptotes for the two exponential curves reveal the counseling contribution, which participants in both treatment groups received in common. Thus, the magnitude of the asymptotic treatment response effectively captures these latter effects of counseling for both TRT and pTRT (shown by the magnitude of treatment-related change quantified by $TQ_{99}$ relative to baseline); whereas, the corresponding time constant for pTRT reveals the timing of the completed treatment benefit from counseling alone. The time difference between the $\tau_{99}$ values for TRT and pTRT quantifies the early acceleratory advantage of therapeutic sound generator use when combined with counseling in TRT.

**Figure 2.** Differences in treatment response dynamics for TRT and pTRT highlight the contributions of counseling and sound generator use in the TRT intervention. Shown here are the exponential models from Figure 1 fitted to the TQ change scores as a function of time in intervention for TRT (blue curve) and pTRT (red curve); corresponding $\tau_{99}$ time constants and $TQ_{99}$ change scores are marked on the respective exponential models, and these values are listed in the inset legend. Shading represents overall differences in the treatment responses to TRT and pTRT. The contribution to TRT from counseling, effectively presented alone when paired with placebo sound generators in the pTRT intervention (shown by red curve), is quantified by the magnitude of the $TQ_{99}$ change score, which is denoted as the "counseling effect." The contribution to TRT from sound generator use is represented by the time difference (in months) between the $\tau_{99}$ value for TRT and that for pTRT; this time difference is denoted as the "sound generator effect." Note that the magnitude of change in the TQ change scores at asymptote (i.e., the time at which the intervention is effectively complete as defined at $\tau_{99}$) is nearly identical for the TRT and pTRT curves (reflecting a common counseling contribution), whereas the time at which the TRT curve becomes asymptotic precedes that for the pTRT curve by 4.4 months (representing the contribution to the TRT intervention from sound generator use, which was not effective in the pTRT intervention). TRT = tinnitus retraining therapy (TRT counseling and sound generator use); $\tau_{99}$ = time constants derived from the exponential model quantify the time points (in months from baseline) at which the TQ change scores improved by 99%; TQ = Tinnitus Questionnaire; pTRT = partial tinnitus retraining therapy (TRT counseling and placebo sound generator use).



## Prior Efforts to Quantify TRT Response Dynamics

Surprisingly, there has been little interest in quantifying the treatment response dynamics for TRT or, for that matter, any treatment option in the tinnitus treatment literature. Although one finds numerous reports in the TRT literature that mention positive treatment-related change associated with TRT at various time points over the course of treatment (variously reported for TRT with bilateral sound generator use at 1 [Hatanaka et al., 2008], 3 [Barozzi et al., 2017; Parazzini et al., 2011], 6 [Bauer & Brozoski, 2012; Ito et al., 2009; Park et al., 2017], or 12 [Korres et al., 2010] months in several recent reports), we know of no formal efforts of the kind reported here to provide a mathematical description of the treatment response dynamics for TRT with bilateral sound generator use. Perhaps the closest effort to ours (and perhaps the only other one to date) is that reported by Henry et al. (2006), who attempted to quantify the trajectory of treatment for TRT and that for a tinnitus masking intervention. Unfortunately, the sound therapy options used in their implementation of TRT included a mix of unilateral and bilateral hearing aids, sound generators, and combination devices used by individuals with and without hearing loss and with varying severity of tinnitus. (This contrasts with our study of a targeted sample of primary tinnitus patients, with similar severity of their tinnitus problems and no significant evidence of hearing loss or sound tolerance concerns, using bilateral sound generators.) The heterogeneous mix of their participants and sound therapy options presents a challenge for interpreting the treatment response dynamics for TRT. What is clear from their analyses is that TRT affected an increased range of treatment change for individuals with a greater than a lesser tinnitus problem. Henry et al. further showed that the TRT treatment response may not reach an asymptote after 18 months, which they noted at that time was consistent with Jastreboff's treatment model. Henry et al. also observed that, early in treatment, TRT response dynamics were relatively delayed with respect to those for the masking intervention; however, later in treatment, the benefit from TRT dwarfed that from masking.

Jastreboff has acknowledged that since the introduction of TRT the prescribed duration of treatment for benefit has declined as the effectiveness of TRT has increased, ostensibly, with improvements in the protocol (Jastreboff, 2015). He stated in 2015 that "The main improvement in TRT has been to shorten the average time until seeing clear improvement from 1 year to 1 month, with a statistically significant improvement seen at, and after, 3 months." (Jastreboff, 2015, p. 309). The treatment response dynamics reported here for TRT implemented with sound generators, used by individuals in the Jastreboff Type I diagnostic category with moderate-to-severe primary tinnitus, are generally consistent with Jastreboff's statement above. We may add to his statement that, on average, the asymptotic benefit from TRT implemented with bilateral sound generators may be expected within the initial 6 months of beginning treatment for this specific group of tinnitus patients.

### Limitations

Notwithstanding the above caveats and limitations previously discussed in the TRTT (Scherer & Formby, 2019; notably missing data associated with participant attrition and missed follow-up visits, which diminished statistical power to reveal differences among the study interventions and to compare individual treatment response dynamics), the analyses reported here benefitted from the rigorous TRTT study design and protocol, which resulted in a rich and nearly ideal data set for evaluating group treatment response dynamics. Moreover, the carefully selected participants in the three TRTT treatment groups were remarkably well matched for their ages, baseline hearing thresholds, tonal pitch match frequencies, loudness discomfort levels, TQ scores, and, ultimately, for their similar sizable ranges of TQ scores, asymptotic treatment benefit (Scherer & Formby, 2019), and daily usage of their sound generators and placebo devices (Gold et al., 2021). However, our well-matched and targeted participant sample may also be considered a potential limitation. In the TRTT, we specifically included individuals with primary tinnitus who were largely unencumbered by confounding problems of hearing loss or sound intolerance; these are common comorbid conditions that often plague a large portion of the population with debilitating tinnitus. Our primary tinnitus sample, therefore, represented distressed, but relatively uncomplicated, patient groups to treat. Thus, inasmuch as we targeted a Jastreboff Category 1 sample in the TRTT, this might limit the generalization of our analyses. Accordingly, we may anticipate in future studies that different treatment response dynamics might be obtained, indeed should be expected, for different samples of participants, outcome measures, control and comparison interventions, and implementations and delivery of TRT (or other interventions implemented with sound generators) by skilled and/or less skilled clinicians in single or multisite trials. Accordingly, the resulting treatment response dynamics, which are unambiguous for the interventions reported here, should be considered in terms of the specific conditions and study sample described in the TRTT (Scherer & Formby, 2019).

## CONCLUSIONS

Sound generators offer a significant advantage for TRT in accelerating the response to treatment (beyond any therapeutic effects from enriched environmental sound), but they seemingly play little or no role in affecting the magnitude of the treatment response at the end of the intervention. The latter appears to be determined primarily by the counseling component of TRT. Thus, sound generator use enhances TRT efficiency, but not its efficacy. The added costs and expeditious utility of sound generators should be weighed accordingly in making a recommendation for their use in TRT.

## Acknowledgments

This research was supported by Awards U01DC007411 (Formby) and U01DC007422 (Scherer) from the National Institute on Deafness and Other Communication Disorders, which had no role in the design and conduct of the TRTT; collection, management, analysis, and interpretation of the data; preparation, review, or approval of this article; and decision to submit this article for publication. The views expressed in this report are those of the authors and do not necessarily reflect the official policies or positions of the Departments of the Navy, Air Force, Army, the Department of Defense (DoD), or the U.S. Government.

The investigators and collaborators comprising the Tinnitus Retraining Therapy Trial Research Group are listed in Scherer and Formby (2019), including the participating military service members and civilian DoD employees who performed the approved study activities as part of their official duties. The data sets used and/or analyzed in this report are available from Scherer upon reasonable request. Trial Registration: ClinicalTrials.gov, Identifier: NCT01177137. Lastly, we thank Richard Tyler and an anonymous reviewer for their thoughtful reviews and constructive criticism.

## References

**American Speech-Language-Hearing Association.** (2006). *Preferred practice patterns for the profession of audiology* [Preferred practice patterns]. http://www.asha.org/policy/PP2006-00274/

**Barozzi, S., Ambrosetti, U., Callaway, S. L., Behrens, T., Passoni, S., & Del Bo, L.** (2017). Effects of tinnitus retraining therapy with different colours of sound. *International Tinnitus Journal, 21*(2), 139–143. https://doi.org/10.5935/0946-5448.20170026

**Bauer, C. A., & Brozoski, T. J.** (2012). Effect of tinnitus retraining therapy on the loudness and annoyance of tinnitus: A controlled trial. *Ear and Hearing, 32*(2), 145–155. https://doi:10.1097/AUD.0b013e3181f5374f

**Billingsley, P.** (1986). *Probability and measure* (2nd ed.). Wiley.

**Chesnaye, M. A., Bell, S. L., Harte, J., Simonsen, L. B., Visram, A., Stone, M. A., Munro, K. J., & Simpson, D. M.** (2021). Efficient detection of cortical auditory evoked potentials in adults using bootstrapped methods. *Ear and Hearing, 42*(3), 574–583. https://doi.org/10.1097/AUD.0000000000000959

**Cima, R. F. F., Mazurek, B., Haider, H., Kikidis, D., Lapira, A., Norena, A., & Hoare, D. J.** (2019). A multidisciplinary European guideline for tinnitus: Diagnostics, assessment, and treatment. *HNO, 67*(Suppl. 1), 10–42. https://doi:10.1007/s00106-019-0633-7

**Cohen, J.** (1988). *Statistical power analysis for the behavioral sciences*. Routledge.

**Efron, N., & Tibshirani, R.** (1993). *An introduction to the bootstrap*. CRC Press. https://doi.org/10.1007/978-1-4899-4541-9

**Erdman, S. A., Scherer, R. W., Sierra-Irizarry, B., & Formby, C.** (2019). The Tinnitus Retraining Therapy Trial's standard of care control condition: Rationale and description of a patient-centered protocol. *American Journal of Audiology, 28*(3), 534–547. https://doi:10.1044/2019_aja-18-0068

**Formby, C., & Scherer, R.** (2013). Rationale for the Tinnitus Retraining Therapy Trial. *Noise & Health, 15*(63), 134–142. https://doi.org/10.4103/1463-1741.110299

**Formby, C., & Scherer, R. W.** (2019). The search for and conduct of the elusive phase 3 randomized clinical trial: Snipe hunting with the military. *JAMA Otolaryngology—Head and Neck Surgery, 145*(7), 595–596. https://doi.org/10.1001/jamaoto.2019.0830

**Gold, S. L., Formby, C., & Scherer, R. W.** (2021). The tinnitus retraining therapy counseling protocol as implemented in the Tinnitus Retraining Therapy Trial. *American Journal of Audiology, 30*(1), 1–15. https://doi.org/10.1044/2020_aja-20-00024

**Hallam, R. S.** (1996). *Manual of the Tinnitus Questionnaire (TQ)*. The Psychological Corporation.

**Hatanaka, A., Ariizumi, Y., & Kitamura, K.** (2008). Pros and cons of tinnitus retraining therapy. *Acta Oto-Laryngologica, 128*(4), 365–368. https://doi:10.1080/00016480701730760

**Henry, J. A., Schechter, M. A., Zaugg, T. L., Griest, S., Jastreboff, P. J., Vernon, J. A., Kaelin, C., Meikle, M. B., Lyons, K. S., & Stewart, B. J.** (2006). Outcomes of clinical trial: Tinnitus masking versus tinnitus retraining therapy. *Journal of the American Academy of Audiology, 17*(2), 104–132. https://doi.org/10.3766/jaaa.17.2.4

**Hoare, D. J., Searchfield, G. D., El Refaie, A., & Henry, J. A.** (2014). Sound therapy for tinnitus management: Practicable options. *Journal of the American Academy of Audiology, 25*(1), 62–75. https://doi.org/10.3766/jaaa.25.1.5

**Hoffman, L.** (2015). *Longitudinal analysis: Modeling within-person fluctuation and change*. Routledge. https://doi.org/10.4324/9781315744094

**Ito, M., Soma, K., & Ando, R.** (2009). Association between tinnitus retraining therapy and a tinnitus control instrument. *Auris Nasus Larynx, 36*(5), 536–540. https://doi.org/10.1016/j.anl.2009.01.003

**Jastreboff, P. J.** (1990). Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neuroscience Research, 8*(4), 221–254. https://doi.org/10.1016/0168-0102(90)90031-9

**Jastreboff, P. J.** (2015). 25 years of tinnitus retraining therapy. *HNO, 63*(4), 307–311. https://doi.org/10.1007/s00106-014-2979-1

**Jastreboff, P. J.** (2016). Tinnitus and decreased sound tolerance. In P. A. Wackym & J. B. Snow Jr. (Eds.), *Ballenger's otorhinology 18 head and neck surgery* (Vol. 31, pp. 391–404). People's Publishing House.

**Jastreboff, P. J., & Hazell, J. W. P.** (2004). *Tinnitus retraining therapy: Implementing the neurophysiological model*. Cambridge University Press. https://doi.org/10.1017/CBO9780511544989

**Konietschke, F., & Pauly, M.** (2014). Bootstrapping and permuting paired t-test type statistics. *Statistics and Computing, 24*(3), 283–296. https://doi:10.1007s11222-012-9370-4

**Korres, S., Mountricha, A., Balatsouras, D., Maroudias, N., Riga, M., & Xenelis, I.** (2010). Tinnitus retraining therapy (TRT): Outcomes after one-year treatment. *International Tinnitus Journal, 16*(1), 55–59.

**Littell, R. C., Milliken, G. A., Stroup, W. W., Wolfinger, R. D., & Schabenberger, O.** (2006). *SAS for mixed models*. SAS Publishing.

**McKenna, L., & Irwin, R.** (2008). Sound therapy for tinnitus—Sacred cow or idol worship? An investigation of the evidence. *Audiology Medicine, 6*(1), 16–24. https://doi.org/10.1080/16513860801899389

**Parazzini, M., Del Bo, L., Jastreboff, M., Tognola, G., & Ravazzani, P.** (2011). Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators. *International Journal of Audiology, 50*(8), 548–553. https://doi:10.3109/14992027.2011.572263

**Park, M. P., Kim, W. J., Ha, J. B., & Han, J. J.** (2017). Effect of sound generators on tinnitus and hyperacusis. *Acta-Oto-Laryngologica, 138*(2), 1–5. https://doi:10.10801/00016489.2017.1386801

**Rietveld, T., & van Hout, R.** (2015). The *t* test and beyond: Recommendations for testing the central tendencies of two independent samples in research on speech, language and hearing pathology. *Journal of Communication Disorders, 58,* 158–168. https://doi.org/10.1016/j.jcomdis.2015.08.002

**SAS.** (2015). *The MI procedure. SAS/STAT 14.1 user's guide*. SAS Institute, Inc.

**Sawilowsky, S.** (2009). New effect size rules of thumb. *Journal of Modern Applied Statistical Methods, 8*(2), 467–474. https://doi.org/10.22237/jmasm/1257035100

**Scherer, R. W., Erdman, S. A., Gold, S., Formby, C., & TRTT Research Group.** (2020). Treatment fidelity in the Tinnitus

Retraining Therapy Trial. *Trials, 21*(1), 670. https://doi.org/10.1186/s13063-020-04530-9

**Scherer, R. W., & Formby, C.** (2019). Effect of tinnitus retraining therapy vs standard of care on tinnitus-related quality of life: A randomized clinical trial. *JAMA Otolaryngology—Head & Neck Surgery, 145*(7), 597–608. https://doi.org/10.1001/jamaoto.2019.0821

**Scherer, R. W., Formby, C., Gold, S., Erdman, S., Rodhe, C., Carlson, M., Shade, D., Tucker, M., Sensinger, L. M., Hughes, G., Conley, G. S., Downey, N., Eades, C., Jyllka, M., Haber-Perez, A., Harper, C., Russell, S. K., Sierra-Irizarry, B., & Sullivan, M.** (2014). The Tinnitus Retraining Therapy Trial (TRTT): Study protocol for a randomized controlled trial. *Trials, 15*(1), 396. https://doi.org/10.1186/1745-6215-15-396

**Scherer, R. W., Sensinger, L. D., Sierra-Irizarry, B., & Formby, C.** (2018). Lessons learned conducting a multi-center trial with a military population: The Tinnitus Retraining Therapy Trial. *Clinical Trials, 15*(5), 429–435. https://doi.org/10.1177/1740774518777709

**Tunkel, D. E., Bauer, C. A., Sun, G. H., Rosenfeld, R. M., Chandrasekhar, S. S., Cunningham, E. R., Jr., Archer, S. M., Blakley, B. W., Carter, J. M., Granieri, E. C., Henry, J. A., Hollingsworth, D., Khan, F. A., Mitchell, S., Monfared, A., Newman, C. W., Omole, F. S., Phillips, C. D., Robinson, S. K., . . . Whamond, E. J.** (2014). Clinical practice guideline: Tinnitus. *Otolaryngology—Head & Neck Surgery, 151*(Suppl. 2), S1–S40. https://doi.org/10.1177/0194599814545325

**Tyler, R. S., & Bentler, R. A.** (1987). Tinnitus maskers and hearing aids for tinnitus. *Seminars in Hearing, 8*(1), 49–60. https://doi.org/10.1055/s-0028-1089904

**Tyler, R. S., Noble, B., Coelho, C., & Ji, H.** (2012). Tinnitus retraining therapy: Mixing point and total masking are equally effective. *Ear and Hearing, 33*(5), 588–594. https://doi.org/10.1097/AUD.0b013e31824f2a6e

**Wicklin, R.** (2009). Rediscovering SAS/IML Software: Modern data analysis for the practicing statistician. In *SAS Global Forum 2009 Forum Proceedings*. SAS Institute, Inc. https://support.sas.com/resources/papers/proceedings10/329-2010.pdf

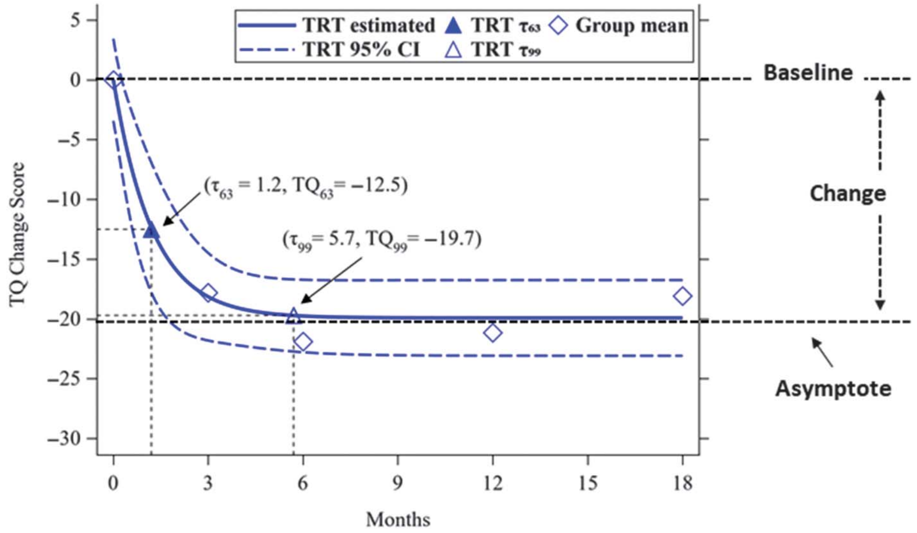
**Wilson, P. H., Henry, J. L., Andersson, G., Hallam, R. S., & Lindberg, P.** (1998). A critical analysis of directive counselling as a component of tinnitus retraining therapy. *British Journal of Audiology, 32*(5), 273–286. https://doi.org/10.3109/03005364000000078

## **Appendix** (p. 1 of 2)

### Analysis of the Treatment Response Dynamics: Implementation of the Exponential Model and Derivation of the Time Constants

The normalized TQ change scores were fit with the general form of the exponential model (with a random intercept effect) illustrated in Figure A1. Associated upper and lower confidence limits are indicated. The asymptote, change, and rate parameters are defined and illustrated with respect to baseline. Of primary interest here are the estimates of rate indexed by time constants, $\tau_{63}$ and $\tau_{99}$ (time in months). These time constants coincide with static points along the fitted exponential that correspond to improvements in TQ change scores by 63% and 99%, respectively, relative to baseline and where 100% is the asymptote. The equations for these change scores, $TQ_{63}$ and $TQ_{99}$, and the respective time constants are shown in Figure A1.

**Figure A1.**



**Appendix** (p. 2 of 2)

## Analysis of the Treatment Response Dynamics: Implementation of the Exponential Model and Derivation of the Time Constants

General form of exponential model:

$$\mathit{TQ\ change\ score} = \mathit{asymptote} + (\mathit{change} \times \exp\ (\mathit{rate} \times \mathit{time})) + \mathit{random\ asymptote} + \mathit{residual}, \text{ where :} \tag{1}$$

*Asymptote:* plateauing estimate of the TQ change score for which one would expect no further improvement in the tinnitus condition with continued duration of treatment.

*Change:* difference between the normalized baseline TQ change score (i.e., intercept = 0 at 0 months of treatment) and the estimate of the asymptotic TQ change score.

*Rate:* an estimate of the treatment-related response dynamics indexed by the rate at which the TQ change score approaches the estimate of the asymptote.

Indices of rate corresponding to 63% and 99% improvement in the tinnitus condition are quantified by time constants denoted by the following pair of equations:

$$\tau_{63} = \frac{1}{\mathit{rate}} \times \log\left(\frac{TQ_{63} - \mathit{asymptote}}{\mathit{change}}\right) \text{ and } \tau_{99} = \frac{1}{\mathit{rate}} \times \log\left(\frac{TQ_{99} - \mathit{asymptote}}{\mathit{change}}\right), \qquad (2) \text{ and } (3)$$

where $TQ_{63}$ = *asymptote* + 0.037 × *Change*, and
$TQ_{99}$ = *asymptote* + 0.01 × *Change*

The actual implementation of the exponential model was achieved using the following simultaneous equation, which incorporated the change scores for each of the interventions in the fitting analysis:

$$\begin{aligned} Y_{ti} = {} & \beta_{0i} + \beta'_{0i} \times \mathit{Group}_{trt} + \beta''_{0i} \times \mathit{Group}_{pTRT} + \left(\beta_{1i} + \beta'_{1i} \times \mathit{Group}_{trt} + \beta''_{1i} \times \mathit{Group}_{pTRT}\right) \\ & \times \exp\left(\beta_{2i} \times \mathit{Time}_{ti} + \beta'_{2i} \times \mathit{Time}_{ti} \times \mathit{Group}_{trt} + \beta''_{2i} \times \mathit{Time}_{ti} \times \mathit{Group}_{pTRT}\right) + U_{0i} + e_{ti}, \end{aligned} \tag{4}$$

where $\mathit{Group}_{trt}$ and $\mathit{Group}_{pTRT}$ are two dummy variables set to a value of 1 for participants assigned to TRT, $\mathit{Group}_{trt} = 1$, or for participants assigned to pTRT, $\mathit{Group}_{pTRT} = 1$. For participants in the SOC group, both $\mathit{Group}_{trt}$ and $\mathit{Group}_{pTRT}$ are set to 0. $Y_{ti}$ is the normalized TQ change score for the ith participant at time *ti* (in months). $\beta_{0i}$ is the asymptote for participant i, which is the plateauing estimate of the TQ change score for which one would expect no further improvement in the tinnitus condition with continued duration of treatment. $\beta'_{0i}$ and $\beta''_{0i}$ are the asymptote effects for TRT and pTRT compared to SOC. $\beta_{1i}$ is the change from asymptote for SOC, which represents the difference between the normalized baseline TQ change score (i.e., intercept = 0 at 0 months of intervention) and the estimate of the asymptotic TQ change score. $\beta'_{1i}$ and $\beta''_{1i}$ represent the change effects for TRT and pTRT, respectively. $\beta_{2i}$ is the rate, an estimate of the treatment-related response dynamics indexed by the rate at which the TQ change score approaches the estimate of the asymptote. $\beta'_{2i}$ and $\beta''_{2i}$ represent the rate effects for TRT and pTRT, respectively. $e_{ti}$ is the random residual ($e_{ti} \sim N(0, s_e^2)$), and $U_{0i}$ ($U_{0i} \sim N(0, s_u^2)$) is the random asymptote that an individual deviates from the fixed group mean asymptote $\beta_{0i}$.