Phase Two Study Examining Magnesium Dependent Tinnitus

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Doctor of Medicine

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Abstract

**Background:** Recent studies in noise-induced and idiopathic sensorineural hearing loss have suggested that magnesium supplementation may lessen both hearing loss and the severity of tinnitus in patients. Further epidemiological evidence indicates that all age groups of Americans fall short of the recommended daily allowance for magnesium by 100 mg daily.

**Purpose:** The purpose of this study was to examine any potential benefit in lessening the severity of tinnitus in patients taking supplemental magnesium.

**Research Design:** The study was a single-arm, open-label, before-and-after study of oral magnesium (532 mg per day) in 26 patients for 3 months. Tinnitus severity was evaluated and recorded daily by the patient using the Tinnitus Distress Rating (TDR) scale of 0 (no tinnitus) to 10 (worst possible tinnitus). The Tinnitus Handicap Inventory (THI) was administered before and at the end of the study, and scores were converted to the grades of the 5-item Tinnitus Severity Scale (TSS). As a phase 2 study, the current design could not distinguish the effect of treatment from a placebo effect or regression to the mean. All data were collected at Mayo Clinic in Scottsdale, Arizona.
**Study Sample:** Patients with moderate to very severe tinnitus (TDR score of 3 through 8).

**Intervention:** Daily magnesium supplementation, 532 mg; patient completion of the THI; and daily self-report of TDR.

**Data Collection and Analysis:** The main outcome measures were mean TDR scale scores and THI scores as converted to TSS grades. The primary analysis was done on the basis of intention to treat.

**Results:** Twenty-six patients were enrolled; 19 completed the study. The extent of handicap, as measured by THI/TSS, for subjects with slight or greater impairment was significantly decreased \((P=.03)\). Patients who ranked slight or greater on the THI/TSS before intervention showed a significant decrease in the severity of their tinnitus at post-testing \((P=.008)\).

**Conclusion:** The results suggest that magnesium may have a beneficial effect on perception of tinnitus-related handicap when scored with the THI.

**Keywords:** Magnesium; Tinnitus; Tinnitus Distress Rating; Tinnitus Handicap Inventory; Tinnitus Severity Scale
Abbreviations

RDA: Recommended Daily Allowance
TDR: Tinnitus Distress Rating
THI: Tinnitus Handicap Inventory
TSS: Tinnitus Severity Scale
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Figure 1. Tinnitus Distress Rating scale.

Figure 2. The Tinnitus Handicap Inventory is a 25-item self-report questionnaire that the patient can complete in about 10 minutes. Answers receive a score of 4 for Yes, 2 for Sometimes, and 0 for No. The Tinnitus Severity Scale (Table 1) is then used to apply a grade to the score.

Figure 3. Change in tinnitus rating in 26 patients from baseline to 3 months after treatment with magnesium.
**Introduction**

Descriptions of tinnitus date back to the time of ancient Egypt, yet science has failed to unravel the mysterious underlying mechanisms that produce these subjective auditory perceptions of sound. Tinnitus is the perception of sound without an external source, and almost 30 million Americans are estimated to be afflicted with tinnitus.\(^1\) For most however, the problem is not as severe enough for them to seek treatment.

Tinnitus is a sensation that patients prefer not to experience, and for most the problem is not fully disabling. Tinnitus is common, affecting 30% of people older than age 55, with an annual incidence of 5%. Disturbing tinnitus does occur in 3% to 5% of individuals with tinnitus.\(^2\) Until recently, treatments available have been limited, yet these new treatments do not provide a total cure for the affliction. The traditional recommendation instructing the patient to “learn to live with it,” has now changed due to significant advances in auditory neuroscience.\(^1\)

These perceptions may be manifestations of damage resulting from noise exposure, ototoxicity, or other abnormal conditions of the auditory system. However, many individuals have idiopathic tinnitus for which no specific cause can be determined. Although often
presenting in conjunction with hearing loss, the magnitude of hearing loss does not necessarily correspond with the severity of tinnitus. In addition, some individuals reporting tinnitus experience concomitant hyperacusis. This relationship suggests these processes may be linked by underlying imbalances at the level of the hair cell. The possible influence of magnesium and its antagonist, calcium, has been discussed in the literature as a contributing factor in the mitigation of noise-induced hearing loss, ototoxicity, and the hyperexcitability of the auditory system. Permanent and temporary changes in auditory function have been linked to nutritional deficiencies of magnesium. Magnesium deficiency has resulted in increased susceptibility to noise-induced hearing loss, ototoxicity, and hyperexcitability of the auditory system.

The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/kg; however, all age groups of Americans fall short of the RDA for magnesium by 100 mg daily. This lack of appropriate magnesium intake may have negative consequences. For example, the putative magnesium mechanism within the auditory system involves a metabolic cellular cascade of events. Specifically, magnesium deficiency leads to increased permeability of the calcium channel in the hair cells with a consequent over-influx of calcium, an increased release of glutamate via exocytosis, and overstimulation of N-methyl-D-aspartate receptors on the auditory nerve fibers. Recent studies of
both noise-induced hearing loss and idiopathic sensorineural hearing loss have suggested that magnesium supplementation may lessen the severity of tinnitus in patients. Magnesium improved hearing recovery and lessened tinnitus in patients with idiopathic sudden hearing loss. More recently, Nageris showed in a well-controlled study that magnesium was a relatively safe and convenient adjunct to corticosteroid treatment for enhancing the improvements of hearing in acute-onset sensorineural hearing loss at a dose of 4 g. The protective effect of magnesium in noise-induced hearing loss has been previously reported. 

Despite these encouraging findings, no controlled study has examined the effect of magnesium supplementation for patients with moderate to severe tinnitus. Additionally, no study to date has examined self-reported tinnitus severity before and after magnesium supplementation. The purpose of this study was to examine any potential lessening of the severity of tinnitus in patients receiving magnesium supplementation.
Methods

Patients aged 18 years or older who were seen for an audiological evaluation at Mayo Clinic in Scottsdale, Arizona, and who had a Tinnitus Distress Rating (TDR) scale score from 3 through 8 (Figure 1) were eligible for the study. The TDR was adapted from an existing pain scale, with the subject rating him- or herself between 0 (no tinnitus) to 10 (worst possible tinnitus). The Tinnitus Handicap Inventory (THI) and Tinnitus Severity Scale (TSS) (Table 1), developed by McCombe et al (2001), were used to grade the severity of each subject’s tinnitus before enrollment in the study and at the end of the study (Figure 2). The THI scores were converted to the grades of the TSS for the purpose of categorizing the numeric values of the THI into a reliable 5-item grading scheme.

Individuals with decreased kidney function within the preceding 3 months (creatinine level >2.2 mg/dL for women and >2.6 mg/dL for men) were excluded from the study (these criterion values are twice the normal creatinine levels according to the Mayo Clinic Arizona laboratory). A review by the Division of Cardiovascular Diseases indicated that daily magnesium supplementation at the level of 532 mg was benign for heart patients whose kidney function was normal. A review by the Mayo Pharmacy indicated that there were no major drug interactions with magnesium at the levels of the current protocol
Figure 1. Tinnitus Distress Rating scale.
**Figure 2.** The Tinnitus Handicap Inventory (THI) is a 25-item self-report questionnaire that the patient can complete in about 10 minutes. Answers receive a score of 4 for Yes, 2 for Sometimes, and 0 for No. The Tinnitus Severity Scale (Table 1) is then used to apply a grade to the score.
<table>
<thead>
<tr>
<th>Score b</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16</td>
<td>Slight</td>
<td>Only heard in a quiet environment, very easily masked. No interference with sleep or daily activities.</td>
</tr>
<tr>
<td>18-36</td>
<td>Mild</td>
<td>Easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities.</td>
</tr>
<tr>
<td>38-56</td>
<td>Moderate</td>
<td>May be noticed, even in the presence of background or environmental noise, although daily activities may still be performed. Less noticeable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>when concentrating. Not infrequently interferes with sleep and quiet activities.</td>
</tr>
<tr>
<td>58-76</td>
<td>Severe</td>
<td>Almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quiet activities affected adversely. Hearing loss is likely to be present, but its presence is not essential.</td>
</tr>
<tr>
<td>Score</td>
<td>Category</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>78-100</td>
<td>Catastrophic</td>
<td>All tinnitus symptoms at level of severe or worse. Should be documented evidence of medical consultation. Hearing loss is likely to be present, but its presence is not essential. Associated psychological problems are likely to be found in hospital or general practitioner records.</td>
</tr>
</tbody>
</table>

- a Data categorized and developed by McCombe et al (2001).
- b Scores derived from the Tinnitus Handicap Inventory
Participants were given a daily magnesium supplement, 532 mg (Mg Plus Protein, 133-mg tablets; Miller Pharmacal Group, Carol Stream, Illinois). After beginning magnesium supplementation, the participants rated themselves daily for 3 months using the TDR. Differences in TDR scores before and after supplementation were compared to determine any effect of supplementation on a participant’s self-rated tinnitus. In addition, all participants completed another THI after 3 months of magnesium supplementation.

The present study received Mayo Clinic Institutional Review Board approval. The data collected for each participant included informed consent, sex, date of birth, hearing threshold at 8 frequencies (250, 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz), weekly diaries of daily TDR ratings of tinnitus, THI questionnaires at baseline and the end of the study, dates of first and last dose of magnesium, number of tablets used, reason for discontinuation, and adverse events. The adverse event data included the date of onset and whether the adverse event led to premature discontinuation of the intervention.

The primary outcome measures were comparisons of TDR scale scores and THI scores as converted to TSS grades at baseline and the end of the study. Patients were included in the primary analysis on the basis of intention to treat. The THI was measured at the time of discontinuation if a patient discontinued the study before 3 months.
The mean hearing thresholds and mean TDR scores before and after treatment were assessed using a paired t test. The effect of magnesium on THI scores/TSS grades was evaluated using a McNemar test. Differences were considered statistically significant if \( P < .05 \).

**Results**

The study comprised 26 eligible and consenting participants. Of these, 2 patients (8%) discontinued the study because of adverse events and subsequently had no follow-up data. Adverse events reported were constipation, syncope, and nausea. Five patients (19%) discontinued for other reasons (lost to follow-up). Thus, 19 patients had complete follow-up data to analyze. The 7 patients who lacked follow-up were used for the intention-to-treat analysis. The mean (SD) follow-up time was 2.74 (0.24) months (range, 2.50-3.42 months). The mean age was 62 years (range, 30-76 years). Ten of 26 participants (37%) were women. There was no significant change in hearing thresholds from 250 Hz through 8,000 Hz for either ear during the duration of the study (Table 2). There was a significant decrease in the severity of tinnitus for subjects on the basis of their THI responses \( (P = .03) \). Those patients whose THI scores translated to “slight” or greater grade on the TSS before the intervention showed a significant decrease in the
# Table 2. Hearing Threshold and Tinnitus Handicap Inventory Results

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Baseline</th>
<th>Post-Mg</th>
<th>Difference</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Hearing Threshold, dB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Right ear</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>23.65 (18.52)</td>
<td>24.04 (18.11)</td>
<td>−0.38 (6.92)</td>
<td>−3.18 to 2.41</td>
<td>.78</td>
</tr>
<tr>
<td>500</td>
<td>25.19 (19.05)</td>
<td>25.58 (20.22)</td>
<td>−0.38 (4.22)</td>
<td>−2.09 to 1.32</td>
<td>.65</td>
</tr>
<tr>
<td>1,000</td>
<td>25.38 (21.63)</td>
<td>26.35 (22.16)</td>
<td>−0.96 (4.48)</td>
<td>−2.77 to 0.85</td>
<td>.28</td>
</tr>
<tr>
<td>2,000</td>
<td>30.19 (23.39)</td>
<td>30.00 (21.07)</td>
<td>0.19 (5.00)</td>
<td>−1.83 to 2.21</td>
<td>.85</td>
</tr>
<tr>
<td>3,000</td>
<td>41.15 (23.97)</td>
<td>41.15 (23.85)</td>
<td>0.00 (3.46)</td>
<td>−1.40 to 1.40</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>4,000</td>
<td>48.46 (24.69)</td>
<td>49.04 (24.78)</td>
<td>−0.58 (3.26)</td>
<td>−1.90 to 0.74</td>
<td>.38</td>
</tr>
<tr>
<td>6,000</td>
<td>53.27 (23.79)</td>
<td>53.27 (22.71)</td>
<td>0.00 (4.00)</td>
<td>−1.62 to 1.62</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>8,000</td>
<td>57.50 (23.16)</td>
<td>58.65 (23.39)</td>
<td>−1.15 (5.53)</td>
<td>−3.39 to 1.08</td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td><strong>Left ear</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>21.92 (18.92)</td>
<td>20.96 (18.55)</td>
<td>0.96 (6.48)</td>
<td>−1.66 to 3.58</td>
<td>.46</td>
</tr>
<tr>
<td>500</td>
<td>24.81 (18.95)</td>
<td>24.81 (17.63)</td>
<td>0.00 (4.24)</td>
<td>−1.71 to 1.71</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>1,000</td>
<td>25.00 (17.78)</td>
<td>24.81 (17.92)</td>
<td>0.19 (4.58)</td>
<td>−1.66 to 2.04</td>
<td>.83</td>
</tr>
<tr>
<td>2,000</td>
<td>30.38 (19.49)</td>
<td>31.54 (19.74)</td>
<td>−1.15 (6.83)</td>
<td>−3.91 to 1.60</td>
<td>.40</td>
</tr>
</tbody>
</table>
### Table 2 (continued)

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Mean (SD) Hearing Threshold, dB</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Post-Mg</strong></td>
<td><strong>Difference</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>3,000</td>
<td>46.92 (22.54)</td>
<td>47.12 (23.63)</td>
<td>−0.19 (7.93)</td>
</tr>
<tr>
<td>4,000</td>
<td>54.04 (22.98)</td>
<td>55.00 (23.62)</td>
<td>−0.96 (6.17)</td>
</tr>
<tr>
<td>6,000</td>
<td>56.73 (25.22)</td>
<td>56.92 (24.98)</td>
<td>−0.19 (4.35)</td>
</tr>
<tr>
<td>8,000</td>
<td>57.88 (26.99)</td>
<td>59.42 (24.47)</td>
<td>−1.54 (5.96)</td>
</tr>
<tr>
<td><strong>Tinnitus Handicap Inventory</strong></td>
<td>34.77 (21.74)</td>
<td>28.69 (24.88)</td>
<td>6.08 (13.89)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Post-mg, after magnesium supplementation; SD, standard deviation.

<sup>a n=26.</sup>
severity of their tinnitus ($P=.008$) (Table 3). Table 4 illustrates a significant decrease in participants’ rating of tinnitus on the TDR at 1 month ($P=.049$), 2 months ($P=.04$), and 3 months of supplementation ($P=.045$). Figure 3 graphically represents the change in TDR in 26 patients from baseline to 3 months after treatment with magnesium. Before magnesium supplementation, 22 of 26 patients (85%) had more than slight impairment on THI/TSS. After supplementation, by intention-to-treat analysis, 14 of 26 patients (54%) continued to have more than slight impairment; by analysis of patients who completed the study, only 7 of 19 patients (37%) had more than slight impairment.
Table 3. Differences in Tinnitus Severity Scale Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Baseline/Post-Mg</th>
<th>Baseline</th>
<th>Post-Mg</th>
<th>Δ</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y/Y N/Y Y/N N/N</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight b</td>
<td>14 0 8 4</td>
<td>22 (85)</td>
<td>14 (54)</td>
<td>0.31</td>
<td>−0.52 to −0.09</td>
<td>.008</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Post-Mg, after magnesium supplementation.

a N=26.

b As defined in Table 1.
Table 4. Tinnitus Distress Rating Scale<sup>a</sup>

<table>
<thead>
<tr>
<th>Self-report</th>
<th>Mean (SD)</th>
<th>Difference From Baseline (SD)</th>
<th>95% CI</th>
<th>P Value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.23 (1.82)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1 mo</td>
<td>5.93 (1.69)</td>
<td>0.30 (0.74)</td>
<td>0.00 to</td>
<td>.049</td>
</tr>
<tr>
<td>2 mo</td>
<td>5.85 (1.70)</td>
<td>0.38 (0.91)</td>
<td>0.02 to</td>
<td>.04</td>
</tr>
<tr>
<td>3 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.79 (1.83)</td>
<td>0.44 (1.07)</td>
<td>0.01 to</td>
<td>.045</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SD, standard deviation; TDR, Tinnitus Distress Rating.

<sup>a</sup> Based on intention-to-treat analysis. N=26.

<sup>b</sup> Five of 26 patients (19% [95% CI, 7%-39%]) had a decrease in TDR by at least 1 point from baseline; 1 of 26 (4% [95% CI, 0%-20%]) had an increase in TDR by 1 point.
Figure 3. Change in tinnitus rating in 26 patients from baseline to 3 months after treatment with magnesium.
Auditory deprivation from hearing loss induces central neural changes that result in tinnitus, with further mechanisms responsible for tinnitus involving peripheral triggers and central plasticity. Currently, treatment is not fully curative, however, sound therapy has been shown as an effective form of tinnitus treatment, and benefits most patients when combined with education and adjunct treatments directed toward factors that exacerbate tinnitus. Medications have emerged to be helpful for specific forms of tinnitus, but are not fully comprehensive in treatment. Clinicians knowledgeable in auditory function and head and neck physiology are well equipped to provide most tinnitus patients with effective treatment, including education, rehabilitation of hearing loss, and identification and treatment of exacerbating factors.  

Tinnitus can be classified as either objective or subjective. Objective tinnitus can be detected by an observer using a stethoscope or ear canal microphone. Objective tinnitus arises from vascular or muscular sources, and usually has a pulsatile quality. Many of these causes are uncommon and are not responsible for most instances of tinnitus. ¹ The significant majority of cases fall under the subjective category.²
In contrast to objective tinnitus, subjective tinnitus is not audible to an observer. This form is more common, with a 5-year incidence of 5.7%. Estimates of subjective tinnitus prevalence range from 8% to 30%, depending on the definition of tinnitus, tinnitus severity, the population sampled, and assessment methodology. In a large population-based study of participants 55 to 99 years old, combining detailed tinnitus questionnaires with audiologic assessment, 30% reported experiencing tinnitus, with prevalence related to audiometric threshold, but not age or gender. Mildly annoying tinnitus was reported in 50% of respondents, and extremely annoying tinnitus was reported in 16%. Tinnitus prevalence in individuals with normal hearing was 26.6% compared with 35.1% in individuals with hearing loss. An estimated 20% of individuals with profound hearing loss do not experience tinnitus. Chronic tinnitus is associated with, and may be triggered by, hearing loss, but they also indicate that hearing loss is not an invariable cause of tinnitus.

Idiopathic subjective tinnitus is the most common form of tinnitus affecting adults. In this case, objective causes have been ruled, such as conductive hearing loss, endolymphatic hydrops, and cerebellopontine angle neoplasms. The pathology underlying idiopathic tinnitus has historically been unknown, and the symptom has been generally viewed as refractory to intervention. Advances in tinnitus research have revealed mechanisms likely responsible, which include tinnitus-
associated pathology of the cochlea or head and neck, and tinnitus susceptible to somatic modulation. 1, 14

Subjective tinnitus can be subtyped based on etiology, the pattern of associated hearing loss, psychoacoustic features, exacerbating factors, psychological comorbidities, and the presence of somatic modulators. 16 Tinnitus subtype classification schemes can be useful in identifying forms of tinnitus that are responsive to specific targeted treatment programs. 1, 16

The two most common types of hearing loss associated with tinnitus are noise-induced hearing loss (NIHL) and presbycusis. NIHL is a significant and growing health problem. 1 Although reduction of exposure to occupational noise has been effective in the last several decades, there has been a notable increase in the incidence of NIHL from recreational and leisure activity in children and adolescents, and military combat–related noise exposure in young adults. Acute transient tinnitus is nearly universal immediately after unprotected exposure to loud acoustic stimuli such as gunfire and amplified music. 20, 21, 22

The prevalence of chronic tinnitus associated with NIHL ranges from 50% to 70%. 23 In a subjective arena, the sensory aspects of acute and chronic tinnitus can be very similar. Chronic tinnitus occurs over time for a significant portion of individuals with a history of exposure to
damaging sounds. It is less known if the pathology of transient acoustic trauma–induced tinnitus is the same as the pathology responsible for chronic tinnitus associated with permanent noise-induced threshold shifts. Chronic tinnitus induced by acoustic trauma occurs at a younger age than tinnitus associated with other types of hearing loss. Consequently, acoustic trauma–induced tinnitus is experienced for a longer portion of the life span than other forms of tinnitus. ¹

NIHL and the associated tinnitus can be preventable. In addition to undertaking proactive methods, such as wearing ear protective hardware, intervention in the periexposure period may prove useful in preventing the onset or progression of NIHL, and possibly the incidence of tinnitus. Intense sound exposure triggers a reduction of blood flow and a cascade of metabolic events in the cochlea, with formation of reactive oxygen and nitrogen species that damage cellular lipids, proteins, and DNA, culminating in increased cell death. ²⁴ Interventions targeting these molecular mechanisms of NIHL include antioxidant therapy such as vitamin E, salicylate, and N-acetylcysteine. ²⁵

In one study, serum magnesium levels have been correlated with NIHL in animals. ²⁶ Controlled studies in humans have shown the prophylactic efficacy of oral magnesium in preventing temporary and permanent NIHL. ²⁷ However, the literature does not explore whether
these interventions are also effective in decreasing the risk of immediate or delayed onset of tinnitus after traumatic injury.

Written accounts indicate medical treatment of tinnitus dates back to the Egyptians (2660-2160 BCE). Early treatments included infusion with oil, frankincense, tree sap, herbs, and soil. The consideration of ancillary psychological factors date back to the Mesopotamian writings. They considered the psychological aspects of tinnitus, possibly the earliest recognition that stress and emotional factors are significant components of tinnitus dysfunction. These early attempts at treatment contained elements that presage modern views of tinnitus pathology. 1, 28

Until more recently, most pharmacologic interventions for tinnitus were empirically determined. Most interventions were based on anecdotal experience and observations of tinnitus relief, which led to further exploration of treatment. Over the past 50 years, pharmacologic treatment of tinnitus has become more scientifically based. Anesthetics (lidocaine, tocainide, mexiletine), anticonvulsants (carbamazepine, gabapentin), and tranquilizers (diazepam, clonazepam, oxazepam) have been investigated as tinnitus treatments.1 These treatments help facilitate neural inhibition. Antidepressants such as trimipramine, nortriptyline, amitriptyline, and selective serotonin reuptake inhibitors have been tested for their ability to ameliorate the comorbid psychological aspects of tinnitus,
including mood disturbance. Considering only well-controlled trials, mixed results have been obtained for all drugs tested to date.

The hypothesis that tinnitus emerges from increased central neural activity after loss of inhibition can be used to guide pharmacologic intervention. Animal models of tinnitus support the loss of inhibition and enhanced neural activity hypothesis. The loss-of-inhibition hypothesis provides a rational basis for numerous pharmacologic interventions, including lidocaine, carbamazepine, alprazolam, and gabapentin.

Currently, the most extensively used pharmacological treatment for tinnitus is antidepressants. Treatment for tinnitus with antidepressants is based on two reasons. There is a well-recognized association between severe tinnitus and mood disorders. The pharmacologic mechanism of action of many antidepressants involves receptors and neurotransmitters that are located in the auditory pathway. Although GABA deficiency seems to contribute to tinnitus pathology, the role of other neurotransmitter systems in triggering or maintaining tinnitus is currently unknown. Serotonin is known to function as a modulator of sensory systems, learning, and memory. The results of the present study indicated that self-reported measures of tinnitus severity using the THI/TSS and the TDR improved significantly with magnesium supplementation over a 3-month period of intervention. In fact, significant improvement in the TDR occurred
as early as 1 month into the study, suggesting that benefit of magnesium supplementation occurred early in treatment and was sustained throughout the 3 months of the study. As illustrated in Figure 3, there was a greater reduction in tinnitus severity (based on THI/TSS results) for subjects who completed the full 3 months of supplementation compared with those who dropped out of the study before completion. For the subjects lost to follow-up, we assumed for the purposes of this analysis that there was no benefit from treatment. These participants were included because if noncompleters doing poorly enough to drop out were not analyzed, then selection bias would be likely. Therefore, subjects with no follow-up were treated as though they had no improvement and were included in the analysis. However, the noncompleters had a significant improvement on the THI/TSS, suggesting a benefit of magnesium in the reduction of severity of tinnitus. The current design, however, cannot distinguish a treatment effect from a placebo effect or regression to the mean. Based on the results of the present study, an investigation using a placebo and double-blinding would be important to control for factors unrelated to the magnesium supplementation itself that may have influenced the results.
Conclusion/Future Directions

The present study indicated that subjects showed significant improvement in their self-rating of tinnitus with a magnesium supplement of 532 mg daily for 3 months. Further investigations should control for the placebo effect.
References


