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The Management and Outcomes of Pharmacological Treatments for Tinnitus

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Abstract: Tinnitus, a phantom sensation experienced by people around the world, currently is endured without a known cure. Some find the condition tolerable, while others are tortured on a daily basis from the incessant phantom noises. For those who seek treatment, oftentimes, they have a comorbid condition (*e.g.*, depression, anxiety, insomnia), which is treated pharmaceutically. These products aim to reduce the comorbities associated with tinnitus thereby minimizing the overall burden present. Because of the phantom nature of tinnitus, it is often compared to neurologic pain. Since pain can be managed with pharmaceutical options, it is reasonable to assume that similar agents might work to alleviate tinnitus. The effects of antidepressants, benzodiazepines, anticonvulsants, and glutamate antagonists are reviewed in this paper. Table **1** summarizes the pharmaceutical products discussed. Due to the variety of comorbid factors and potential causes of tinnitus, there may not be one pharmaceutical treatment that will combat every type of tinnitus. Nevertheless, a product that finally addresses the true cause of tinnitus, and not just its comorbidities, will benefit millions of people worldwide.

Keywords: Angiotensin-converting enzyme (ACE), anticonvulsants, antidepressants, benzodiazepines, COX2, cyclooxygenase (COX)1, glutamate antagonists, tinnitus, vitamins.

INTRODUCTION

Tinnitus is a medical term used to describe a sensation of sound when no external source is present. It is also called an auditory phantom sensation. For some patients, the sensation is relatively tolerable, soft-sounding, and intermittent. For others, the noise can be loud, incessant, and life-changing. Often, there may be a sudden onset accompanying noise trauma, or a gradual progression with age. It may sound like a hissing, sizzling, ringing, or roaring noise. The sensation may be perceived in one ear, both, or central in the head. Both subjective and objective forms of tinnitus exist, with objective tinnitus being much more rare. The focus of this review will be on the subjective form of tinnitus and how pharmacological treatments aim to ameliorate this debilitating and world-wide affliction.

In the United States, 25.3% of adults experience tinnitus, with 7.9% experiencing it frequently [1]. A Norwegian study found that 21.3% of men and 16.2% of women experience tinnitus of varying degrees [2]. Roughly 4.4% of men and 2.1% of women report high intensity tinnitus. Another study in England saw a prevalence of 10.1% adults with tinnitus [3]. Ranges of 0.5% to 2.8% were found for moderately annoying to life-altering levels of tinnitus. The above studies noted that the findings are consistent throughout the world, resulting in 10-20% of the global population experiencing tinnitus, with 1-2% claiming severe tinnitus [1]. With roughly 50 million Americans and an even larger global community affected by this symptom, it is disconcerting that there is still no Food and Drug Administration (FDA)/ European Medicines Agency (EMA) approved drug on the market to specifically treat tinnitus, much less an ideal drug.

EMOTIONAL/AFFECTIVE COMPONENT OF TINNITUS

Tinnitus has much comorbidity, which is often exacerbated by the incessant phantom sound. Oftentimes, individuals have accompanying symptoms including: frustration, irritability, anxiety, depression, hearing difficulties, hyperacusis, insomnia, and concentration difficulties. In addition, severe depression can aggravate tinnitus. This list is not exhaustive, but already indicative of a huge burden and an impact on the quality of life sufferers can experience. Many pathways in the brain are associated with these comorbid factors. Distress and mood networks, including the orbitofrontal cortex, the posterior cingulate cortex, the anterior cingulate cortex, and the bilateral posterior parahippocampal-hippocampal interface, have been shown to activate in patients who suffer from tinnitus [4-7]. Both auditory and non-auditory structures are co-activated at different levels, including the amygdala, hippocampus, anterior insula, anterior cingulate, and thalamus [8]. Since

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Table 1. Pharmaceutical treatment effects on tinnitus.

Drugs	Authors	Subjects	Placebo Controlled	Dosage	Results	Side Effects
Lidocaine	Melding, *et al*. (1978)	78	Open-label	1-2 mg per kg of body weight intravenously for 3-4 minutes	Highly effective in patients with Organ of Corti damage	None
Nortriptyline	Sullivan *et al*. (1989)	19	Placebo-washout	Maximum 50 to 150 mg per day	Tinnitus loudness and severity decreased	Dry mouth, dyspepsia, constipation, orthostatic hypotension
	Sullivan *et al*. (1993)	92	Placebo controlled	50 to 150 mg/mL for six weeks	Depression and tinnitus loudness decreased	Anticholinergic side effects, sedation
Amitriptyline	Podoshin *et al*. (1995)	218	Placebo controlled	10 mg 3x/day for 10 weeks	Improvement in more than 40%	Sedation
	Bayar *et al*. (2001)	37	Placebo controlled	50 to 100 mg daily for six weeks	Decreased tinnitusintensity and subjective relief	Sedation, dryness of mouth
	Mendis *et al*. (2008)	1	Case study	10 mg for three days	Neurologic foot pain resolved	Tinnitus
Imipramine	Tandon *et al*. (1987)	475	Chart review	150 to 250 mg per day	Depression improved	Tinnitus
	Evans *et al*. (1981)	1	Case study	15 to 45 mg per day	No improvement in depression	Tinnitus
Sertraline	Zoger *et al*. (2006)	76	Placebo controlled	25 to 50 mg daily for 16 weeks	Improved loudness, severity	Sexual side effects
Paroxetine	Robinson *et al*. (2005)	115	Placebo controlled	Maximum of 50 mg per day for 100 days	No better than placebo	Sexual dysfunction, drowsiness, dry mouth, sweating, insomnia, gastrointestinal distress, tremor, headache
Alprazolam	Johnson *et al*. (1993)	36	Placebo controlled	0.25 or 0.5 mg for one week, increased to maximum of 1.0 mg for some for 56 days	Reduction in loudness	Excessive drowsiness; more dreams
	Jalali *et al*. (2009)	36	Placebo controlled	0.5 mg 1-3 times per day for 8 weeks	No improvement	None
Clonazepam Ginkgo biloba	Han *et al*. 2012)	38	Open-label	0.5 mg Clonazepam; 4.0 mg GB increased from 1 to 4 doses per day for 5 weeks	Clonazepam more effective than GB; tinnitus annoyance, duration, and loudness decreased	Drowsiness
Gabapentin	Bauer *et al*. (2006)	39	Placebo controlled	Maximum 2,400 mg for 20 weeks	Decrease in annoyance	Dizziness, fatigue
	Witsell *et al*. (2006)	76	Placebo controlled	1800 mg daily for five weeks	No significant difference	Mouth sores, decreased libido
Amino-oxyacetic Acid	Reed *et al*. (1985)	10	Placebo controlled	50 to 75 mg four times a day for one week	Subjective lessening of tinnitus in 3/10	Worsening of tinnitus upon withdrawal; dizziness, lightheadedness, disequilibrium, nausea, and headache at higher doses (400 mg/day)
Lamotrigine	Simpson *et al*. (1999)	31	Placebo controlled	25 to 100 mg daily for 8 weeks	No significant difference	Nausea, vomiting, headache

Table 1. contd…

Drugs	Authors	Subjects	Placebo Controlled	Dosage	Results	Side Effects
Carbamazepine	Donalson I (1981)	62	Placebo controlled	100 mg	No significant difference	Tinnitus returned rapidly post-injection
Memantine	Figueiredo *et al*. (2008)	43	Placebo controlled	5 to 10 mg 1-2 times per day for 90 days	No significant difference	Dizziness, high blood pressure, insomnia, stomachache
Flupirtine	Salembier *et al*. (2006)	24	Open-label	100 mg twice a day for three weeks	No significant difference	Amnesia and concentration disorders
Neremexane	Suckfull *et al* (2011)	320	Placebo controlled	25 to 75 mg daily for 16 weeks	Decreased annoyance and impact on life at higher dosage	Dizziness, headache, vertigo, fatigue, hypertension
Acamprosate	Azevedo *et al*. (2007) Sharma *et al*. (2012)	50 40	Placebo controlled Placebo controlled	333 mg 3x daily for three months 333 mg TDS 3x daily for 45 days	Improvement over placebo Significant improvement over placebo	Epigastralgia, choking Worsening intensity (2 participants)
Cyclobenzaprine	Coelho at al. (2011)	49	open-label	max high dose: 30 mg; max low dose: 10 mg	high dosage saw a reduction in THI	dry mouth, sleepiness, constipation
	Vanneste *et al*. (2013)	95	open-label	10 mg 2x/day for 4 weeks	reduction in distress and intensity	worsening intensity
Naltrexone	Vanneste *et al*. (2013)	106	open-label	up to 50 mg for four weeks	tinnitus distress reduced in some	none
Deanxit	Meeus *et al*. (2011)	28	placebo-controlled	1 mg per day for three weeks	3/28 report tinnitus improvement	none
Betahistine	Sonmez *et al*. (2013)	68	placebo-controlled	48 mg per day for three months	slight improvement in loudness and on THI	pyrosis, nausea
Pramipexole	Sziklai *et al*. (2011)	40	placebo-controlled	maximum dosage: 0.7 mg 3x/day for 4 weeks	35% of pramipexole group improved	dizziness, allergic reactions
Piribedil	De Azevedo *et al*. (2009)	56	Placebo-controlled	50mg daily	No difference from placebo	Nausea, dizziness
Simvastatin	Canis *et al*. (2011)	94	placebo-controlled	40 mg/day for 4 months	reported improvement but not significant	worsening tinnitus
Vitamin B12	Berkiten *et al*. (2013)	83	placebo-controlled	1 g/mL injected daily for 5 days, then once a month for 12 months	no significant change	N/A
Zinc	Coelho *et al*. (2013)	89	placebo-controlled	220 mg zinc sulphate daily for 4 months	no significant change	indigestion

chronically depressed tinnitus patients may respond, for example, to a different treatment than those with acute noise-induced tinnitus without depressive symptoms, it may be useful to organize tinnitus patientsinto multiple subgroups to optimize treatment. Therapy options targeting specific tinnitus patient subgroups will be discussed later in this paper.

PHARMACOLOGICALLY TREATABLE

Tinnitus was originally thought to have a cochlear origin. However, severing the vestibulocochlear nerve was often ineffective in disrupting the phantom sound, suggesting an alteration to the neuronal activity in the central nervous system [9]. Where the most common cause of tinnitus is age-related hearing loss, many other common causes of tinnitus include noise trauma, ototoxic drugs, and head and neck injuries [10]. These incidents can cause problems anywhere along the auditory pathway. Because of the variety of triggers and pathways associated with tinnitus, it is reasonable to assume that more than one cause exists. Moller [11] suggested that in order to find the cause, it is important to find the anatomical structure involved. Knowing more about the particular abnormalities associated with each form

of tinnitus would provide insight to the variety of causes of tinnitus. Finally, reviewing the development of these features would direct research towards finding the mechanism(s) responsible.

Tinnitus is often studied in relation to pain disorders, as central neuropathic pain also has no known cause [12-15]. Similar to tinnitus, pain disorders cause phantom sensations and these have been studied in more detail than tinnitus. Likewise, there is much literature on depression and other emotional disorders associated with tinnitus. These disorders are related to tinnitus through the non-classical pathway of the auditory system, which may be activated in some forms of tinnitus, and through the somatosensory and limbic systems [16-18].

As pharmacological treatments can modulate the neural activity effectively, it is logical that such types of treatments could and would be effective for tinnitus. Of course, it is difficult to localize a treatment and there are almost always side effects that accompany administration of a particular drug. Lidocaine, given intravenously to target the voltage-gated sodium channels, effectively reduced tinnitus in 70% of patients [19]. Unfortunately, when switched to an oral dosage, the results were not promising. Nevertheless, there is support for the treatment of tinnitus using pharmacological methods.

PHARMACOLOGICAL OPTIONS

A major problem with pharmacological tinnitus research is that animal data rarely translate to humans, which is analogous to what has been seen in other treatments for tinnitus [20, 21]. For example, memantine seems efficacious in rats [22], but not in humans [23], which is similar to findings with carbamazepine [24, 25], and baclofen [26].

Without comparable animal studies, human pharmacological trials have no solid guidance. Therefore, most pharmacological studies in humans are solely based on theoretical or clinical underpinnings. Often, pharmacologically treatable co-morbidities are addressed, such as in depression. Sometimes medications that are efficacious in neuropathic pain are tried because of the clinical [12-14], pathophysiological [14, 15] and surgical treatment similarities [27-30] between tinnitus and pain. Several tricyclic antidepressants, anticonvulsants and naltrexone have been tried for the aforementioned reasons. Other pharmacological approaches, *e.g*., muscle relaxants, address the sensorimotor modulation of tinnitus [31].

Furthermore, researchers havestudied glutamatergic hyperactivity [32, 33] and GABA-ergichypoactivity [34] noted in animal research. These studies have triggered the use of memantine, GABA-ergic drugs, and acamprosate for clinical trials. Some medications attempted to improve rheology to the cochlea, as cochlear hypoperfusion was assumed to be an important cause of tinnitus,based on trials with Ginkgo biloba. Still, other studies assume tinnitus is a consequence of auditory neuropathy and attempt to treat it with Vitamin B12. In sum, due to the lack of reliable animal data available for translation to human subjects, a variety of theoretical and clinical motivations are used to justify the use of pharmacological agents.

Antidepressants

Because of the chronic and debilitating nature of tinnitus for some patients, depression is not an uncommon associated condition. Several researchers have looked to antidepressants as a possible treatment for patients with tinnitus and co-existing depression. Tricyclic antidepressants and selective serotonin-reuptake inhibitors were found to be ineffective for tinnitus [35]. In addition, side effects of sedation, sexual dysfunction, and dry mouth were reported. However, two studies looking at the tricyclic antidepressant, nortriptyline, found that patients suffering from depression and severe tinnitus improved with treatment in contrast to the placebo group [36, 37]. The two studies by Sullivan *et al*. [36, 37] were very similar, with an improved methodology and larger sample size in the latter. The 1993 study gave an initial bedtime dosage of 25mg, which was increased by an additional 25mg per week. At 100mg, blood levels were assessed and monitored to stay between 50-150 ng/mL for six weeks. Depression and tinnitus loudness decreased more in patients who were severely depressed. Despite these potentially positive effects, all of the participants had depressive symptoms or major depression before treatment, which limits the results to a subgroup of tinnitus patients. Furthermore, the measures between these groups were not statistically significant. Anticholinergic side effects and sedation were reported by those who used nortriptyline.

Another tricyclic antidepressant, amitriptyline, was tested by Podoshin *et al*. [38]. One group was given 10mg of amitriptyline hydrochloride for 10 weeks, while a second group used a biofeedback device; each group had an associated placebo group. Amitriptyline decreased tinnitus in 27.5% of subjects at rest and in 15.8% of subjects during activity [38]. However, a greater percentage of biofeedback users (43.5%) saw improvement during rest. Amitriptyline showed no significant advantage over placebo treatment. Side effects from amitriptyline (*e.g*., sedation) were minimized by administering a low dosage. Nonetheless, seven patients discontinued treatment. Later, another study with 20 subjective tinnitus patients and 17 placebo subjects was conducted – neither group suffered from depression [39]. Test subjects received 50mg of amitriptyline per day the first week and 100 mg per day the following five weeks. Only minor side effects of sedation and dryness of mouth were reported. Tinnitus severity was reported to decrease following treatment in 95% of the test group and only 12% in the placebo group.

Contrary to the above potentially promising studies, tricyclic antidepressants have also been shown to induce tinnitus. Typically, tinnitus will resolve within seven days of terminating the use of amitriptyline; however, there have been cases where tinnitus continued for more than seven months post-treatment [40]. Imipramine administration appeared to *cause* tinnitus in 1% of subjects [41]. Evans and Golden [42] suspected that the administration of imipramine causes a neurologic response or change in blood flow, which creates an autonomic imbalance. Case studies report tinnitus starting between three days and three weeks post treatment.

A randomized, double-blind, placebo-controlled study looked at the effects of sertraline on tinnitus patients who were at high risk for severe and disabling tinnitus [43].

Subjects were given 25 mg/day for the first week and 50mg/day for the following 15 weeks. Scores on the Tinnitus Severity Questionnaire decreased more in test subjects than in the placebo group. Depression and anxiety scores also improved. These improvements were seen in only some of those who completed the study; a high dropout rate of 17% was experienced after onset of sertraline administration. Those who discontinued the study had less comorbid depressive and anxiety disorders than those who participated in the study.

In a double-blind placebo controlled study, chronic tinnitus patients were given up to 10mg/day of paroxetine the first week, increasing up to 50mg/day [44]. The study treatment lasted 100 days in total. Twenty-six patients dropped out due to adverse side effects. Of the 115 subjects who completed the study, the maximum dosage was taken, on average, for 31 days. One significant treatment effect was the decrease in reported aggravation caused by tinnitus, which was seen more in the test subjects than the placebo group. However, baseline and post-treatment measures indicated that treated and placebo subjects did not significantly differ on tinnitus, psychological, or depressive measures.

Meeus, De Ridder, and van de Heyning [45] looked at the combination of Deanxit (0.5 mg of flupentixol and 10 mg of melitracen) and Clonazepam (1 mg) and its effect on 28 tinnitus patients. Flupentixol is used as an anti-psychotic medication and melitracen is an anti-depressant. Clonazepam treats seizures, anxiety, and pain disorders. Original recruitment of 35 participants was reduced to 28 for a variety of reasons (*i.e*., forgetting the pill and seeing no improvement). Their prospective, double-blind, randomized, placebo-controlled, crossover design administered the treatment daily for three weeks. Group 1 received three weeks of treatment (clonazepam + deanxit), one week of washout, and three weeks of placebo (clonazepam + placebo).Group 2 received treatment in the opposite order.When asked how their tinnitus changed after therapy, three out of the 28 tinnitus patients reported improvement in tinnitus, while zero patients reported improvement post-placebo. This indicates that clonazepam + deanxit or deanxit alone is more effective than clonazepam alone.

One study looked at whether pramipexole (dopamine receptor agonist) has any influence on presbycusis-related tinnitus [46]. In a randomized, prospective, placebo-controlled, double-blinded study, 40 participants completed the protocol. Some participants dropped out before completion due to dizziness, noncompliance, allergic reactions, and accidental intake of sedatives. Twenty received pramipexole and 20 received placebo tablets. Dosage was increased from 0.088 mg 3x/day to 0.7 mg 3x/day for the first three weeks, and then reduced back to 0.088mg 3x/day by the end of the fourth week. At the end of the trial, 45% of the placebo group reported improvement in tinnitus loudness. One-fourth of the pramipexole group experienced tinnitus cessation, and a total of 35% of the pramipexole group saw significant improvement on Tinnitus Handicap Inventory (THI).

Piribedil, a nonergot D2/D3 dopamine receptor agonist, was tested on 100 participants who had tinnitus for at least two months [47]. Pre-treatment testing included electro-cochleography and otoacoustic emissions. For 90 days, participants received either 50mg once a day or placebo. Treatments were switched after a 30 day washout period. Nineteen participants dropped out because of side effects (nausea, dizziness) and another 25 withdrew consent before starting treatment. Results on the Tinnitus Handicap Inventory and visual analog scale revealed no significant difference post-treatment and no significant difference between treatment and placebo findings. In a review by Salvi *et al*. (2009), the authors concluded that certain drugs targeting dopamine receptors may benefit tinnitus sufferers, but further research is needed to better explain and support previous findings [48].

Benzodiazepines

Benzodiazepines, the main group of anxiolytics, reduce anxiety and induce sleep, among other effects. Due to the co-occurrence of anxiety and tinnitus, certain benzodiazepines have been administered as possible tinnitus treatment options. Alprazolam has been prescribed as an anxiolytic and antidepressant. A double-blind study looked at the effects of alprazolam on 40 subjects who took 0.25mg to 0.5mg for one week at bedtime [49]. The dosage was increased to either twice or three times a day, depending on patient tolerance, for a total of 12 weeks. The results obtained at weeks 4 and 12 indicated a reduction in loudness for 76% of the test group in contrast to 5% of the control group. Jalali *et al*. [50] also studied the effects of alprazolam on tinnitus relief. After following a 1.5mg/day regiment, test subjects expressed no benefit in regards to their tinnitus.

Han *et al*. [51] reviewed the effects of clonazepam and Ginkgo biloba in an open-label, randomized, crossover study with 38 subjects. The initial dosage of 0.5mg clonazepam and 4.0mg Ginkgo biloba was steadily increased every three days until a maximum of four tablets daily was taken. After five weeks, tinnitus was assessed and it was found that clonazepam was more effective than Ginkgo biloba in reducing tinnitus [51]. Tinnitus annoyance, duration, and loudness were all reduced between pre- and post-drug measurements using the Tinnitus Handicap Inventory. Ginkgo biloba showed no significant reduction in tinnitus. Forty-two percent of subjects on clonazepam reported side effects, the most common being drowsiness.

Anticonvulsants

Acoustic trauma patients have been known to suffer from tinnitus. One study administered gabapentin to acoustic trauma patients with chronic, moderate-to-severe tinnitus at a maximum dosage of 2,400mg/day over the course of 20 weeks [52]. Gabapentin appeared to be more helpful than placebo in reducing tinnitus annoyance for patients with acoustic trauma. However, the gabapentin showed no overall effect on the entire group. Rated loudness or intrusiveness showed no significant difference in comparison to control subjects. That same year, Witsell *et al*. [53] found that a dosage of 1800mg/day of gabapentin for five weeks did not have any significant impact or improvement over the placebo, as measured by the Tinnitus Handicap Inventory.

Anticonvulsants have been tested in regards to their effectiveness to reduce/treat tinnitus. A specific cohort with

cochlear lesions, who showed improvement from lidocaine injections, was treated with 25mg of amino-oxyacetic acid four times a day [54]. Upon stopping treatment, the patients noticed a worsening in tinnitus symptoms. Only four subjects reported a lessening in tinnitus, overall. Lamotrigine and carbamazepine showed relatively poor improvement [55, 56].

Glutamate Antagonists

Subjects in a prospective, randomized, double-blind, crossover study received memantine at dosages of 10 mg/day for the first two weeks, 15mg/day the following week, and 20mg/day until the 90th day [23]. No significant difference was seen between memantine and placebo groups. Similarly, flupirtine taken 2 x 100mg/day showed little improvement for tinnitus sufferers [57]. Neramexane at 25mg/day was not effective; however, those patients who could tolerate the higher doses of 50mg/day and 75mg/day saw improvement over the placebo group for tinnitus annoyance and impact on life [58].

Other Compounds

Sonmez, Kulahli, Vural, Sahin& Aydin [59] wanted to test the effects of an anti-vertigo drug, Betahistine, on tinnitus patients because of its vasoactive effects on the inner ear. Forty-eight milligrams of Betahistine per day for three months was compared to 10 sessions of ozone treatment twice a week. For the ozone sessions, 100 mL of the patient's blood was extracted and then administered intravenously as a blood-gas mixture with a 1:1 volume of oxygen and ozone. Results indicated no significant improvement on tinnitus loudness for the two test groups, nor the control group. Scores on the Tinnitus Handicap Inventory improved for about half the patients in the ozone and betahistine groups and about one-third of the control group. Side effects included pyrosis and nausea in the betahistine group. No clinical benefit was seen for betahistine over ozone, other than being non-invasive and less expensive.

Simvastatin, a cholesterol-lowering medication, was tested on tinnitus patients to see if lowering the plasma LDL levels might relieve symptoms [60]. Ninety-four participants completed the study. The test group, including 58 participants, received 40 mg of simvastatin per day for four months, while another group (N = 36) received 120 mg of Ginkgo biloba per day for four months. After the four months, these participants were used as the control group. Although 46% of participants in the simvastatin group reported improvement, 21% reported worsening tinnitus and there was no statistically significant difference between pre- and post-measures. No significant difference was seen for the participants in the Ginkgo biloba group, either.

Since acamprosate has a similar chemical structure to GABA, and GABA may beinvolved in the formation of tinnitus, the effects of acamprosate on tinnitus were explored. Acamprosate, typically used to treat alcohol dependency, was given to tinnitus sufferers at a lower dosage than what is used with alcohol dependent individuals. When given 333 mg/day for three months, 87% of tinnitus subjects showed improvement after 90 days of treatment [61]. The placebo group improved 44% in the same period. Thirteen percent of the participants reported no improvement. The researchers emphasized that treatment should last at least three months; yet, no cure is guaranteed.

Sharma *et al*. [62] conducted a prospective, randomized double-blind, placebo controlled, cross over study. Forty participants received 333mg transdermal system (TDS) acamprosate or placebo three times a day. After 45 days, participants had a washout week followed by another 45 days of the opposite treatment (placebo for those who just completed the acamprosate treatment and acamprosate for those who just took the placebo). Of all the participants included in this study, 92.5% had improvement in their tinnitus scores; however, 77.5% of them reported less than 50% improvement. Six participants said improvement was greater than 50% and five patients declared tinnitus cessation. Side effects of treatment included worsening symptoms in two patients. In addition, 12.5% of participants taking placebo reported improvement. It is important to keep in mind that this experiment focused on participants whose tinnitus had a sensorineural origin and their conclusions are specific to that specific tinnitus subgroup.

Naltrexone, an opioid antagonist, is usually prescribed for opioid and alcohol addiction. However, it has also been tried with people who suffer from chronic pain disorders. Since pain and tinnitus appear to have similarities, as previously stated, naltrexone was tested on a group of people suffering from tinnitus. One-hundred and sixteen participants completed a placebo-controlled trial [63]. Over the course of four weeks, 86 participants, split into three groups, received 5, 12.5, or 50 mg of naltrexone. Thirty participants did not receive treatment. Ten participants dropped out because they did not take the treatment or did not attend appointments (leaving 76 subjects in the naltrexone group). In the 50mg group, six out of 16 participants had a significant reduction in tinnitus distress.Intensity did not change in any group. Placebo participants saw no reduction in distress or intensity.

Muscle Relaxants

Coelho *et al*. [64] looked at muscle relaxants to see their effects on tinnitus patients. The drugs tested were: cyclobenzaprine (14 subjects at high dosage, 6 subjects at low dosage), orphenadrine (12 subjects), tizanidine (3 subjects), and eperisone (14 subjects). Maximum dosages per group over a 14 week period were as follows: 30 mg (high) or 10 mg (low) of cyclobenzaprine, 200 mg of orphenadrine, 24 mg of tizanidine, and 50 mg of eperisone. Administration of low dose cyclobenzaprine and eperisone stopped after 12 weeks. When comparing baseline and week 12 results, only subjects taking cyclobenzaprine at a high dosage saw a reduction on the THI. Tinnitus severity decreased, but these results were not producible at a lower dosage. Adverse events across drugs included: dry mouth, sleepiness, and constipation, and several others. A placebo-controlled study also looked at the effects of cyclobenzaprine on tinnitus patients [65]. Participants in the drug group received 10 mg twice a day for four weeks. Results, pre- and post-treatment saw a significant decrease in distress (24% of participants) and intensity (25% of participants). However, 10 patients reported worsening intensity. Greatest results

were seen in those with little distress and tonal, unilateral tinnitus.Interestingly, Coelho *et al*. [64] could not find significant results at a lower dosage (10 mg) of cyclobenzaprine, but Vanneste *et al*. [65] did see a decrease in distress and intensity when participants took 20 mg per day in a shorter amount of time. The larger sample size in the study by Vanneste *et al*. may have played a role in these findings.

Vitamins

In addition to pharmacological medications, certain studies have looked at the use of vitamins to treat tinnitus. Vitamin B12 deficiency is associated with axonal degeneration, demyelination, and neuronal death. Berkiten *et al*. [66] investigated the relationship among hearing loss, tinnitus, and B12 deficiency. Participants were considered B12 deficient if their serum cobalamin was below 180 pg/mL. Sixty-three subjects received vitamin B12 treatment, which consisted of 1 g/mL injected intramuscularly once a day for five days, followed by treatments once a month for 12 months. Although eight participants receiving treatment reported some relief from tinnitus, scores on the visual analog scale were not statistically significant pre- and post-treatment. Severity of tinnitus also did not change significantly. The researchers concluded that vitamin B12 replacement therapy was not effective in treating this cohort of tinnitus participants.

A treatment for tinnitus using zinc sulphate capsules was administered to participants 60 years and older, as individuals over 60 years of age often have zinc deficiency [67]. Eighty-nine participants were randomized into two groups. Participants either received 220 mg of zinc sulphate or placebo treatment once a day for four months. Following a washout period of 30 days, those who had taken the zinc capsules received placebo treatment and those who had received placebo treatment were switched to zinc capsules. Few participants saw improvement in loudness or annoyance. Results on the Tinnitus Handicap Questionnaire post-treatment were not significantly different than those seen post-placebo. What is more, 2% saw improvement with placebo. Indigestion was reported as an adverse event from zinc intake.

FUTURE POSSIBILITIES

Certain drugs can cause tinnitus [41]. If the drugs that have tinnitus as a side effect are reviewed, perhaps it would provide information about the pathophysiology of tinnitus. A first attempt of looking at tinnitus from this angle was already done [68]. When looking at drugs that cause tinnitus as a side effect, cyclooxygenase (COX)1 and COX2 were more common than chance in being targeted in the tinnitus network. Hyperacusis and hearing impairment also shared networking neighborhoods with COX1 and COX2. Considering that these are targets of salicylates, which have ototoxic effects, a relationship with tinnitus can be presumed. Future investigations may focus on COX1/COX2 and other specific targets throughout the tinnitus network. SLC6A4 and 5HTA1, related to serotonin, are possible emergent targets to pursue, as well, because of serotonergic-related effects on the central nervous system. It might also be of interest to further review angiotensin-converting enzyme (ACE) and its relation to tinnitus, as ACE inhibitors were specific to the tinnitus network. ACE-targeting drugs may impact brain activity and induce tinnitus. As previously mentioned, tinnitus can be divided into several subgroups, so one target in the brain is not going to resolve all symptoms, but there is enough evidence to support pursuing individual targets.

RESEARCH AND DEVELOPMENT CONSIDERATIONS

A few thoughts have been proposed as to why a treatment has yet to be discovered. For one, lack of clinical trials with clear methodology and analytic procedures has left much unclear. There is still limited understanding of tinnitus because of inadequate animal models and lack of serendipitous discoveries. No standardized protocol for FDA/EMA approval exists; therefore, the first drug to prove effective will have to pave the way through the approval and legalization process.

MEDICAL NEED

As previously mentioned, tinnitus affects the global community, with 1-2% reporting to experience severe tinnitus [1]. Comorbidities, such as depression, anxiety, irritability, *etc.*, can exacerbate the condition for many afflicted with this condition. The combination of increasing industrial and leisure noises with longer lifespans and hearing loss dramatically impacts the tinnitus sufferers of today and of the future. In 2012, the United States Veterans Administration Annual Benefits Report reported tinnitus as the most prevalent service-connected disability [69]. Additionally, the number of prescriptions written each year in the US and Europe is over four million, all of which are off-label and have not been FDA approved to treat tinnitus [70]. Many patients turn to phone applications or self-medicate to find some form of relief. Because of the limited treatment currently available for patients, many clinicians are eager to have a product that would provide significant relief to tinnitus patients. At this point, individuals suffering from severe tinnitus would probably accept even the smallest amount of relief; however, a drug that could completely eliminate this phantom sensation should be the ultimate goal.

CONCLUSIONS

Tinnitus presents a global challenge and yet the time until a solution arrives is unknown. It may be that a pharmaceutical treatment has not yet been discovered because of the heterogenetic nature of the tinnitus. Certain subtypes of tinnitus may respond to drugs better than other subtypes. Regardless of the “off-label” drug prescribed, they all focus on comorbid factors of tinnitus and do not directly address the tinnitus. These drugs may offer coping strategies and minor relief, but they are not a cure. A better understanding of the underlying mechanisms and more translational research are important for future domination of this intolerable condition.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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