Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://www.ijpca.org/

Short Communication

# Pharmacotherapy of tinnitus

**Sunil Chaudhry**[1,*]

[1]*Bioclinitech Technologies Pvt. Ltd, Mumbai, Maharashtra, India*

ARTICLE INFO

*Article history:*
Received 26-12-2020
Accepted 31-12-2020
Available online 13-01-2021

*Keywords:*
Tinnitus
Sytematic review
Hearing impairment
Antidepressants
Benzodiazepines

ABSTRACT

Tinnitus can vary widely with regard to pitch, loudness, description of sound, special localization, and temporal pattern. Tinnitus is sometimes the first sign of hearing loss in older people. It also can be a side effect of various medications (antibiotics, cancer drugs, quinine medications, antidepressants, aspirin) If the condition is left unattended for a prolonged period, it can also lead to psychological problems. Extensive reviews of randomized clinical trials have revealed that only nortriptyline, amitriptyline, alprazolam, clonazepam, and oxazepam are more beneficial than placebo.



## 1. Introduction

Tinnitus, originating from the Latin word 'tinnire' ('to ring'), is a perception of sound in proximity to the head with the absence of an external source. It may be described as buzzing, ringing, roaring, whistling or hissing and can be variable and complex.[1] Tinnitus is a very common complaint and affects 7% of population and has been associated with a range of physical and emotional disorders. The prevalence of tinnitus among those over 65 years of age ranges from 12% to 15%. In children the prevalence is 13%.[2] Tinnitus annoyance was stronger in the middle-age groups of women and men (45-59 years of age) than in younger patients and decreased again in older men (≥60 years of age), but not in older women.[3] Findings have shown that hearing loss, age, head injury, dizziness, meningitis, sinus and middle ear infections, mastoiditis, and migraine play a significant role in determining the annoyance level of tinnitus.[4] It has been estimated that 80% of all patients with hearing loss have tinnitus, and very likely 80% of all patients with tinnitus have hearing loss—thus indicating a high correlation, but certainly not causation. Tinnitus and auditory hallucinations are sensations of hearing in the absence of external sounds. Three main types can be identified:[1] objective tinnitus, which is caused by sounds generated somewhere in the body; subjective tinnitus, which is the perception of meaningless sounds without any physical sound being present; and auditory hallucinations, which are perceptions of meaningful sounds, such as music or speech. The latter two types are phantom sensations. Tinnitus is acute if the patient has experienced it for less than 3 months and is considered sub-acute after 3 months. It is termed "chronic" when the patient has experienced it for 6 months or more. Anxiety, depression, and insomnia are commonly found in patients with tinnitus. Non objective tinnitus is only heard by the patient. It is mainly nonpulsatile. Tinnitus may be objective in which case an observer (the physician) can also hear the sound, especially with a stethoscope. These sounds are frequently pulsating and may be due to a vascular tumour such as a glomus tumour, or due to an anterior-venous fistula.[5]

## 2. Mechanisms for Tinnitus Generation

1. Role for serotonin (5-HT) in persistent tinnitus was postulated by Simpson and Davies, based on the

* *Corresponding author.*
*E-mail address*: sunil.r.chaudhry@gmail.com (S. Chaudhry).

https://doi.org/10.18231/j.ijpca.2020.030

consideration that disrupted or modified 5-HT function might cause a reduction in auditory filtering abilities and in tinnitus habituation.
2. Intense noise and ototoxic agents initially damage the basal turn of the cochlea, and outer hair cells (OHCs), and only later affect inner hair cells (IHCs) if continued or repeated, IHCs being more resistant to such damage.
3. Tinnitus may be caused by increased neural activity in the auditory brainstem, where the brain processes sounds, causing some auditory nerve cells to become over-excited. The basis of this theory is that many with tinnitus also have hearing loss. Increased spontaneous discharge rate in subcortical auditory neurons and increased neural synchrony and hyperactivity in the auditory cortex (AC) are correlates of tinnitus..
4. Tinnitus generation made the assumption, either implicit or explicit, that it was associated with spontaneous overactivity of the cochlear nerve. Increased neural activity at levels above the cochlear nerve may be implicated in tinnitus generation.
5. Burst-firing can occur in the auditory nerve after exposure to kanamycin, and in the inferior colliculus after salicylate administration.[6]

### 2.1. Conditions that might cause tinnitus include

Ménière's disease, Loud noise exposure, Migraine headaches, Head injury, Brain infections like meningitis, syphilis, Lyme disease etc. Anemia, Hypertension Stress, Too much wax in the ear, Certain types of tumors. Tinnitus can also occur due to the discontinuation of therapeutic doses of benzodiazepines. It can sometimes be a protracted symptom of benzodiazepine withdrawal and may persist for many months. Medications such as bupropion may also result in tinnitus. Aminoglycoside antibiotics (like gentamycin, amikacin etc.), aspirin, loop diuretics, cancer chemotherapeutic agents etc can lead to tinnitus. Tinnitus can cause insomnia, and that tinnitus-related disability should be considered distinct from any disability associated with hearing loss.[7]

### 2.2. Diagnosis

Imaging techniques, including brain electrical activity mapping (BEAM), single photon emission computer tomography (SPECT), positron emission tomography (PET), magneto-electroencephalography (MEG), and functional MRI, offer the potential of an insight into the medical significance of tinnitus, underlying mechanisms of tinnitus production, and specifically neurologic/neurotologic implications both for tinnitus diagnosis/treatment.[8]

## 3. Management of Tinnitus

### 3.1. Lifestyle changes

1. Avoid exposure to loud noise
2. Foods do not directly cause tinnitus, but alcohol reduction may be helpful.
3. Caffeine reduction e.g. coffee, tea, colas, energy drinks.
4. Stress reduction e.g. regular exercise, yoga, or meditation.
5. Play soothing music or white noise at night if difficulty getting to sleep when there is no background noise.

### 3.2. Discontinuing ototoxic medications (e.g. NSAIDs, loop diuretics, antibiotics, beta-blockers)

### 3.3. Drug therapy for Tinnitus

#### 3.3.1. Benzodiazepines

Benzodiazepines, the positive allosteric modulators of the $GABA_A$ receptor are expected to potentiate the inhibitory neurotransmission and lessen tinnitus symptoms by reducing hyperactivity. Alprazolam reduced tinnitus loudness, measured with a tinnitus synthesizer and visual analog scale, in 76% of subjects, whereas only 5% showed a reduction in tinnitus loudness in the control group. In a prospective, randomized, single-blind clinical trial involving few patients per group, clonazepam significantly reduced tinnitus loudness and annoyance (visual analog scale) relative to the control group**.** Of all the benzodiazepines studied, only oxazepam and clonazepam were significantly more effective than antihistamines in suppressing chronic tinnitus.

#### 3.3.2. Antidepressants

As a treatment for tinnitus (case reports–fluoxetine and paroxetine, retrospective reviews–imipramine and selective serotonin reuptake inhibitors, single blind trials of amitriptyline and double blind placebo controlled trials of trimipramine, nortriptyline, paroxetine. Sertraline have reported some benefit.

In a randomized, double-blind, placebo-controlled study in patients without severe hearing loss but with depression, anxiety and a high risk for developing severe tinnitus, sertraline was shown to be significantly more effective than placebo in reducing tinnitus loudness or pitch.

**Sulpiride**, a dopamine D2 antagonist and atypical antipsychotic drug, significantly reduced tinnitus perception, modulating the auditolimbic dopaminergic pathway.

D2/D3 agonist, **Pramipexole**, produced a beneficial effect on psychoacoustic measures of tinnitus in presbycusis patients in a dose schedule accepted for the treatment of Parkinson's disease in elderly people.

*3.3.3. Carbamazepine*

Anticonvulsants reduce neuronal hyperexcitability through three main pharmacological mechanisms of action: halting depolarization by blocking voltage-dependent sodium channels, augmenting GABA action, and lessening glutamate transmission may provide tinnitus relief in roughly half the patients that respond positively to lidocaine. Carbamazepine and its analouge, oxcarbazepine are effective in decreasing tinnitus severity, but they are not significantly more effective than placebo.

*3.3.4. Gabapentin*

Enhances the stimulate release of GABA, increases GABA levels in patients 6 weeks' treatment with gabapentin 300 mg bid is effective in patients with acoustic tinnitus.

*3.3.5. Betahistine*

Betahistine is a weak histamine H1 receptor agonist and a potent histamine H3 receptor antagonist. One postulated mechanism of action of the drug is reduction of endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlea The daily dosage of 48 mg of betahistine during 120 consecutive days is useful to reduce or eliminate tinnitus in patients with vestibular disorders. A significant clinical improvement ($p<0.0001$) was seen in 30.5% of the patients treated with betahistine, when compared to 17.1% of patients who improved in the control group. In Ménière's disease patients there was tinnitus reduction with betahistine dimesylate (36 mg/day), as well as with a combination of 20 mg of cinnarizine and 40 mg of dimenhydrinate, and there was not statistically significant difference between the two treatment groups

*3.3.6. Lignocaine*

Lignocaine is thought to act centrally, probably at the level of the brainstem and reticular formation and suppresses this hyperactivity by virtue of its membrane stabilizing properties. Lignocaine iv is superior to a placebo in suppressing tinnitus. Further, the dose used was 3-4 mg/kg (maximum-200 mg). High positive response rates (~70%) have beenreported in some studies. Tocainide, an analogue of lidocaine that can be taken orally, was evaluated as a potential long-term therapy for tinnitus. Preliminary results were encouraging, several randomized, controlled studies found that tocainide had little benefit for tinnitus

*3.3.7. Melatonin*

A hormone produced Melatonin, a hormone produced by the pineal gland, may be a promising treatment option for tinnitus. by the pineal gland, may be a promising treatment option for tinnitus. Melatonin offers minimal risk of toxicity with modest daily doses such as 1 to 3 mg, as well as a low cost and favorable adverse effect profile for older adults. In addition to potential benefits in the treatment of tinnitus, melatonin also may have beneficial neurogenerative properties.

Zinc has a role in cochlear physiology and in the synapses of the auditory system, there is a plausible mechanism of action for this treatment. Zinc influences the biophysiological function of neural membranes and transmission. In the cochlea, levels of zinc are higher than in any other regions of the body. 50 mg of zinc per day for 4 months, Age > 60 seems to be sufficient. With decreasing serum zinc levels, tinnitus occurs at lower frequencies. In cases responding to therapy, the zinc replacement therapy may sometimes have to be continued for about 6 months. There were no severe adverse effects associated with zinc.

*3.3.8. Acamprosate*

Acamprosate had no beneficial effects after 30 days of treatment, a modest benefit at 60 days and a significant effect at 90 days. It presumably blocks excitatory glutamatergic N-methyl-d-aspartate (NMDA) receptors while enhancing $\gamma$-aminobutyric acid (GABA)-mediated nerve inhibition). However, some studies indicate that acamprosate enhances NMDA function. Acamprosate is an effective drug in treating the severity of sensorineural tinnitus without causing much of the side effects.

*3.3.9. Memantine*

Blocks the NMDA receptor used by glutamate and reduces its effect. A study on Memantine for tinnitus showed a strong suppressive effect on glutamate activity when the medication was applied by transtympanic perfusion.

*3.3.10. Neramexane*

Neramexane inhibits the excessive nerve excitation in the auditory pathway between the inner ear and cerebral cortex via NMDA antagonistic activity. Neramexane inhibits the nerve excitation in the inner ear via nicotinic acetylcholine receptor antagonistic activity. NMDA receptor antagonists have been reported to afford protection from hearing loss caused by free-radical-induced damage to the hair cells.

*3.3.11. Gacyclidine*

A non-competitive NMDA receptor antagonist, is a phencyclidine derivative with neuroprotective properties. For lasting effective treatment, controlled intracochlear and long-term delivery of the drug seems to be necessary.

*3.3.12. Misoprostol*

It inhibits the release of inflammatory cytokines. In a small, placebo-controlled, semi-crossover study, tinnitus was improved (reduced severity, improved sleep and concentration) in 33% of subjects during misoprostol treatment (escalating to 800 $\mu$g/day).

Sensorineural tinnitus, in patients having hyperlipidemia, can be successfully dealt with by treating hyperlipidemia with lipid lowering agent atorvastatin.

Neurokinin receptors are present in the inner ear, which has a potential therapeutic target for treating tinnitus. Vestipitant is an antagonist of the neurokinin-1 receptor, which usually binds substance P. Vestipitant and the combination of paroxetine are currently under clinical trials for treating patients with tinnitus. [9–15]

#### *3.3.13. Herbs*

50 mg Ginkgo biloba extract given 3 times daily for 12 weeks is no more effective than placebo in treating tinnitus.

Gushen Pian as is a novel Chinese medicinal herb, which is being used in the treatment of sensorineural hearing loss and tinnitus.

Panax ginseng, is considered that oxidative stress is the cause for idiopathic tinnitus and patients may take benefits from oral antioxidant therapy.

Garlic's effect on tinnitus is attributable to improve blood flow of cochlea as a result of its antiplaque formation ability and stabilizing blood pressure. [16,17]

## 4. Conclusion

Due to its diverse aetiology, pharmacotherapy of tinnitus has met with limited success. Cognitive and behavioral therapy, sound therapy, music therapy, tinnitus retraining therapy, massage and stretching of the neck and masticatory muscles have been associated with significant improvement in tinnitus. Electrical stimulation of the cochlea with trains of pulses at 5,000 pulses per second can substantially or completely suppress tinnitus with either no perception or only a transient perception of the stimulus. Drug therapies can be suited adjuvants to the other modalities of treatment. Surgical procedure for the treatment such as auditory nerve section, cochlear destruction has been tried with varying efficacy.

## 5. Source of Funding

None.

## 6. Conflict of Interest

The authors declare that there is no conflict of interest.

## References

1. Atik A. Pathophysiology and Treatment of Tinnitus: An Elusive Disease. *Indian J Otolaryngol Head Neck Surg*. 2014;66(1):1–5.
2. Makar SK, Biswas A, Shatapathy P. The Impact of Tinnitus on Sufferers in Indian Population. *Indian J Otolaryngol Head Neck Surg*. 2014;66(1):37–51.
3. Seydel C, Haupt H, Olze H, Szczepek AJ, Mazurek B. Gender and chronic tinnitus: differences in tinnitus-related distress depend on age and duration of tinnitus. *Ear Hear*. 2013;34(5):661–72.
4. Sindhusake D, Golding M, Wigney D, Newall P, Jakobsen K, Mitchell P. Factors Predicting Severity of Tinnitus: A Population-Based Assessment. *J Am Acad Audiol*. 2004;15(04):269–80. doi:10.3766/jaaa.15.4.2.
5. Møller AR. Pathophysiology of tinnitus. *Otolaryngol Clini N Am*. 2003;36(2):249–66. doi:10.1016/s0030-6665(02)00170-6.
6. Baguley DM. Mechanisms of tinnitus. *Drugs Future*. 2009;34(5):381–400.
7. Audiology Information Series, Tinnitus, American Speech Language information ; 2017.
8. Shulman A. Tinnitology: Recent Advances for Both Diagnosis and Treatment. *Int Tinnitus J*. 1998;4(1):5–9.
9. Salvi R, Lobarinas E, Sun W. Pharmacological treatments for tinnitus: New and old. *Drugs Future*. 2009;34(5):381. doi:10.1358/dof.2009.034.05.1362442.
10. Gerami, Hooshang, Nemati. Evaluation of Carbamazepine and Oxcarbazepine on Tinnitus Otolaryngology. *Med J Mashhad Univ Med Sci*. 2016;55(1):46–51.
11. Tabrizi AG, Naini AS, Baradaran N. Short-Term Effect of Gabapentin on Subjective Tinnitus in Acoustic Trauma Patients. *Iran J Otorhinolaryngol*. 2017;29(91):95–100.
12. Robinson SK, Viirre ES, Stein MB. Antidepressant therapy in tinnitus. *Hearing Res*. 2007;226(1-2):221–31. doi:10.1016/j.heares.2006.08.004.
13. Person OC, Puga MES, da Silva E, Torloni MR. Zinc supplementation for tinnitus. *Cochrane Database Syst Rev*. 2016;doi:10.1002/14651858.cd009832.pub2.
14. Hall DA, Wegner I, Smit AL, McFerran D, Stegeman I. Betahistine for tinnitus. *Cochrane Database Syst Rev*. 2018;doi:10.1002/14651858.CD013093.
15. Park SY. Pharmacological Treatments for Tinnitus. *Hanyang Med Rev*. 2016;36(2):113–9. doi:10.7599/hmr.2016.36.2.113.
16. Mahmoudian-Sani MMR, Hashemzadeh-Chaleshtori M, Samani A. Qian YangGinkgo biloba in the treatment of tinnitus: An updated literature review. *Int Tinnitus J*. 2017;21(1):58–62.
17. Bagherihagh A, Khosravi MH. Herbal Medicine in the Management of Tinnitus. *Head Neck Surg*. 2019;doi:10.5772/intechopen.81320.

## Author biography

**Sunil Chaudhry,** Honorary Medical Director

**Cite this article:** Chaudhry S. Pharmacotherapy of tinnitus. *Int J Pharm Chem Anal* 2020;7(4):188-191.