Treatment of Tinnitus with Migraine Medications: A Randomized Clinical Trial

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Background and Rationale

Tinnitus can be categorized into objective and subjective types. In objective tinnitus, there is a physical explanation for the sound, such as abnormal blood flow or muscular contractions (e.g., palatal myoclonus). In contrast, subjective tinnitus is only perceived by the individual and is far more common. Emerging research has identified a significant relationship between subjective tinnitus and migraine, with studies reporting that 26–47% of patients with tinnitus experience concomitant headache, particularly unilateral migraines.

Several observational and questionnaire-based studies have demonstrated that patients with both tinnitus and migraine report lower quality of life, greater symptom burden, and a higher prevalence of comorbid conditions such as hyperacusis, vertigo, pain syndromes, and depressive symptoms. Migraine laterality (left-sided or bilateral) and type (migraine with aura, cluster headache) have also been shown to influence symptom severity. Other case series suggest that the intensity of tinnitus may increase during migraine episodes, potentially due to shared mechanisms such as central sensitization or cortical hyperexcitability.

Additional large-scale studies in young adults have found statistically significant associations between tinnitus and migraine, especially in those with migraine with aura. This supports the hypothesis that migraine and tinnitus may share underlying pathophysiological pathways.

Currently, there is no FDA-approved pharmacologic treatment for tinnitus. Existing management strategies are limited to lifestyle modifications, cognitive behavioral therapy (CBT), and sound therapy. Psychoactive medications are sometimes used off-label to alleviate the psychological distress associated with tinnitus, though they are not curative. Among them, tricyclic antidepressants like nortriptyline have shown promise in reducing tinnitus severity, even in patients without comorbid depression. The neural circuits implicated in tinnitus overlap with those affected in mood, anxiety, and pain disorders — particularly in limbic and fronto-subcortical regions — suggesting a shared neurological basis involving maladaptive cortical plasticity.

We hypothesize that patients may benefit from medications targeting migraine-related neural dysregulation, even in the absence of formal headache diagnosis. This includes agents like nortriptyline, topiramate (a sodium-calcium channel blocker), verapamil (a calcium channel blocker), and paroxetine (a selective serotonin reuptake inhibitor). These medications may help modulate cortical excitability and reduce the perception and intensity of tinnitus.

This randomized, placebo-controlled trial aims to evaluate the efficacy of nortriptyline plus topiramate and verapamil plus paroxetine in reducing tinnitus symptoms. We will assess changes in tinnitus severity using a visual analog scale (VAS) and the Tinnitus Functional Index (TFI), as well as the frequency and duration of tinnitus episodes. Secondary outcome measures include the impact on comorbid symptoms such as motion sensitivity, photophobia, phonophobia, facial pain, neck stiffness, and headache-related features.

Our goal is to generate high-quality clinical evidence for migraine-prophylactic pharmacotherapy as a novel treatment strategy for subjective tinnitus.

Objectives

Aim 1: To determine if tinnitus symptoms improve with specific migraine regimens compared to those taking no medication based on number of tinnitus episodes per week, duration of tinnitus episodes, and tinnitus severity.

Aim 2: The doses at which these medications should be given for tinnitus not yet been determined; thus, one aim would be to further elucidate this.

Aim 3: To study the effect of the medications on presence and duration of other concomitant symptoms, presence of migraine related symptoms and clinical features such as sensitivity to motion, light, sound, pain in face or scalp, neck stiffness, and headaches as secondary outcomes.

Study Design

This study is a randomized controlled study. There will be three arms in the experiment. The first will be the placebo group, the second will be the nortriptyline (7.5 mg) plus topiramate (10 mg) group, and the third will be the verapamil (30 mg) plus paroxetine (4 mg) group. Both medication combinations may include dosage increases, as will be explained in the following paragraph. The placebo pill's ingredient is microcrystalline cellulose.

The symptomatic survey scores from each arm will be compared before and after treatment. This will be a double-blinded trial to avoid bias. One unblinded research staff member will be in charge of randomization, treatment assignment tracking, and coordinating with the pharmacy to ensure proper labeling and blinding. Simple randomization, using a computer-generated number sequence, will be performed in a 1:1:1 ratio for the two treatment groups and the placebo group.

During the 2-month study course, each patient assigned to the treatment groups will receive nortriptyline plus topiramate or verapamil plus paroxetine. Failure to improve with one combination will not result in crossover to another group. Files containing treatment group assignments and follow-up survey results will be stored securely on REDCap servers.

An unblinded clinical team member will serve as the data safety monitor. This individual will oversee symptom progression and provide safety oversight, including recommendations for dose adjustments or withdrawal if adverse effects occur.

Patients receiving nortriptyline plus topiramate will begin treatment at 7.5 mg nortriptyline and 10 mg topiramate taken at bedtime. A baseline tinnitus visual analog scale (VAS) score and tinnitus functional index (TFI) score will be obtained. A designated, unblinded study physician will contact participants weekly by phone to assess VAS improvement and potential side effects. If symptoms do not improve by at least 20% compared to baseline VAS, patients will be instructed to increase their dosage by 7.5 mg nortriptyline and 10 mg topiramate, respectively, for one week. If improvement is ≥20%, dosage will be maintained until the next check-in.

This dose adjustment protocol will continue until the maximum dosage is reached (60 mg for nortriptyline and 80 mg for topiramate). Participants will attend in-person visits at the beginning of the trial (Week 0), Week 4, and Week 8. During these appointments, a blinded physician will administer a VAS and oversee completion of TFI and secondary outcome questionnaires using a tablet device. All responses will be securely stored in REDCap.

Blood pressure and ECG readings will be obtained at each in-person visit. TFI and secondary outcome measures will be analyzed at the end of the trial by the principal investigator, who remains blinded to treatment assignment. Weekly symptom reports and monthly safety data (blood pressure, ECG results) will be reviewed by the unblinded safety monitor to assess for any adverse effects. Based on clinical judgment, the safety monitor may recommend dosage changes or participant withdrawal from the trial.

The same experimental design will apply to the verapamil plus paroxetine group, with different starting doses. Verapamil will begin at 30 mg and increase by 30 mg weekly until symptom improvement, up to a maximum dose of 240 mg. Paroxetine will start at 4 mg and increase by 4 mg weekly up to a maximum dose of 32 mg. With both treatment combinations, gradual titration is required to reach therapeutic levels. Dosage reductions must also be tapered to avoid withdrawal effects.

The placebo group will receive capsules identical in size and shape to the treatment groups. Participants in this group will follow the same weekly dose escalation protocol unless they report ≥20% symptom improvement.

All participants will be asked to report potential side effects. These reports will be reviewed by the clinical team and communicated to the unblinded safety monitor, who will oversee patient safety and determine the need for dose modifications or early withdrawal. At the end of the 2-month study period, participants who are symptom-free will undergo a tapering schedule to discontinue medication. Participants who continue to experience symptoms may be offered additional treatment outside the context of the trial based on the clinical discretion of the lead investigator. Because there is currently no standard of care for this condition, individualized follow-up care will be based on best available treatment options.

Primary and Secondary Endpoints

Efficacy will be evaluated using validated survey instruments that assess tinnitus severity and its impact on daily life.

- The **primary endpoint** is the change in **Tinnitus Functional Index (TFI)** score from baseline to the end of treatment.
- **Secondary endpoints** include:
    - Midpoint TFI (Week 4)
    - **Perceived Stress Scale (PSS)**
    - **Sleep Quality Index (PSQI)**
    - **Patient Health Questionnaire (PHQ-9)**
    - Self-reported symptoms related to tinnitus and vestibular migraine, including:
        - Sensitivity to motion
        - Sensitivity to light
        - Sensitivity to sound
        - Pain in the face or scalp
        - Neck stiffness
        - Headaches

Side effects will be assessed and recorded during follow-up appointments and weekly phone calls.

At the end of the trial:

- **Treatment success** is defined as a >20% improvement in TFI score compared to baseline.
- **Treatment failure** is defined as an improvement of <20% in TFI score compared to baseline.

Statistical Analysis Plan (SAP)

To determine the statistical significance the three arms of the experimental groups will be compared using ANOVA.

The primary statistical method used to compare the three groups is ANOVA. Multiple instruments will be used to determine the difference between treatment and control (placebo) groups. The primary outcomes measure is the tinnitus functional index (TFI) score before and after treatment. ANOVA will be used to compare secondary outcome variables including perceived stress scale, sleep quality index, and patient health questionnaire scores, number and duration of tinnitus episodes, and presence and duration of migraine related symptoms and clinical features such as sensitivity to motion, light, sound, pain in face or scalp, neck stiffness, and headaches.

Bonferroni correction will be necessary because both experimental groups (nortriptyline plus topiramate and verapamil plus paroxetine) will be compared to control outcomes and also to each other. Thus, comparisons will be made between all three groups using two groups at a time.

Based on our pilot data, we hypothesized that the mean change in tinnitus functional index (TFI) after 2 months of treatment would be 70% (± 10%) among patients receiving nortriptyline+topiramate, 50% (± 10%) among patients receiving verapamil+paroxetine, and 20% (± 10%) among patients receiving placebo. A sample size of 10 patients per group would yield at least 80% power to test this hypothesis using two-sided t tests at 1.7% significance level, adjusted for an attrition rate of 20% (Bonferroni correction was applied to adjust the significance level for multiple treatment comparisons). Thus, the proposed sample size of 21 patient per group would provide more than adequate power to test the hypothesis.

Eligibility: Patients with tinnitus

<u>Inclusion Criteria:</u>

1) Patients with moderate to severe tinnitus.
2) Male or female between the ages of 25 to 85 years.

3) Subject must be compliant with the medication and attend study visits.

4) Must be able to read and write in the English language to provide consenting.

Exclusion Criteria:

1) Pregnancy will result in automatic exclusion from the study. Rule out of pregnancy will be done by a urine pregnancy test to confirm the situation for all women who are of childbearing potential.

2) Subject with history of an adverse reaction to medication being prescribed.

3) Subject suffers from a medical condition or has history that may be concerning to the investigator's clinical opinion.

4) All contraindications for the medications which prevent subjects from randomization will be considered as exclusion criteria.

Outcome Measures

The criteria for evaluation of efficacy in treatment will be the administration of surveys that measure severity of tinnitus and impact on daily life of the subject. The primary endpoint is the comparison of tinnitus functional index (TFI) scores before and after treatment. Secondary endpoints include additional questionnaires including the perceived stress scale, sleep quality index, patient health questionnaire, mid-point TFI, and questions that address the presence and duration of other signs and symptoms related to tinnitus, vestibular migraine, presence of migraine related symptoms and clinical features such as sensitivity to motion, light, sound, pain in face or scalp, neck stiffness, and headaches. Side effects will be assessed and recorded during follow-up appointments and regular phone calls to patients.

At the end of the trial, treatment success will be defined as an improvement in TFI score of >20% as compared to baseline TFI score. Treatment failure will be defined as an improvement in TFI score of <20%.