ARE MEDICATIONS EFFECTIVE IN MANAGING TINNITUS?: A REVIEW OF THE LITERATURE

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and recommend that it be accepted as fulfilling the Audiology Doctoral Project requirement for the Degree of Doctor of Audiology.

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Final approval and acceptance of this Audiology Doctoral Project is contingent upon the **candidate's submission of the final copies of the** Audiology Doctoral Project to the Graduate College.

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DEDICATION

I want to dedicate this paper to my cohort who has been alongside me throughout all of our graduate school endeavors. I would also like to dedicate this paper to my family, and my friends who have been there to comfort me and cheer me on from the sidelines during this process. And to my wonderful husband, John, this is dedicated to you. I am eternally grateful for all you have done as you have supported me, cried with me, cheered me on, and most importantly kept me alive throughout my graduate career. In addition to my human support system, I would also like to dedicate this paper to my cat, Mystical, who was often found purring on my lap while I studied, especially during a pandemic. Without their unrelenting support and encouragement, I would not be where I am today.

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ABSTRACT

Objective: The purpose of this project was to evaluate the claims and efficacy of medications marketed towards tinnitus relief for adult humans. The information presented in this literature review provides insight to clinicians regarding medications that have been trialed in adults to treat tinnitus.

Methods: This literature review was conducted following steps modeled after Cronin et al. (2008). Articles were identified using the following online databases: PubMed, Ovid, the University of Arizona's online library and a review of reference lists from excluded Cochrane reviews, systematic reviews, and surveys that were identified during the search process.

Results: This review identified 19 articles that fit the search criteria. These articles were categorized into the following nine drug classifications: anticonvulsive/antiepileptic, benzodiazepines, vitamins/minerals/antioxidants/herbals, anesthetics, antagonist drugs, vasodilators, antidepressants, anti-inflammatories/corticosteroids, and anticoagulants/antithrombotic.

Conclusions: Future research is needed to validate the effectiveness of the medications reviewed in this project. Treatment approach for tinnitus is complex as tinnitus is multifaceted. Without the exact knowledge of etiology and mechanisms involved, treatment results for tinnitus are unpredictable. Starting or stopping any medication is not recommended without a physician's approval.

BACKGROUND

Tinnitus, derived from the Latin term *tinnire* (to ring), is the perception of a sound in the absence of an external source (Baguley et al., 2013). Tinnitus perception is known to vary across individuals who experience it. For example, some may perceive tinnitus in one ear while others experience it in both ears (Gans, 2015). The volume, pitch, consistency, and type (ringing, buzzing, chirping, etc.) of sound can also vary among those who experience tinnitus (Gans, 2015). Tinnitus can be classified as subjective or objective (Peifer et al., 1999). The more common of these types is subjective tinnitus which occurs when the sound is only heard by the person experiencing tinnitus (Peifer et al., 1999). Objective tinnitus occurs when another person can hear the sound that the person is experiencing by use of a stethoscope or by placing their ear close to the ear of the person who has tinnitus (Peifer et al., 1999). While rare, objective tinnitus can be treated as it often has an identifiable cause (Peifer et al., 1999).

Tinnitus is a poorly understood common complaint with an unclear prevalence ranging from 5.1 to 42.7% in adults (Lockwood et al., 2002; McFerran et al., 2019). Gans (2015) estimated that 260 million people are affected by tinnitus, globally. Individuals can experience tinnitus so severe that it negatively impacts their quality of life, disturbs their sleep, and impacts their work performance. This bothersome tinnitus occurs in approximately 1-3% of the general population (Eggermont & Roberts, 2004). Chronic (or persistent) tinnitus is largely associated with hearing loss stemming from noise exposure or the natural aging process (Eggermont & Roberts, 2004). Tinnitus is not a disease but is typically an underlying symptom of an auditory pathology such as hearing loss, retrocochlear lesions, ototoxic medication, head injury or depression (Baguley et al., 2013). The pathophysiologic cause of tinnitus is still unknown (Peifer et al., 1999).

There is no "gold standard" for measuring tinnitus nor is there an objective way for diagnosing subjective tinnitus (Guijo et al., 2019; Han et al., 2017). However, psychoacoustic methods, such as acuphenometry, can be used to subjectively measure tinnitus by defining the minimum masking levels (MML), the loudness and the pitch, and the residual inhibition (Guijo et al., 2019). The MML is achieved by determining the lowest level of stimuli, such as low or high frequency narrow band or white noise, that is needed to "mask" or cover-up tinnitus perception (Suzuki et al., 2018). Similarly, the pitch (frequency) and loudness (intensity) of an individual's tinnitus can be subjectively matched using pure tones. Residual inhibition is a phenomenon that occurs when individuals experience a brief reduction in their tinnitus following cessation of a masker, such as pure tones or narrow band noise (Roberts, 2007). These psychoacoustic measures can help define the characteristics of an individual's tinnitus which can assist in determining if and what kind of sound therapy will provide relief the tinnitus. In addition to psychoacoustic approaches, self-reports and questionnaires are common methods used to document the perceived severity and the impact that the tinnitus has on an individual (Guijo et al., 2019). The *Tinnitus Handicap Inventory* (THI), *Tinnitus Functional Index* (TFI), and *Tinnitus Handicap Questionnaire* (THQ) are commonly used subjective measurement assessments (Guijo et al., 2019; McCormack et al., 2016).

There are many interventions (sound therapy, cognitive behavioral therapy, tinnitus retraining therapy, etc.) aimed to reduce tinnitus-associated psychological distress and improve quality of life but there are no medications currently available that are approved by the U.S. Food and Drug Administration for the management of tinnitus (McFerran et al., 2019; Coelho et al., 2016). Research exploring the efficacy of medications used to treat tinnitus has yielded varying

results. The goal of this study was to explore the claims and efficacy of these medications marketed towards tinnitus relief in adult humans.

METHODS

A literature review was chosen as the method to review the published literature on medical management of subjective tinnitus. A literature review allows a variety of articles (i.e., non-peer reviewed articles) to be included. This literature review was conducted by modeling steps proposed by Cronin et al. (2008) for writing a literature review and by modeling a literature review by Hall and Walton (2004).

The following databases were used to establish and identify the literature: PubMed, Ovid, and the University of Arizona's online library. Searches were performed in September and October 2020 using various combinations of the following terms: "noise-induced tinnitus," "tinnitus," "medication," "treatment," "drug," "tinnitus/prevention & control," "tinnitus/drug therapy*," "tinnitus/therapy*," "pharmacology," "pharmacological," "management," "anti-inflammatory," "anti-depressant," and "Hearing Loss, Noise-Induced/drug therapy." Research articles dated within the last 22 years were included in the search. Cochrane reviews, systematic reviews, and surveys were excluded. However, the references in the reviews and surveys, identified during the search, were reviewed to find additional relevant studies. Animal studies were rejected as the goal of the current literature review was to examine the efficacy of medications used to treat tinnitus in humans. As this review is focused on medical management of tinnitus, articles that discussed sound therapy, cognitive behavioral therapy (CBT), and/or any other type of treatment of tinnitus were rejected.

RESULTS

Nineteen studies met inclusion criteria for the current literature review. The nine major drug classifications identified as treatments used to treat tinnitus in this review were

1. anticonvulsive/antiepileptic,
2. benzodiazepines,
3. vitamins/minerals/antioxidants/herbals,
4. anesthetics,
5. antagonists drugs,
6. vasodilators,
7. antidepressants,
8. anti-inflammatories/corticosteroids, and
9. anticoagulants/antithrombotic.

The articles included in this review are detailed in Tables 1-9 and are sorted by drug classification. Five of the studies examined more than one drug and four of these studies examined drugs within different drug classifications (Han et al., 2012; Procházková et al., 2018; Elzayat et al., 2018; Sönmez et al., 2013). These studies are therefore listed in more than one of the tables.

Anticonvulsive/Antiepileptic

This literature review identified two studies that explored anticonvulsive/antiepileptic medications as a treatment for tinnitus (see Table 1). Dehkordi et al. (2011) completed a randomized, double-blind, placebo-controlled, clinical trial, in Iran from March 2006 to May 2008. These researchers studied the effectiveness of gabapentin (an adjunctive antiseizure medication) as a treatment for participants with subjective, idiopathic tinnitus. They chose this

medication as gabapentin is known to be effective in treating nerve injuries and one of the suspected etiologies of tinnitus is nerve injury (Dehkordi et al., 2011). This study included 80 adults who had non-pulsatile tinnitus which had persisted for at least two months. Each participant completed the Tinnitus Severity Index (TSI) and tinnitus loudness ratings before and after treatment. Half of the participants received gabapentin in ascending doses, starting with 600 mg/day, and progressing to a maximum of 1,800 mg/day over a period of 8 weeks and the other half received a placebo that followed the same schedule. While their study did not yield results showing a significant difference between the active-treatment and placebo groups in either the TSI values or loudness scores, Dehkordi et al. (2011) found that participants in the active-treatment group who had concomitant hypertension, diabetes, and/or dyslipidemia reported an improvement in symptoms.

Simpson et al. (1999) investigated lamotrigine, an antiepileptic agent, as a treatment for tinnitus in a double blind, placebo-controlled, crossover clinical trial. Simpson et al. (1999) chose lamotrigine in their study for its multiple actions of inhibiting glutamate release and sodium channel antagonist activity. Simpson et al. (1999) included 31 participants whose tinnitus had persisted for at least six months. One group received a daily 25 mg tablet of lamotrigine for 2 weeks. This was increased to 50 mg for the following 2 weeks and then to 100 mg for 4 weeks. The other group received a daily placebo tablet for 8 weeks. There was no washout period before the two groups began the trial for the second drug (lamotrigine or placebo). Improvement in tinnitus symptoms was measured by questionnaires, visual analog scales (VAS), and a battery of audiologic measurements. Participants completed these assessments before treatment and at 4-, 8-, 12-, and 16-weeks following treatment. One participant taking the placebo withdrew before completion of the study due to complaints of dizziness and rash. One participant taking the

lamotrigine withdrew before completion of the study due to complaints of nausea, vomiting, and headache. Twelve participants indicated that they preferred lamotrigine but the audiologic data collected by Simpson et al. (1999) did not reveal any significant correlation between the responses of the treatment and the placebo groups; thus, the researchers indicated that there was a strong placebo effect.

Benzodiazepines

One research study investigating benzodiazepines as a tinnitus treatment was identified in this literature review (see Table 2). Han et al. (2012) used an open label, randomized, crossover study to investigate clonazepam (a benzodiazepine) in addition to Ginkgo biloba (an antioxidant). Similar to Simpson et al. (1999), this study utilized a crossover design thus participants served as their own control. They chose to investigate clonazepam based on positive results of previous studies which utilized short-acting benzodiazepines and "...less rigorous studies..." which utilized clonazepam as a treatment option for tinnitus (Han et al., 2012, p. 821). They enrolled 38 adults who had been experiencing tinnitus symptoms for at least two months. Participants were randomized into either a Ginkgo biloba-first group or a clonazepam-first group. Participants in the Ginkgo biloba-first group were given an initial daily dose of 40 mg tablet of Ginkgo biloba. Over the course of three weeks, the participants increased the dose by one tablet every 3 days to a maximum of four tablets daily until they perceived a satisfactory decrease in tinnitus loudness or intolerable side effects. Participants in the clonazepam-first group started the first three weeks with an initial daily dose of a 0.5 mg of clonazepam and continued to follow the same regimen as the Ginkgo biloba-first group. After the first three weeks, all participants underwent a two-week washout period before beginning a trial of the other drug with the same regimen. Participants in this study completed the Tinnitus Handicap

Inventory (THI), tinnitus pitch and loudness matching, and Visual Analogue Scales (VAS) of tinnitus loudness, duration, and annoyance as a baseline measurement (before the first treatment arm and after the two-week washout period as a baseline for the second treatment arm) and following each treatment arm. Twenty-seven participants dropped out before completing the first part of the study due to complaints about drowsiness, time consumption, no improvement, reconsideration of participation, concerns of adverse reactions, and loss of contact. The following side effects were reported from 42.1% of the participants in the clonazepam group: drowsiness and dizziness. Despite the large number of participants who dropped out of the study, Han et al. (2012) found significant improvement in all tinnitus related scores after the clonazepam trials. However, they did not find any significant improvements after the Ginkgo biloba trials.

Vitamins/Minerals/Antioxidants/Herbals

Many researchers have examined the use of natural supplements as a treatment method for tinnitus symptoms. This literature review identified four articles that investigated vitamins, minerals, antioxidants and/or herbal medications as a treatment for tinnitus symptoms (see Table 3). Han et al. (2012) utilized Ginkgo biloba in their cross-over study and the details of this study are discussed in the previous section. They chose to use Ginkgo biloba in their study based on previous "...large, well controlled, double-blind, placebo-controlled clinical studies..." in which Ginkgo biloba was found to be "...no more effective than placebo in alleviating tinnitus" despite it being "...widely promoted as an effective tinnitus treatment." (Han et al., 2012, p. 821). These authors found no relief following the Ginkgo biloba trials.

Rojas-Roncancio et al. (2016) were specifically interested in the treatment effects of manganese when used in conjunction with Lipoflavonoid Plus®. They chose Lipoflavonoid Plus®

based on previous studies which resulted in improvement of tinnitus perception (Rojas-Roncancio et al., 2016). They chose to incorporate manganese in their study based on a study which reported a high level of radical-free markers in participants with tinnitus and the proposed suggestion that antioxidant treatments could reduce levels of reactive oxygen species (Rojas-Roncancio et al., 2016). They recruited 40 participants whose tinnitus had persisted for at least six months. Half of the participants took three daily pills of Lipoflavonoid Plus® for six months while the other half took three daily pills of Lipoflavonoid Plus® with 8 mg of manganese for six months. Only 12 participants were able to complete this study as the remainder either experienced undesired side effects (i.e., nausea, vomiting, shaking, and worsening of tinnitus) or were lost to follow-up. Tinnitus symptoms were measured before and after treatment using the Tinnitus Handicap Questionnaire, Tinnitus Primary Functions Questionnaire, and tinnitus loudness and annoyance ratings. Minimum Masking Level (MML), tinnitus loudness matching, and audiograms were performed by an audiologist. Only one participant in the manganese group revealed an improvement on the questionnaires and one other participant in this group revealed a decrease in the loudness and annoyance ratings. In the Lipoflavonoid Plus® only group, two participants revealed a decrease in loudness and one participant revealed an improvement in annoyance. Rojas-Roncancio et al. (2016) were unable to conclude that manganese or Lipoflavonoid Plus® were an effective treatment for tinnitus symptoms.

Polanski et al. (2016) conducted a prospective, randomized, double-blinded, placebo-controlled clinical trial to assess the treatment effects of antioxidants on tinnitus in elderly participants. They chose to utilize antioxidants in their study based on the known primary function of neutralization and clearance of free radicals which are toxic and harmful to cells and tissues (Polanski et al., 2016). There were 58 participants who were 60 years or older included in

this trial. All participants included had clinical complaints of tinnitus associated with sensorineural hearing loss. The duration of the tinnitus was not documented. Participants were randomly selected to one of four groups and were treated with one of the following regimens for six months: (a) dry extract of Ginkgo biloba (120 mg/day), (b) α-lipoic acid (60 mg/day) plus vitamin C (600 mg/day), (c) papaverine hydrochloride (100 mg/day) plus vitamin E (400 mg/day), and (d) placebo (starch capsules). No significant differences were found between before and after measures using the Tinnitus Handicap Inventory Questionnaire. Thus, the researchers concluded there was no benefit from the use of antioxidant agents for their group of adults who were experiencing tinnitus.

Similar to Han et al. (2012), Procházková et al. (2018) compared the treatment effects of two different interventions. Procházková et al. (2018) investigated an antioxidant [Ginkgo biloba extract (Egb 761®)] and a haemorheological agent/vasodilator (pentoxifylline) as treatment for tinnitus in a randomized, double-blind, double-dummy, parallel-group, reference controlled single-center trial (Singh et al., 2008; Ward & Clissold, 2012). They chose Egb 761® due to its ability to lower the inflammatory process and enhance blood flow in the cochlea and brain (Procházková et al., 2018). The recruited 202 participants in this study who have experienced chronic tinnitus symptoms for at least three months. This trial was completed over a twelve-week period. Half of the participants were randomly selected to receive one film-coated tablet of 120 mg EGb 761® together with one pentoxifylline-like placebo tablet twice a day while the other group received one extended-release tablet of 600 mg pentoxifylline together with one EGb 761®-like placebo tablet twice. Participants completed an 11-Point Box Scale for tinnitus loudness and annoyance by tinnitus, as a baseline and daily during this study. Additionally, the participants completed The Mini-TQ (an abridged version of the Tinnitus

Questionnaire), the Hospital Anxiety and Depression Scale (HADS), and the Sheehan Disability Scales (SDS) as a baseline and following the treatment period. Although Procházková et al. (2018) found that adults in the EGb 761® group improved scores on all tinnitus-related scales (unlike Han et al., 2012) and the pentoxifylline group also revealed improved scores, there were no significant differences between the two groups. Some adverse reactions, such as gastrointestinal problems, worsening of tinnitus symptoms, and infections, were reported in both groups with the pentoxifylline group resulting in a higher incidence of adverse reactions. Five participants were not included in the final analysis due to adverse events, lost to follow-up, discontinuation, or withdrawal from the trial. This study did not utilize a placebo only control group for comparison. Furthermore, all the participants in this study were white/Caucasian. Therefore, further research is needed to validate the results found in this study.

Anesthetics

Three articles focusing on lidocaine, an anesthetic, as a tinnitus treatment were found in this literature review (see Table 4). Each study used a unique method of administration of the lidocaine. Savastano (2004) investigated the use of an intradermal injection of lidocaine as a treatment for tinnitus symptoms. She chose to utilize lidocaine in her study based on its "...efficacy...in controlling tinnitus" which is "...well documented." (Savastano, 2004, p. 13). She specifically chose an intradermal injection as this was a novel delivery method as a treatment method for tinnitus (Savastano, 2004). Previous delivery methods include intravenous and transtympanic which have been documented as having adverse reactions (Savastano, 2004). A total of 68 adults with tinnitus were included in this study. Twenty participants were allocated to the control group. The treatment group received 40 mg of lidocaine in 1 mL of saline in the external auditory canal in four locations (superior, posterior, inferior and anterior) while the

control group received saline injections in the same locations. Participants in this study completed self-evaluation scales of subjective disturbance and tinnitus loudness as a baseline and at the following intervals post injection: 2 hours, 2 days, and 10 days. All participants in the treatment group reported improved scores of disturbance and reduced tinnitus loudness. Participants in this study were separated into two groups based on initial tinnitus intensity measurements of either less than "10 dB" (Group A) or greater than "10 dB" (Group B). Savastano (2004) concluded that all participants who received treatment revealed significant improvement two hours following treatment and two days following treatment when assessed with the self-evaluation scale of disturbance. Significant improvement was also found for the tinnitus intensity measurements two hours following treatment, especially in Group B. It is noteworthy that disturbance levels and tinnitus intensity measurements worsened (not exceeding initial results) by the tenth day in both groups. Savastano (2004) noted that the improvement appeared to be unstable which could lead to repeated weekly injections for desired results.

O'Brien et al. (2019) used a transdermal patch to administer lidocaine as a treatment for participants with chronic subjective tinnitus in a pilot, prospective efficacy, single center, un-blinded, quasi-experimental protocol designed study. O'Brien et al. (2019) chose to investigate a transdermal patch as a tinnitus treatment option based on a previous case study which found temporary relief from tinnitus, and they noted that there have not been any previous published studies investigating this method of treatment. They recruited 30 adults who had been experiencing non-fluctuating tinnitus symptoms for at least six months. Participants were given a patch of 5% transdermal lidocaine to apply to their skin and alternate between 12 hours on and 12 hours off for one month. During the second month, participants were given the option to (a) stop using the patch, (b) continue with one patch, or (c) increase to two patches daily. During the

third month, the participants were able to choose from the same three for a maximum of three patches per day. Participants completed the Tinnitus Functional Index (TFI) as a baseline and at the following intervals post treatment: 1 month, 2 months, and 3 months. Before completion of the first month, nine participants dropped out of this study due for a variety of reasons (i.e., patch irritation, skin reactions, poor cosmesis, lack of insurance coverage, and inability to comply with the regulations). Four participants chose to increase their dose after the first month while three participants chose to revert back to one patch due to worsening of symptoms. Before completion of the second month, eight participants dropped out due to loss to follow-up or withdrawal of consent. Four participants dropped out before completion of the third month for the same reasons. After the first month, O'Brien et al. (2019) found clinically significant improvement on the Tinnitus Functional Index (TFI) scores in participants. However, the researchers noted that their findings may be confounded due to the small sample size and large dropout rate.

Elzayat et al. (2018) compared the treatment effects of two different intratympanic injections in a prospective, controlled, randomized, double-blind study that included 44 adults with non-pulsatile, subjective, idiopathic tinnitus associated with hearing loss less than 30 dB HL. Group A received a combination intratympanic injection consisting of 2% lidocaine and 8 mg/2 ml dexamethasone (a corticosteroid) while group B received an intratympanic injection consisting solely of 8 mg/2 ml dexamethasone. They chose lidocaine for its mechanisms of central and peripheral actions on the auditory system in participants with idiopathic subjective non-pulsatile tinnitus (Elzayat et al., 2018). Participants completed the Tinnitus Handicap Inventory (THI), Arabic Tinnitus Questionnaire (ATQ), and loudness matching test as a baseline and at the following intervals post treatment: 3 months and 6 months. Elzayat et al. (2018) found a 73.8% improvement in the Arabic Tinnitus Questionnaire (ATQ), Tinnitus Handicap Index

(THI), and tinnitus loudness scale in the group that was administered the lidocaine with the dexamethasone. They noted this improvement remained stable for 8 weeks following treatment. All participants in this treatment group experienced a moderate degree of vertigo and nausea. Four of the 22 participants in this group complained of attacks of vomiting.

Antagonist Drugs

The present literature review identified four studies that examined antagonist drugs as a treatment for tinnitus symptoms (see Table 5). Figueiredo et al. (2008) focused on the use of memantine, an NMDA (N-methyl-D-aspartate) receptor antagonist, as a treatment for tinnitus in a prospective, randomized, placebo-controlled, double-blind crossover study. They chose to investigate memantine following a study in which rats with salicylate- and quinine-induced tinnitus revealed non-statistically significant beneficial effects when memantine was used as a treatment (Figueiredo et al., 2008). Additionally, animal studies have found that NMDA receptors have been shown to be expressed in the cochlea after tinnitus has been induced and the application of NMDA antagonists directly into cochlear fluid blocks salicylate-induced tinnitus (Figueiredo et al., 2008). In their study, Group M initially received memantine for 90 days with dosage increasing from 5 mg daily to 20 mg daily following this specific regimen:

1. days 1 to 7: 5 mg in the morning,
2. days 8 to 14: 5 mg in the morning and 5 mg at night,
3. days 15 to 21: 5 mg in the morning and 10 mg at night, and
4. days 22 to 90: 10 mg in the morning and 10 mg at night.

Group P initially received a placebo for 90 days with a similar regimen (Figueiredo et al., 2008). Both groups completed a 30-day washout period before receiving the other intervention. Participants completed a Brazilian Portuguese version of the Tinnitus Handicap Inventory (THI)

as a baseline measurement and following treatment (90 days). The researchers found no significant improvement in the Tinnitus Handicap Inventory (THI) scores in the treatment group when compared to the placebo group and thus concluded that the evidence to support memantine as a treatment for tinnitus was insufficient.

Hong et al. (2018) investigated the use of nitrous oxide, another NMDA inhibitor, as a treatment to reduce bothersome tinnitus in a randomized, placebo-controlled crossover trial. Similar to Figueiredo et al. (2008), Hong et al. (2018) investigated nitrous oxide for its role in maintaining the NMDA receptor synapses throughout the auditory system. Included in this study were 40 adults who had subjective, idiopathic, non-pulsatile, bothersome tinnitus symptoms for at least six months. Half of the participants initially received an inhalation of 50% nitrous oxide concentration for 40 minutes while the other half of the participants received an inhalation of 50% nitrogen and 50% oxygen for 40 minutes. The participants then had the other intervention after a 14-day washout period. Improvement in tinnitus was measured using the Tinnitus Functional Index (TFI), the Patients' Global Impression of Change (PGIC) and the Global Bothersome Scale (GBS). Participants were assessed before the treatment and one week following each intervention. No significant changes were found in the scores of the TFI, PGIC and GBS when comparing the results following the treatment and placebo interventions in either group. The researchers concluded that nitrous oxide was no more effective than the placebo for a treatment of tinnitus symptoms.

Azevedo and Figueiredo (2005) found significant improvement in tinnitus in a prospective, randomized, double-blind clinical trial using acamprosate. One theory of tinnitus pathophysiology suggests an excessive release of the excitatory neurotransmitter, glutamate in the central and peripheral auditory pathways which leads to an overexpression of NMDA

(Azevedo & Figueiredo, 2005). Azevedo and Figueiredo (2005) explored acamprosate, which is typically used in alcoholism treatment, as it acts as an inhibitory agent in the GABA system and acts as an excitatory agent in the glutamatergic system. Azevedo and Figueiredo (2005) enrolled 50 adults with sensorineural tinnitus in this study. For 90 days, half of the participants received 333 mg of acamprosate three times a day while the other half received a placebo three times a day. Participants completed a tinnitus disturbance questionnaire as a baseline and at the following intervals post intervention: 30 days, 60 days, and 90 days. After 90 days, 86.9% of the participants in the treatment group reported improvement in tinnitus using the self-evaluation scale of subjective disturbance. Nearly half (47.8%) of these participants reported that their tinnitus had improved by at least 50%. The improvement seen in the treatment group was significantly greater than the reported improvement (44.4%) in the placebo group. Significant improvement in the tinnitus disturbance scores was found at each of the follow-up evaluations in the treatment group. No significant variance of results was observed in the placebo group.

In a double-blinded, prospective clinical study, Stidham et al. (2005) explored the use of botulinum toxin A as a treatment for tinnitus. Another theory of tinnitus suggests that sustained activation of the limbic system and autonomic nervous system cause the symptomatic response of tinnitus (Stidham et al., 2005). The motivation for Stidham et al. (2005) to utilize botulinum toxin A as a treatment option for tinnitus is its ability to block the autonomic pathway. Stidham et al. (2005) recruited 30 adults with non-pulsatile, subjective tinnitus for at least two months and randomized them into two treatment arms. Treatment arm 1 received subcutaneous injections of botulinum toxin A in the following 3 areas: 1 cm above the superior aspect of the auricle, 1 cm behind the superior aspect of the auricle, and 1 cm behind the inferior aspect of the auricle. Treatment arm 2 received subcutaneous injections of saline in the same locations. After four

months, the two treatment arms received the opposite injection. Participants completed the Tinnitus Handicap Inventory (THI) as a baseline and at the following post intervention intervals: 1 month, and 4 months. Tinnitus and hearing rating scales were completed daily after each injection for a month. Stidham et al. (2005) found improvement in tinnitus irritation in 7 of the 26 (27%) participants following treatment while only 2 of the participants (8%) reported improvement following the placebo as measured using the Tinnitus Handicap Inventory (THI) and subjective tinnitus rating scale. Significant improvement in THI scores was observed when comparing the baseline scores to the scores 4 months following botulinum toxin A injections. Stidham et al. (2005) postulated that there may be a delayed response to this intervention. They indicated that further research, including a larger sample size, is needed before definitive conclusions regarding the potential benefits of botulinum toxin A as a treatment of tinnitus can be made.

Vasodilators

This literature review identified three articles that focused on the use of vasodilators as a treatment for tinnitus (see Table 6). Sönmez et al. (2013) examined betahistine and ozone (O_3) as treatments for tinnitus in a randomized, prospective, controlled study. Betahistine, commonly used to treat vertiginous symptoms in patients with balance disorders, is a vasodilator and a H1-receptor agonist (Jeck-Thole, & Wagner, 2006). Ozone possesses both anti-inflammatory and vasodilating properties (Elvis & Ekta, 2011). Ozone is a non-metal oxide typically used as a treatment in inflammatory pathologies when ischemia is an etiologic factor (Sönmez et al., 2013). Sixty-eight adults experiencing tinnitus for at least six months, were included in this study. Fifty-three participants were randomized into two treatment groups. Fifteen participants served as a control group after choosing not to receive any treatment despite being eligible.

The betahistine group received daily 48 mg tablets for three months. The ozone group received ten sessions of ozone treatment intravenously twice a week. Participants completed the Tinnitus Handicap Inventory (THI), and tinnitus loudness and frequency matching as a baseline and at the following intervals post intervention: 3 months and 6 months. Statistically significant improvement was found on the scores of the THI following intervention with ozone and betahistine; however, no statistically significant differences were found when comparing the THI scores to the control group. The researchers were unable to provide sufficient evidence supporting betahistine or ozone as treatments for tinnitus.

In a prospective, randomized, placebo-controlled, double-blind study, Hester et al. (1998) evaluated the effectiveness of cyclandelate (a vasodilating agent primarily used as treatment for peripheral vascular diseases) in the treatment of tinnitus. They chose to investigate cyclandelate as a treatment option for tinnitus following previous studies which found improvement in tinnitus symptoms; however, these studies were not randomized or controlled. Fifty-nine adults, with constant tinnitus for at least one year, were enrolled but only 29 completed the study. The experimental group received 400 mg cyclandelate to be taken three times daily for three months while the control group received a lactose placebo to be taken following the same regimen. Participants completed tinnitus pitch and loudness matching evaluations as a baseline and following the intervention. A subjective rating of tinnitus loudness was completed by each participant before intervention and every 30 days during the three-month study. Improvement in the tinnitus scores was reported by four participants in the treatment group. However, these participants stated they would not continue this treatment after the study. No significant changes were found when comparing the initial and final tinnitus pitch and loudness matching evaluations. Adverse reactions relating to gastrointestinal problems were observed within the

experimental group. Additionally, there was a large drop-out rate due to adverse reactions, illness, non-realistic expectations, non-compliance, and relocation.

As mentioned previously, Procházková et al. (2018) investigated pentoxifylline as a treatment for tinnitus symptoms. This study also explored Ginkgo biloba as a treatment for tinnitus and related results are discussed previously. Several studies have suggested that pentoxifylline may be a vasodilator (Sonkin, 1992). Similar to Hester et al. (1998), Procházková et al. (2018) found significant improvement on the Mini-TQ, the 11-Point Box Scales for tinnitus loudness and annoyance, the Hospital Anxiety and Depression Scale (HADS) score, and the Sheehan Disability Scale (SDS) following treatment with pentoxifylline. Thirty-six adverse reactions, such as gastrointestinal problems, worsening of symptoms, and infections, were observed in twenty-seven participants who received pentoxifylline.

Antidepressants

People who experience tinnitus often endure depression (Berthold et al., 2011). Two articles that explored antidepressants as a treatment for tinnitus were found in this literature review (see Table 7). In a randomized, double-blind, placebo-controlled study, Zöger et al. (2006) explored sertraline, a selective serotonin reuptake inhibitor (SSRI), as a treatment for 76 adults with tinnitus symptoms. They hypothesized that there is a shared neurobiological mechanism between tinnitus and mood disorders and thus the anti-depressive medication actions in tinnitus would be independent of its effect on depressed mood (Zöger et al., 2011). The treatment group received a daily 25 mg tablet of sertraline for the first week which was increased to a daily tablet of 50 mg tablet of sertraline for the following 15 weeks. The control group received a daily placebo for 16 weeks. Participants completed the Tinnitus Severity Questionnaire (TSQ) and Visual Analogue Scale (VAS) on tinnitus loudness and annoyance as a

baseline and at the following intervals post intervention: one week, two weeks, four weeks, eight weeks, twelve weeks, and sixteen weeks. The researchers found that sertraline was more effective than the placebo. They also implied that this effect could be explained by a reduction in psychiatric symptoms.

Trazadone was investigated by Dib et al. (2007) as a treatment for tinnitus in a prospective, double blind, randomized, placebo-controlled study. Dib et al. (2007) chose to investigate trazadone as a treatment option for tinnitus due to its double mechanism of action for the increase in serotonin levels in the synapses of the central auditory pathway. They recruited 104 eligible participants of which 85 completed the study. Forty-three participants were randomized to the treatment group while 42 participants received a placebo. The treatment group received a daily 50 mg tablet of trazadone for 60 days while the control group received a daily placebo tablet for 60 days. Participants completed analogue scales related to tinnitus intensity, discomfort, and life quality impact by tinnitus as a baseline and following intervention. Both groups reported an improvement in all three measurements. However, there were no statistically significant differences between the two groups. Thus, the researchers concluded that trazadone, in the dose used in their study, was not effective controlling tinnitus.

Anti-inflammatories/Corticosteroids

The present literature review identified three articles that explored anti-inflammatories or corticosteroids as a treatment option for tinnitus symptoms (see Table 8). Araújo et al. (2005) investigated dexamethasone as a treatment for tinnitus when administered as an intratympanic injection in a randomized, prospective, single-blind study. The researchers enrolled 36 adults with severe, disabling tinnitus who were randomized into either a treatment group or a control group. Four participants reported perception of tinnitus in both ears and therefore the

intervention was administered bilaterally to them. The treatment group received weekly 0.5 mL intratympanic injections of 4 mg/mL dexamethasone on the side(s) in which tinnitus was experienced for 4 weeks. The control group received weekly 0.5 mL intratympanic injections of isotonic sodium chloride (saline) for 4 weeks. Participants completed a questionnaire regarding the status of their tinnitus and a Visual Analogue Scale (VAS), relating to tinnitus intensity, as a baseline and following intervention. Results of these assessments revealed significant improvement in 29% of ears in the control group and 33% of ears in the treatment group. However, there were no statistically significant differences between the two groups. Thus, the researchers attributed the improvement to a "placebolike" effect.

As discussed previously Elzayat et al. (2018) also explored an intratympanic injection of dexamethasone, with and without lidocaine, as a treatment option for tinnitus. They chose the addition of dexamethasone due to its high concentration in the perilymph with no observed systemic adverse effects encountered. In their study, Elzayat et al. (2018) one group of participants (Group A) was injected with a combination of dexamethasone and lidocaine while another group (Group B) was injected with just dexamethasone. Group B revealed a 50.0% improvement on the Tinnitus Handicap Inventory (THI), and a 46.4% improvement on the Arabic Tinnitus Questionnaire (ATQ) and the tinnitus loudness scale. All participants in Group B experienced a mild degree of vertigo for a short duration and a moderate degree of nausea. Two of the 22 participants in this group complained of attacks of vomiting. Their results yielded improvement in both groups. The group that was administered the combination of dexamethasone and lidocaine revealed better improvement in tinnitus symptoms. However, unlike Araújo et al. (2005) no control group was utilized in this study.

Sönmez et al. (2013), as mentioned previously under the vasodilators section, also investigated the anti-inflammatory properties of ozone as a treatment option for tinnitus. They chose ozone as it has been suggested that ozone avoids the outer cell damage. In this randomized, prospective, controlled study, statistically significant improvement was found on the scores of the Tinnitus Handicap Inventory (THI) following intervention with ozone. However, no statistically significant differences were found when comparing these THI scores to the control group. The researchers were unable to provide sufficient evidence supporting ozone as treatments for tinnitus.

Anticoagulants/Antithrombotic

This literature review identified one article that focused on the use of anticoagulants and antithrombotic medications as a treatment option for tinnitus symptoms (see Table 9). Specifically, sulodexide was investigated by El Beaino et al. (2018), in a randomized, double-blinded controlled trial. This medication has both anticoagulant and antithrombotic effects. The researchers recruited 124 adults with non-pulsatile tinnitus present for at least one year. For 40 days, the treatment group took one 25 mg tablet of sulodexide twice daily while the control group took one placebo tablet twice daily. Participants completed the Tinnitus Handicap Inventory (THI) and the Mini-Tinnitus Questionnaire (Mini-TQ) as a baseline and following the intervention. The following adverse reactions were found in the treatment group: 9 cases of epigastric pain, 7 cases of constipation (a known side effect of sulodexide), and 2 cases of headache and anticoagulation. The participants in the treatment group showed statistically significant improvement on the THI and the Mini-TQ scores.

DISCUSSION

Tinnitus is a common chronic health problem that affects approximately 260 million people, globally (Maes et al., 2013; Gans, 2015). The present literature review explored the claims and efficacy of medications marketed towards tinnitus relief in adult humans. Literature reviews provide readers with a comprehensive view of current literature and understanding of a topic (Cronin et al., 2008). They can also draw attention to areas which may need further research. The current author chose to perform a literature review in order to include studies of various treatment methods and studies that may not have been peer-reviewed (Grant & Booth, 2009).

Dib et al. (2007) noted that there are a number of central nervous system structures involved in tinnitus and thus isolating the role of each structure is a challenge. The researchers of the articles identified in this literature review had specific motivation for evaluating their chosen medication. The inspiration of each article will be discussed below. Another challenge presented when assessing treatments for tinnitus symptoms is the fact that researchers are asking participants to draw their attention to their tinnitus which can increase the participants' perception of the severity or bothersome factors of their tinnitus (Hong et al., 2018). Consequently, the placebo effect has been documented to be as large as 40% reported from participants during tinnitus investigations (Hong et al., 2018). The present literature review identified articles with varying medications (treating specific target areas), treatment regimens, and test measures. While a few studies in the current literature review yielded results that revealed improvement in tinnitus symptoms, further research should be completed to account for sample sizes, placebo effect and special population reactions, as discussed below.

Anticonvulsive/Antiepileptic

Neither of the studies that focused on anticonvulsive/antiepileptic medications identified in the present literature review were able to conclude that these medications were effective in treating tinnitus symptoms (Dehkordi et al., 2011; Simpson et al., 1999). The loss of inhibition of γ-amino butyric acid (GABA) has been implicated as a potential underlying cause of inappropriate changes in neuroplasticity which is expressed as tinnitus (Brozoski et al., 2007). The medication used in the study conducted by Dehkordi et al. (2011) targets and binds to calcium channel proteins and inhibits the release of the neurotransmitter GABA. Similarly, tinnitus has been found to be correlated with the downregulation of glutamate decarboxylase 65 (GAD65) in the auditory cortex (Miyakawa et al., 2019). The medication used by Simpson et al. (1999) blocks sodium channels and inhibits the release of glutamate through selective inhibition of voltage-dependent ion channels which leads to a reduction in excitability of the nervous system.

Benzodiazepines

Benzodiazepines aide the inhibitory processes of the neurotransmitter GABA (Han et al., 2012). Han et al. (2012) postulated that benzodiazepines could reduce tinnitus symptoms by reducing hyperactivity in the auditory central nervous system. Participants in their study reported improved tinnitus related scores following the benzodiazepine trial of clonazepam. Further research on the effectiveness of clonazepam as a treatment for tinnitus is needed as this study had a small sample size of only 38 participants and no placebo was utilized. Furthermore, 42.1% of participants reported side effects, such as dizziness and drowsiness, from clonazepam. Han et al. (2012) postulated that tinnitus relief may possibly be due to the reduction in auditory neuronal activity and the sedative effects of clonazepam. While comparing their own study with previous

studies, Han et al. (2012) noted that some individuals with tinnitus may benefit from one type of benzodiazepine but not another type of benzodiazepines (Johnson, Brummett, & Schleuning, 1993; Lechtenberg & Shulman, 1984). They also acknowledged that the long-term benefit of using benzodiazepines as a treatment for tinnitus is an area in which further research is needed.

Vitamins/Minerals/Antioxidants/Herbals

Three of the four studies that explored vitamins/minerals/antioxidants/herbals as a treatment option for tinnitus symptoms were unable to conclude effective results in treating tinnitus symptoms (Rojas-Roncancio et al., 2016; Polanski et al., 2016; Han et al., 2012). Rojas-Roncancio et al. (2016) explored the treatment effect of adding manganese to Lipoflavonoid Plus® compared to Lipoflavonoid Plus® used alone. Roth et al. (2013) suggested that manganese could aid enzymes that target toxic products of oxygen metabolism (as cited in Rojas-Roncancio et al., 2016). Savastano et al. (2007) noted that antioxidant treatment may have reduced levels of reactive oxygen species in individuals with tinnitus (as cited in Rojas-Roncancio et al., 2016). Similarly, Polanski et al. (2016) chose to explore three different antioxidants (Ginkgo biloba, α-lipoic acid plus vitamin C, and papaverine hydrochloride plus vitamin E) for their role in neutralization and clearance of free radicals.

Han et al. (2012) found results analogous to Polanski et al. (2016) regarding the use of ginkgo biloba as a treatment for tinnitus symptoms. However, Han et al. (2016) chose to use gingko biloba in their study as a placebo based on a meta-analysis of randomized trials indicating the lack of benefit ginkgo biloba provides to individuals with tinnitus.

The one study that found improvement in tinnitus symptoms following treatment with Ginkgo biloba chose to use this intervention in their study based on the “perfusion-enhancing properties that act in the brain and inner ear” which are assumed to contribute to the clinical

benefits (Procházková et al., 2018). As tinnitus is known to impact psychological and social aspects of sufferers, these researchers were also interested in the anxiolytic and antidepressant-like effects of EGb 761®, as well as its influence on neuroplasticity, involving neurogenesis and synaptogenesis. In direct contrast to the findings of Polanski et al. (2016) and Han et al. (2012), participants in this study reported improvement in tinnitus related scales and anxiety and disability scores following the use of Ginkgo biloba (Procházková et al., 2018). Further research would be needed to validate these findings due to the conflicting results and the fact that no placebo control group was utilized in this study. Additionally, Procházková et al. (2018) acknowledged that their study consisted of all white/Caucasian participants which suggests that the results may not generalize to a larger, more diverse population.

Anesthetics

All three of the studies that investigated anesthetics as a treatment option for tinnitus reported improvement in tinnitus symptoms following intervention (Savastano, 2004; O'Brien et al., 2019; Elzayat et al., 2018). Each of these articles incorporated a different administration route of lidocaine. Savastano (2004) chose an intradermal injection of lidocaine at four sites in the external auditory canal. She indicated that lidocaine, when administered intravenously or by transtympanic injection, has been known to temporarily suppress tinnitus, as documented as early as 1935 by Barany. However, she also noted the adverse reactions, such as toxicity in the cardiovascular and central nervous system (CNS), peripheral nerve damage, and misdiagnosed allergic reactions, following intravenous treatment of lidocaine. Adverse reactions following transtympanic injection of lidocaine include slight neurosensorial deafness in the low frequencies, vertigo, vomiting, and taste disturbances (Savastano, 2004). In the dosage and administration methods used in her study, Savastano (2004) did not observe any of these adverse

reactions within the 10-day follow-up period. She did find significant improvement in the level of disturbance and tinnitus loudness scores following intradermal injection of lidocaine. Further research is needed to determine the long-lasting effects of this treatment, how often it should be administered for sustained tinnitus improvements, and if results will generalize to a larger population.

Similar to Savastano (2004), O'Brien et al. (2019) explored lidocaine due to the known suppression of tinnitus effects. O'Brien et al. (2019) also noted adverse reactions, such as disequilibrium, parenthesia, arrhythmia, and worsening of tinnitus, associated with lidocaine intervention, specifically intravenously administered lidocaine. They explored the use of transdermal lidocaine patches for the steady and controlled release of the medication. Furthermore, they indicated that these patches are safe for outpatient use and do not require cardiac or neurologic monitoring. In this study, the participants were responsible for the purchase of their patches. Further research on the effectiveness of transdermal lidocaine patches as a treatment for tinnitus is needed as only nine participants of the small sample size of 30 completed this study and no placebo was utilized. Additionally, the authors of this study indicated that the reported improved tinnitus scores may be due to a placebo effect.

Elzayat et al. (2018) investigated tinnitus treatment effects of adding lidocaine to dexamethasone in an intratympanic injection. They indicated that previous research of intratympanic injections of lidocaine has resulted in improvement in tinnitus and possible transient slight sensorineural hearing loss in the low frequencies (Szabados et al., 1985; Sakata et al., 1984). Elzayat et al. (2018) found significant improvement on all the scores in the group that was administered with dexamethasone with lidocaine. This improvement remained stable for 8 weeks following treatment. Due to the small sample size, 44 participants, and the fact that no

placebo was utilized in this study, further research would be needed to determine the efficacy of adding lidocaine to dexamethasone in an intratympanic injection as a treatment for tinnitus.

Antagonist Drugs

Two of the four studies that explored the use of antagonist medications as a treatment option for tinnitus symptoms were unable to conclude effective results in treating tinnitus symptoms (Figueiredo et al. 2008; Hong et al., 2018). Particularly, Figueiredo et al. (2008) investigated the use of memantine as a treatment for tinnitus following a study in which tinnitus induced rats were treated with memantine (Lobarinas et al., 2006). These rats revealed beneficial effects on tinnitus-related behavior; however, the results were not statistically significant (Lobarinas et al., 2006). Figueiredo et al. (2009) did not find significant differences between the Tinnitus Handicap Inventory (THI) scores of participants in the treatment group and the control group.

Hong et al. (2018) focused on the use of nitrous oxide, an NMDA (N-methyl-D-aspartate) receptor antagonist, as a treatment for tinnitus following a study in which nitrous oxide was found to be effective in preventing acute excitotoxic tinnitus in rats (Guitton & Dudai, 2007). Hong et al. (2018) noted that NMDA receptors that are maintained throughout the auditory pathway generally promote excitation at synapses and overactivation of these receptors seen in chronic damage to the auditory system can lead to abnormal spontaneous neural firing along the auditory pathway which leads to further damage (Hong et al, 2018). Hong et al. (2018) did not find significant improvement in the Tinnitus Functional Index (TFI), Patients' Global Impression of Change (PGIC), or the Global Bothersome Scale (GBS) in either the treatment or control groups or when comparing the groups.

One of the studies that reported improvement in tinnitus symptoms following treatment with antagonist medications was completed by Azevedo and Figueiredo (2005). They explored acamprosate, which acts as an inhibitory agent in the GABA (Gamma-Amino-Butiric Acid) system and acts as an excitatory agent in the glutamatergic system, as a treatment option for tinnitus. This treatment option supplements the theory that tinnitus arises from excessive glutamatergic activity through NMDA (N-methyl-D-aspartate) receptors and/or the hyperactivity resulting from the loss of GABA-mediated inhibition. Although Azevedo and Figueiredo (2005) revealed significant positive results, further research will be needed to determine longevity of treatment effects and if their research will generalize to a larger population, especially given their small sample size of 50 participants.

Following the theory that tinnitus arises from sustained activation of the limbic and autonomic nervous system, Stidham et al. (2005) chose to investigate botulinum toxin A as a treatment for tinnitus for its suspected ability to block acetylcholine and to inhibit the release of neurotransmitters and neuropeptides which are important in the autonomic nervous system. Stidham et al. (2005) found non-statistically significant improvement on the tinnitus scores following the treatment trials and statistically significant improvement on the tinnitus handicap inventory when comparing baseline evaluations to the 4-month follow-up after treatment with botulinum toxin A. They noted that their small sample size was a weakness in their study. A larger study is needed to replicate results to determine if botulinum toxin A is a suitable treatment option for tinnitus.

Vasodilators

The three articles that explored vasodilators as a treatment for tinnitus yielded varying results. Following the theory that tinnitus is caused by a disturbance of cochlear

microcirculations, Sönmez et al. (2013) investigated the use of betahistine and ozone, both of which possess vasodilating properties, as a treatment for tinnitus (Elvis & Ekta, 2011). No significant differences were found within or between the betahistine, ozone, and control groups when reviewing tinnitus loudness scores after six months. Significant improvement in THI scores was found in the betahistine and ozone groups but these findings were not significantly different than those in the control group. Thus, Sönmez et al. (2013) concluded that the evidence to support ozone and betahistine as a treatment for tinnitus was insufficient.

Hester et al. (1998) chose to further explore cyclandelate, a vasodilating drug, as a treatment for tinnitus following a non-randomized or controlled study by Memin (1987), which revealed a decrease in severity and frequency in patients' tinnitus symptoms. Cyclandelate is used to treat various peripheral vascular disorder and symptoms, such as tinnitus, which are thought to be linked to cerebrovascular insufficiency (Hester et al., 1998). Some of the participants in the experimental group reported significant improvement in subject tinnitus loudness scores. However, negative adverse reactions (gastrointestinal problems) were observed, and a significant percentage of participants stated they would not continue to use this treatment.

Procházková et al. (2018) investigated pentoxifylline due to its high frequency of being prescribed as a treatment option for tinnitus in European countries (Langguth, Salvi, & Elgoyhen, 2009). Significant improvement in tinnitus loudness and annoyance scores was reported from the participants that took pentoxifylline after 12 weeks of treatment. Non-significant improvement was found in the Hospital Anxiety and Depression Scale of these participants. Procházková et al. (2018) noted that their large sample size was a strength of their study. However, they did not include a placebo and thus it is difficult to know if the positive

findings in their study were due to a placebo-like effect. Further research is needed to validate the efficacy of using pentoxifylline as a treatment for tinnitus.

Antidepressants

The two studies that focused on antidepressants yielded varying results (Zöger et al., 2006; Dib et al., 2007). Zöger et al. (2006) chose to explore antidepressants as a treatment for tinnitus as they hypothesized that there is a shared neurobiological mechanism between tinnitus and mood disorders. They found improved scores on the Tinnitus Severity Questionnaire (TSQ) and perceived tinnitus loudness as noted on the Visual Analog Scale (VAS) in both the placebo and the treatment groups. However, sertraline was shown to be more effective than the placebo as determined by the greater reduction in TSQ scores. The treatment group did not reveal any significant improvement in the tinnitus annoyance scale, according to the VAS, following the 16-week follow-up. The treatment group also revealed greater improvement in anxiety symptoms as noted by the clinician's rating, via the Hamilton Anxiety Scale (HAS), and the self-administered scale, via the Comprehensive Psychopathological Rating Scale (CPRES-S-A). Improvement of depression in the treatment group was only reported via the self-administered scale. Zöger et al. (2006) postulated that the improvement in tinnitus may be due to a reduction of comorbid psychiatric symptoms. Further research is needed to determine if sertraline is an effective treatment option for individuals who experience tinnitus regardless of comorbid psychiatric conditions.

Dib et al. (2007) investigated trazodone as a treatment for tinnitus following the theory that tinnitus could be caused by altered serotonin levels and alterations in receptors along the auditory pathway. They chose trazodone for its ability to block 5-HT2A e 5-HT2C serotonin receptors in the post-neuronal synapses and promote serotonin reuptake pre-synaptic inhibition.

Tinnitus intensity, level of discomfort, and life quality were assessed using Visual Analog Scales (VAS) before and after treatment. Dib et al. (2007) found significant improvement in these scores in both the treatment and the control groups with no significant differences between the two groups. Thus, they were unable to conclude that trazodone is an efficient treatment option for tinnitus.

Anti-inflammatories/Corticosteroids

The three articles that explored anti-inflammatories/corticosteroids as a treatment for tinnitus yielded varying results (Araújo et al., 2005; Elzayat et al., 2018; Sönmez et al., 2013). Araújo et al. (2005) explored dexamethasone as a follow-up to previous research which yielded positive results but did not utilize a control group (Sakata et al., 1982; Sakata et al., 1996). Araújo et al. (2005) attributed the improvement in tinnitus scores to a placebo effect, which they stated is common in any tinnitus treatment. Because there were no statistically significant differences between the two groups, Araújo et al. (2005) were unable to conclude that dexamethasone is an effective treatment for tinnitus.

Elzayat et al. (2018) explored dexamethasone as a treatment for tinnitus following research that yielded varying results of the use of intra-tympanic lidocaine, corticosteroids and/or aminoglycosides as a treatment for tinnitus in patients with Ménière's disease (Barrs, 2004). Elzayat et al. (2018) further postulated that steroids may suppress the irritability or hypersensitivity of the sensory cells in the cochlea and reduce the inflammation caused by immune-mediated, autoimmune dysfunction, and/or direct effect on the inner ear neuro-epithelium. Further research would be needed to determine the efficacy of an intra-tympanic injection of dexamethasone as a treatment for tinnitus, due to the small sample size and the fact that no placebo was utilized in this study.

Sönmez et al. (2013) hypothesized that the anti-inflammatory properties and well-being effect of ozone would affect tinnitus perception in their participants. They further postulated that with this type of treatment damage to the outer cell hair cells, which occurs due to cochlear perfusion damages or oxidative stress, would be avoided. Results of the Tinnitus Handicap Inventory (THI) revealed statistically significant improvement in participants that received ozone treatment. However, there were no statistically significant differences between this group and the control group which received no intervention at all. Due to this and the fact that ozone treatment is expensive, invasive, and requires special equipment, Sönmez et al. (2013) were unable to support the use of ozone as an effective treatment for tinnitus.

Anticoagulants/Antithrombotic

The one article identified in this review that explored anticoagulants/antithrombotic medications as a treatment for tinnitus revealed positive findings (El Beaino et al., 2018). El Beaino et al. (2018) chose to explore the effectiveness of sulodexide as an isolated treatment for tinnitus following previous research that utilized sulodexide in combination with melatonin for participants with tinnitus (Neri et al., 2009; Ferrari et al., 2015). In their study, El Beaino et al. (2018) found statistically significant improvement in Tinnitus Handicap Inventory (THI) scores and Mini-Tinnitus Questionnaire (Mini-TQ) scores following treatment of sulodexide. El Beaino et al. (2018) concluded that sulodexide should be further researched in a larger-scale trial to confirm or contradict the efficacy of the use of sulodexide as a treatment for tinnitus.

CONCLUSION

The economic and emotional impact of tinnitus is relatively large especially considering the estimated prevalence of 10-15% of adults in the United States experiencing tinnitus (Salvi et al., 2009; Tunkel et al. 2014). The purpose of this literature review was to explore the claims and

efficacy of medications marketed towards tinnitus relief medications that have been trialed in adult humans with tinnitus. Using a literature review of studies conducted over the last 22 years, nineteen different articles using one or two interventions from nine classes of drug treatments were identified. Nine of the nineteen studies identified in the present literature review revealed improvement in tinnitus symptoms as measured by various methods detailed previously (Han et al., 2012; Procházková et al., 2018; Savastano, 2004; O'Brien et al., 2019; Elzayat et al., 2018; Azevedo & Figueiredo, 2005; Stidham et al., 2005; Zöger et al., 2006; El Beaino et al., 2018). However, tinnitus and its etiology are multifaceted (i.e., noise-trauma, ototoxicity, aging, genetics) which presents a challenge for treatment (Salvi et al., 2019). Further research is needed to validate the claims made by these researchers for various reasons (i.e., larger, and more diverse sample sizes, integration of a placebo, longer duration of medication). This literature review provides clinicians with information regarding medications that have been trialed in adults to treat tinnitus. Finally, the present author does not recommend starting or stopping any medications without discussion with a physician.

TABLES

Table 1: Anticonvulsive/Antiepileptics

Authors/Year	Title	Participants	Methods and Measures	Results
Dehkordi, et al., 2011	Efficacy of Gabapentin on Subjective Idiopathic Tinnitus: A Randomized, Double-blind, Placebo-Controlled Trial	80 participants age 20-85 years; 31 men and 49 women; 40 in placebo group and 40 in treatment group; non-pulsatile tinnitus for at least two months	Gabapentin in ascending doses, starting with 600 mg/day and progressing to a maximum of 1,800 mg/day over a period of 8 weeks MRI; Loudness score; Tinnitus Severity Index (TSI); Audiologic testing	"No significant differences between the gabapentin and control groups in mean decreases in TSI value and loudness score"
Simpson et al., 1999	The Assessment of Lamotrigine, an Antiepileptic Drug, in the Treatment of Tinnitus	31 participants age 18-75 years; 19 men and 12 women; tinnitus present at least six months	One group received lamotrigine (25 mg daily for 2 weeks, 50 mg for 2 weeks and 100 mg for 4 weeks); The other group received a daily placebo tablet for 8 weeks; There was no washout period before the two groups began trial of other drug following the same regimen Questionnaires; Audiologic measures; Visual Analog Scale (VAS)	Treatment effective in "very few" participants

Table 2: Benzodiazepines

Authors/Year	Title	Participants	Methods and Measures	Results
Han et al., 2012	Clonazepam quiets tinnitus: A randomised crossover study with *Ginkgo Biloba*	38 participants; age 16-80 years; 27 men and 11 women; tinnitus present for at least two months	One group received Ginkgo biloba for three weeks starting with and initial daily 40 mg tablet of Ginkgo biloba. Participants increased the dose by one tablet every 3 days to a maximum of four tablets daily until they perceived a satisfactory decrease in tinnitus loudness or intolerable side effects; The other group followed the same regimen starting with an initial dose of a 0.5 mg tablet of clonazepam; Both groups underwent a two-week washout period before beginning a trial of the other drug Tinnitus pitch and loudness matching; Tinnitus Handicap Inventory; Visual Analogue Scales of loudness, duration, and annoyance	Scores from the tinnitus handicap inventory and the visual analogue scales of loudness, duration, and annoyance significant improved after the clonazepam trials; See Table 3 for results related to Ginkgo biloba

Table 3: Vitamins/Minerals/Antioxidants/Herbals

Authors/Year	Title	Participants	Methods and Measures	Results
Rojas-Roncancio et al., 2016	Manganese and Lipoflavonoid Plus® to treat tinnitus: A randomized controlled trial	40 participants; mean age of 56 years; 20 in treatment group and 20 in control group; tinnitus present for at least six months	Treatment group took manganese pills of 8 mg (corresponding to 8 mg of elemental manganese) together with Lipoflavonoid Plus'" pills three times a day for 6 months; Control group took only Lipoflavonoid Plus® pills three times a day for 6 months Tinnitus Handicap Questionnaire; Tinnitus Primary Functions Questionnaire; Subjective loudness/annoyance rating; Audiologic measures; Tinnitus loudness matching	Unable to conclude that either manganese or Lipoflavonoid Plus® is an effective treatment for tinnitus
Polanski et al., 2016	Antioxidant therapy in the elderly with tinnitus	58 participants; age 60 years and older	Six-month treatment of one of the following treatment groups: 1. dry extract of G. biloba (120 mg/day) 2. α-lipoic acid (60 mg/day) plus vitamin C (600 mg/day) 3. papaverine hydrochloride (100 mg/day) plus vitamin E (400 mg/day), and 4. placebo (starch capsules) Tinnitus Handicap Inventory (THI) Questionnaire	No benefit from the use of antioxidant agents for tinnitus

Table 3. Continued

Authors/Year	Title	Participants	Methods and Measures	Results
Procházková et al., 2018	Ginkgo biloba extract Egb 761® versus pentoxifylline in chronic tinnitus: A randomized, double-blind clinical trial	197 participants; age 30 years or more; tinnitus present for at least three months	One group received one film-coated tablet of 120 mg EGb 761® together with one pentoxifylline-like placebo tablet twice a day for 12 weeks while the other group received one extended-release tablet of 600 mg pentoxifylline together with one EGb 761®-like placebo tablet twice a day for 12 weeks 11-Point Box Scale; abridged Tinnitus Questionnaire (Mini-TQ); Hospital Anxiety and Depression Scale (HADS); Sheehan Disability Scale (SDS); otological examination; EEG measurements	Overall improved scores on all tinnitus-related scales for both groups with no significant differences between the two groups. Some adverse reactions were observed in both groups with the pentoxifylline group resulting in the most adverse events
Han et al., 2012	Clonazepam quiets tinnitus: A randomised crossover study with *Ginkgo Biloba*	38 participants; age 16-80 years; 27 men and 11 women; tinnitus present for at least two months	One group received Ginkgo biloba for three weeks starting with and initial daily 40 mg tablet of Ginkgo biloba. Participants increased the dose by one tablet every 3 days to a maximum of four tablets daily until they perceived a satisfactory decrease in tinnitus loudness or intolerable side effects; The other group followed the same regimen starting with an initial dose of a 0.5 mg tablet of clonazepam; Both groups underwent a two-week washout period before beginning a trial of the other drug Tinnitus pitch and loudness matching; Tinnitus Handicap Inventory; Visual Analogue Scales of loudness, duration, and annoyance	Ginkgo biloba did not reveal any significant improvements as measured by scores from the tinnitus handicap inventory and the visual analogue scales of loudness, duration, and annoyance; For results related to clonazepam, see Table 2

Table 4: Anesthetics

Authors/Year	Title	Participants	Methods and Measures	Results
Savastano, 2004	Lidocaine intradermal injection-A new approach in tinnitus therapy: Preliminary report.	68 participants; age 21-68 years; Treatment group received; 20 participants in the control group	Treatment group received 40 mg of lidocaine in 1 mL of saline in the external auditory canal in four locations (superior, posterior, inferior and anterior); Control group received saline injections in the same locations Self-evaluation scale of subjective disturbance and tinnitus intensity measurements	All participants in the treatment group reported improved scores of disturbance and tinnitus loudness. Participants in the treatment group who experienced tinnitus at intensity levels greater than 10 dB reported better tinnitus loudness outcomes
O'Brien et al., 2019	Transdermal lidocaine as treatment for chronic subjective tinnitus: A pilot study	30 participants; age 18 years and older with average age of 60 years; tinnitus present for at least six months	Participants were given a patch of 5% transdermal lidocaine to apply to their skin and alternate between 12 hours on and 12 hours off for one month. During the second month, participants were able to stop using the patch, continue with one patch, or increase to two patches daily. The participants were able to choose from the same options during the third month for a maximum of three patches per day. Tinnitus Functional Index (TFI)	Participants reported improved tinnitus scores on the Tinnitus Functional Index (TFI) after the first month of treatment. However, due to the small sample size and large dropout rate, the results may be misrepresented.

Table 4. Continued

Authors/Year	Title	Participants	Methods and Measures	Results
Elzayat et al., 2018	Evaluation of adding lidocaine to dexamethasone in the intra-tympanic injection for management of tinnitus: A prospective, randomized, controlled double-blinded trial	44 participants; age 30-65 years; tinnitus is non-pulsatile	Group A received a 1 ml intratympanic injection consisting of 2% lidocaine and 8 mg/2 ml dexamethasone (1:1 ratio); group B received a 1 ml intratympanic injection consisting solely of 8 mg/2 ml dexamethasone; Procedure was completed weekly for three weeks Tinnitus questionnaire: Arabic self-assessment tinnitus distress scale; Tinnitus Handicap Inventory (THI); Tinnitus Loudness Measure; Visual Analog Scale (VAS); audiometry; immittance	Participants in both groups showed improved tinnitus symptoms with group A having better results

Table 5: Antagonist Drugs

Authors/Year	Title	Participants	Methods and Measures	Results
Figueiredo et al., 2008	Tinnitus treatment with memantine	60 participants; tinnitus present for at least two months	Group M initially received memantine for 90 days with dosage increasing from 5 mg daily to 20 mg daily following a specific regimen; Group P initially received a placebo for 90 days with a similar regimen; Both groups completed a 30-day washout period before receiving the other intervention Tinnitus Handicap Inventory (THI); Audiologic measures	The researchers concluded that the evidence to support memantine as a treatment for tinnitus was insufficient
Hong et al., 2018	Effect of Nitrous Oxide as a treatment for subjective, idiopathic, nonpulsatile bothersome tinnitus: A randomized clinical trial	40 participants; age 18-65 years; non-pulsatile tinnitus present for at least six months	Half of the participants initially received an inhalation of 50% nitrous oxide concentration for 40 minutes while the other half of the participants received an inhalation of 50% nitrogen and 50% oxygen for 40 minutes. The participants then had the other intervention at least 14 days later. Tinnitus Functional Index (TFI); Patients' Global Impression of Change (PGIC); Global Bothersome Scale (GBS)	Treatment was no more effective than placebo as a treatment for tinnitus symptoms

Table 5. Continued

Authors/Year	Title	Participants	Methods and Measures	Results
Azevedo et al., 2005	Tinnitus treatment with acamprosate: Double-blind study	50 participants; age 35-82 years; tinnitus present for at least one month	Treatment group (n=25) received 333 mg acamprosate TID for 90 days; Control group (n=25) received placebo for 90 days Self-evaluation scale of subjective disturbance; Progression of tinnitus scale; Audiologic measures	Participants in the treatment group reported significant improvement in tinnitus symptoms
Stidham et al., 2005	Evaluation of botulinum toxin A in treatment of tinnitus	30 participants; age 31-73 years; non-pulsatile tinnitus present for at least 5 months	Treatment arm 1 initially received botulinum toxin A injection and after four months they received a placebo injection of saline; Treatment arm 2 initially received a placebo injection of saline and after four months they received an injection of botulinum toxin A; Injections were administered subcutaneously into 3 sites: 1 cm above superior aspect of auricle, 1 cm behind superior aspect of auricle, and 1 cm behind inferior aspect of auricle Tinnitus Handicap Inventory (THI); Tinnitus matching test (pitch/intensity); Tinnitus rating scale (TRS); Hearing rating scale; Patient questionnaires; Audiologic measures	Participants reported improved Tinnitus Handicap Inventory (THI) scores and patient subjective results after receiving the botulinum toxin A injection

Table 6: Vasodilators

Authors/Year	Title	Participants	Methods and Measures	Results
Sönmez et al., 2013	The evaluation of ozone and betahistine in the treatment of tinnitus	68 participants; age 20-75 years; tinnitus present for at least six months	Participants were randomized into two treatment groups; Fifteen participants denied treatment and were allocated to the control group; The betahistine group received daily 48 mg tablets; The ozone group were administered 10 sessions of ozone intravenously for two weeks Tinnitus matching (pitch/intensity); Tinnitus Handicap Inventory (THI); Audiologic measures	The researchers concluded that the evidence to support ozone and betahistine as a treatment for tinnitus was insufficient
Hester et al., 1998	Cyclandelate in the management of tinnitus: A randomized, placebo-controlled study	59 participants; age 19-74 years; 42 men and 17 women; non-pulsatile tinnitus present for at least one year	Experimental group received 400 mg cyclandelate to take three times daily for three months; Control group received a lactose placebo for three months Tinnitus matching (pitch/intensity); Subjective questionnaire; Audiologic measures	Some of the participants in the experimental group reported significant improvement in subject tinnitus scores. However, negative adverse reactions were observed, and a significant percentage of participants stated they would not continue to use this treatment

Table 6. Continued

Authors/Year	Title	Participants	Methods and Measures	Results
Procházková et al., 2018	Ginkgo biloba extract Egb 761® versus pentoxifylline in chronic tinnitus: A randomized, double-blind clinical trial	197 participants; age 30 years or more; tinnitus present for at least three months	One group received one film-coated tablet of 120 mg EGb 761® together with one pentoxifylline-like placebo tablet twice a day for 12 weeks while the other group received one extended-release tablet of 600 mg pentoxifylline together with one EGb 761®-like placebo tablet twice a day for 12 weeks 11-Point Box Scale; abridged Tinnitus Questionnaire (Mini-TQ); Hospital Anxiety and Depression Scale (HADS); Sheehan Disability Scale (SDS); otological examination; EEG measurements	Overall improved scores on all tinnitus-related scales for both groups with no significant differences between the two groups. Some adverse reactions were observed in both groups with the pentoxifylline group resulting in the most adverse events

Table 7: Antidepressants

Authors/Year	Title	Participants	Methods and Measures	Results
Zöger et al., 2006	The effects of sertraline on severe tinnitus suffering-A randomized, double-blind, placebo-controlled study	76 participants; age 18-65 years	Treatment group received a daily 25 mg tablet of sertraline for the first week which was increased to a daily tablet of 50 mg tablet of sertraline for the following 15 weeks; Control group received placebo for 16 weeks Tinnitus Severity Questionnaire (TSQ); Visual Analog Scale (VAS) of tinnitus loudness and tinnitus annoyance; Hamilton Depression Rating Scale; Hamilton Anxiety Rating Scale; Comprehensive Psychopathological Rating Scale (CPRS-S-A); Assessment of Side Effects Questionnaire; Audiologic measures	Results showed that sertraline was more effective than the placebo. The researchers also implied that this effect could be explained by a reduction in psychiatric symptoms
Dib et al., 2007	Tinnitus treatment with trazodone	85 participants; age 45-80 years; tinnitus present for at least one year	Treatment group (n=43) received a daily 50 mg tablet of trazadone for 60 days; Control group (n=42) received a daily placebo tablet for 60 days Visual Analog Scale (VAS) of tinnitus intensity, life quality impact and level of discomfort; Audiologic measures	Both groups reported improvement of tinnitus symptoms but there was no statistically significant difference between the two groups. The researchers concluded that trazadone was not efficient controlling tinnitus with the dosage used in the study.

Table 8: Anti-inflammatories/Corticosteroids

Authors/Year	Title	Participants	Methods and Measures	Results
Araújo et al., 2005	Intratympanic dexamethasone injections as a treatment for severe, disabling tinnitus: Does it work?	36 participants; age 20-80 years	Treatment group was administered weekly 0.5 mL intratympanic injections of 4 mg/mL dexamethasone on the side(s) in which tinnitus was experienced for 4 weeks; Control group was administered weekly 0.5 mL intratympanic injections of isotonic sodium chloride (saline) for 4 weeks Visual Analog Scale (VAS) of tinnitus intensity; Tinnitus questionnaire focused on duration, laterality, subjective hearing loss, known etiology and previous treatments; Lab bloodwork; Audiologic measures	A small portion of participants in each group showed significant improvement in tinnitus symptoms. However, there were no statistically significant differences between the two groups. Thus, the researchers attributed the improvement these participants experienced to a "placebolike" effect.
Elzayat et al., 2018	Evaluation of adding lidocaine to dexamethasone in the intra-tympanic injection for management of tinnitus: A prospective, randomized, controlled double-blinded trial	44 participants; age 30-65 years; tinnitus is non-pulsatile	Group A received a 1 ml intratympanic injection consisting of 2% lidocaine and 8 mg/2 ml dexamethasone (1:1 ratio); group B received a 1 ml intratympanic injection consisting solely of 8 mg/2 ml dexamethasone; Procedure was completed weekly for three weeks Tinnitus questionnaire: Arabic self-assessment tinnitus distress scale; Tinnitus Handicap Inventory (THI); Tinnitus Loudness Measure; Visual Analog Scale (VAS); audiometry; immittance	Participants in both groups showed improved tinnitus symptoms with group A having better results

Table 8. Continued

Authors/Year	Title	Participants	Methods and Measures	Results
Sönmez et al., 2013	The evaluation of ozone and betahistine in the treatment of tinnitus	68 participants; age 20-75 years; tinnitus present for at least six months	Participants were randomized into two treatment groups; Fifteen participants denied treatment and were allocated to the control group; The betahistine group received daily 48 mg tablets; The ozone group were administered 10 sessions of ozone intravenously for two weeks Tinnitus matching (pitch/intensity); Tinnitus Handicap Inventory (THI); Audiologic measures	The researchers concluded that the evidence to support ozone and betahistine as a treatment for tinnitus was insufficient

Table 9: Anticoagulants/ Antithrombotic

Authors/Year	Title	Participants	Methods and Measures	Results
El Beaino et al., 2018	Sulodexide monotherapy in chronic idiopathic subjective tinnitus: A randomized controlled trial	124 participants; age 30-75 years; non-pulsatile tinnitus present for at least one year	Treatment group took one 25 mg tablet of sulodexide twice daily for 40 days; Control group took one placebo tablet twice daily for 40 days Tinnitus Handicap Inventory (THI); Mini-Tinnitus Questionnaire (Mini-TQ)	Participants in the treatment group showed improvement in tinnitus related scores

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