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# Efficacy of Nortriptyline-Topiramate and Verapamil-Paroxetine in Tinnitus Management: A Randomized Placebo-Controlled Trial

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## Abstract

*Objective.* To evaluate the efficacy of 2 drug combinations on tinnitus severity and associated stress, depression, sleep, and anxiety.

*Study Design.* A randomized, double-blind, placebo-controlled clinical trial conducted between 2019 and 2023 for an 8-week duration.

*Setting.* Single institution tertiary care center.

*Methods.* The study recruited adult patients with moderate to severe tinnitus for 6 months or more. In total, 81 patients were assessed for eligibility, 78 were enrolled and randomized, and 67 were included in the per-protocol analysis. Patients were randomized into 3 groups (1:1:1). Group NT received nortriptyline-topiramate, group VP received verapamil-paroxetine, and group P received placebo.

*Results.* A total of 19 patients in group NT, 22 in group VP, and 26 patients in group P were included in the per-protocol analysis. In group NT, the Tinnitus Functional Index (TFI) score decreased from 58.4 ± 13.9 (baseline) to 46.3 ± 17.5 (end-of-trial) ($P < .001$). Similarly, in group VP, the TFI score decreased from 54.6 ± 17.5 to 42.2 ± 16.1 ($P = .004$). However, group P did not demonstrate any significant decrease in the TFI score from 51.2 ± 18.6 to 45.2 ± 20.1 ($P = .086$). The between-arm analysis did not yield any statistical significance decrease in the TFI score (analysis of variance, $P = .265$).

*Conclusion.* Both combinations of drugs were promising in improving tinnitus severity. However, larger-scale trials with longer follow-up periods are warranted to validate our findings between groups.

## Keywords

migraine, nortriptyline-topiramate, randomized clinical trial, tinnitus, verapamil-paroxetine

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Tinnitus, derived from the Latin verb "tinnire" meaning "to ring," denotes the perception of a phantom sound in the absence of an external stimulus.[1] Untreated tinnitus may lead to symptoms of depression, anxiety, impaired sleep, and result in poorer health-related quality of life.[2] Additionally, the health care cost for managing tinnitus poses a considerable burden on a nation's health care system.[3-5] This strain is further exacerbated by the lack of effective treatment strategies, contributing to long-term disability payments reaching $1.2 billion per year in the United States in 2012.[6] While the US Food and Drug Administration has not approved any pharmaceutical agent for tinnitus treatment, researchers have shown significant interest in investigating various nonpharmacological methods and drug classes to treat tinnitus.[7] The clinical trials examining tinnitus treatments displayed considerable variability in methodology, lack of control groups, short duration, and high dropout rates among other limitations. Therefore, the existing evidence is of poor quality and contradictory, and ongoing investigations are needed to explore the effect of these drugs on tinnitus.[8]

As a result, there is a need for well-designed, randomized, double-blind clinical trials to further evaluate the efficacy of pharmaceutical interventions on tinnitus. On this basis, we pursued a double-blind randomized clinical trial to evaluate the effectiveness of combinations involving

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nortriptyline plus topiramate (NT) or verapamil plus paroxetine (VP) in reducing tinnitus severity compared to a placebo. These medication combinations were selected based on the senior author's clinical experience. We have previously experimented with various combinations and developed these specific regimens based on our clinical findings (Supplemental Figure S1, available online).[9-11] The secondary objective was to compare the impact of both combinations versus placebo on tinnitus-related comorbidities, such as stress, anxiety, sleep, and quality of life (Supporting Information). The choice of these medication combinations was based on increasing evidence of an epidemiological and pathophysiological association between migraine and tinnitus.[11-15]

## Materials and Methods

### Study Design

We conducted an 8-week parallel-arm, double-blind, randomized (1:1:1), placebo-controlled trial to investigate the efficacy of NT and VP in treating patients with moderate to severe tinnitus (Tinnitus Functional Index [TFI]>25). The study was conducted at the neurotology clinic of the UC Irvine Medical Center, was approved by the Institutional Review Board, and registered on ClinicalTrials.gov (NCT04404439). After consenting, participants were randomized among 3 parallel arms: Group NT; Group VP; and Group P, a placebo (Microcrystalline Cellulose; PH105) group, in the same colored and shaped capsule. The capsules were supplied by our on-site hospital pharmacy as single capsules, each containing the initial dosage of the medications. Notably, all 3 treatment groups experienced dose escalation from the initial dosage during the study as explained in **Figure 1**. Moreover, participants were contacted by a blinded physician via telephone once per week during the trial and in-person visits were scheduled for Week 0 (the beginning of the trial), Week 4, and Week 8. If during these weekly contacts, the patient reported <20% improvement in tinnitus compared to the baseline Visual Analog Scale (VAS) obtained at the beginning of the trial, the physician instructed the patient to increase the dosage by adding 1 capsule per day. Conversely, if a patient reported ≥20% improvement as compared to the baseline VAS, the team member advised the patient to maintain the same dosage of medication for 1 week until the next weekly check-in. Furthermore, at the clinical assessment visits, patients completed a tablet-based assessment of tinnitus symptoms. The questionnaire results were securely transferred to a REDCap database. A data safety monitor addressed any reported side effects throughout the study.

### Participants

The study recruited English-speaking adult patients, between the ages of 18 and 85 years with chronic (>6 months) moderate to severe tinnitus. Additionally, they had to be compliant with the medication regimen and attend study visits. Patients underwent comprehensive otolaryngologic assessments, including an audiogram, and provided informed consent. In addition, patients underwent a magnetic resonance imaging of the internal auditory canals (if unilateral tinnitus or asymmetric hearing loss, and not already performed). Exclusion criteria included pregnancy, psychosis, neurological neoplasm, active ear disease affecting hearing, allergies or adverse reactions to study medications, concerning medical conditions like arrhythmia, and any contraindications to the study drugs.

### Primary, Secondary, and Safety Endpoints

The study's primary outcome was measured using a TFI, evaluating the negative impact of tinnitus across 8 domains: Intrusive, Sense of control, Cognitive, Sleep, Auditory, Relaxation, Quality of life, and Emotional. Changes ≥13 points in TFI were considered the Minimal Clinically Important Difference (MCID).[16] Secondary outcomes included Perceived Stress Scale (PSS), Patient Health Questionnaire (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), and Generalized Anxiety Disorder (GAD-7) scores, collected at clinical visits. The MCID for PSS was an improvement of ≥11 points,[17] ≥5 points for PHQ-9,[18] ≥3 points for PSQI,[19] and ≥4 points for GAD-7.[20]

### Statistical Analyses

The study endpoint analyses included within-arm changes from baseline (Week 0) to the end of treatment at 8 weeks and between-arm differences for TFI, PSS, PHQ-9, PSQI, and GAD-7. The within-arm analyses were based on a per-protocol estimand and tested with paired 2-tailed *t* tests. The between-arm analyses were based on a per-protocol estimand and tested with analysis of variance (ANOVA) analysis. The use of the per-protocol estimand ensured that changes in outcome measures were representative of participants using the treatment as directed, enhancing the accuracy of the analysis. The relative benefit change (RBC) was calculated as the difference between the rate of experiencing the outcome (in this case, the MCID improvement) in the active intervention group and the placebo group, divided by the rate of experiencing the outcome in the active intervention group [RBC = (Improvement rate in the active intervention group – Improvement rate in the placebo group)/Improvement rate in the active intervention group]. An intention-to-treat analysis was also conducted with identical methods and analyses, with the addition of 4 patients in group NT, 6 in group VP, and 1 in group P. For missing observations, the last value was carried forward to avoid bias. Analysis was conducted in R version 4.3.0, with *P* values less than .05 indicating significance.

## Results

Of the 81 patients screened for enrollment, 78 were eligible for randomization. Three patients were excluded as they

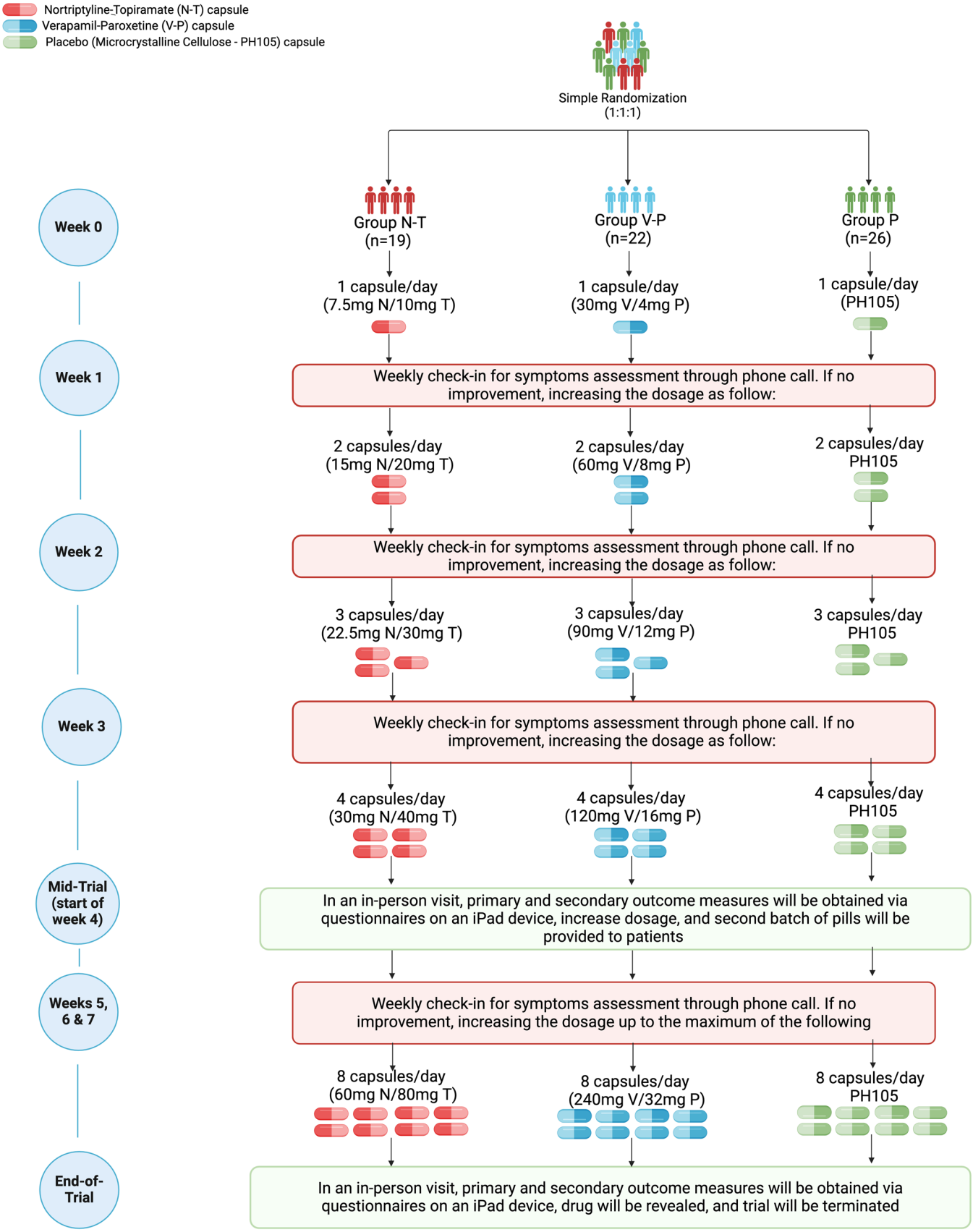


**Figure 1.** Flowchart of patients' randomization, recruitment, and follow-up during the 8-week course of the trial.

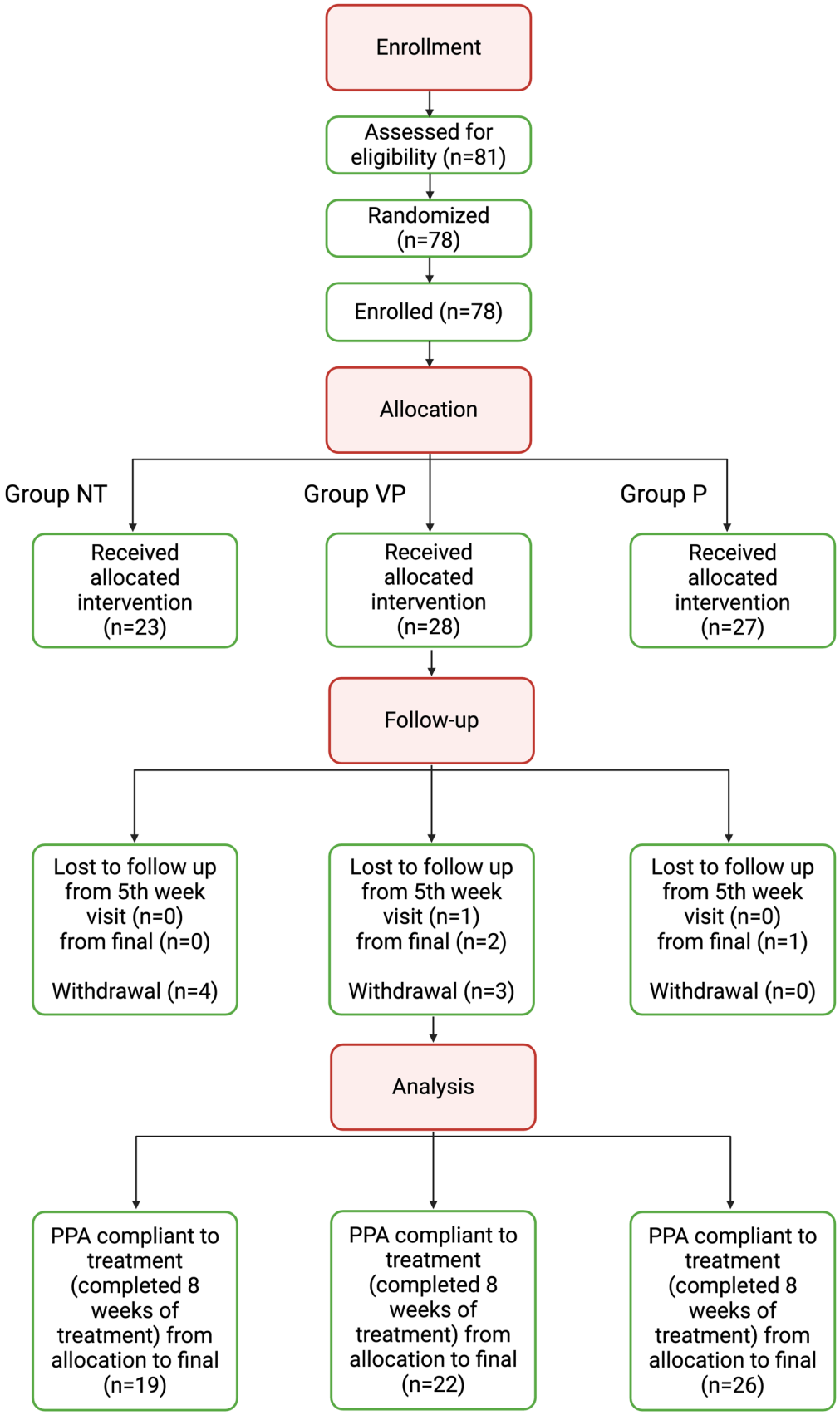


**Figure 2.** Participant flow diagram. Within-arm and between-arm comparisons were performed with PPA for those who were compliant with the treatment. NT, nortriptyline plus topiramate; P, placebo; PPA, per-protocol analysis; VP, verapamil plus paroxetine.

exhibited mild tinnitus on their TFI score.[21] The randomized patients were distributed into 3 groups: 23 in group NT, 28 in group VP, and 27 in group P. Four patients withdrew from group NT during the trial for reasons including abdominal pain, uncontrolled blood pressure unrelated to the study medication, discomfort with the blinding process, and 1 patient withdrew without providing a reason. In group VP, 1 patient was lost to follow-up at the fourth-week visit, 2 were lost at the end-of-trial visit, and 3 patients withdrew during the trial due to tiredness, erectile dysfunction, and blurry vision. In group P, 1 patient failed to attend the last trial visit without explanation. In the end, 19 patients from group NT, 22 from group VP, and 26 from group P were included in the per-protocol analysis (**Figure 2**). The mean age of patients in group NT was 58.1 ± 14.1, 59.7 ± 14.2 in group VP, and 58.3 ± 12.2 in group P ($P = .93$). Similarly, sex distribution was not statistically significant between groups ($P = .26$) (**Table 1**). In patients who completed the trial, 1 patient in the NT group reported a metallic taste as a side effect. In the VP group, 1 patient-reported fatigue and insomnia, another reported fatigue, and a third reported erectile dysfunction. In the intention-to-treat analysis, 23 patients from group NT, 28 from group VP, and 27 from group P were included. The mean age of patients in group NT was 58.1 ± 14.1, 59.6 ± 14.2 in group VP, and 58.2 ± 12.1 in group P ($P = .913$). Similarly, sex distribution was not statistically significant between groups ($P = .666$).

**Table 1.** Demographics of Patients Included in the Per-Protocol Analysis and Average Value of Different Studied Scores at Each Time Point Throughout the Trial

| | NT group (n = 19) | VP group (n = 22) | P group (n = 26) |
|---|---|---|---|
| Age | 58.1 ± 14.1 | 59.7 ± 14.2 | 58.3 ± 12.2 |
| Sex | | | |
| Female | 4 (21.0%) | 10 (45.5%) | 9 (34.6%) |
| Male | 15 (79.0%) | 12 (54.5%) | 17 (65.4%) |
| TFI | | | |
| Initial | 58.4 ± 13.9 | 54.6 ± 17.5 | 51.2 ± 18.6 |
| Mid-trial | 48.2 ± 17.9 | 49.7 ± 16.8 | 47.9 ± 19.4 |
| End-of-trial | 46.3 ± 17.5 | 42.2 ± 16.1 | 45.2 ± 20.1 |
| PSS | | | |
| Initial | 16.7 ± 8.1 | 12.3 ± 7.1 | 12.5 ± 5.3 |
| Mid-trial | 13.8 ± 8.9 | 12.4 ± 7.4 | 12.5 ± 5.3 |
| End-of-trial | 13.8 ± 8.9 | 10.3 ± 6.1 | 12.0 ± 5.4 |
| PHQ-9 | | | |
| Initial | 8.8 ± 5.8 | 5.8 ± 3.5 | 5.0 ± 3.2 |
| Mid-trial | 6.4 ± 5.5 | 5.7 ± 3.7 | 4.3 ± 3.0 |
| End-of-trial | 5.7 ± 4.2 | 5.2 ± 3.5 | 4.3 ± 3.1 |
| PSQI | | | |
| Initial | 12.8 ± 2.2 | 14.3 ± 2.1 | 12.8 ± 2.3 |
| Mid-trial | 13.0 ± 2.9 | 13.7 ± 1.6 | 13.2 ± 2.7 |
| End-of-trial | 12.5 ± 3.1 | 13.7 ± 2.4 | 12.9 ± 2.2 |
| GAD-7 | | | |
| Initial | 6.7 ± 4.5 | 5.4 ± 4.3 | 4.2 ± 3.9 |
| Mid-trial | 4.1 ± 4.7 | 4.1 ± 4.1 | 4.0 ± 3.8 |
| End-of-trial | 4.2 ± 5.0 | 2.7 ± 2.9 | 4.3 ± 3.1 |

Abbreviations: GAD-7, General Anxiety Disorder-7; NT, nortriptyline-topiramate, P, placebo; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; TFI, Tinnitus Functional Index; VP, verapamil-paroxetine.

## *TFI*

### *Per-Protocol Analysis*

The initial TFI scores were not significantly different between the 3 comparison groups (ANOVA, $P = .373$). Within-group results showed that by the end-of-trial, the TFI scores of 46.3 ± 17.5 for group NT (paired $t$ test, $P < .001$; 95% confidence interval [CI] = −18.561, −5.646; $d = 0.903$), and 42.2 ± 16.1 for group VP (paired $t$ test, $P = .004$; 95% CI = −20.437, −4.359; $d = 0.684$) significantly decline from the initial timepoint. The placebo group showed no significant improvements, with end-of-trial TFI scores of 45.2 ± 20.1 (paired $t$ test, $P = .086$; 95% CI = −12.935, 0.916; $d = 0.350$) (**Figure 3**). Between-group comparisons revealed that TFI score changes (ΔTFI) demonstrated no significant difference (ANOVA, $P = .265$).

Among the groups, 8 (42.1%) patients in group NT, 9 (40.9%) in group VP, and 6 (23.1%) in group P achieved MCID improvements. In addition, the absolute changes in TFI scores were 12.1 ± 13.4, 12.4 ± 18.1, and 6.0 ± 13.5 in group NT, group VP, and group P, respectively (**Figure 4**). The RBC of TFI was 45.3% for patients in group NT and 43.5% for patients in group VP compared to placebo.

### *Intention-to-Treat Analysis*

The initial TFI scores were not significantly different between the 3 comparison groups (ANOVA, $P = .243$). Within-group results showed that by the end-of-trial, the TFI scores of 49.65 ± 19.97 for group NT (paired $t$ test, $P = .056$; 95% CI = −18.434, 0.246; $d = 0.421$), and 45.33 ± 16.43 for group VP (paired $t$ test, $P = .061$; 95% CI = −19.932, 0.470; $d = 0.370$) did not show a significant decline from the initial timepoint. The placebo group showed no significant improvements, with end-of-trial TFI scores of 44.96 ± 19.76 (paired $t$ test, $P = .162$; 95% CI = −14.070, 2.481; $d = 0.277$). Between-group comparisons revealed that ΔTFI demonstrated no significant difference (ANOVA, $P = .590$).

Among the groups, 8 (34.8%) patients in group NT, 8 (28.6%) in group VP, and 6 (22.2%) in group P achieved MCID improvements. In addition, the absolute changes in TFI scores were 9.09 ± 14.37, 9.73 ± 16.99, and 5.79 ± 13.31 in group NT, group VP, and group P, respectively.

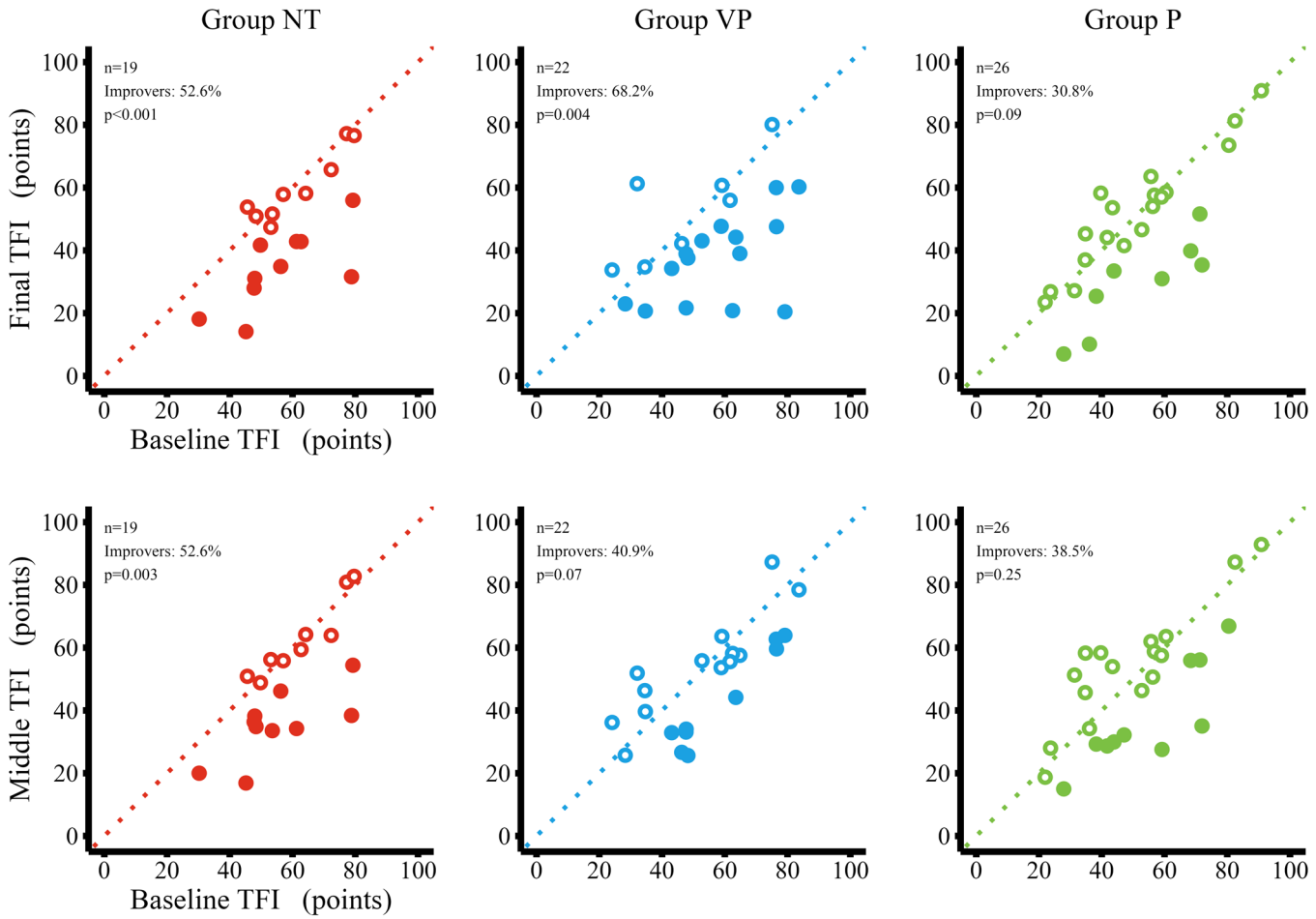


**Figure 3.** Scatterplots represent changes in TFI scores for each treatment-compliant patient from baseline to mid-trial (lower panels) and end-of-trial versus baseline (upper panels) for each arm. Solid dots represent patients with ≥15% improvement in tinnitus. NT, nortriptyline-topiramate, P, placeb; TFI, Tinnitus Functional Index; VP, verapamil-paroxetine.

## Discussion

Within the active treatment-compliant groups (group NT and group VP), the TFI scores showed a significant statistical reduction from baseline to end-of-trial in comparison to placebo, indicating meaningful improvements in tinnitus severity within the migraine medication groups and the therapeutic effect associated with active interventions. Additionally, 42.1% and 40.9% of patients in group NT and group VP, respectively, demonstrated clinically significant improvement in TFI scores when compared to placebo (23.1%), highlighting the clinical relevance of the observed improvement within the groups. However, it is important to note that this discrepancy between clinical and between-group comparison findings could be due to the overlap in standard deviations among the groups, sample size, or duration of the study. The intention-to-treat analysis revealed no significant differences in the within-arm analysis, suggesting that treatment adherence may have a more pronounced effect on tinnitus severity. In addition, no significant differences were found in the between-group analysis, highlighting the need for a larger sample size.

This study represents the first clinical trial to investigate the efficacy of medication combinations in treating tinnitus, rather than a single medication, while also addressing the risk of bias observed in previous studies. These biases included inadequate randomization, allocation concealment, lack of blinding, large losses to follow-up, and the use of non-standardized questionnaires.[22-25] Of the 81 patients screened for enrollment, 78 were eligible for randomization. Withdrawals and loss to follow-up occurred with 11 patients, resulting in 67 patients included in the final per-protocol analysis. The dropout rate was 14% which is less than what was reported in other studies using drugs for tinnitus treatment.[26] This finding indicated that the combination of medications was generally well-tolerated by patients. In addition, this attrition rate was relatively balanced among groups, minimizing potential bias in the analysis.

Investigating the efficacy of antidepressants in tinnitus patients, regardless of comorbid depression, stems from the shared neurobiological mechanisms observed between tinnitus and mood and anxiety disorders, as well as pain syndromes.[27-31] Neuroimaging studies have highlighted

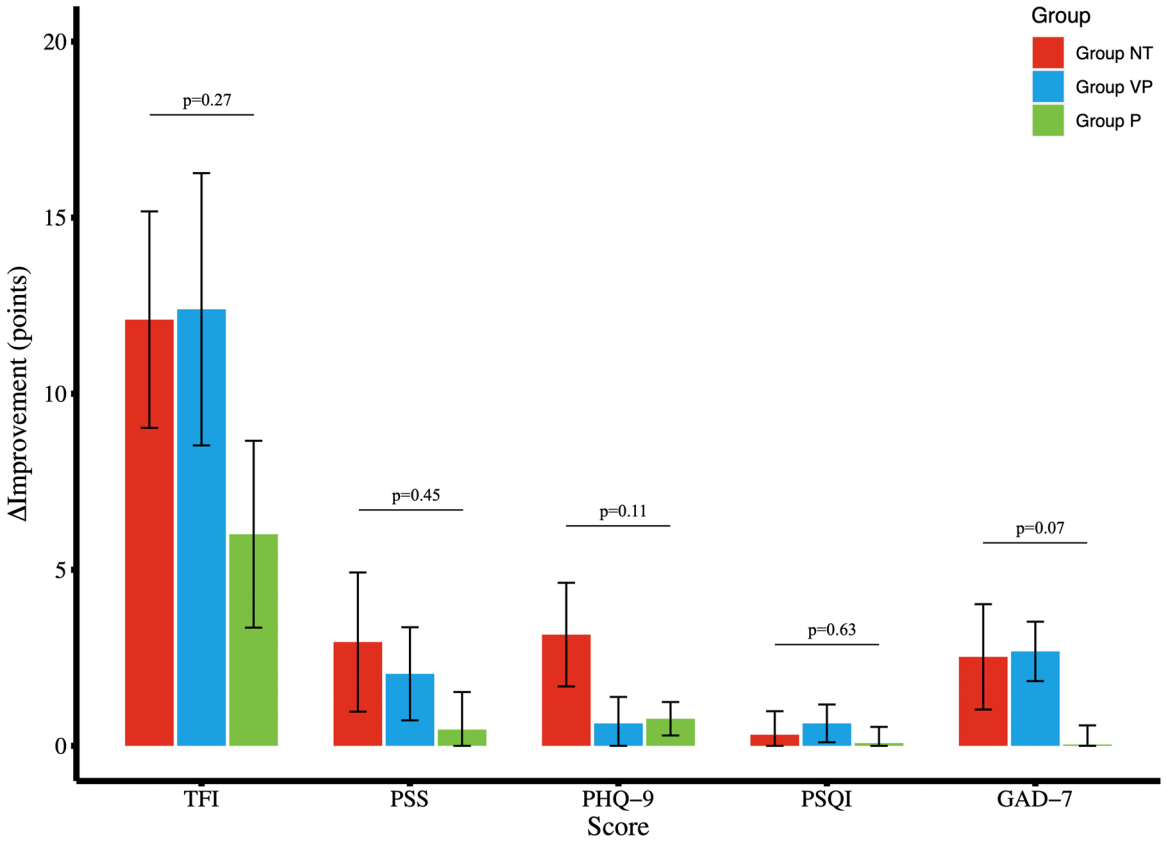


**Figure 4.** Comparison of the mean difference in TFI, PSS, PHQ-9, PSQI, and GAD-7 scores for each arm from baseline to end-of-trial between the 3 groups (ANOVA). The error bar represents the standard error of the mean. ANOVA, analysis of variance; GAD-7, Generalized Anxiety Disorder-7; NT, nortriptyline-topiramate, P, placebo; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; TFI, Tinnitus Functional Index; VP, verapamil-paroxetine.

the involvement of both auditory (rich in serotonin receptors) and nonauditory brain areas, particularly the limbic system, in the pathophysiology of tinnitus.[28,32] However, our hypothesis was based on the migraine prophylactic effects of these drugs.[33,34] While some argue that antidepressants primarily target the emotional and psychological tinnitus comorbidities, a clinical trial conducted by Sullivan et al demonstrated that the impact of nortriptyline on tinnitus may be independent of depression and anxiety symptoms.[35] Despite observing an important RBC in PSS scores of 70.8% in group NT, and a less important relative change of 15.4% in group VP compared to the placebo, neither the within-arm nor between-arm analyses showed any statistically significant changes in the PSS scores across all groups (Supporting Information). These findings suggest that the improvement in tinnitus symptoms within groups NT and VP cannot be attributed to a reduction in stress levels.

Our proposed theory for the pathophysiology of fluctuating or loud tinnitus suggests that it may be linked to altered electrical activity or spreading cortical depression due to migraine.[11] This phenomenon is thought to induce neurogenic inflammation through the release of neuropeptides (eg, substance P and calcitonin gene-related peptide) from the trigeminal ganglion. Consequently, this process can lead to cochlear vascular changes, neurogenic inflammation, cochlear nerve sensitization, and increased central sensitivity, ultimately contributing to increased tinnitus perception.[11,36] Based on this theory, we decided to investigate verapamil and topiramate as a potential treatment for tinnitus. Topiramate exerts an effect centrally on sensitization mechanisms and pain activation. It modulates cortical hyperexcitability by diminishing the progression of cortical spreading depression. In addition, topiramate is believed to suppress the release of neuropeptides involved in the central pain pathway, such as the caudal trigeminal nucleus and subsequent neurogenic dural vasodilatation.[37] Verapamil is also efficacious in migraine prophylaxis. Although its precise mechanisms of action are not fully understood, it is believed to induce vasodilation in cerebral arteries and interact with serotonergic systems implicated in migraine pathogenesis and subsequent tinnitus perception.[38] Moreover, the idea that multiple signaling pathways may be involved in the generation and modulation of tinnitus has led researchers to suggest combinations of medications that target multiple receptors, rather than single receptors, for more effective control over tinnitus symptoms.[39]

There is a strong correlation between the severity of tinnitus and symptoms of depression, anxiety, sleep disturbances, and poor quality of life.[2] Our within-arm

analysis revealed that pre-treatment PSS scores in both NT ($P = .15$) and VP ($P = .14$) groups remained unchanged throughout the trial, yet improvements were noted in tinnitus symptoms. Similarly, there was no statistically significant change in PSQI scores among patients in all study groups. These findings suggest that additional nonpharmacological interventions may be necessary to address stress and improve sleep quality in tinnitus patients such as cognitive behavioral therapy and sound therapy. This neurointegrative approach can potentially break the vicious cycle of tinnitus exacerbation caused by stress and poor sleep (partly due to the activation of atypical migraine), leading to better overall outcomes in patients.

Several limitations warrant consideration in our study. First, the use of per-protocol analysis introduced a risk of selection bias, potentially leading to an overestimation of the treatment effects. Furthermore, this approach may limit the generalizability of our findings to real-world clinical practice. Although we used per-protocol analysis, we meticulously reported withdrawal reasons and adverse effects, aiming to maintain the validity of the interpretation of our results. Nonetheless, excluding the nonadherent patient may have increased the risk of type 1 error. To mitigate this concern, we also included the intention-to-treat analysis. Additionally, our follow-up period was limited to 8 weeks, highlighting the need for a longer duration to assess the maintenance of the observed results. A larger patient cohort may be necessary to detect statistically significant differences between groups, especially considering the overlap of standard deviations in the scores observed in our analysis. Despite this limitation, it is important to note that we observed a clinically significant difference between groups, underscoring the importance of our findings. Finally, although a higher proportion of patients in the active treatment groups met the MCID for TFI, there were indeed a few high responders in each group that might have influenced the mean TFI changes. However, the data demonstrate that patients in the active groups consistently experienced higher improvements in the TFI compared to placebo (median calculated as −8.08, −10.18, and −2.14 in the NT, VP, and P groups, respectively).

## Conclusion

We observed a statistically significant decrease in tinnitus severity captured by the TFI scores within-arm comparison in both groups NT and VP, which was not observed in the placebo group. Specifically, 8 (42.1%) patients in group NT, 9 (40.9%) in group VP, and 6 (23.1%) in group P achieved MCID improvements. Although the results did not yield statistical significance between groups, the RBC demonstrated a clinical improvement in the intervention groups compared to placebo. Therefore, both combinations of drugs might be promising in improving tinnitus symptoms. Moving forward, larger-scale trials with longer follow-ups are warranted to validate our findings.

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## Author Contributions

**Mehdi Abouzari**, study conception and design, data collection, data analysis, interpretation of the data, drafting of the manuscript, and final approval of the version to be published; **Karen Tawk**, study conception and design, data collection, data analysis, interpretation of the data, drafting of the manuscript, and final approval of the version to be published; **Joshua K. Kim**, data analysis, interpretation of the data, drafting of the manuscript, and final approval of the version to be published; **Eva D. Larson**, data collection, drafting of the manuscript, and final approval of the version to be published; **Harrison W. Lin**, data collection, interpretation of the data, drafting of the manuscript, and final approval of the version to be published; **Hamid R. Djalilian**, study conception and design, study supervision, drafting of the manuscript, and final approval of the version to be published.

## Disclosures

**Competing interests:** Hamid R. Djalilian is an advisor and holds equity in NeuroMed Care LLC, Elinava Technologies, and Cactus Medical LLC.

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## Supplemental Material

Additional supporting information is available in the online version of the article.

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