ORIGINAL ARTICLE
NEURO-OTOLOGY AND VESTIBULAR DISORDERS
DOI: 10.5152/B-ENT.2021.20151

Analysis of factors affecting the success of betahistine treatment in patients with idiopathic subjective tinnitus

Mehmet Murat Gunay[1], Deniz Baklaci[2], Ihsan Kuzucu[3]

[1]Department of Otolaryngology, Kahta State Hospital, Adıyaman, Turkey
[2]Department of Otolaryngology, Bülent Ecevit University Faculty of Medicine, Zonguldak, Turkey
[3]Department of Otolaryngology, Medisun Private Hospital, Ankara, Turkey

Cite this article as: Gunay MM, Baklaci D, Kuzucu I. Analysis of factors affecting the success of betahistine treatment in patients with idiopathic subjective tinnitus. B-ENT 2020; 16(3): 158-63.

ABSTRACT

Objective: This study aimed to evaluate betahistine treatment efficacy and factors affecting the success of betahistine treatment in patients with subjective idiopathic tinnitus.

Methods: A total of 91 patients diagnosed with subjective idiopathic tinnitus were included in the study. The study group consisted of 61 patients treated with betahistine for three months. The control group consisted of 30 patients who did not receive any treatment. The severity of tinnitus and its effects on quality of life (QOL) and sleep were evaluated using the Tinnitus Handicap Inventory (THI) and Visual Analog Scale.

Results: According to the THI results, there was clinical improvement in 25 of 61 patients (41%) treated with betahistine and in 6 of 30 patients (20%) in the control group, which indicated a significant difference ($p<0.05$). Compared with the control group, there was a statistically significant decrease regarding the duration of tinnitus and annoyance in the treatment group ($p<0.05$). According to the multivariate analysis, improvement in tinnitus was increased by the absence of a history of betahistine use within the past year, by having a normal level of vitamin B12, by every one-year reduction in age, and by having stable tinnitus loudness.

Conclusion: Betahistine treatment applied for three months in patients with subjective idiopathic tinnitus improves the QOL and reduces the severity of tinnitus.

Keywords: Betahistine, THI, tinnitus, treatment, VAS

Introduction

Tinnitus is defined as a phantom auditory perception in one or both ears or the head in the absence of any external stimulus (1). The perceived sound is often expressed as humming, ringing, whistling, buzzing, hissing, or clicking. Tinnitus can be categorized as subjective or objective. Subjective tinnitus is the most common type and is audible only to patients, whereas objective tinnitus is rarely seen and can be heard by both the patient and the observer (2). A total of 30-40% of adults experience tinnitus in their lifetimes, and the incidence increases with age (3, 4). Complaints caused by tinnitus can be evaluated in a wide range from hardly noticeable to serious. Approximately 3-4% of the population has severe tinnitus complaints leading to distress and negatively affecting the quality of life (QOL) (1, 5).

Tinnitus is a multifactorial disorder; however, its etiology has not yet been clarified. It is considered to be a result of aberrant neural activity and generates at any location along the auditory pathway from the cochlea to the auditory cortex (1). There are also other theories indicating the possible role of the disturbances of cochlear microcirculation and intracochlear calcium, outer hair cell damage, cochlear neurotransmission, and retro-cochlear and central mechanisms (6, 7).

Treatment is necessary in cases with severe tinnitus that interferes with the QOL, but there is no consensus on the optimum treatment modality. Various treatments have been proposed for tinnitus, such as pharmacological agents, intratympanic injection of steroids, tinnitus retraining therapy, hearing aid fitting, sound masking, transcranial stimulation of the brain, acupuncture, and surgical destruction of the vestibular system

Corresponding Author: Deniz Baklaci, doktorent@gmail.com
Received: November 19, 2020 **Accepted:** January 18, 2021
Available online at www.b-ent.be

CC BY 4.0: Copyright@Author(s), "Content of this journal is licensed under a Creative Commons Attribution 4.0 International License."

(8-14). Medications frequently used include anticonvulsants, antidepressants, vasomodulators, and Ginkgo biloba (8-10). Betahistine is another pharmacological agent that may have beneficial effects in the treatment of tinnitus (15-17). Nevertheless, a recent review suggested that there was still no sufficient evidence on whether betahistine was effective in treating tinnitus.

The purpose of this study was to evaluate the influence of various factors on betahistine treatment efficacy in patients with subjective idiopathic tinnitus (18).

Methods

This retrospective, nonrandomized controlled study was accepted with the decision number 2019/10-27 by the Ethics Committee of the university. No written informed consent was received from the patients before inclusion owing to the retrospective design of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. There was no conflict of interest or source funding.

We retrospectively reviewed the medical data of patients who presented to our clinic between May 2019 and December 2019 with subjective tinnitus. Patients underwent a neurotological evaluation, which included clinical history as well as an ear, nose, and throat (ENT) examination and audiological and radiological assessments. Hearing was assessed using pure tone audiometry, speech recognition, and tympanometry. Magnetic resonance imaging (MRI) was conducted in patients with unilateral tinnitus complaints and asymmetric sensorineural hearing loss during the audiological evaluation. Blood tests, including complete blood count, biochemical parameters, lipid panel, thyroid function, vitamin B_{12}, prothrombin time, and activated partial thromboplastin time analyses, were performed.

The study included 91 patients aged between 18 and 65 years who presented to the outpatient clinic with the complaint of nonpulsatile tinnitus and were diagnosed with subjective idiopathic tinnitus according to anamnesis, ENT examination, and audiological and radiological evaluation. The study group consisted of 61 patients with subjective tinnitus who were treated with betahistine. The control group consisted of 30 patients diagnosed with subjective idiopathic tinnitus who did not receive betahistine treatment owing to contraindications, such as gastrointestinal hemorrhage caused by peptic ulcer, uncontrolled or severe bronchial asthma, and hypersensitivity to the drug. The patients who did not accept medical treatment were also included in the control group.

Main Points:

- Betahistine is one of the most prescribed drugs to reduce the severity and manage the complaints associated with subjective idiopathic tinnitus.
- The factors affecting the success of betahistine treatment in patients with subjective idiopathic tinnitus were evaluated.
- It was shown that 48 mg daily betahistine treatment applied for three months in patients with subjective idiopathic tinnitus can improve the quality of life and reduce the severity of tinnitus in select patients.
- Improvement in tinnitus was increased by the absence of a history of betahistine use within the past year, a normal level of vitamin B12, every one-year reduction in age, and stable tinnitus loudness.

Patients with objective tinnitus, middle ear disease, chronic suppurative otitis media, serous otitis media, otosclerosis, Meniere's disease, conductive type hearing loss, a history of neurotological surgery, head trauma, acoustic trauma, epilepsy, neuropsychiatric diseases, depression, and systemic diseases except hypertension (HTN) or diabetes mellitus (DM) under control and pregnant and lactating women were excluded. In addition, two patients who were diagnosed with cerebellopontine angle tumors on the basis of posterior fossa MRI (one with meningioma and the other with acoustic neuroma) were excluded. Both had unilateral subjective tinnitus complaints.

All patients were evaluated in terms of smoking and alcohol consumption, comorbidities (HTN and DM), hyperlipidemia (HPL), medications used, and noise exposure in the workplace. The history of betahistine use for subjective idiopathic tinnitus in the past year was also recorded.

The severity of tinnitus and its effects on the QOL and sleep were statistically evaluated using the Tinnitus Handicap Inventory (THI) and the Visual Analog Scale (VAS) (19-22). The adapted Turkish version of THI was used (23). VAS was used to measure subjective distress caused by tinnitus in the domains of severity of tinnitus (VAS-1), frequency and duration of tinnitus (VAS-2), annoyance (VAS-3), concentration difficulty (VAS-4), and sleep disturbances (VAS-5), in which higher scores indicated a greater level of distress. In addition, we recorded the duration and intensity of tinnitus, distribution on the basis of the time of day, and progression of tinnitus loudness from the onset of symptom to presentation at the outpatient clinic. We classified tinnitus loudness as progressive or stable. In terms of duration, we divided all the cases into acute (<3 months), subacute (3-6 months), and chronic tinnitus (>6 months). According to the distribution based on the time of day, we classified the cases as all-time continuous, all-time intermittent, or only at night. For intensity, we used the categories of only in a quiet environment, suppressed by environmental sounds, and not suppressed by environmental sounds.

In the study group, all patients with tinnitus received 24 mg betahistine twice a day after meals for three months. Any other tinnitus medication was stopped. Treatment with betahistine was well tolerated with no severe adverse effects that would make it necessary to terminate the drug in any of the patients in the study group.

The patients with comorbidities continued to use their regular medications. In the control group, no medical treatment for tinnitus was given to the patients. The THI and VAS scores were obtained at the beginning of the study, and a follow-up evaluation was undertaken three months after the onset. The improvement criterion was at least a 10-point reduction in THI.

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA) was used for statistical analyses. Data were expressed as mean, standard deviation

Table 1. Clinical characteristics of the patients

Characteristics	Control group (n=30) n	%	Study group (n=61) n	%	p
Sex					
Female	14	46.7	21	34.4	0.259
Male	18	53.3	40	65.6	
Noise exposure in the workplace					
Absent	24	80	48	78.7	0.885
Present	6	20	13	21.3	
Smoking					
Absent	22	73.3	43	70.5	0.778
Present	8	26.7	18	29.5	
Alcohol consumption					
Absent	30	100	59	96.7	1.000
Present	0	0	2	3.3	
Comorbidities					
Absent	27	90	48	78.7	0.183
Present	3	10	13	21.3	
Hypertension					
Absent	29	96.7	53	86.9	0.262
Present	1	3.3	8	13.1	
Diabetes mellitus					
Absent	28	93.3	56	91.8	1.000
Present	2	6.7	5	8.2	
Hyperlipidemia					
Absent	25	83.3	46	75.4	0.391
Present	5	16.7	15	24.6	
Vitamin B12 deficiency					
Absent	27	90	52	85.2	0.744
Present	3	10	9	14.8	
Medications used					
Absent	30	100	54	88.5	0.091
Present	0	0	7	11.5	
Side					
Unilateral	25	83.3	46	75.4	0.391
Bilateral	5	16.7	15	24.6	
History of betahistine use					
Absent	27	90	52	85.2	0.744
Present	3	10	9	14.8	
Hearing loss					
Absent	29	96.7	56	91.8	0.659
Present	1	3.3	5	8.2	

p<0.05

(SD), percentage (%), median, and minimum and maximum values. Shapiro-Wilk test was used to check the normality of the data. Chi-square and Fisher's exact tests were employed for the comparison of categorical data between groups. Mann-Whitney U and Wilcoxon tests were employed for non-parametric variables, and Student's *t*-test and paired samples *t*-test were used for parametric variables. A logistic regression analysis was undertaken to investigate the predictive role of the variables associated with response to treatment in multivariate analyses. P-<0.05 were considered statistically significant.

Results

The study group consisted of 61 patients (40 males, 65.6% and 21 females, 34.4%) with ages varying between 18 and 65 years (mean 40.69±14.48 years), and the control group comprised 30 patients (16 males, 53.3% and 14 females, 46.7%) with ages varying between 20 and 63 years (mean 37.00±13.03 years). There was no statistically significant difference between the study and control groups in terms of age, sex, noise exposure in the workplace, smoking, alcohol consumption, comorbidities (HTN and DM), HPL, vitamin B_{12} deficiency, medications used, tinnitus side, or history of betahistine use (p>0.05) (Table 1). The mean bone conduction pure tone thresholds (average of 500, 1,000, and 2,000 Hertz) were within normal limits, and there was no significant difference between the groups (p>0.05). There was also no statistically significant difference in terms of the duration of tinnitus and the progression of tinnitus loudness. However, in the study

Table 2. Comparison of the characteristics of tinnitus between groups

Characteristics of tinnitus	Control group (n=30) n	%	Study group (n=61) n	%	p
Progression of tinnitus loudness					
Stable	25	83.3	47	77	0.488
Progressive	5	16.7	14	23	
Duration					
Acute	11	36.7	28	45.9	0.625
Subacute	3	10	7	11.5	
Chronic	16	53.3	26	42.6	
Distribution based on the time of day					
All-time continuous	15	50	18	29.5	0.016
All-time intermittent	5	16.7	29	47.5	
Only at night	10	33.3	14	23	
Intensity					
Only in quiet environment	12	41.4	17	27.9	0.004
Not suppressed by environmental sounds	14	48.3	16	26.2	
Suppressed by environmental sounds	3	10.3	28	45.9	

p<0.05

Table 3. Comparison of tinnitus VAS scores between groups

VAS scores	Day 0 mean±SD median (min-max)	At third month mean±SD median(min-max)	p
VAS-1			
Control group (n=30)	6.13±1.80 6 (2-10)	4.13±3.32 5.5 (0-9)	0.001
Study group (n=61)	5.98±1.81 6 (2-10)	4.21±3.93 5 (0-9)	0.000
p**	0.575	0.948	
VAS-2			
Control group (n=30)	5.63±2.58 5 (1-10)	4.18±3.32 6 (0-9)	0.004
Study group (n=61)	5.26±2.45 5 (1-10)	2.90±1.69 4 (0-9)	0.000
p**	0.475	0.015	
VAS-3			
Control group (n=30)	6.93±2.44 8 (1-10)	4.43±3.61 5.25 (0-9)	0.000
Study group (n=61)	6.49±2.40 7 (1-10)	2.93±1.46 3 (0-9)	0.000
p**	0.257	0.004	
VAS-4			
Control group (n=30)	4.57±2.61 4.25 (1-9)	3.28±1.17 3 (0-9)	0.008
Study group (n=61)	4.60±2.57 4.5 (1-9)	3.38±3.13 3 (0-10)	0.000
p**	0.956	0.917	
VAS-5			
Control group (n=30)	5.53±3.20 6.5 (1-10)	3.33±3.25 2.5 (0-9)	0.000
Study group (n=61)	5.56±3.26 6 (1-15)	3.51±3.31 3 (0-10)	0.000
p**	0.997	0.860	

**p<0.05; VAS, Visual Analog Scale.

Table 4. Factors increasing improvement in tinnitus

Factors	Odds ratios	95% confidence interval	p
Every one-year reduction in age	1.090	1.045-1.138	0.000
No vitamin B12 deficiency	5.172	1.066-25.100	0.041
No history of betahistine use	6.362	1.141-35.483	0.035
No progression of tinnitus loudness	7.572	1.991-28.802	0.003

p<0.05

group, all-time intermittent and suppressed by environmental sounds tinnitus types were seen at a statistically significantly higher rate than in the control group (p<0.05).

In the study group, unilateral tinnitus was present in 46 patients (75.4%): 24 patients had it in the left ear, and 22 patients had it in the right ear. Tinnitus was present for at least one month, with the mean duration of a symptom being calculated as 4.63±2.33. A total of 28 patients (45.9%) in this group had acute tinnitus, seven (11.5%) had subacute, and 26 (42.6%) had chronic tinnitus. Tinnitus was classified as all-time continuous in 18 patients (29.5%), all-time intermittent in 29 (47.5%), and only at night in 14 (23%). Tinnitus was stable in 47 patients, whereas 14 patients reported progression in tinnitus loudness from the onset of the disease to presentation at the clinic (Table 2).

Evaluation of THI and VAS scores

The comparison between the initial and three-month THI scores revealed clinical improvement in 25 of 61 patients (41%) treated with betahistine and in six of 30 patients (20%) in the control group, indicating a significant difference (p<0.047). There was also a statistically significant improvement in all VAS scores in the betahistine treatment group (p<0.05). Compared with the control group, there was a statistically significant decrease in the VAS-2 and VAS-3 scores of the study group (p<0.05). The mean and SD for the VAS scores are presented in Table 3.

In the univariate analysis, the factors affecting the improvement in tinnitus according to the THI score were determined as age, smoking, DM, and history of betahistine use (p<0.05). Comparing the effect of tinnitus characteristics (duration and intensity of tinnitus, distribution based on the time of day, and progression of tinnitus loudness), there was no statistically significant difference.

The multivariate logistic regression analysis showed age, vitamin B_{12} deficiency, history of betahistine use, and progression of tinnitus loudness as being related to improvement in tinnitus (Table 4). Although DM was a statistically significant factor in improvement according to the univariate analysis, it was not included in the multivariate logistic regression analysis model because none of the patients with DM in this group showed significant improvement. The multivariate analysis revealed that having no history of betahistine use in the past year, having a normal level of vitamin B_{12}, and having stable tinnitus loudness increased the improvement in tinnitus. In addition, every one-year decrease in age resulted in a 1.09-fold increase in the treatment success.

Discussion

Although tinnitus is a very common complaint and reduces the QOL in 3-4% of the population, there is not yet a consensus on the medical therapy of tinnitus (1, 5). As yet, no drug has been approved for tinnitus by the European Medicines Agency or the United States Food and Drug Administration (18). Nonetheless, drug therapies are frequently used to reduce the severity of tinnitus or manage complaints associated with this condition (8-10, 15-18). Betahistine is one of the most prescribed drugs for tinnitus both across the world and in Turkey. In England, over 100,000 prescriptions for betahistine are being filled every month for tinnitus (18). In this study, the betahistine treatment efficacy and the factors affecting the success of betahistine treatment in patients with subjective idiopathic

tinnitus were investigated through comparison with a group of patients who received no treatment. Betahistine dihydrochloride is a histamine-like drug that acts as an antagonist at H3 receptors and as a partial agonist at H1 receptors (22). It has been used for vertigo and tinnitus since it was first marketed in 1967. Betahistine improves endothelial permeability and local capillary dilatation with the H1 receptors located in the inner ear and increases the blood flow and reciprocal decrease in endolymphatic pressure (24). It also promotes and facilitates central vestibular compensation (25, 26). Betahistine is a generally well-tolerated drug with a similar risk of adverse effects to those of placebo treatments and is suitable for long-term treatment (18). With these favorable properties, betahistine presents as a good choice in the treatment of tinnitus (15, 27). However, in a systematic review in 2018, Wegner et al. (18) concluded that there was not sufficient evidence to suggest that betahistine had an effect on subjective idiopathic tinnitus when compared with placebo. In another recent review, no specific drug therapy with a sufficient level of evidence for the treatment of chronic tinnitus was found (28).

Sönmez et al. (17) compared betahistine and ozone in the treatment of chronic subjective tinnitus. In 26 patients who received betahistine treatment, there were statistically significant differences in THI but not for tinnitus loudness in terms of the pre- and post-treatment measures. However, there was no statistically significant difference when the treatment and control groups were compared. Similar to our study, the patients received 24 mg betahistine twice a day for three months, and no serious side effect was reported. The authors concluded that betahistine affected cochlear microcirculation, which could be responsible for the early stage of tinnitus; therefore, betahistine was more effective in patients who received this therapy in their early onset of complaints, but the authors were not able to further investigate this issue because their study sample consisted of only patients with chronic tinnitus cases (17). In our study, we also evaluated the effectiveness of betahistine treatment. We divided the patients into three groups of acute, subacute, and chronic tinnitus, but we observed no statistically significant difference between these groups ($p>0.05$). Thus, we consider that the effect of betahistine should not be limited to the regulation of cochlear microcirculation and that central compensation is among the considerable effects of betahistine.

Ma et al. (15) investigated whether betahistine mesylate combined with flunarizine hydrochloride was effective in treating tinnitus. They determined significant improvement in tinnitus loudness but not for the subjective tinnitus improvement rate in the betahistine treatment group. They observed the efficacy of these drugs after one week of treatment. In our study, compared with the control group, there was a significantly higher reduction in the THI and VAS scores in the betahistine treatment group.

In other words, it was determined that 48 mg daily betahistine treatment for three months in patients with subjective idiopathic tinnitus can reduce subjective idiopathic tinnitus and improve QOL in selected patients. Orhan et al. investigated the effect of betahistine, trimetazidine, and Gingko biloba in 90 patients with tinnitus and reported a statistically significant improvement in the betahistine group, but trimetazidine was more effective (29).

The results of our study and the literature show that betahistine can be preferred as a reliable drug with negligible side effects in patients with tinnitus, but there are still questions concerning which selective patients should receive this treatment and at which stage. Furthermore, the factors that affect the efficacy of treatment need to be further elucidated. Unfortunately, none of the studies in the literature examined the factors affecting the success of betahistine treatment in patients with subjective tinnitus. In the multivariate analysis in our study, we detected four parameters related to improvement in tinnitus: age, history of betahistine use, vitamin B_{12} deficiency, and progression of tinnitus loudness. Increased incidence of tinnitus with age is already known, but the effect of age on the drug therapy has not been evaluated in the literature (4). In our study, the response of young patients to betahistine treatment was found to be higher. However, the improvement rate was approximately six times lower among patients receiving betahistine treatment for tinnitus for at least one month within the last one year. We consider that it would be more appropriate to switch to other therapeutic methods in patients who use betahistine for tinnitus. The normal level of serum vitamin B_{12} increases the improvement rate by five times according to our study results. For this reason, we recommend that vitamin B_{12} level should be checked in patients with tinnitus and that vitamin B_{12} supplements should be provided if deficiency is detected. Similarly, in a study including 57 patients with chronic tinnitus, it was found that the incidence of vitamin B_{12} deficiency was significantly more in patients with tinnitus. Moreover, improvement in tinnitus and associated complaints were detected in 12 patients after vitamin B_{12} replacement therapy. In the light of these results, routine vitamin B_{12} serum levels determination is recommended by the authors when evaluating patients for chronic tinnitus (30). On the contrary, Berkiten et al. found no relationship between tinnitus severity and vitamin B_{12} deficiency. In addition, there was no effect of vitamin B_{12} replacement treatment in patients with tinnitus and hearing levels except for those with a hearing level at 250 Hz in pure tone audiometry (31). Finally, considering the results of our multivariate analysis, we can conclude that applying betahistine as a unimodal modality will not be sufficient in the management of cases with progressive tinnitus loudness.

Despite the strengths of this study, such as the relatively large sample size and the presence of a control group, there are also several limitations. First, the retrospective nature of the study and the lack of a control group to receive another treatment can be considered as weaknesses in the study design. In addition, because the follow-up evaluation of the patients was made immediately after the completion of the treatment, it is not possible to comment on whether treatment efficacy is temporary or permanent. Studies with a longer follow-up are needed. Finally, the VAS and THI scores are not sufficient to assess all the changes from the pretreatment to the post-treatment period in patients with tinnitus.

Further large randomized controlled studies are required to elucidate the direct effects of betahistine on patients with

subjective idiopathic tinnitus as well as to elucidate the indirect effects that may result from improvements in the QOL.

In conclusion, to apply an effective pharmacological or non-pharmacological therapeutic approach, the key step is the detection of possible causes in each individual case. However, our results indicate that betahistine has beneficial effects on patients with subjective idiopathic tinnitus in terms of reducing the severity of the condition and improving the QOL. In addition, concerning possible benefits that can be achieved before starting betahistine treatment, the patient's age, history of betahistine use in the past year, serum level of vitamin B_{12}, and progression of tinnitus loudness should be taken into consideration. In light of these results, the decision of whether to start betahistine treatment should be made on an individual basis for each patient.

Ethics Committee Approval: This study was approved by Ethics committee of Aksaray University Medical School, (Approval No: 2019/10-27).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Supervision – D.B., İ.K.; Design – M.G., D.B.; Supervision – D.B., İ.K.; Resources – M.G., D.B; Materials – M.G., D.B.; Data Collection and/or Processing – M.G., D.B.; Analysis and/or Interpretation – D.B., İ.K.; Literature Search – M.G., D.B.; Writing Manuscript – M.G., D.B.; Critical Review – D.B., İ.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 1990; 84: 221-54. [CrossRef]
2. Schleuning AJ 2nd. Management of the patient with tinnitus. Med Clin North Am 1991; 756: 1225-37. [CrossRef]
3. Zarenoe R, Torbjörn. Quality of life in patients with tinnitus and sensorineural hearing loss. B-ENT 2014; 10: 41-51. [CrossRef]
4. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med 2010; 123: 711-8. [CrossRef]
5. Michikawa T, Nishiwaki Y, Kikuchi Y, et al. Prevalence and factors associated with tinnitus: a community-based study of Japanese elders. J Epidemiol 2010; 20: 271-6. [CrossRef]
6. Zenner HP, Ernst A. Cochlear-motor, transduction and signal-transfer tinnitus: models for three types of cochlear tinnitus. Eur Arch Otorhinolaryngol 1993; 249: 447-54. [CrossRef]
7. Mazurek B, Stöver T, Haupt H, Gross J, Szczepek A. Die Rolle der kochleären Neurotransmitter in Bezug auf Tinnitus [The role of cochlear neurotransmitters in tinnitus]. HNO 2007; 55: 964-71. [CrossRef]
8. Hoekstra CE, Rynja SP, van Zanten GA, Rovers MM. Anticonvulsants for tinnitus. Cochrane Database Syst Rev 2011; 6: CD007960. [CrossRef]
9. Robinson S. Antidepressants for treatment of tinnitus. Prog Brain Res 2007; 166: 263-71. [CrossRef]
10. Von Boetticher A: Ginkgo biloba extract in the treatment of tinnitus: a systemic review. Neuropsychiatry Dis Treat 2011; 7: 441-7. [CrossRef]
11. Jastreboff PJ. 25 years of tinnitus retraining therapy. HNO 2015; 63: 307-11. [CrossRef]
12. Yakunina N, Lee WH, Ryu YJ, Nam EC. Tinnitus suppression effect of hearing aids in patients with high-frequency hearing loss: a randomized double-blind controlled trial. Otol Neurotol 2019; 40: 865-71. [CrossRef]
13. Tyler RS, Perreau A, Powers T, et al. Tinnitus sound therapy trial shows effectiveness for those with tinnitus. J Am Acad Audiol 2020; 31: 6-16. [CrossRef]
14. Tutar B, Atar S, Berkiten G, Üstün O, Kumral TL, Uyar Y. The effect of transcutaneous electrical nerve stimulation (TENS) on chronic subjective tinnitus. Am J Otolaryngol 2020; 41: 1023-6. [CrossRef]
15. Ma FR, Xin Y, Zhao YM, Lü JQ. Efficacy of betahistine mesilate combined with flunarizine hydrochloride for treating tinnitus. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2006; 41: 269-73.
16. Ganança MM, Caovilla HH, Gazzola JM, Ganança CF, Ganança FF. Betahistine in the treatment of tinnitus in patients with vestibular disorders. Braz J Otorhinolaryngol 2011; 77: 499-503. [CrossRef]
17. Sönmez O, Külahlı I, Vural A, Sahin MI, Aydın M. The evaluation of ozone and betahistine in the treatment of tinnitus. Eur Arch Otorhinolaryngol 2013; 270: 1999-2006. [CrossRef]
18. Wegner I, Hall DA, Smit AL, McFerran D, Stegeman I. Betahistine for tinnitus. Cochrane Database Syst Rev 2018; 12: CD013093. [CrossRef]
19. Skarżyński PH, Rajchel JJ, Gos E, et al. A revised grading system for the Tinnitus Handicap Inventory based on a large clinical population. Int J Audiol 2020; 59: 61-7. [CrossRef]
20. Adamchic I, Langguth B, Hauptmann C, Tass PA. Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus. Am J Audiol 2012; 21: 215-25. [CrossRef]
21. Aytac I, Baysal E, Gulsen S, et al. Masking Treatment and its Effect on Tinnitus Parameters. Int Tinnitus J 2017; 21: 83-9. [CrossRef]
22. Timmerman H. Histamine agonists and antagonists. Acta Otolaryngol Suppl 1991; 479: 5-11. [CrossRef]
23. Aksoy S, Firat Y, Alpar R. The tinnitus handicap inventory: a study of validity and reliability. Int Tinnitus J 2007; 13: 94-8.
24. Ihler F, Bertlich M, Sharaf K, Strieth S, Strupp M, Canis M. Betahistine exerts a dose-dependent effect on cochlear stria vascularis blood flow in guinea pigs in vivo. PLoS One 2012; 7: e39086. [CrossRef]
25. Dutia MB. Betahistine, vestibular function and compensation: in vitro studies of vestibular function and plasticity. Acta Otolaryngol Suppl 2000; 544: 11-4. [CrossRef]
26. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. CNS Drugs 2001; 15: 853-70. [CrossRef]
27. Gryczyńska D, Drobik-Wasiewicz K, Malicka M, Kotecki M. Szumy uszne i ich leczenie u dzieci [Therapy of tinnitus in children]. Otolaryngol Pol 2007; 61: 784-8. [CrossRef]
28. Zenner HP, Delb W, Kröner-Herwig B, et al. A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. Eur Arch Otorhinolaryngol 2017; 274: 2079-91. [CrossRef]
29. Orhan I, Aydın S, Altın G, Yılmaz F. Tinnituslu hastalarda trimetazidin, betahistin ve ginkgo biloba ekstresi etkinliğinin karşılaştırılması [An efficacy comparison of betahistin, trimetazidine and ginkgo biloba extract in patients with tinnitus]. Kulak Burun Bogaz Ihtis Derg 2013; 23: 143-7. [CrossRef]
30. Shemesh Z, Attias J, Ornan M, Shapira N, Shahar A. Vitamin B12 deficiency in patients with chronic-tinnitus and noise-induced hearing loss. Am J Otolaryngol 1993; 14: 94-9. [CrossRef]
31. Berkiten G, Yildirim G, Topaloglu I, Ugras H. Vitamin B12 levels in patients with tinnitus and effectiveness of vitamin B12 treatment on hearing threshold and tinnitus. B-ENT 2013; 9: 111-6.