

EXPERT OPINION

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Current pharmacological treatments for tinnitus

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Introduction: Tinnitus, the phantom perception of sound, is a highly prevalent disorder and treatment is elusive.

Areas covered: This review focuses on clinical research regarding pharmacological treatments for tinnitus. The authors searched PubMed databases for English language articles related to pharmacological treatment of tinnitus, published through August 2012. The keywords "tinnitus AND pharmacological treatment" and "tinnitus AND drugs" were used. The search focused on clinical trials, but was complemented by other articles and information from clinical trial registries.

Expert opinion: Despite the significant unmet clinical need for a safe and effective drug for tinnitus relief, there is currently no EMA- or FDA-approved drug on the market. Even a drug that produces a small but significant effect would have a huge therapeutic impact. At present, evidence-based pharmacological approaches are limited to the treatment of comorbidities such as depression, anxiety, or insomnia. In the last few years there have been significant advances in the understanding of the pathophysiology of the different forms of tinnitus, the establishment of valid animal models, and the development of clinical trial methodology. A glimpse of hope is appearing in the horizon as an increasing number of pharmaceutical industries now have compounds targeting tinnitus in their pipeline.

Keywords: auditory system, hearing, meta-analysis, pharmacotherapy, randomized controlled trial, systematic review, tinnitus, treatment

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1. Introduction

Tinnitus is a common and distressing symptom that is characterized by the perceived sensation of sound without a corresponding external stimulus. Tinnitus can take the form of buzzing, hissing or ringing, or a combination of these or other characteristics. It can be heard in one or both ears, but it can also be referred to the head. Tinnitus can occur continuously, intermittently, or have a pulsatile character. The intensity of the phantom sound can vary from a subtle noise just above hearing threshold to high-intensity sounds, which cannot be masked by any external noise.

Tinnitus can be classified as being either objective or subjective. In the objective form, which is rare, a real sound is generated by an internal biological source, reaching the ear through conduction in body tissues. The source can be vascular turbulence, pulsations, or spasm of the muscles in the middle ear, Eustachian tube, or soft palate. Objective tinnitus can often be heard by an observer, using a stethoscope. In contrast, subjective tinnitus refers to a phantom auditory sensation for which no objective sound can be identified and only the person who has the tinnitus can hear it. Subjective tinnitus is by far the most common form and its pharmacological treatment is the subject of the present review.

Based on recent data, tinnitus occurs in 25.3% of American adults (50 million people) with 7.9% experiencing it frequently (16 million people) [1]. Epidemiological studies reveal comparable prevalence rates for Europe [2]. In a large Norwegian

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Article highlights.

- Tinnitus represents a highly prevalent disorder causing a significant burden.
- There is currently not a single FDA- or EMA-approved drug on the market.
- A wide variety of drugs with different therapeutic uses have been tested with some effect in a limited subset of patients.
- At present, evidence-based pharmacological approaches are limited to the treatment of comorbidities such as depression, anxiety or insomnia.
- There is a pressing need and a huge potential market for a drug or a combination of drugs for tinnitus relief.
- Big pharmaceutical companies are increasingly entering the hearing and tinnitus field.

This box summarizes key points contained in the article.

survey of more than 50,000 adults, 21.3% of men and 16.2% of women reported being bothered by their tinnitus, with 4.4% and 2.1%, respectively, reporting high tinnitus intensity [3]. Although most epidemiological studies are based on data from the USA or Europe, studies investigating the extent of tinnitus in other regions of the world are emerging, indicating that tinnitus is a significant health problem across the world [4-6]. Most important risk factors for tinnitus are hearing loss, increasing age and male gender. Prevalence rates are expected to increase due to demographic development, warfare and increasing occupational and leisure noise.

Tinnitus is clinically heterogeneous, with respect to its etiology, its perceptual characteristics and its accompanying symptoms [7]. In addition to acoustic (the unwanted sound, i.e., most commonly known as the perception of 'ringing in the ears') and attentional (the extent to which the person is aware of the sound) components, tinnitus also involves emotional, cognitive, and memory components. Many patients with tinnitus report symptoms such as frustration, annoyance, insomnia, anxiety, depression, irritation and concentration difficulties, and these symptoms are highly relevant for the perceived tinnitus severity [7]. Thus, tinnitus represents a highly prevalent and potentially distressing condition that transcends the classical definition of an otological illness to encompass a range of symptoms that are likely to place a huge burden on patients and significantly impair quality of life. In fact, for 1 in 100 adults, tinnitus markedly affects their ability to lead a normal day-to-day life [8] and the extent of this disability leads many people to seek help. It has been estimated that 13 million people suffering from tinnitus symptoms in Western Europe and in the United States approach their doctor for medical advice [8].

1.1 Pathophysiology of tinnitus

Although often arising from peripheral hearing loss, tinnitus persists after auditory nerve transection, suggesting the critical involvement of central mechanisms. In recent years, animal studies and neuroimaging data have contributed to a

more detailed identification of tinnitus-related neuronal alterations in the central nervous system [9]. Governed by mechanisms of homeostatic plasticity [10], reduced auditory input is compensated at various structures along the central auditory pathway by reduced inhibitory and increased excitatory function. This in turn leads to increased neuronal firing rates, increased neuronal synchrony, and tonotopic reorganization [11]. These activity changes in the central auditory pathways are mediated by alterations in GABAergic, glycinergic, and glutamatergic neurotransmission [12-14]. Serotonergic axons may also modulate tinnitus-related activity in auditory pathways via the thalamic reticular nucleus [15] or other mechanisms [16,17]. In addition to deprived auditory input, abnormal somatosensory afferent input from the neck and face region (e.g., in patients with temporomandibular joint disorder) can influence activity in the central auditory pathways [18] and can be responsible for tinnitus generation [19].

Magnetoencephalographic (MEG) studies have shown that tinnitus is related to gamma band activity in the auditory cortex, along with decreased alpha and increased theta activity [20,21]. However, these changes of synchronized oscillatory activity in the auditory pathways are probably necessary but not sufficient for the conscious perception of the phantom sound. It is assumed that tinnitus is only perceived if the abnormal activity in the auditory cortex is functionally connected to a network of higher order brain 'neuronal global workspace' areas [22]. In accordance, MEG studies have demonstrated a global tinnitus network of long-range cortical connections involving auditory and non-auditory regions and including the right parietal cortex, the right frontal lobe and the anterior cingulate cortex [23]. Moreover, tinnitus has an affective component, since in some patients it is accompanied by stress, depression and anxiety. Therefore, in addition to the perceptual network, a distress network is activated which comprises the medial temporal lobe (amygdala and hippocampus), parahippocampal areas, insula and the anterior cingulate cortex [24]. Salience and mnemonic networks are also activated, evidenced by enhanced activity of the amygdala in positron emission tomography imaging, by changes in the hippocampal area and by transient tinnitus diminution after suppression of the amygdalo-hippocampal complex by amytal [25]. Thus, there is compelling evidence for a distributed tinnitus brain network, which includes sensory auditory areas together with cortical regions involved in perceptual, emotional, mnemonic, attentional and salience functions [22].

1.2 Animal models of tinnitus

Several tinnitus animal models have been established. In most animal models, salicylate and noise trauma are used for tinnitus induction. Conditioned response methods and gap-startle reflex methods are used to assess behavioral correlates of tinnitus. Even if the development of animal models has already provided important insight into the neuronal mechanisms involved in the pathophysiology of tinnitus [9],

their validity for the different aspects of tinnitus is still a matter of debate [26].

Since the behavioral validation is currently still restricted to the perceptual aspects of acute tinnitus, the available models probably reflect tinnitus-related alterations in central auditory pathways leading to the phantom percept. It remains to be determined whether the transition from acute into chronic tinnitus and its emotional and cognitive aspects are also reflected.

1.3 Tinnitus measurement

For the development and the evaluation of therapeutic interventions of tinnitus, valid and reliable measurement of tinnitus is critical. This is complicated by the fact that tinnitus is a purely subjective phenomenon and that psychoacoustic measurements of tinnitus (e.g., loudness matching) do not explain the subjectively perceived severity of the symptom. Therefore, a comprehensive evaluation has to include the assessment of both perceptual aspects of tinnitus (e.g., loudness, pitch), and of subjective tinnitus severity (e.g., tinnitus related functional impairment or tinnitus handicap). Tinnitus loudness can be assessed by psychoacoustic methods and by subjective rating scales (e.g., visual analogue scales (VAS) or numeric rating scales) [27]. Several validated questionnaires are available for assessment of tinnitus severity [28-30]. The different measurements provide complementary information and should be used in parallel for a comprehensive evaluation of treatment-induced changes [31,32].

1.4 Heterogeneity of tinnitus

A further challenge in the development of effective therapeutics is the heterogeneity of tinnitus. Different triggering events can lead to tinnitus, such as noise exposure or administration of specific pharmacological agents, ear or head injuries, some diseases of the ear and ear infections. Moreover, the manifestation of tinnitus can vary, ranging from intermittent tinnitus perception with little impact on daily life to a very bothersome tinnitus that occurs 24 h a day preventing sleep, leading to the inability to perform intellectual work and to social isolation. Tinnitus is also often associated with other symptoms, such as hyperacusis and distortion of sounds and several affective disorders, such as anxiety, phonophobia and depression [7]. With such differences in etiology and symptoms, it is expected that different subtypes of tinnitus exist that differ in their pathophysiology and in the response to specific treatments.

Specific underlying pathophysiological mechanisms have already been identified for specific clinical factors such as the perceived localization, the duration or the frequency composition [33]. Differential diagnosis of triggering events [19] and temporal onset [23,34] should allow for a more rational and effective pharmacological approach. The fact that a subgroup of patients who have intermittent tinnitus that sounds like a typewriter receive significant relief from the use of carbamazepine [35] indicates that stratifying tinnitus patients benefits treatment. Efforts toward establishing tinnitus subgroups are

under way [36-38], and will most likely aid the identification of responders to specific drugs and the selection of patients in future clinical trials. Thus, the most probable future scenario is that there will be different treatment approaches for the different forms of tinnitus.

1.5 Tinnitus: a clinically unmet need

The available treatments for the management of the tinnitus patient are diverse. The most widely established treatment methods are counseling (providing information about tinnitus and giving recommendations how to cope with it), cognitive behavioral therapy (CBT), and various forms of sound therapies (environmental sound, hearing aids, noise generators). Frequently, these approaches are applied in combination [39]. Whereas beneficial effects of CBT on subjective tinnitus severity (but not on tinnitus loudness) have been clearly demonstrated in randomized controlled trials [40], the efficacy of sound therapy [41] and hearing aids [42] remains to be determined. A similar situation applies for the Tinnitus Retraining Therapy, a specific combination of directive counseling and sound therapy [43]. In addition, pharmacological treatments are widely used, even if there is no approved tinnitus drug on the market. Over 4 million prescriptions are written each year for tinnitus relief in Europe and the United States, but these are all off-label prescriptions from a wide variety of therapeutic drugs (Table 1) [8].

Based on a more detailed understanding of the pathophysiological mechanisms of tinnitus, various new therapeutic approaches have been developed. These new approaches, which are all still at an early development stage, aim at direct interference with the neuronal correlates of tinnitus by neurobiofeedback, specific individualized auditory stimulation, cochlear implants (for unilateral deaf patients with tinnitus), and electrical stimulation of brain structures either through implanted electrodes or with transcranial magnetic stimulation.

Although most patients benefit from the currently available therapies to some degree, a big fraction of them are left untreated and in despair with the notion that “they have to learn to live with their tinnitus.” Thus, tinnitus is still today a clinically unmet need and most patients would welcome a drug, which abolishes or reduces their phantom sound [44]. In a recent survey in the United States, more than 20% of the patients were willing to pay US\$ 25,000 for complete reduction of their tinnitus [44]. Most clinicians who treat tinnitus patients would welcome a more effective drug therapy as well [45]. Since in some individuals, tinnitus causes irritability, agitation, stress, depression, insomnia and interferes with normal life, leading to suicidal attempts in severe cases, even a drug that produces a small but significant effect would have a huge therapeutic impact. However, disappearance of tinnitus should be the ultimate goal [46].

The hearing field is being increasingly recognized by big pharma companies as a huge and still untapped market. The “Action on Hearing Loss” in the UK estimated in 2005 that

Table 1. Off-label drugs used in the treatment of tinnitus.

<ul style="list-style-type: none"> • Antiarrhythmics Lidocaine Tocainide Flecainide Mexiletine 	<ul style="list-style-type: none"> • Antidepressants Amitriptyline Trimipramine Nortriptyline Paroxetine Sertraline Fluoxetine
<ul style="list-style-type: none"> • Anticonvulsants Carbamazepine Gabapentine Lamotrigine Pregabalin Valproic Acid 	<ul style="list-style-type: none"> • Muscle relaxants Baclofen Cyclobenzaprine
<ul style="list-style-type: none"> • Anxiolytics Clonazepam Alprazolam Diazepam 	<ul style="list-style-type: none"> • Others Misoprostol Atorvastatin Nimodipine Furosemide Cyclandelate Sulpiride Naltrexon Vardenafil Melatonin Herbal products Vitamins Minerals
<ul style="list-style-type: none"> • Glutamate receptor antagonists Acamprosate Caroverine Memantine 	

a novel tinnitus drug could have a product value of US \$689 million in its first year of launch [8]. The market value of hearing loss, which is closely related to tinnitus is even estimated at US \$ 2 billion [47]. However, there is no FDA- or EMA-approved drug on the market which targets tinnitus or hearing loss. This may soon change, since the big pharma companies have recently started to enter the hearing field [47].

1.6 Methodological quality of clinical trials in tinnitus

Many of the clinical trials in tinnitus have critical methodological limitations including: inappropriate outcome measures and statistical methods, insufficient sample sizes, poorly defined interventions, problems with study blinding and randomization and insufficient reporting of study details [48-50]. The heterogeneous quality of pharmacological tinnitus treatment studies is echoed by all Cochrane Review analyses [51-54] and has to be considered in the interpretation of the results, particularly in elder studies. Very recently efforts have been made to improve the methodological quality of clinical trials in tinnitus by describing basic methodological recommendations for trial design, performance and reporting [31,32].

2. Pharmacological treatment

2.1 Tinnitus can be pharmacologically treated

Current pathophysiological models assume that tinnitus results from alterations of neuronal activity in the central nervous

system. Since neuronal excitability can be modulated by different neurotransmitters, neuromodulators, and compounds acting on voltage-gated channels, there is no *a priori* reason to believe that tinnitus cannot be pharmacologically treated. The best proof is the transient dose-dependent reduction of tinnitus in up to 70% of patients after intravenous application of the voltage-gated sodium channel blocker lidocaine [55,56].

Unfortunately, because of poor bioavailability after oral intake, lidocaine is only effective when applied intravenously. Moreover, the effect is short-lasting and side effects are considerable [57]. Oral antiarrhythmic drugs like tocainide, flecainide, and mexiletine have been investigated for tinnitus, however without much success [49,58]. Novel local anesthetics like tonaicaine and sameridine with longer duration of action have been discussed for the treatment of tinnitus [56]. A preliminary report has shown some positive results in tinnitus patients with an intradermal lidocaine injection [59]. The pharmaceutical company Epicept has a lidocaine patch formulation currently at Phase II for tinnitus. However, the challenge of the transdermal approach will be to achieve the systemic concentrations needed to suppress tinnitus.

2.2 Treatment of acute tinnitus

There is a consensus among clinicians and researchers that different neuronal mechanisms are involved in the onset of tinnitus and in the transition from acute to chronic tinnitus. Therefore, treatment approaches will probably vary with the duration of the disease. There is no pathophysiologically founded border between “acute” and “chronic” tinnitus. The currently used distinction is arbitrary and varies between 3 and 6 months.

In the majority of cases, acute tinnitus resolves spontaneously. Thus therapeutic strategies could aim to provide an environment that facilitates tinnitus recovery. For example, in the case of acute tinnitus associated with sudden hearing loss or noise trauma, treatment strategies which restore hearing function are expected to have beneficial effects on tinnitus. In sudden sensorineural hearing loss up to 65% of patients experience spontaneous recovery of pre-loss hearing, others experience no recovery at all. The high variability suggests that there are different forms of sudden sensorineural hearing loss with different etiologies. Among others, vascular, inflammatory, and infectious mechanisms are probably involved. Accordingly, proposed treatments include systemic or intratympanic steroids [60-62], vasodilators [63], and antiviral agents [64,65]. Good evidence is only available for steroids [66], with intratympanic steroids being equivalent to high-dose oral prednisone therapy as primary therapy. As salvage therapy, intratympanic steroids may offer the potential for some degree of additional hearing recovery, although it remains uncertain if this improvement is clinically significant [67].

Another specific form of acute tinnitus is that associated with noise-induced hearing loss produced by exposure to loud sounds (levels of 85 dBA and higher [68]), e.g., after a blast or a rock concert. Single, repeated, or continuous

exposure to high levels of noise can cause noise-induced hearing loss and tinnitus. Excessive noise can cause immediate and direct irreversible structural damage to the hair cell bundles and can generate in a second phase potentially reversible or preventable excitotoxic effects on the sensory nerve terminals [69]. Hair cells die by apoptosis and cannot be replaced. Loss of hair cells leads to loss of spiral ganglion neurons, which depend on hair cells for the production of survival factors such as the neurotrophin NT-3 and brain-derived neurotrophic factor. Accumulation of free radicals, excitotoxicity mediated by glutamate receptors, and activation of apoptosis are predictable players in the loss of cells [70]. Animal experiments suggest that various growth factors and drugs directed against apoptosis, excitotoxicity and oxidative stress can provide valuable protection from hearing loss and tinnitus if applied during exposure [71] and also probably immediately after exposure. Several of these otoprotectants are currently in clinical development for preventing noise-induced hearing loss and associated tinnitus, with mixed results. Daily supplements of 4 g of oral Mg granulate (6.7 mmol Mg aspartate) significantly reduced hearing loss post noise as compared to placebo in a double-blind placebo-controlled study involving 300 young and healthy military recruits [72]. In a placebo-controlled crossover study 2 weeks treatment with 1200 mg/day of the glutathione prodrug N-acetylcysteine (NAC) protected male workers from noise-induced temporary threshold shift [73]. In contrast, 900 mg NAC 30 min before exposure to 2 h of loud music (mean noise level of 98.1 dB) had no beneficial effects on temporary threshold shifts as compared to placebo [74]. Results of several further still-unpublished studies in humans [75] suggest that NAC has at best very small effects on hearing protection in humans [47]. The combination of NAC with alpha-phenyl-tert-butyl nitron (HPN-07), a compound that reacts with free radicals, has shown synergistic effects preclinically [76] and is currently tested in a Phase I trial [47]. SPI-1005 (ebselen), an antioxidant, developed by Sound Pharmaceuticals is currently tested in Phase II trials in college students listening to music with their iPods [77] and in chemotherapy-induced hearing loss [78].

AM-101, a NMDA antagonist, has been developed by Auris Medical for the treatment of acute tinnitus and shown to be safe [79]. In a recent double-blind, randomized, placebo-controlled Phase II trial, 248 subjects with persistent tinnitus no older than 3 months from acute noise trauma, otitis media or sudden deafness received three intratympanic injections of AM-101 at a high dose, a low dose or placebo over three consecutive days. AM-101 failed to significantly reduce minimal masking levels, but the higher dose of AM-101 (810 µg/mL) showed substantial and statistically significantly better reduction than placebo in tinnitus loudness, sleep impact and tinnitus impairment in patients suffering from acute tinnitus with established cochlear origin. In contrast, the subgroup of sudden deafness-related tinnitus did not show conclusive results [80].

Summarizing, there is consensus among clinicians that acute tinnitus, especially if it co-occurs with acute hearing loss, deserves specific attention and that there might be a short therapeutic window for specific pharmacological interventions. The most widely used treatment strategies are intratympanic or high-dose oral steroid administration. Apart from steroids, there are yet no treatments available which have shown repeated efficacy in controlled trials. This might be due to etiological heterogeneity of acute hearing loss and a high rate of spontaneous recovery. Further clinical trials to validate treatments of acute tinnitus are urgently needed.

2.3 Treatment of chronic tinnitus

There is no specific pharmacological compound which has been approved for the treatment of chronic tinnitus. But a large variety of drugs approved for other indications are used for the treatment of tinnitus in clinical practice (see Table 1). Some of these compounds have also been investigated in clinical trials. Here we will discuss the most relevant results, sorted by the type of drug tested.

2.3.1 Antidepressants

Antidepressants are frequently proposed for the management of chronic tinnitus [81]. The main reason for the large use of antidepressants is the frequent co-occurrence of depressive disorders and tinnitus as well as the overlap in symptomatology and pathophysiology of tinnitus and depression [82]. Moreover, antidepressants are among the most effective drugs for the treatment of chronic neuropathic pain syndromes, which in turn resemble tinnitus in many aspects [22,83]. Among all antidepressants that have been investigated for tinnitus, a particular interest has been paid to tricyclic antidepressants, mainly because of their beneficial effects on chronic pain syndromes [84]. In two placebo-controlled studies, one single-blind [85] and one double-blind [86] study involving subjects with severe tinnitus and depressive symptoms, nortriptyline significantly reduced depression scores, tinnitus disability scores, and tinnitus loudness relative to placebo. There was a significant correlation between the reduction in tinnitus disability scores and depression scores, suggesting that nortriptyline is especially effective in severely depressed tinnitus patients, but has less benefit in non-depressed individuals with tinnitus [87]. One study has compared amitriptyline with placebo and found after 6 weeks of 100 mg amitriptyline a significant reduction of tinnitus complaints and tinnitus loudness compared to the placebo group [88]. In another study, where amitriptyline was compared with biofeedback, 27.5% of patients reported improvement. However, this was less effective than biofeedback *per se* [89]. A small double-blind placebo crossover study did not demonstrate a difference between trimipramine and placebo treatment [90]. It should also be noted that the induction and worsening of tinnitus has been reported in relation to tricyclics [91-94] but also to other antidepressants [95] as side effect of both treatment and discontinuation.

The selective serotonin reuptake inhibitors (SSRI) paroxetine and sertraline have been also tested in tinnitus. In a randomized double-blind placebo controlled study of patients without severe hearing loss, but with depression, anxiety, and a high risk for developing severe tinnitus, sertraline was significantly more effective than placebo in reducing tinnitus loudness and tinnitus severity [96]. In a double-blind, placebo-controlled study involving chronic tinnitus patients, few of whom suffered from depression, the paroxetine group showed little difference from placebo on tinnitus loudness matching, Tinnitus Handicap Questionnaire (THQ) scores, and other measures; however the paroxetine group showed a significant improvement on tinnitus aggravation compared to the control group [97].

Very recently a combination of paroxetine and vestipitant, a neurokinin-1 receptor antagonist with anxiolytic properties was investigated in a crossover trial. Neither the combination nor vestipitant alone had a potential effect against chronic tinnitus [98]. No data are available for the serotonin reuptake enhancer tianeptin, the serotonin-norepinephrine reuptake inhibitors (SNRI) duloxetine and venlafaxine, the norepinephrine-dopamine reuptake inhibitor bupropion, the dual acting drug mirtazapine or the melatonin agonist agomelatine.

In the interpretation of the effect of antidepressants on tinnitus, it has to be considered that the scales used for the measurement of tinnitus correlate highly with depression scales [99]. Thus, the observed reduction of tinnitus severity under antidepressant treatment might – at least partially – be a pure consequence of the antidepressant effect of the investigated drugs. Nevertheless, available data provide converging evidence that tinnitus patients with depression and anxiety may gain benefit from antidepressant treatment and clearly suggest that the use of an antidepressant in this patient group is highly indicated. However, available results do not allow for determining whether one specific compound is superior to others [81]. Therefore, in clinical practice, selection of the antidepressant drug should be guided by the patient's comorbidities and the side-effect profile of the specific drug.

2.3.2 Benzodiazepines

Since benzodiazepines are positive allosteric modulators of the GABA_A receptor and since reduced inhibitory neurotransmission is thought to be critical for the development of tinnitus [12], benzodiazepines would be expected to have a positive effect on tinnitus by increasing inhibitory neurotransmission. Furthermore, due to their anxiolytic and sleep-inducing properties, benzodiazepines should have beneficial effects on comorbid anxiety and insomnia.

In a small double-blind placebo-controlled study, 12 weeks of alprazolam administration at an individually adjusted dosage reduced tinnitus loudness in 76% of subjects – measured with a tinnitus synthesizer and a visual analog scale – whereas only 5% showed a reduction in tinnitus loudness in the control group [100]. In a further trial (crossover, randomized, triple-blind, placebo-controlled, 30 patients), 1.5 mg

alprazolam/day resulted in a significant improvement in the VAS score (0 representing “no tinnitus” and 100 representing “the worst imaginable tinnitus”) as compared to placebo, but not in the tinnitus handicap inventory (THI) score and tinnitus loudness [101]. Diazepam, evaluated in a double-blind triple crossover trial involving 21 tinnitus patients, had no effect on tinnitus loudness [102]. In a prospective, randomized, single-blind clinical trial involving 10 patients per group, clonazepam significantly reduced tinnitus loudness and annoyance (VAS) relative to the control group [103]. A potential beneficial effect of clonazepam is further suggested by a retrospective study analyzing medical records from over 3000 patients taking clonazepam (0.5 – 1 mg/day, 60 – 180 days) for vestibular or cochleovestibular disorders, where 32% reported an improvement in their tinnitus [104]. In a recent open-label, randomized, crossover study effects of 3 weeks treatment with clonazepam and Ginkgo biloba were compared in 38 patients with chronic tinnitus (tinnitus duration more than 2 months). Starting with one tablet daily (clonazepam 0.5 mg; Ginkgo biloba 40 mg), subjects were instructed to increase the dose by one tablet every 3 days to a maximum of four tablets daily until they perceived a satisfactory decrease in tinnitus loudness or intolerable side effects. During clonazepam patients reported significant improvements in tinnitus loudness, annoyance and THI score, whereas Ginkgo biloba showed no significant differences on any of these measures [105]. The non-benzodiazepine hypnotics zopiclon, eszopiclon, zaleplon and zolpidem (Z-substances) have not yet been systematically investigated for the treatment of tinnitus.

Summarizing, there are some hints for a potential short-term benefit of benzodiazepines in tinnitus treatment. However given the side-effect profile of benzodiazepines, especially the risk of drug dependency, the available data are by far not sufficient to recommend the use of benzodiazepines for the treatment of tinnitus. Moreover, caution is warranted since protracted tinnitus has been reported after discontinuation of benzodiazepines [106,107].

2.3.3 Non-benzodiazepine anticonvulsants

Anticonvulsants are increasingly used in the treatment of several non-epileptic conditions, including various psychiatric disorders and pain syndromes. Some of them have also been investigated for the treatment of tinnitus. Diverse pharmacological mechanisms of action are responsible for the therapeutic effects of antiepileptics; among them, effects on voltage-gated sodium and calcium channels, and on synaptic transmission – mainly mediated by gamma amino butyric acid type A (GABA_A) receptors. Since antiepileptics reduce neuronal excitability, they represent potential candidates for the treatment of tinnitus as well [108].

Carbamazepine reduces neural firing by binding to voltage-gated sodium channels and stabilizes the sodium inactivation state. Based on the assumption that carbamazepine resembles lidocaine in its mechanism of action, several studies have

investigated the effect of carbamazepine in tinnitus patients who previously had responded to intravenous lidocaine [109-111]. A positive response to carbamazepine has been reported at a dosage of 600 – 1000 mg daily in about half of the patients. However, these effects could not be confirmed in placebo-controlled studies [112,113]. A significant benefit from carbamazepine has been reported for a rare group of patients who have intermittent tinnitus that sounds like a typewriter, or ear clicking [35,114].

Gabapentin is an anticonvulsant which acts on voltage-gated calcium channels and is used for the treatment of seizures, neuropathic pain, and migraine. One controlled trial has shown a significant improvement in tinnitus annoyance and loudness for a subgroup of participants with tinnitus related to acoustic trauma [115]. A second study did not detect improvement in tinnitus handicap, but did report a significant improvement in tinnitus annoyance when compared to placebo [116]. However, further controlled trials did not report any benefit of the compound on tinnitus annoyance or loudness [117,118]. In a very recent study gabapentine was not superior to placebo on the group level, but beneficial effects were reported in a subgroup of tinnitus patients with comorbid hypertension, diabetes and dyslipidemia [119].

However, potential beneficial effects in *post-hoc* defined subpopulations have to be interpreted with caution till they are replicated by prospective studies. Accordingly, systematic reviews conclude that there is insufficient evidence for the effect of gabapentin on tinnitus [54,120].

Pregabalin resembles gabapentin in its mechanisms of action and is approved for the treatment of partial seizures, neuropathic pain, and generalized anxiety disorder [121,122]. Beneficial effects on sleep have also been reported [123]. There are no data available for the use of this compound in tinnitus patients. However, based on its clinical profile, pregabalin could potentially be considered for the treatment of tinnitus-related anxiety and insomnia.

Lamotrigine inhibits voltage-sensitive sodium channels and is a membrane stabilizer. It has been investigated in a double-blind placebo-controlled crossover clinical trial on 33 tinnitus patients and failed to demonstrate a beneficial effect [124]. Valproic acid is one of the most frequently prescribed anti-epileptic drugs and acts by multiple mechanisms. It has not been systematically investigated for tinnitus and has only been reported as useful in case reports [125,126].

The use of anticonvulsants for tinnitus treatment has also been reviewed recently in a Cochrane metaanalysis, which comes to the conclusion that studies performed so far only show small effects of doubtful clinical significance and that there is no evidence for a large positive effect of anticonvulsants in the treatment of tinnitus [54].

2.3.4 Antiglutamatergic compounds

Glutamate receptor antagonists have been tried in tinnitus sufferers with the goal to reduce excitatory neurotransmission. Increased glutamatergic neurotransmission may play a role in

the periphery in acute tinnitus, but also in the central auditory pathways in chronic tinnitus. Blocking glutamatergic neurotransmission after noise overexposure is thought to prevent noise-induced excitotoxic injury of hair cells [127]. Caroverine, an antagonist of non-NMDA and NMDA receptors, has been applied both systemically and topically, with contradictory results [128-130].

Oral treatment with the putative non-selective NMDA receptor antagonist acamprosate, which is approved for the treatment of alcohol dependency, has been tried in a double-blind study [131]. Acamprosate had no beneficial effects after 30 days of treatment, a modest benefit at 60 days, and a significant effect at 90 days. Approximately 87% of the subjects in the acamprosate group showed some improvement, including three subjects in which tinnitus disappeared, compared to 44% in the placebo group. These results were confirmed in a recent randomized double-blind placebo-controlled crossover trial in which 6 weeks of acamprosate treatment resulted in a significant improvement of a tinnitus severity score as compared to placebo treatment [132]. A further large clinical trial has been completed [133], but results are not yet published.

The non-selective NMDA antagonist memantine was no more effective than placebo in a prospective randomized double-blind crossover 90-day treatment study using the THI to assess efficacy [134]. The memantine analog neramexane, which blocks both NMDA and $\alpha 9\alpha 10$ nicotinic cholinergic receptors [135], has been tested in a Phase II study [136]. Neramexane failed to demonstrate a significant difference to placebo at the predefined study endpoint after 16 weeks of treatment. However, 4 weeks after the end of treatment, THI-12 scores in the group receiving 50 mg neramexane/day were significantly better improved than those of the placebo control group. Based on this finding several Phase III clinical trials [137] have been performed. Results are not yet published, but have been reported to be not sufficient for approval of the drug.

2.3.5 Dopaminergic-antidopaminergic drugs

Dopaminergic pathways in limbic and prefrontal areas may be involved in mediating salience and emotional aspects of tinnitus. Dopamine has also an inhibitory function in the cochlea suggesting a potential role in the early phase of tinnitus. Thus, both dopaminergic and antidopaminergic drugs have been proposed for the treatment of tinnitus. In one double-blind placebo-controlled study, the dopamine antagonist sulpiride significantly reduced subjective ratings of tinnitus and tinnitus visual analog scores. Effects were more pronounced when sulpiride was combined with either hydroxyzine (an antihistamine, and anxiolytic) or melatonin [138,139]. The dopamine agonist piribedil was investigated in a double-blind placebo-controlled crossover study, where it was not superior to placebo [140]. Pramipexole, an agonist of D2/D3 receptors, has been investigated in presbycusis patients with tinnitus in a randomized, prospective, placebo-controlled double-blind trial at a dose

schedule accepted for the treatment of Parkinson's disease. Four weeks of pramipexole treatment reduced both the tinnitus handicap inventory score and tinnitus loudness significantly more than placebo treatment [141].

2.3.6 Muscle relaxants

Baclofen, a GABA_B agonist with muscle relaxant effects, has been shown to reduce tone exposure-induced hyperexcitability in the inferior colliculus of rats [142]. Based on these findings, baclofen was investigated in a double-blind randomized placebo controlled trial [143]. In this trial 3 weeks of baclofen at increasing dosage (up to 60 mg/day) was not more effective than placebo in improving tinnitus symptoms, but caused more frequently side effects. Very recent animal data showed a reduction of behavioral signs of tinnitus after application of L-baclofen [144] and suggest that L-baclofen should be reconsidered as a potential drug treatment for tinnitus [145].

In a recent open-label exploratory study, the effect of various muscle relaxants on tinnitus has been assessed. Whereas treatment with orphenadrine (100 mg/day), tizanidine (24 mg/day), eperisone (50 mg/day) and cyclobenzaprine at a dose of 10 mg/day were not effective, cyclobenzaprine at a dosage of 30 mg/day resulted in a significant reduction of the THI score [146]. These results were confirmed in a further open-label trial, in which 25% of the 65 investigated patients reported a clear response to cyclobenzaprine [147].

2.3.7 Other

Some other drugs have been tested with either limited efficacy or needing further controlled trials. These include the HMG-CoA reductase atorvastatin [148], the vasodilator cyclandelate [149,150], the loop diuretic furosemide [151], some herbal products like ginkgo biloba [152,153], melatonin [154], the prostaglandin E1 analog misoprostol [155], the L-type calcium blocker nimodipine [156], the phosphodiesterase type 5 inhibitor vardenafil [157], and minerals including zinc [158,159].

3. Expert opinion

Why are there no approved tinnitus drugs in spite of the existence of such a huge market for a clinically unmet need?

One reason is probably that the lack of serendipitous discoveries of effective treatments has severely limited insight into tinnitus pathology. Nevertheless, the empirical approach that has been used for most central nervous system disorders should not be precluded in the case of tinnitus. Most innovative central nervous system-acting drugs were discovered serendipitously [160]. Advances in the understanding of tinnitus pathophysiology reveal a large number of similarities with other disorders of the central nervous system, such as neuropathic pain, epilepsy, headache, anxiety and depression. Thus, any new compound under development for any of these conditions should also be tested in the case of tinnitus patients.

The high variability in treatment outcome encountered in most clinical trials may be attributed to the heterogeneity of

tinnitus. Thus, a challenge for future tinnitus research consists in the identification of meaningful criteria for differentiating pathophysiological distinct subtypes of tinnitus. Clinical characteristics [37], etiological factors [19,80], and imaging data [33,38] have been proposed as useful strategies for subtyping. Moreover, standardized assessment of patients in clinical trials and pooling of these longitudinal data in large databases has been suggested as a strategy for identifying clinically meaningful subtypes [36].

Large-scale screening of compounds for their potential use in tinnitus is limited by the lack of *in vitro* bioassays and by the still-limited validity of the currently available animal models [26]. Different animal models have been developed and validated for the perceptual aspects of acute tinnitus [161-166], but not for its emotional and cognitive impairments. Moreover, their validity for predicting effectiveness of a drug on severity of chronic tinnitus in humans remains to be determined. However, animal models may prove useful for discovery validation even if they do not recapitulate all disease aspects. In the research of more complex central nervous diseases such as depression or schizophrenia, animal models have proven useful, even if they can serve only as models of disease mechanisms but not of the disease itself. Thus, the search for drugs to treat tinnitus should not wait for a complete understanding of the neural correlates of tinnitus nor the refinement of the animal models.

An additional challenge in the design of drugs for the treatment of tinnitus derives from the fact that modern drug discovery mainly focuses on the identification of new chemical entities interacting with discrete molecular targets. This is a reductionist approach which requires the knowledge of defined sites of drug action with a known clinical relevance. This is not the scenario we are facing in the case of tinnitus. Tinnitus cannot be seen solely as a pathology of increased excitation or decreased inhibition at different relays along the auditory pathway. We are rather dealing with dynamic overlapping brain networks as the neuronal correlate of tinnitus [22,167]. Further complexity is added by recent findings of state dependency of receptor effects: thus, for example, it has been shown that GABA_A receptors, which are targeted in tinnitus patients with the aim to increase inhibitory GABAergic pathways, can be excitatory in the mature cortex depending on the excitability of the network the neuron is embedded in [168].

Thus it seems rather unlikely that all forms of tinnitus will be cured by one single drug acting selectively at a single molecular target [169]. Considering that tinnitus is a complex network pathology, one might expect that – similar to other complex CNS-pathologies [170] – a combination of different drugs may be more effective than a single drug alone [171]. Such a combination treatment could consist of different drugs, even if each one in isolation has shown only some limited benefit for tinnitus suppression. This notion is supported by a recent report in which deanxit, the combination of the antidepressant melitracen and the antipsychotic

flupentixol, has proven superior to placebo in a crossover trial as add-on medication to clonazepam [172].

Given that promiscuous or dirty drugs are probably more efficient than highly selective ones, can they be designed rationally? Drug combinations have been used with compounds already known to be effective in the disease of interest, or where there is a clear rationale for the combination [170]. However, such limited combination testing samples only a tiny fraction of the combinatorial pharmacological space and is unlikely to result in the selection of optimal combinations among the very large number of possibilities. The complexity imposed by finding the right combination of targets to aim, exploring dosage ranging, considering drug interactions, and finally ensuring safety seems to exclude the rational development of combination therapies.

The use of network science has recently been proposed to deal with this high degree of complexity. Following network biology principles, drug discovery approaches may involve the rational identification of combinations of small molecules that perturb networks in a desired fashion [173]. Network concepts have already been applied in drug discovery studies in anti-cancer drugs [174]. Moreover, drug-target networks linking approved or experimental drugs to their protein targets have helped to organize and visualize the considerable knowledge that exists concerning the interplay between diseases, drug targets, and drugs [175]. Finally, large-scale network analysis of side-effect databases has been proven successful for predicting new molecular targets for known drugs based on their side-effect profile [176].

Finally, because the first tinnitus drugs are yet to be approved, regulatory agencies such as the Food and Drug Administration or the European Medicines Agency lack standardized protocols for their approval process. Therefore, the first pharmaceutical industry to develop a tinnitus drug will have to lead the way. This will be most successful as a collaborative effort with tinnitus researchers providing

informed direction to drug companies and developing better lines of communication. A recent initiative to develop international methodological standards for clinical trials in tinnitus represents a first step in this direction [32].

4. Conclusions

Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA- or EMA-approved drug on the market. A wide variety of drugs with different therapeutic uses have been used off-label with some effect in a limited subset of patients. At present, evidence-based pharmacological approaches are limited to the treatment of comorbidities such as depression, anxiety or insomnia. Most patients and clinicians are waiting for a drug that can suppress or significantly reduce tinnitus. Thus, there is a pressing need to develop a drug or a combination of drugs for tinnitus relief. With the big pharmaceutical companies increasingly entering the hearing and tinnitus field, this scenario will most likely change in the near future.

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