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Review

Pharmacological Treatments for Tinnitus

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Pharmacotherapy has been constantly chosen by the clinician among the available treatment options for tinnitus. Medications that have been prescribed off-label to treat tinnitus can be grouped into several categories: benzodiazepines, antidepressants, anticonvulsants, N-methyl-D-aspartate (NMDA) receptor antagonists, dopamine receptor modulators, muscle relaxants, and others. In this article, a wide variety of compounds once used in the treatment of tinnitus and evidenced by clinical trials are reviewed with respect to the mechanisms of action and the drug efficacy. Only a few of the various pharmacological interventions investigated have some beneficial effects against tinnitus: clonazepam, acamprosate, neramexan, and sulpiride. Sertraline and pramipexole were effective in subgroups of patients with psychiatric symptoms or presbycusis. However, no agents have been identified to provide a reproducible long-term reduction of tinnitus in excess of placebo effects. In rodent tinnitus models, L-baclofen, memantine, and KCNQ2/3 channel activators have been demonstrated to reduce tinnitus development. Limitation of the use of an effective high dosage during a longer treatment duration due to dose-dependent side effects of the centrally acting drugs may influence the results in clinical studies. More effective and safer innovative agents should be developed based on the further understanding of tinnitus neural mechanisms and valid animal models, and should be supported by improved clinical trial methodology. The management of tinnitus patients through a tailored treatment approach depending on the detailed classification of tinnitus subtypes will also lead to better treatment outcomes.

Key Words: Anticonvulsant; Antidepressants; Benzodiazepines; Dopamine Receptor Agonist; NMDA Receptor Antagonists

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INTRODUCTION

Chronic subjective tinnitus is a prevalent symptom, not a disease in adults. Epidemiologic studies of general populations have estimated tinnitus prevalence at 10-15% of the adult population. Approximately 1-2% are severely affected and 0.5% are unable to lead a normal life [1-3]. Briefly, one in ten adults has clinically significant subjective tinnitus and one in hundred is severely affected. In addition, there is a high incidence of tinnitus associated with both noise-induced and age-related hearing loss [1]. Tinnitus-related distress interferes with quality of life in severe tinnitus sufferers, but the cure remains a challenging territory until now. The difficulties in the treatment of tinnitus lie in multiple etiologies, heterogeneous symptoms, limited understanding of the pathophysiology, and complicating psychological factors. Although the exact mechanisms should continue to be under active investigation, it is relatively well-known that the generation of tinnitus signal is associated with abnormal neuronal hyperactivity, synchrony, and reorganization in the central auditory pathways. However, all tinnitus signals would not cause persistent tinnitus perception unless the auditory system is pathologically linked to the brain regions responsible for emotions or consciousness.

A comprehensive diagnostic assessment to identify the etiology and comorbidities is the basis of every successful tinnitus manage-

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ment [4]. Among the several treatment options available to tinnitus patients, pharmacotherapy has been constantly chosen by the clinician for decades. Medications that have ever been prescribed off-label to treat tinnitus patients are grouped into several categories: benzodiazepines, antidepressants, anticonvulsants, N-methyl-D-aspartate (NMDA) receptor antagonists, dopamine receptor modulators, muscle relaxants, and others (Table 1). Many of the agents have been used empirically without evidence, not supported by clinical trials. Apart from the poorly designed methodology, lack of a consistent outcome measure and substantial placebo effects on tinnitus have been thought to contribute to the low level evidence. In this article, a wide variety of compounds once used in the treatment of tinnitus and evidenced by clinical trials are reviewed. The mechanisms of action and the efficacy of the drugs will be discussed to provide clinicians with the useful information that may help them select the appropriate treatment.

PHARMACOLOGICAL TREATMENT

1. Benzodiazepines

Tinnitus perception has been hypothesized to arise partly from spontaneous neural hyperactivity in the central auditory system. Benzodiazepines, the positive allosteric modulators of the GABAA receptor are expected to potentiate the inhibitory neurotransmission and lessen tinnitus symptoms by reducing this hyperactivity. As they have also beneficial effects on comorbid anxiety and insomnia which are common in tinnitus patients, there remains the possibility that the effect of these drugs is the result of a general anxiolytic effect rather than a direct effect on the neurophysiological cause of tinnitus [5]. Six clinical trials of benzodiazepines revealed that benzodiazepine use for subjective tinnitus does not have a robust evidence base [6] (Table 2). Clonazepam has the most evidence to support its use [7-9]. The effectiveness of alprazolam is equivocal [10,11]. Diazepam had no effect and oxazepam was effective in only one study [7,12]. Benzodiazepines carry a risk of misuse or abuse and have a considerable list of adverse effects such as sedation, drowsiness, memory impairment, and unsteadiness. Clonazepam is relatively less likely to lead to abuse because of its longer half-life [6].

Table 1. Off-label drugs used in pharmacological treatments for tinnitus

Drug class	Agents
Benzodiazepines	Clonazepam, Alprazolam, Oxazepam, Diazepam
Antidepressants	Amitriptyline, Nortriptyline, Sertraline, Paroxetine
Anticonvulsants	Cabamazepine, Gabapentine, Lamotrigine
NMDA receptor antagonists	Acamprosate, Neramexane, Caroverine, Memantine
Dopamine receptor modulators	Sulpiride, Piribedil, Pramipexole
Muscle relaxants	Baclofen, Cyclobenzaprine
Miscellaneous drugs	Ginkgo biloba extract, Melatonin

NMDA, N-methyl-D-aspartate.

2. Antidepressants

Antidepressants have been frequently used for the management of tinnitus because of a high comorbidity of tinnitus and depression. It has been long disputed whether tinnitus is more likely to occur in psychologically disturbed people or whether tinnitus causes the psychological disturbance. There is also debate about whether psychoactive drugs act on the central auditory system to reduce tinnitus directly or whether they act by treating comorbid depression. It has been hypothesized that some drugs may have direct effect on tinnitus since many receptors on which psychoactive drugs operate are also present within the central auditory pathways [13]. Also, it should be considered in the assessment of antidepressant effect on tinnitus in that the scales for tinnitus severity correlate highly with the depression scales [6]. In all clinical trials of tricyclic antidepressants (trimipramine, nortriptyline, and ami-

Table 2. Outcomes in benzodiazepine clinical trials

Drug	Study (year)	Outcome measure	Conclusion
Diazepam	Kay (1981)	VAS	Not effective, inconclusive
Diazepam Oxazepam Clonazepm	Lechtenberg & Shulman (1984)	Self-rating scale	Both oxazepam and clonazepam were highly effective.
Alprazolam	Johnson et al. (1993)	VAS, matched loudness	Alprazolam provides therapeutic relief for some patients.
Clonazepam	Bahmad et al. (2006)	VAS	Clonazepam reduces tinnitus annoyance & intensity.
Alprazolam	Jalali et al. (2009)	THI, VAS, matched loudness	Insufficient evidence to support overall superiority of alprazolam vs placebo.
Clonazepam	Han et al. (2012)	THI, VAS, matched loudness	Clonazepam is effective in treating tinnitus.

THI, tinnitus handicap inventory; VAS, visual analog scale.

Table 3. Outcomes in antidepressant clinical trials

Drug	Study (year)	Outcome measure	Conclusion
Trimipramine	Mihail et al. (1988)	Self-rating severity scale	There was evidence of a strong placebo effect.
Nortriptyline	Sullivan et al. (1993)	Tinnitus interference scale, internal disability VAS, tinnitus matching	Nortriptyline decreases depression, functional disability, and tinnitus loudness associated with severe chronic tinnitus.
Amitriptyline	Podoshin et al. (1995)	Severity rating, tinnitus matching	The better effect at rest could be explained by the sedative effect of the drug which improved the ability to rest and sleep.
Amitriptyline	Bayar et al. (2001)	Subjective ratings, matched frequency and intensity	Amitriptyline therapy was effective in decreasing tinnitus.
Paroxetine	Robinson et al. (2005)	Tinnitus matching, tinnius handicap questionnaire	No evidence of the efficacy of paroxetine in the treatment of chronic tinnitus in nondepressed patients.
Sertraline	Zöger et al. (2006)	Questionnaire, VAS	Sertraline is more effective than placebo in the treatment of refractory tinnitus. Approximately 20% of this effect may be explained by reduction of psychiatric symptoms.
Trazodone	Dib et al. (2007)	VAS (intensity, discomfort)	In the dose used, trazodone was not efficient in controlling tinnitus.

triptyline), there was no evidence that those drugs are effective or ineffective in the management of tinnitus although there was a slight improvement in tinnitus due to methodological bias [14-17]. The trials of selective serotonin reuptake inhibitors (paroxetine, sertraline, and trazodone) showed no benefit for most outcome measures in non-depressed patients [18-20] (Table 3). Nevertheless, the use of an antidepressant in tinnitus patients with depression and anxiety is highly indicated because this patient group can be benefited from antidepressant treatment. Overall, there is no high-quality evidence on the effect of antidepressants on tinnitus reduction. The common side effects include sedation and dry mouth.

3. Anticonvulsants

Anticonvulsants, i.e. antiepileptics are increasingly used in several non-epileptic conditions including psychiatric disorders and pain syndromes. They also represent potential candidates for the treatment of tinnitus on the assumption that tinnitus is related to central auditory hyperactivity [6]. 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 [21]. Carbamazepine reduces neural firing by binding to voltage-gated sodium channels and stabilizes the neuronal membrane. A significant benefit from carbamazepine has not been confirmed in placebo-controlled studies [22, 23]. Gabapentin is an anticonvulsant that mimics the chemical structure of GABA, but does not acts on GABA receptors. Although the exact mechanisms of action have not been fully described, gabapentin is thought to increase GABA biosynthesis and to interact with voltage-gated calcium channels to reduce calcium current after chronic application [24,25]. The side effects of gabapentin are relatively less than for other GABAergic drugs. There is insufficient evidence supporting the effectiveness of gabapentin for tinnitus [26-29]. Lamotrigine that suppresses glutamate release and inhibits voltage-dependent sodium channel failed to demonstrate a beneficial effect on tinnitus [30]. Valproic acid, one of the most frequently prescribed antiepileptics has not been systematically investigated for tinnitus. Anticonvulsant studies performed so far only showed small effects of doubtful clinical significance and there is no evidence for a large positive effect of anticonvulsants in the treatment of tinnitus [6,21] (Table 4). Side effects are experienced by a relatively large portion of the patients (18%) [21]. Retigabine, an approved novel antiepileptic drug, is a KCNQ2-5 channel activator. Voltage-gated Kv7 (KCNQ) channels are potassium channels activated at resting membrane potentials, and provide a powerful brake on neuronal excitability. Recent research on KCNQ2/3 channel activators have produced promising results in preventing the development of tinnitus in mouse models [31,32]. It has been reported that a reduction in KCNQ2/3 channel activity results in tinnitus-specific hyperactivity in the dorsal cochlear nucleus and initiates the development of tinnitus. A pharmacological manipulation that shifts the voltage dependence of Kv7 to more negative voltages prevented the development of tinnitus after noise exposure [32]. Another KCNQ2/3 channel activator, a more potent and less toxic than retigabine in rodents, has been shown to reduce the development of tinnitus in the noise-exposed mouse model of tinnitus, providing a clinical candidate for preventing tinnitus [31].

4. N-methyl-D-aspartate (NMDA) receptor antagonists

Glutamate is a major excitatory neurotransmitter within the cochlea and central auditory pathways. Disturbances of glutamatergic transmission have been implicated in various disorders of the

Table 4. Outcomes in anticonvulsant clinical trials

Drug	Study (year)	Outcome measure	Conclusion
Carbamazepine	Donaldson (1981)	Tinnitus change percentage	A non-significant positive effect in 45% as compared to 21% in the placebo group.
Carbamazepine	Hulshof & Vermeij (1985)	Self-assessment score	Carbamazepine had less effect than the placebo (a non-significant negative effect).
Lamotrigine	Simpson et al. (1999)	Questionnaire, VAS, matched loudness	Questionnaires indicated that lamotrigine was effective in a very few patients.
Gabapentin	Witsell et al. (2007)	THI	Insufficient evidence to support the effectiveness of gabapentin.
Gabapentin	Piccirillo et al. (2007)	THI	Gabapentin is no more effective than placebo. A beneficial effect of gabapentin in a subgroup with normal hearing.
Gabapentin	Bakhshaee et al. (2008)	TQ score, matched loudness, severity index	Insufficient evidence to support the effectiveness of gabapentin in the treatment of tinnitus.
Gabapentin	Ciodaro et al. (2015)	THI	The combination of gabapentin and lidocaine would to be superior to placebo or gabapentin alone.

TQ, tinnitus questionnaire.

Table 5. Outcomes in NMDA antagonist clinical trials

Drug	Study (year)	Outcome measure	Conclusion
Caroverine	Denk et al. (1997)	Severity rating, matched loudness	Caroverine is an effective drug for the therapeutic suppression of cochlear synaptic tinnitus.
Caroverine	Domeisen et al. (1998)	VAS (severity), matched loudness	The null hypothesis that caroverine does not have a therapeutic effect on tinnitus cannot be rejected.
Acamprosate	Azevedo et al. (2007)	VAS (loudness, annoyance)	The drug effect is delayed at least 1 month and the beneficial effect increases steadily from 1 month to the end of this study (3 months).
Acamprosate	Sharma et al. (2012)	VAS (loudness), quality of life score	Acamprosate is an effective drug in treating the severity of tinnitus without much side effects.
Memantine	Figueiredo et al. (2008)	THI	No evidence to recommend memantine for the treatment of tinnitus.
Neramexane	Suckfüll et al. (2011)	THI-12	Significantly better scores in the 50 mg/d group (late effect). The 50 mg/d dose is concluded to be the appropriate standard dose for further clinical development.

central nervous system and also in the development of tinnitus. These alterations may change the balance between the excitatory and inhibitory neurotransmission in the central auditory pathways. The NMDA receptor (NMDAR) is a specific type of ionotropic glutamate receptor, named after the agonist molecule N-methyl-D-aspartate that binds selectively to it. The NMDARs projecting from the medial geniculate body to the amygdala are hypothesized to be of importance in a pathophysiological model of tinnitus, in which the connections between the auditory, limbic, and autonomic nervous systems play a crucial part in the emergence of tinnitus [33]. Caroverine, an antagonist of non-NMDA and NMDA receptors, has shown contradictory results [34,35]. Acamprosate, the putative non-selective NMDAR antagonist and GABA agonist, which is approved for the treatment of alcohol dependency, resulted in significant improvement of tinnitus [36,37]. The non-selective NMDA antagonist memantine was no more effective than placebo [38]. Recent research demonstrated that memantine significantly reduced tinnitus-like behaviors caused by salicylate or acoustic trauma in rats [39,40]. The memantine analog neramexane, which blocks both NMDA and α9α10 nicotinic cholinergic receptors, showed a trend towards improvement of tinnitus in the medium- and high-dose neramexane groups in a Phase II study. However, several Phase III studies have reported no sufficient evidence for approval of the drug [6] (Table 5).

5. Dopamine receptor modulators

The dopaminergic pathway which includes the prefrontal area, primary temporal area, temporo-parietal associative area, and limbic system has been proposed as the structure that supports the neurophysiological model of tinnitus perception. The cerebral areas where tinnitus is perceived are the identical areas where dopamine is localized in. The studies using imaging techniques have identified three zones where tinnitus is perceived: the prefrontal area associated with attention and stress; the primary temporal area in relation to hearing; and the limbic system that controls emotions, learning, memory, and motivated behavior [41]. Increased activity in the hypothesized auditolimbic dopaminergic pathway is potentially involved in emotional aspects of tinnitus and may produce the distress in tinnitus sufferers. This theory provides a means to modulate the dopamine actions using dopaminergic agonistic and antagonistic drugs [42]. Sulpiride, a dopamine D2 antagonist and atypical antipsychotic drug, significantly reduced

tinnitus perception, modulating the auditolimbic dopaminergic pathway [42]. Piribedil, a dopamine D2/D3 agonist approved for Parkinsonism, was not superior to placebo. Instead, the incidence of side effects such as nausea and dizziness was relatively high, resulting in treatment interruption in all cases [43]. Another 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. A decrease in D2/D3 receptor density and function in advanced age may contribute to the onset and persistence of tinnitus [44]. The dopamine concept of tinnitus perception has opened possibilities for dopamine supplementation or receptor modulation using agonists or antagonists, weighing the agonists more strongly.

6. Muscle relaxants

Baclofen, a $GABA_B$ agonist with muscle relaxant effects, was not more effective than placebo in a clinical trial in which a clinically available racemic baclofen was probably used [45]. However, in rats with acoustic trauma, a reduction of tinnitus behavior has been observed after application of L-baclofen [46]. L-baclofen has been reported to be more potent than both D-baclofen and racemic baclofen in reducing sound-evoked hyperexcitability in neurons of the inferior colliculus, and in relieving the symptoms of trigeminal neuralgia with better tolerated side effects [47]. Cyclobenzaprine, a muscle relaxant that modulates muscle tension, has been used to relieve skeletal muscle spasms and associated pain in acute musculoskeletal conditions. It is known to be a tricyclic antidepressant analog which inhibits the uptake of norepinephrine, resulting in increased synaptic norepinephrine concentration [48]. In a pilot study without a placebo, high-dose cyclobenzaprine resulted in a significant reduction in the tinnitus handicap inventory score [49].

7. Miscellaneous drugs

Ginkgo biloba extract has been widely prescribed in peripheral vascular disease and cerebral insufficiency. The standardized extract of ginkgo biloba should contain the active chemical components of 24-25% flavonoids and 6% terpenoid fraction containing ginkgolides and bilobalide. The flavonoids have antioxidant properties, while ginkgolide B has potent PAF antagonism. Many of the central nervous system effects of the extract have been dependent on the combination of its antioxidant and PAF antagonistic actions. It is also a vasodilator, which may be the obvious reason for thinking that it would be useful in the management of tinnitus [50]. However, two most systematic double-blind and placebo controlled clinical trials have yielded negative results suggesting that ginkgo biloba extracts are of little more use in the treatment of tinnitus than a placebo [51,52]. Melatonin synthesized by the pineal gland is an endogenous antioxidant, which also seems to affect sleep, mood, reproduction, immunity, and aging. Melatonin treatment showed beneficial effect on tinnitus, especially in the subgroup of patients complaining of sleep disturbance. Melatonin alone or in combination with other drugs could offer useful perspectives in the management of patients suffering from tinnitus and sleep disturbance [53].

CONCLUSION

Among the various pharmacological interventions that have been investigated, only clonazepam, acamprosate, neramexan, and sulpiride showed some beneficial effects against tinnitus. Sertraline and pramipexole were effective in subgroups of patients with psychiatric symptoms or presbycusis. However, no agents have been identified to provide a reproducible long-term reduction of tinnitus in excess of placebo effects. In rodent tinnitus models, L-baclofen, memantine, and KCNQ2/3 channel activators have been demonstrated to reduce tinnitus development. Possibly, limitation of the use of an effective high dosage during a longer treatment duration due to dose-dependent side effects of the centrally acting drugs may influence the negative results in clinical studies. It is imperative that more effective and safer innovative agents are developed based on the further understanding of tinnitus neural pathophysiology and valid animal models, and supported by improved clinical trial methodology. Finally, the management of tinnitus patients through a tailored treatment approach depending on the detailed classification of tinnitus subtypes will also lead to better treatment outcomes.

CONFLICTS OF INTEREST

The author has no financial conflicts of interest to declare.

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