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Review of Pharmacological Therapy for Tinnitus

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Abstract: This article provides a review of studies investigating the pharmacological treatment of tinnitus. Tinnitus continues to be a significant and costly health problem without a uniformly accepted treatment. A wide variety of studies exploring prescription, supplement, and vitamin therapies are assessed for efficacy of treatment and for establishing consistencies in symptom definition, assessment, and outcome measures. This review reveals no compelling evidence suggesting the efficacy of any pharmacological agent in the treatment of tinnitus. Analysis of prior investigations provides insight to appropriate methods for future work, which are outlined.

Key Words: medication; nutritional supplements; pharmacotherapy; tinnitus; treatment

Tinnitus remains a major chronic health condition in developed countries. It is reported to occur in up to 30% of individuals in those nations, with 10–15% of individuals experiencing symptoms significant enough to require medical attention [1]. Of the 342,903 US veterans receiving disability pensions in 2004, 84% received payment for a tinnitus disability. In that year, it was the third most prevalent disability among veterans, after hearing loss and generalized musculoskeletal disability. Auditory disabilities taken together resulted in more than $1 billion of payment by the US Department of Veterans Affairs in fiscal year 2004 alone [2]. Accessible, efficient, and effective treatment for this potentially disabling symptom remains elusive.

No universally accepted classification or treatment of tinnitus exists. The symptom itself is highly variable and often difficult for patients to describe. In addition, its presence in isolation or in the setting of specific disease entities, such as hearing loss, Ménière's disease, or trauma, is inconsistent. Therefore, therapy tends to be individualized and can range from placebo to surgery, with a multitude of options found between. Finally, consensus on accepted outcomes for treatment is lacking, owing to the subjective nature of tinnitus. All these issues lay the foundation for a heterogeneous body of literature on the topic that is largely devoid of compelling evidence for any particular treatment protocol.

Though success rates of 80% tinnitus control are reported with such treatment modalities as biofeedback [3] and tinnitus retraining therapy [4], these modalities of therapy are time consuming for providers and patients alike. Further, they are extremely resource-intensive and require specialized training. As a result, despite their efficacy, widespread use for such a common problem is unlikely and economically unfeasible. Thus, the potential for a safe and effective oral pharmacological intervention has the hope of offering widely accessible and acceptable treatment for tinnitus patients. This form of therapy can be self-administered and self-monitored, reducing the impact on medical resources for treatment. Additionally, such therapy may also benefit by reducing the causes of tinnitus and not just providing symptomatic relief.

In 1992, Murai et al. [5] performed the last dedicated review of pharmacological treatment of tinnitus. Since then, Dobie [6] reviewed well-controlled, randomized clinical trials for all treatments of tinnitus. Most recently, Seidman and Babu [7] reviewed the role of alternative nutritional and medicinal treatment. Although not establishing consensus, these studies identified some agents with promise, but the lack of uniform symptom definitions, outcome measures, and statistical power of the studies reviewed renders interpreting these conclusions

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challenging. Further complicating matters is that large-scale, well-controlled clinical trials of pharmacological agents are expensive and time consuming if conducted properly. Much of the available clinical data, therefore, comes from small studies with significant design flaws.

Until recently, the lack of animal models for tinnitus has further limited our ability to define the role of pharmacological agents in preparation for clinical study. Currently, no drug exists with an indication for tinnitus, though several are used "off-label," and side effects can be an issue that limits compliance. In comparison, multiple nutritional supplements are sold individually or in combination with claims of tinnitus relief. Though these claims may be based on some science, their marketing and manufacturing is minimally regulated, with side effects and drug interactions poorly characterized. Thus, the pharmacological treatment of tinnitus remains a realm of pseudoscience and supplements.

As a result, our objectives here are to review the basic and clinical science evidence for the pharmacological treatment of tinnitus, to assess for consensus on symptom definition and outcome reporting, and to chart a course for future efforts.

MATERIALS AND METHODS

We searched MEDLINE (1966–2005) for English-language studies combining the word *tinnitus* with the term *medical treatment*, *pharmacologic*, or *pharmacological*. We excluded studies not focused on tinnitus, nonpharmacological articles, and studies addressing a particular neurootological disease. Of the 59 results remaining, primary focus was given to summarizing developments since previous reviews [5–7]. We supplemented sources by personal files and cross-referenced articles of the primary search. We reviewed studies for basic and clinical science evidence for the pathophysiology and treatment of tinnitus, symptom definition, outcome measure, statistical power, and potential for future research.

We considered evidence in light of study type, design, clarity, and applicability of findings. Heller [1] reviewed classification systems of tinnitus, although none are universally used. Therefore, we reviewed studies in our effort for their inclusion of the symptom location, character, loudness, pitch, impact on daily life, association with hearing loss or other neurootological disease, and verification with such measures as audiometry, pitch matching, loudness matching, and masking level. We also gave attention to the presence of specific, defined outcome measures, including changes in audiometric tests or quality-of-life measures, such as the tinnitus handicap inventory (THI) [8].

RESULTS

Pharmacological Agents Commonly Used for Tinnitus

Antidepressants

Tricyclic antidepressants decrease presynaptic reuptake of norepinephrine and serotonin, whereas selective serotonin reuptake inhibitors (SSRIs) decrease reuptake of serotonin only. Although the anticholinergic, antihistaminic, and adrenergic activities of tricyclic antidepressants are postulated to play a role in the mitigation of tinnitus [9], no basic science studies have demonstrated a plausible biological mechanism.

The results of clinical studies on antidepressants in the treatment of tinnitus are summarized in Table 1. In a small study, trimipramine failed to demonstrate any subjective or audiometric benefit over placebo [9]. A trial of nortriptyline demonstrated statistically significant subjective and objective improvements within both treatment and placebo groups but essentially no differences between groups [10]. However, a follow-up study from the same trial (and apparently the same data set) demonstrated a statistically significant decrease in tinnitus-related disability via the multidimensional pain inventory (MPI) tinnitus interference questionnaire and in tinnitus loudness via audiometric matching at the frequency of tinnitus as compared with placebo [11]. Both studies highlighted the effectiveness of nortriptyline treatment of the depression associated with the tinnitus. Compared to placebo, amitriptyline demonstrated a statistically significant decrease in a subjective measure of tinnitus intensity in a single-blind prospective trial [12]. However, comparisons were made before and after treatment within groups but not between groups. A retrospective look at SSRI use in patients with tinnitus reported a statistically significant improvement on a tinnitus severity index over time in 23 of 30 patients [13]. However, no control group was included, nor was mention made of when patients began SSRI use relative to their initial tinnitus severity index score.

Symptom definition in these studies was highly variable. No standard approach to describing central, peripheral, or mixed tinnitus; severity; duration; frequency; or impact on quality of life is evident. A wide variety of subjective questionnaires was used. Audiometric analysis was more consistent and typically involved pure-tone thresholds, speech discrimination, uncomfortable loudness levels, and tinnitus frequency and intensity matching. Outcomes measures were heterogeneous. Subjective outcomes ranged from a simple yes or no response to the question, "Has your tinnitus improved?" [10] to longer multipart questionnaires, such as the Iowa Tinnitus Handicap Questionnaire [11]. Audiometric outcomes

Table 1. Studies of Antidepressants

Study	Study Design	Agent	No. of Subjects	Subject Characteristics	Outcome	Result
Mihail et al. [9]	Prospective, randomized, double-blind, placebo-controlled, crossover	Trimipramine	19	Subjective tinnitus, unilateral or bilateral, quality and duration, audiometry, otological disease ruled out	7-point scale, frequency matching, intensity matching, masking level	NS difference in all outcome measures
Dobie et al. [10]	Prospective, randomized, double-blind, placebo-controlled	Nortriptyline	92	Age 50–80 years, significant THQ score, no treatable disease, major depression, depressed symptoms, no other mental illness, audiometry	Tinnitus improved?	Active: 43% Placebo: 30%
					Loudness scale	Active[a]: 4.7 to 3.9* Placebo[a]: 4.5 to 3.4*
					Intensity matching	Active[a]: 15.7 to 10.8* Placebo[a]: 18.6 to 17.9[NS]
					Multiple questionnaires	NS difference between active and placebo on all tinnitus outcomes
Sullivan et al. [11]	Prospective, randomized, double-blind, placebo-controlled	Nortriptyline	92	Age 50–80 years, significant THQ score, no treatable disease, major depression, depressed symptoms, no other mental illness, audiometry	Hamilton depression	Active: 10.6 Placebo: 14.3*
					MPI tinnitus disability	Active: 1.8 Placebo: 2.4*
					Intensity matching	Active: 13.6 dB Placebo: 20.0 dB*
Bayar et al. [12]	Prospective, randomized, single-blind, placebo-controlled	Amitriptyline	37	Subjective tinnitus, no active Ménière's, no known cause of tinnitus, no depression, laterality noted, duration and character	10-point scale	For amitriptyline: AD 4.3 to 1.3* AS 4.4 to 1.8*
					Intensity matching	For amitriptyline: AD[a] 33.1 to 15.9* AS[a] 41.3 to 27.9* NS improvements in placebo group
Folmer & Shi [13]	Retrospective	SSRI	30	Not defined	Tinnitus severity index 10-point scale	42.0 to 36.5*[a] NS change

AD = right ear; AS = left ear; MPI = multidimensional pain inventory; NS = not statistically significant; SSRI = selective serotonin reuptake inhibitor; THQ = Tinnitus Handicap Questionnaire.
* Statistically significant.
[a] Numerical ranges in the Result column represent pretreatment to posttreatment values.

tended to focus on tinnitus frequency and intensity matching. No discussion of statistical power was mentioned in any study, and studies involved between 19 and 92 subjects.

GABA-Active Drugs

γ-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter of the central nervous system, and its formation is catalyzed by glutamic acid decarboxylase (GAD). Decreased GABA activity is postulated as a potential causative factor for tinnitus that results from abnormal activation of central nervous system auditory pathways. The inferior colliculus projects auditory information via the ventral medial geniculate body of the thalamus in the classic auditory pathway. However, projections also occur via the dorsal and medial thalamic nuclei via the nonclassic pathway that subsequently projects to the amygdala and association cortices. This nonclassic pathway receives somatosensory input, which may be abnormally redirected to auditory regions of the central nervous system and perceived as tinnitus [14]. Salicylate toxicity, a known cause of reversible tinnitus in humans, also results in GAD upregulation and increased GABA receptor affinity in the inferior colliculus of rats [15]. GABA inhibition at the level of the inferior colliculus in rats is also associated with development of audiogenic seizures [16]. In an analysis of inferior colliculus hyperexcitability, various GABAergic agents were found to have very different effects on modulating evoked potentials, suggesting agonist-receptor variability with potential clinical implications for treatment. In other words, not all GABA-active agents may produce similar effects on tinnitus. Finally, single-photon emission computed tomography (SPECT) imaging has suggested a loss of GABA inhibition in the amygdala-hippocampus formation in humans with tinnitus [17].

The results of clinical studies of GABA receptor–binding pharmacological agents are presented in Table 2. Alprazolam, a drug that potentiates GABA activity at GABA-A receptors, was found to decrease both subjective loudness and intensity matching of tinnitus in a double-blind, placebo-controlled, prospective study [18]. No statistical comparison was made between treatment and placebo groups, only within those groups. The study lacked details of patient selection, crossover of treatment and placebo groups, and a discussion of the potential impact of drowsiness, caused by the sedating action of alprazolam, on loss of blinding. Baclofen (Lioresal), a GABA analog with binding to the GABA-B receptor, was found to be no more effective than placebo in a double-blind, placebo-controlled, prospective trial [19]. The study did demonstrate a statistically significant improvement on the THI within the treatment group, but this was not considered clinically significant,

Table 2. Studies of GABA-Active Drugs

Study	Study Design	Agent	No. of Subjects	Subject Characteristics	Outcome	Result
Johnson et al. [18]	Prospective, randomized, double-blind, placebo-controlled	Alprazolam	40	Constant tinnitus >1 year's duration, no Ménière's, Tinnitus Data Registry, audiometry	10-point scale	NS improvements in placebo group
					Intensity matching	For alprazolam: 7.0 to 5.5[*a]
						For alprazolam: 7.1 to 3.5[*a]
Westerberg et al. [19]	Prospective, randomized, double-blind, placebo-controlled	Baclofen	63	Constant tinnitus, nonpulsatile, no active Ménière's, no other treatment, audiometry	10-point scale, loudness match, pitch match, maskability	Essentially NS differences in all measures between groups
					THI	Within baclofen group, THI 47.4 to 42.9*
Shulman et al. [20]	Prospective	Gabapentin, clonazepam	30	Central, severe tinnitus, confirmed by SPECT, anxiety and/or depression	7-point intensity	2.4 improvement*
					7-point annoyance	2.8 improvement*
					THI	Not reported
					Improved yes/no?	19/21 yes (90%)
					Improved perfusion by SPECT imaging	10/10 yes (100%)

NS = not statistically significant; SPECT = single-photon emission computed tomography; THI = tinnitus handicap inventory.
* Statistically significant.
[a] Numerical ranges in the Result column represent pretreatment to posttreatment values.

and treatment was associated with significant side effects leading to withdrawal from the study by 26% of participants. A prospective study reported 90% improvement in those completing treatment with combined gabapentin and clonazepam in a select group of patients with severe, disabling tinnitus verified by decreased perfusion on SPECT imaging of the amygdala-hippocampus region [20]. However, improvement was defined on subjective analog scales from 0 to 7, no control or placebo was used, and the 30% of patients who dropped out of the study for various reasons were not included in analysis.

No consistent symptom definition was identified in these studies, and all populations were essentially convenience samples from clinics or databases. Subjective outcomes measures ranged from yes or no responses on tinnitus improvement, to visual analog scales, to the 25-question THI. The Lioresal trial used loudness matching, pitch matching, and maskability as audiometric outcomes. The gabapentin and clonazepam trial used SPECT imaging with ^{99}Tc-HMPAO to identify increased perfusion in the medial temporal lobe system as evidence of treatment success. Statistical power was specifically mentioned in the Lioresal trial, as 90 patients were calculated as the minimum number necessary to afford a power of 80% to detect a clinically significant difference between treatment groups. The final enrollment in the trial was 63. The population in the three studies ranged from 40 to 63 subjects.

Prostaglandins

Prostaglandin synthesis has been demonstrated in the cochlea [21]. In guinea pigs, a model of prostaglandin activity suggested that prostaglandins may act as neuromodulators of cochlear afferent transmission [22].

Studies addressing the use of misoprostol in the treatment of tinnitus are summarized in Table 3. The first demonstrated a subjective report of 33% response to active treatment as compared to 0% with placebo treatment and showed that responders to medication had statistically significantly decreased subjective rating-scale scores of tinnitus after 16 days of treatment, as compared to the scores of nonresponders [23]. Although audiometric data were recorded, results were not included. No statistical comparison was made between active and placebo groups. The other two studies were prospective, double-blind, placebo-controlled trials by the same authors in different patient populations with similar results. The studies found a statistically significant decrease in loudness matching and a statistically insignificant decrease in subjective rating of tinnitus in patients with hypertension or diabetes mellitus (or both) [24] or the absence of systemic or other known otological disease [25].

The first study had essentially no symptom definition

Table 3. Studies of Prostaglandins: Misoprostol

Study	Study Design	Agent	No. of Subjects	Subject Characteristics	Outcome	Result
Briner et al. [23]	Prospective, randomized, single-blind, placebo-controlled, semi-crossover	Misoprostol	24	"Severe" tinnitus	Improved yes/no? 10-point scale	Active: 33% yes Placebo: 0% yes Difference between responders and nonresponders between days 16–20 (2.7) and days 21–25 (2.58)*
Akkuzu et al. [24]	Prospective, randomized, double-blind, placebo-controlled	Misoprostol	42	Subjective tinnitus >6 months' duration, HTN and/or DM, audiometry	10-point scale Loudness matching	NS difference 13 (46%) in active vs 2 (14%) in placebo with 15 dB or greater improvement*
Yilmaz et al. [25]	Prospective, randomized, double-blind, placebo-controlled	Misoprostol	40	Subjective tinnitus >6 months' duration, no systemic disease, no known cause of tinnitus, audiometry	10-point scale Loudness matching	NS difference 18 (64%) in active vs 4 (36%) in placebo with 15 dB or greater improvement*

DM = diabetes mellitus; HTN = hypertension; NS = not statistically significant.
* Statistically significant.

[23], whereas the most recent two were limited to subjective tinnitus of greater than 6 months' duration with fairly specific inclusion and exclusion criteria. Subjective outcome measures were limited to yes or no improvement replies and visual analog scales, without any tools to measure impact of tinnitus on functioning. Audiometric outcomes in the most recent trials included tinnitus frequency and intensity matching. Statistical power was alluded to in all trials, though not formally discussed, and was the subject of a critique on the study of prostaglandins in tinnitus [26]. Enrollment ranged from 24 to 42 subjects.

Other Pharmacological Agents

Several other drugs, including the anticonvulsants carbamazepine and lamotrigine; the vasodilator cyclandelate; the smooth-muscle relaxant Caroverine; tocainide; and melatonin, have been reviewed previously without clear evidence of significant treatment benefit that outweighs potential risks [6]. Intravenous lidocaine is not reviewed because of its transient effect. More recently, the anticoagulant sodium enoxaparin was compared to combination therapy of corticosteroids, vasoactive agents, multivitamins, and anticoagulants, with a reported abatement of tinnitus symptoms [27]. However, the study did not include any statistical analysis comparing groups, offered no placebo, had a total of 20 subjects in each group, and was not blinded. A recent novel study compared subcutaneous periauricular injections of botulinum toxin A with placebo in a double-blind, prospective, crossover, randomized, controlled trial and reported significant differences between groups along with a significant decrease in THI scores between pretreatment and 4-month post–botulinum toxin A therapy [28]. The study identified having limited power, with a total of 26 subjects completing injections and follow-up, and the differences in groups incorporated those improved, those worsened, and those unchanged, without specifically addressing the statistical difference in improvement alone.

Nutritional Supplements Commonly Used in Treating Tinnitus

B Vitamins

The evidence linking various vitamin B deficiencies and treatments with tinnitus are largely anecdotal [7]. In a double-blind, placebo-controlled, prospective trial of 48 patients treated with nicotinamide (vitamin B_3), results were no better than those from placebo [29]. A statistically significant increased incidence of vitamin B_{12} deficiency was identified in patients with chronic tinnitus and noise-induced hearing loss (NIHL) as compared with NIHL and normal subjects, with reported improved symptoms after replacement therapy [30]. However, this study was not designed to measure treatment effects.

Zinc

Zinc is an essential nutrient that can influence neurotransmission and is present in highest concentration in the human cochlea [31]. The reported incidence of zinc deficiency in patients with tinnitus is inconsistent, with some reporting a positive correlation [31–35] and others finding no relationship [36,37]. No substantial basic science evidence demonstrates the role of zinc in the pathogenesis or treatment of tinnitus.

The clinical trials of the use of zinc in tinnitus are summarized in Table 4. Two prospective, placebo-controlled studies found conflicting results. The first reported no significant difference between Zn^{2+}, 22 mg three times daily, and placebo [37]. However, a more recent study reported a statistically significant improvement in subjective rating of tinnitus both within the Zn^{2+} 50-mg daily treatment group and in comparison with placebo [35]. Unclear was whether this trial was blinded; 9 of the original sample of 50 patients dropped out and were not included in data analysis; and no significant change in loudness matching was found. Two additional, nonplacebo-controlled studies investigated the incidence of zinc deficiency in patients with tinnitus along with the potential for improvement with zinc replacement. The first study reported a significantly increased incidence of zinc deficiency in tinnitus as compared with healthy controls and a significant decrease on a subjective rating scale with Zn^{2+} 34–68 mg daily over 2 weeks [32]. The second study found no strong relationship of zinc deficiency and tinnitus and failed to demonstrate significant improvement with Zn^{2+} 220 mg daily for 2 months, although a trend toward improved symptoms in elderly patients with hearing loss was noticed [36]. In those with normal hearing, zinc deficiency may play a role in the development of tinnitus, and zinc supplementation may be helpful in those cases [33,37].

The two placebo-controlled trials of zinc were noticeably thorough with symptom definition, including laterality, constant versus intermittent, quality, pitch, association with disease process, and association with audiometric data. All studies used an analog subjective tinnitus rating scale—either from 0 to 7 or from 0 to 10—as the main outcome measure, with one trial [35] using loudness matching as an additional outcome measure. No discussion of statistical power was mentioned in any study, and enrollment ranged from 40 to 96 subjects.

Ginkgo biloba

EGB761 is the most common isolate of *Ginkgo biloba*, one of the most ancient medicinal plants recently reported to increase body circulation and having benefits

Table 4. Studies of Zinc

Study	Study Design	Agent	No. of Subjects	Subject Characteristics	Outcome	Result
Paaske et al. [37]	Prospective, randomized, double-blind, placebo-controlled	Zinc	48	Tinnitus needing treatment, unilateral or bilateral, duration and quality, functional impact, audiometry	10-point scale	NS difference
Ochi et al. [33]	Prospective, healthy controls	Zinc	96	No prior treatment, no known cause of tinnitus	10-point scale	Decrease after treatment*; decreased zinc levels in tinnitus subjects as compared to controls*
Yetiser et al. [36]	Prospective	Zinc	40	"Severe" tinnitus, multiple origins (presbycusis, trauma, ototoxicity)	Subjective scale, THQ, frequency matching, intensity matching	NS increased incidence of low zinc levels; NS benefit on any outcome measure
Arda et al. [35]	Prospective, randomized, placebo-controlled	Zinc	41	No known cause of tinnitus, unilateral or bilateral, duration and quality, audiometry	7-point questionnaire	For zinc[a]: 5.25 to 2.82* For placebo[a]: 5.15 to 4.23 NS Zinc vs placebo*
					Intensity matching	NS

NS = not statistically significant; THQ = Tinnitus Handicap Questionnaire.
* Statistically significant.
[a] Numerical ranges in the Result column represent pretreatment to posttreatment values.

for vascular insufficiency and cognitive function [7]. Improvement in blood circulation to the organ of Corti has been suggested as a mechanism for ameliorating tinnitus [38]. In a rodent model, EGB761 resulted in a statistically significant decrease in the behavioral manifestation of tinnitus induced by sodium salicylate toxicity at a dose as low as 25 mg/kg/day [39].

The clinical trials of *Ginkgo biloba* use for treating tinnitus are summarized in Table 5. One trial demonstrated a statistically significant decrease in tinnitus loudness matching as compared with results from placebo [40]. The statistical significance was recorded as $p < .05$ one-tailed, yet the reason for using a one-tailed analysis or whether significance would be maintained with a two-tailed analysis remains unclear. In addition, all participants started the trial with 10 days of intravenous *Ginkgo biloba* treatment before being randomly assigned to oral therapy versus placebo. Finally, only 22 of 60 patients completed all phases of evaluation, although all subjects were analyzed on an intention-to-treat basis. The remaining trials showed no benefit as compared to placebo, and each had unique features that merit review.

To isolate subjects likely to respond to treatment, one study [38] started with an open trial of 80 patients, all of whom received treatment. Only those who reported some improvement (n = 21) were invited into a randomized, placebo-controlled, crossover study. Even with this selection, no significant improvement on subjective scores of tinnitus was found as compared to results from placebo. A subsequent trial used a different preparation of *Ginkgo biloba*, LI 1370, at a dose of 150 mg/day [41]. This was a large trial involving age, gender, and duration-of-symptoms matching analysis that revealed no differences in subjective rating scales of loudness, annoyance, and quality-of-life impact. However, this study was done completely by mail or phone, and no physical or audiometric evaluation was performed on patients. The most recent randomized, controlled trial showed no significant improvement with *Ginkgo biloba* by itself and also no benefit when considered in a meta-analysis along with other trials in the literature [42]. This is consistent with other reviews of *Ginkgo biloba* and tinnitus [43,44].

Overall symptom definition was vague in these studies, and no study presented a systematic method by which to identify significant otological disease as a cause of tinnitus. All studies used some kind of subjective analog rating scale as an outcome measure. The THI was used as a quality-of-life outcome in the most recent study [42], and a similar questionnaire was used in the largest study [41]. Audiometric loudness matching was a primary outcome measure in only one study [40]. Discussion of statistical power along with recruitment

Table 5. Studies of *Ginkgo biloba*

Study	Study Design	Agent	No. of Subjects	Subject Characteristics	Outcome	Result
Holgers et al. [38]	Open trial, then prospective, randomized, double-blind, placebo-controlled, crossover	*Ginkgo* EGB761	80 20	No definition	Visual analog scales: loudness, awareness, annoyance	21/80 (25%) responders NS benefit for responders during RCT on any outcome
Drew & Davies [41]	Prospective, randomized, double-blind, placebo-controlled	*Ginkgo* LI 1370	1121	Stable tinnitus >1 year's duration, no major illness, no other treatments, mail/telephone study, no physical evaluations	Visual analog scales: 6-point loudness, 5-point annoyance, 73-point questionnaire	NS difference in all outcome measures
Morgenstern & Biermann [40]	Prospective, randomized, double-blind, placebo-controlled	*Ginkgo*	60	Chronic tinnitus	Loudness matching	Decrease in volume at 4, 8, and 12 weeks ($p < .05$ one-tailed) for treatment vs placebo*
Rejali et al. [42]	Prospective, randomized, single-blind, placebo-controlled; meta-analysis	*Ginkgo*	66	Subjective tinnitus, no middle-ear disease, no outer-ear disease	THI, Glasgow Health-Status Inventory, hearing change	NS differences on RCT outcomes; meta-analysis with 21.6% benefit from active and 18.4% benefit from placebo NS

NS = not statistically significant; RCT = randomized clinical trial; THI = tinnitus handicap inventory.
* Statistically significant.

of adequate subjects was obtained in two studies [41,42], both reporting no effect of treatment. Enrollment ranged from 20 to 1,121 subjects. The doses used in the studies were substantially lower than those demonstrating benefit in the animal model.

CONCLUSIONS

Currently, no pharmacological agent is specifically indicated for tinnitus. Similarly, despite their widespread use and in the absence of compelling clinical evidence, none of the commonly advocated nutritional supplements are any more effective than is placebo in tinnitus control. Despite this lack of conclusive evidence, much can be gathered from the available research on the pharmacological management of tinnitus. Over the last decade, basic science models of tinnitus have been developed. These models have advanced our understanding of tinnitus as a central phenomenon and can be used to refine the exploration for effective pharmacotherapy.

Antidepressants likely have a role in the management of tinnitus concomitant with major depression or depressed symptoms and can help in ameliorating comorbidities in severe or chronic cases of tinnitus. In particular, the sedating tricyclic medications are useful in patients with insomnia. Other antidepressants, such as SSRIs, likely are similarly effective, although a placebo-controlled, prospective study of SSRI medications is needed.

GABA receptor–binding medications, such as benzodiazepines, appear to be reasonable candidates for tinnitus therapy, given the inhibitory role of GABA in the central nervous system. In particular, several animal studies suggested that changes in the GABA-A-receptor binding in the brainstem and inferior colliculus may be responsible for tinnitus, though the relationships are complex. The available clinical studies using benzodiazepines are of short duration and have limited patient numbers. Studies with larger power, longer follow-up, and consideration for potential dependency are needed. Benzodiazepines may prove to be counterproductive in the long run if suppression of neural plasticity is indeed something that will prevent reconditioning of nonclassic auditory pathways, as theorized in tinnitus retraining therapy [4]. Another GABA-active drug, baclofen, showed promise in a limited animal study, although the single clinical study with significant design limitations demonstrated no better efficacy than that of placebo. Currently, no clinical study has used gabapentin alone, though this seems a logical choice for chronic therapy, given its limited side-effect profile and lack of addiction potential.

Prostaglandins and other vasodilators have been studied clinically. Once again, these were small studies

of a mixed group of patients, having mixed results. Often the effects were limited by a high rate of side effects. In particular, the studies on misoprostol failed to show subjective improvements, and the clinical significance of decreased tinnitus loudness matching is doubtful. However, these studies were also underpowered and did not address quality-of-life outcomes that may be evident with treatment.

Of all the nutritional supplements, zinc has had the longest history and has been subjected to the most clinical study. The zinc studies have similar characteristics, although a trend toward helping elderly patients with zinc deficiency was identified [36]. Thus, though zinc deficiency can be a cause of tinnitus, zinc replacement in tinnitus sufferers with normal zinc levels is of little benefit. In tinnitus sufferers who have normal hearing, zinc may be of benefit. However, more standardized definition of zinc deficiency along with higher-powered studies are needed to address this potential treatment.

The results of studies on *Ginkgo biloba* as a whole tend to argue against any benefit for the treatment of tinnitus. Though a single basic science study demonstrated reduction in salicylate-induced tinnitus, it was for a single extract at relatively high doses (25–100 mg/kg/day). Clinical investigations, including a large number of subjects as well as meta-analysis, failed to show any benefit over placebo. However, a standard preparation was not used in all studies, and dosages varied widely. At best we can say that no benefit has accrued for the given dose and extract used in these studies. Again, there is room for a future well-designed, dose-dependent study.

The use of vitamin supplementation has also not demonstrated efficacy. No basic science studies support the use of any vitamin supplementation. Clinical studies are limited. Niacin (B_6) was shown in one study to be no better than placebo. Riboflavin (B_{12}) deficiency was demonstrated in sufferers with noise-induced hearing loss and tinnitus as compared to those without tinnitus. However, no clinical evidence supports supplementation. A wide variety of antioxidants have also been studied. Many have been shown to reduce noise-induced hearing loss in animal models, and the effects are both peripherally and centrally mediated [45]. Currently, no clinical studies demonstrate benefit for hearing loss or tinnitus. Though they may not prove useful in treating tinnitus, antioxidants may help to reduce the noise-induced injuries that precipitate tinnitus.

DISCUSSION

No evidence supports a specific treatment of subjective tinnitus. Given the lack of adequate basic science models, disparity in symptom definitions and outcome measures, and overall lack of power of past studies, it is also not possible to exclude most (if not all) of the reviewed treatments from future analysis.

The lack of strong animal models for tinnitus limits basic science research. Such models as conditioned lick suppression in the presence of sound [46] still rely on salicylate toxicity that may not accurately mimic the wide range of potential causes of tinnitus. Still, this seems the most practical approach at this time. An experiment using a behavioral avoidance task during sound was able to reduce false-positive avoidance (presumably caused by tinnitus) with the use of *N*-methyl-D-aspartate receptor-blocking agents that may play a role as local therapeutics [47].

A consistent approach to studying pharmacological agents in tinnitus is needed. Following are suggestions to enhance the validity and applicability of future efforts.

Symptom Definition

Given the likely wide range of potential causes of tinnitus, a thorough definition of the patient population must be established. Studies should include a table that offers information on age, gender, subjective versus objective tinnitus, laterality, constant versus intermittent, location (central versus cochlear), duration, hearing function, any known tinnitus causing disease, psychiatric illness, systemic illness, current medications for tinnitus, past medications for tinnitus, and baseline measures of the impact of tinnitus on quality of life. Such validated questionnaires as the THI [8] are recommended. Specific selection, inclusion, and exclusion criteria should be presented, and convenience samples should be avoided. Very likely, different treatments for tinnitus will emerge for different groups of patients on the basis of comorbid illness and tinnitus duration, severity, or location. Effective definition of the study population will enable important post hoc analyses to reveal these potential treatments.

Outcomes

Subjective tinnitus is subjective; outcomes measures, audiometric or not, will be as well. However, every effort should be made to use subjective measures that have clinical significance, with an a priori decision on the defined level of improvement that constitutes a relevant outcome. Given that a placebo can result in a 30–40% response rate for tinnitus, similar findings with treatment should be presented with caution [10,48]. Outcomes that are likely to be clinically significant are those associated with a meaningful improvement in a patient's life. Small improvements may be meaningless to those with mild tinnitus but very important to those whose tinnitus is disabling. Visual analog scales are

useful but should record variables of annoyance and awareness in addition to simply loudness. Another potential important outcome may be a subject's willingness to continue treatment. Again, widely recognized categorical scales and scored questionnaires that measure quality-of-life impact are recommended. Statistical analysis should compare effects within all treatment arms as well as between arms. Baseline and final data should be reported along with their analysis. Side effects of active and placebo treatment should be carefully documented and analyzed for possible effects on subjects discontinuing the trial. Long-term follow-up is sorely lacking in the current literature.

Design

Once outcome measures are decided, a formal inquiry of statistical power should be reported to determine the required number of subjects in all treatment arms. Studies should be prospective, randomized, double-blind, placebo-controlled, crossover investigations with adequate washout time between placebo and active treatment. Description of methods should allow replication and reasonable verification of blinding. Statistical comparison of baseline characteristics of treatment groups should address any significant differences. Subjects should be analyzed on an intention-to-treat basis. The study design by Holgers et al. [38] may be particularly useful in tinnitus to identify drug responders in an initial open study for subsequent inclusion in a randomized, placebo-controlled trial.

Basic science models for tinnitus, though limited, should be used to guide more productive study of pharmacological treatments for tinnitus. Better-designed, more systematic studies of tinnitus treatment are possible. Given the prevalence and economic impact of this disorder, such studies should be pursued. As more than 70% of patients with noise-induced hearing loss also suffer from tinnitus, efforts to reduce the impact of environmental noise on hearing should continue, including the use of pharmacological agents.

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