

EXPERT OPINION

1. Introduction
2. Pharmacological treatment
3. Expert opinion
4. Conclusions

Current pharmacological treatments for tinnitus

Berthold Langguth[†] & Ana Belén Elgoyhen

[†]*Department of Psychiatry and Psychotherapy, University of Regensburg, Germany*

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

Expert Opin. Pharmacother. [Early Online]

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

informa
healthcare

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 tonicaine 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 agomelatin.

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 pramipexole 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.

Acknowledgements

B Langguth is supported by the Deutsche Forschungsgemeinschaft, the American Tinnitus Association and the Tinnitus Research Initiative. He received consultancy and speaker honoraria from Autifony, ANM, Astra Zeneca, Merz, Novartis, Pfizer, Lundbeck and Servier. AB Elgoyhen is supported by the Tinnitus Research Initiative and a Howard Hughes International Scholar Grant.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. *Am J Med* 2010;123:711-18
2. Axelsson A, Ringdahl A. Tinnitus—a study of its prevalence and characteristics. *Br J Audiol* 1989;23:53-62
3. Krog NH, Engdahl B, Tambs K. The association between tinnitus and mental health in a general population sample: results from the HUNT Study. *J Psychosom Res* 2010;69:289-98
4. Lasisi AO, Abiona T, Gureje O. Tinnitus in the elderly: profile, correlates, and impact in the Nigerian Study of Ageing. *Otolaryngol Head Neck Surg* 2010;143:510-15
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
6. Khedr EM, Ahmed MA, Shawky OA, et al. Epidemiological study of chronic tinnitus in Assiut, Egypt. *Neuroepidemiology* 2010;35:45-52
7. Langguth B. A review of tinnitus symptoms beyond 'ringing in the ears': a call to action. *Curr Med Res Opin* 2011;27:1635-43
8. Vio MM, Holme RH. Hearing loss and tinnitus: 250 million people and a US \$10 billion potential market. *Drug Discov Today* 2005;10:1263-5
9. Lobarinas E, Sun W, Stolzberg D, et al. Human brain imaging of tinnitus and animal models. *Semin Hear* 2008;29:333-49
10. Norena AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neurosci Biobehav Rev* 2011;35:1089-109
11. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. *Trends Neurosci* 2004;27:676-82
- **A highly cited review of the neuronal changes in the central auditory system after deprivation from sensory input**
12. Yang S, Weiner BD, Zhang LS, et al. Homeostatic plasticity drives tinnitus perception in an animal model. *Proc Natl Acad Sci USA* 2011;108:14974-9
13. Richardson BD, Brozoski TJ, Ling LL, Caspary DM. Targeting inhibitory neurotransmission in tinnitus. *Brain Res* 2012; in press
14. Brozoski T, Odintsov B, Bauer C. Gamma-aminobutyric acid and glutamic acid levels in the auditory pathway of rats with chronic tinnitus: a direct determination using high resolution point-resolved proton magnetic resonance spectroscopy (H-MRS). *Front Syst Neurosci* 2012;6:9
15. Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron* 2010;66:819-26
16. Simpson JJ, Davies WE. A review of evidence in support of a role for 5-HT in the perception of tinnitus. *Hear Res* 2000;145:1-7
17. Caperton KK, Thompson AM. Activation of serotonergic neurons during salicylate-induced tinnitus. *Laryngoscope* 2010;120(Suppl 4):S203
18. Roberts LE, Eggermont JJ, Caspary DM, et al. Ringing ears: the neuroscience of tinnitus. *J Neurosci* 2010;30:14972-9
19. Vielsmeier V, Strutz J, Kleinjung T, et al. Temporomandibular joint disorder complaints in tinnitus: further hints for a putative tinnitus subtype. *PLoS One* 2012;7:e38887
20. Llinas RR, Ribary U, Jeanmonod D, et al. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA* 1999;96:15222-7
- **The concept of thalamocortical dysrhythmia has been highly influential for pathophysiological models of tinnitus**
21. Weisz N, Wienbruch C, Dohrmann K, Elbert T. Neuromagnetic indicators of auditory cortical reorganization of tinnitus. *Brain* 2005;128:2722-31
- **The first description of altered cortical oscillations in people with tinnitus**
22. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proc Natl Acad Sci USA* 2011;108:8075-80
- **A description of the neuronal correlates of tinnitus as abnormal activity in distributed dynamically changing cortical networks**
23. Schlee W, Hartmann T, Langguth B, Weisz N. Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neurosci* 2009;10:11
24. Vanneste S, Plazier M, van der Loo E, et al. The neural correlates of tinnitus-related distress. *Neuroimage* 2010;52:470-80
25. De Ridder D, Fransen H, Francois O, et al. Amygdalohippocampal involvement in tinnitus and auditory memory. *Acta Otolaryngol Suppl* 2006(556):50-3
26. Eggermont JJ. Hearing loss, hyperacusis, or tinnitus: What is modeled in animal research? *Hear Res* 2012; in press
27. Adamchic I, Langguth B, Hauptmann C, Tass PA. Psychometric evaluation of Visual Analog Scale for the assessment of chronic tinnitus. *Am J Audiol* 2012; in press
28. Zeman F, Koller M, Figueiredo R, et al. Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? *Otolaryngol Head Neck Surg* 2011
29. Adamchic I, Tass PA, Langguth B, et al. Linking the Tinnitus Questionnaire and the subjective Clinical Global Impression: which differences are clinically important? *Health Qual Life Outcomes* 2012;10:79
30. Meikle MB, Henry JA, Griest SE, et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear* 2012;32:153-76
31. Langguth B, Goodey R, Azevedo A, et al. Consensus for tinnitus patient assessment and treatment outcome measurement: tinnitus Research Initiative meeting, Regensburg, July 2006. *Prog Brain Res* 2007;166:525-36
- **A consensus on standards for patient assessment and outcome measurements from an international expert group**
32. Landgrebe M, Azevedo A, Baguley D, et al. Methodological aspects of clinical trials in tinnitus: a proposal for an

Expert Opin. Pharmacother. Downloaded from informahealthcare.com by 195.37.16.230 on 11/05/12 For personal use only.

- international standard. *J Psychosom Res* 2012;73:112-21
- **The proposal for an international standard for clinical trial methodology of tinnitus treatment studies**
33. Vanneste S, De Ridder D. The auditory and non-auditory brain areas involved in tinnitus. an emergent property of multiple parallel overlapping subnetworks. *Front Syst Neurosci* 2012;6:31
 34. Schlee W, Kleinjung T, Hiller W, et al. Does tinnitus distress depend on age of onset? *PLoS One* 2011;6:e27379
 35. Mardini MK. Ear-clicking "tinnitus" responding to carbamazepine. *N Engl J Med* 1987;317:1542
 36. Landgrebe M, Zeman F, Koller M, et al. The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome. *BMC Med Inform Decis Mak* 2010;10:42
 37. Tyler R, Coelho C, Tao P, et al. Identifying tinnitus subgroups with cluster analysis. *Am J Audiol* 2008;17:S176-84
 38. Schecklmann M, Lehner A, Poepl TB, et al. Cluster analysis for identifying sub-types of tinnitus: a positron emission tomography and voxel-based morphometry study. *Brain Res* 2012; in press
 39. Cima RF, Maes IH, Joore MA, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *Lancet* 2012;379:1951-9
 40. Martinez-Devesa P, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev* 2010;CD005233
 41. Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database Syst Rev* 2010;CD006371
 42. Schaette R, Konig O, Hornig D, et al. Acoustic stimulation treatments against tinnitus could be most effective when tinnitus pitch is within the stimulated frequency range. *Hear Res* 2010;269:95-101
 43. Phillips JS, McFerran D. Tinnitus Retraining Therapy (TRT) for tinnitus. *Cochrane Database Syst Rev* 2010;CD007330
 44. Tyler RS. Patient preferences and willingness to pay for tinnitus treatments. *J Am Acad Audiol* 2012;23:115-25
 45. Hall DA, Lainez MJ, Newman CW, et al. Treatment options for subjective tinnitus: self reports from a sample of general practitioners and ENT physicians within Europe and the USA. *BMC Health Serv Res* 2011;11:302
 46. Langguth B. Tinnitus: the end of therapeutic nihilism. *Lancet* 2012;379:1926-8
 47. Dolgin E. Sound medicine. *Nat Med* 2012;18:642-5
 48. Hoare DJ, Kowalkowski VL, Kang S, Hall DA. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. *Laryngoscope* 2011;121:1555-64
 49. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999;109:1202-11
 50. Hesser H. Methodological considerations in treatment evaluations of tinnitus distress: a call for guidelines. *J Psychosom Res* 2010;69:305-7
 51. Bennett MH, Kertesz T, Yeung P. Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus. *Cochrane Database Syst Rev* 2007;CD004739
 52. Baldo P, Doree C, Lazzarini R, et al. Antidepressants for patients with tinnitus. *Cochrane Database Syst Rev* 2006;CD003853
 - **A cochrane metaanalysis of the effects of antidepressants on tinnitus**
 53. Hilton M, Stuart E. Ginkgo biloba for tinnitus. *Cochrane Database Syst Rev* 2004;CD003852
 - **A cochrane metaanalysis of the effects of ginkgo biloba on tinnitus**
 54. Hoekstra CE, Rynja SP, van Zanten GA, Rovers MM. Anticonvulsants for tinnitus. *Cochrane Database Syst Rev* 2011;CD007960
 - **A cochrane metaanalysis of the effects of anticonvulsants on tinnitus**
 55. Melding PS, Goodey RJ, Thorne PR. The use of intravenous lignocaine in the diagnosis and treatment of tinnitus. *J Laryngol Otol* 1978;92:115-21
 56. Trellakis S, Lautermann J, Lehnerdt G. Lidocaine: neurobiological targets and effects on the auditory system. *Prog Brain Res* 2007;166:303-22
 - **This review summarizes the putative neurobiological mechanisms by which lidocaine suppresses tinnitus**
 57. Gil-Gouveia R, Goadsby PJ. Neuropsychiatric side-effects of lidocaine: examples from the treatment of headache and a review. *Cephalalgia* 2009;29:496-508
 58. Darlington CL, Smith PF. Drug treatments for tinnitus. *Prog Brain Res* 2007;166:249-62
 59. Savastano M. Lidocaine intradermal injection—a new approach in tinnitus therapy: preliminary report. *Adv Ther* 2004;21:13-20
 60. Slattery WH, Fisher LM, Iqbal Z, et al. Intratympanic steroid injection for treatment of idiopathic sudden hearing loss. *Otolaryngol Head Neck Surg* 2005;133:251-9
 61. Slattery WH, Fisher LM, Iqbal Z, Liu N. Oral steroid regimens for idiopathic sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2005;132:5-10
 62. Shim HJ, Song SJ, Choi AY, et al. Comparison of various treatment modalities for acute tinnitus. *Laryngoscope* 2011;121:2619-25
 63. Narozny W, Kuczkowski J, Kot J, et al. Prognostic factors in sudden sensorineural hearing loss: our experience and a review of the literature. *Ann Otol Rhinol Laryngol* 2006;115:553-8
 64. Stokroos RJ, Albers FW, Tenverget EM. Antiviral treatment of idiopathic sudden sensorineural hearing loss: a prospective, randomized, double-blind clinical trial. *Acta Otolaryngol* 1998;118:488-95
 65. Westerlaken BO, Stokroos RJ, Dhooge IJ, et al. Treatment of idiopathic sudden sensorineural hearing loss with antiviral therapy: a prospective, randomized, double-blind clinical trial. *Ann Otol Rhinol Laryngol* 2003;112:993-1000
 66. Hu A, Parnes LS. Intratympanic steroids for inner ear disorders: a review. *Audiol Neurootol* 2009;14:373-82
 67. Spear SA, Schwartz SR. Intratympanic steroids for sudden sensorineural hearing loss: a systematic review. *Otolaryngol Head Neck Surg* 2011;145:534-43

68. Lim DJ. Effects of noise and ototoxic drugs at the cellular level in the cochlea: a review. *Am J Otolaryngol* 1986;7:73-99
69. Puel JL, Ruel J, Guitton M, Pujol R. The inner hair cell afferent/efferent synapses revisited: a basis for new therapeutic strategies. *Adv Otorhinolaryngol* 2002;59:124-30
70. Holley MC. Keynote review: the auditory system, hearing loss and potential targets for drug development. *Drug Discov Today* 2005;10:1269-82
71. Lynch ED, Kil J. Compounds for the prevention and treatment of noise-induced hearing loss. *Drug Discov Today* 2005;10:1291-8
72. Attias J, Weisz G, Almog S, et al. Oral magnesium intake reduces permanent hearing loss induced by noise exposure. *Am J Otolaryngol* 1994;15:26-32
73. Lin CY, Wu JL, Shih TS, et al. N-Acetyl-cysteine against noise-induced temporary threshold shift in male workers. *Hear Res* 2010;269:42-7
74. Kramer S, Dreisbach L, Lockwood J, et al. Efficacy of the antioxidant N-acetylcysteine (NAC) in protecting ears exposed to loud music. *J Am Acad Audiol* 2006;17:265-78
75. Kopke RD, Jackson RL, Coleman JK, et al. NAC for noise: from the bench top to the clinic. *Hear Res* 2007;226:114-25
76. Ewert DL, Lu J, Li W, et al. Antioxidant treatment reduces blast-induced cochlear damage and hearing loss. *Hear Res* 2012;285:29-39
77. Ebselen in College Students. Available from: (<http://clinicaltrials.gov/ct2/show/NCT01444484?term=ebselen&rank=1>) 2012
78. Ebselen in Chemotherapy induced hearing loss. Available from: <http://clinicaltrials.gov/ct2/show/NCT01451853?term=ebselen&rank=2> 2012
79. Muehlmeier G, Biesinger E, Maier H. Safety of intratympanic injection of AM-101 in patients with acute inner ear tinnitus. *Audiol Neurootol* 2011;16:388-97
80. Van de Heyning P, Cox T, Maier H, et al. Efficacy and safety of AM-101 in the treatment of acute inner ear tinnitus - a double blind, randomised, placebo controlled phase II study [abstract]. *Abstract Book of the 6th TRI Meeting* 2012. 6:19
81. Robinson SK, Viirre ES, Stein MB. Antidepressant therapy in tinnitus. *Hear Res* 2007;226:221-31
82. Langguth B, Landgrebe M, Kleinjung T, et al. Tinnitus and depression. *World J Biol Psychiatry* 2011;12:489-500
83. Tonndorf J. The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus. *Hear Res* 1987;28:271-5
84. Mico JA, Ardid D, Berrocoso E, Eschaliere A. Antidepressants and pain. *Trends Pharmacol Sci* 2006;27:348-54
85. Sullivan MD, Dobie RA, Sakai CS, Katon WJ. Treatment of depressed tinnitus patients with nortriptyline. *Ann Otol Rhinol Laryngol* 1989;98:867-72
86. Sullivan M, Katon W, Russo J, et al. A randomized trial of nortriptyline for severe chronic tinnitus. Effects on depression, disability, and tinnitus symptoms. *Arch Intern Med* 1993;153:2251-9
87. Katon W, Sullivan M, Russo J, et al. Depressive symptoms and measures of disability: a prospective study. *J Affect Disord* 1993;27:245-54
88. Bayar N, Boke B, Turan E, Belgin E. Efficacy of amitriptyline in the treatment of subjective tinnitus. *J Otolaryngol* 2001;30:300-3
89. Podoshin L, Ben-David Y, Fradis M, et al. Idiopathic subjective tinnitus treated by amitriptyline hydrochloride/biofeedback. *Int Tinnitus J* 1995;1:54-60
90. Mihail RC, Crowley JM, Walden BE, et al. The tricyclic trimipramine in the treatment of subjective tinnitus. *Ann Otol Rhinol Laryngol* 1988;97:120-3
91. Feder R. Tinnitus associated with amitriptyline. *J Clin Psychiatry* 1990;51:85-6
92. Mendis D, Johnston M. An unusual case of prolonged tinnitus following low-dose amitriptyline. *J Psychopharmacol* 2008;22:574-5
93. Tandon R, Grunhaus L, Greden JF. Imipramine and tinnitus. *J Clin Psychiatry* 1987;48:109-11
94. Langguth B, Landgrebe M, Wittmann M, et al. Persistent tinnitus induced by tricyclic antidepressants. *J Psychopharmacol* 2010;24:1273-5
95. Clewes J. A case report of onset of tinnitus following discontinuation of antidepressant and a review of the literature. *Prim Care Companion CNS Disord* 2012;14
96. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering—a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2006;26:32-9
97. Robinson SK, Viirre ES, Bailey KA, et al. Randomized placebo-controlled trial of a selective serotonin reuptake inhibitor in the treatment of nondepressed tinnitus subjects. *Psychosom Med* 2005;67:981-8
98. Roberts C, Inamdar A, Koch A, et al. A randomized, controlled study comparing the effects of vestipitant or vestipitant and paroxetine combination in subjects with tinnitus. *Otol Neurotol* 2011;32:721-7
99. Langguth B, Kleinjung T, Fischer B, et al. Tinnitus severity, depression, and the big five personality traits. *Prog Brain Res* 2007;166:221-5
100. Johnson RM, Brummett R, Schleuning A. Use of alprazolam for relief of tinnitus. A double-blind study. *Arch Otolaryngol Head Neck Surg* 1993;119:842-5
101. Jalali MM, Kousha A, Naghavi SE, et al. The effects of alprazolam on tinnitus: a cross-over randomized clinical trial. *Med Sci Monit* 2009;15:155-60
102. Kay NJ. Oral chemotherapy in tinnitus. *Br J Audiol* 1981;15:123-4
103. Bahmad FM Jr, Venosa AR, Oliveira CA. Benzodiazepines and GABAergics in treating severe disabling tinnitus of predominantly cochlear origin. *Int Tinnitus J* 2006;12:140-4
104. Gananca MM, Caovilla HH, Gananca FF, et al. Clonazepam in the pharmacological treatment of vertigo and tinnitus. *Int Tinnitus J* 2002;8:50-3
105. Han SS, Nam EC, Won JY, et al. Clonazepam Quiets tinnitus: a randomised crossover study with Ginkgo Biloba. *J Neurol Neurosurg Psychiatry* 2012;83:821-7
106. Busto U, Fornazzari L, Naranjo CA. Protracted tinnitus after discontinuation of long-term therapeutic use of

- benzodiazepines. *J Clin Psychopharmacol* 1988;8:359-62
107. Busto U, Sellers EM, Naranjo CA, et al. Withdrawal reaction after long-term therapeutic use of benzodiazepines. *N Engl J Med* 1986;315:854-9
 108. Eggermont JJ. Tinnitus: neurobiological substrates. *Drug Discov Today* 2005;10:1283-90
 109. Melding PS, Goodey RJ. The treatment of tinnitus with oral anticonvulsants. *J Laryngol Otol* 1979;93:111-22
 110. Sanchez TG, Balbani AP, Bittar RS, et al. Lidocaine test in patients with tinnitus: rationale of accomplishment and relation to the treatment with carbamazepine. *Auris Nasus Larynx* 1999;26:411-17
 111. Shea JJ, Harell M. Management of tinnitus aurium with lidocaine and carbamazepine. *Laryngoscope* 1978;88:1477-84
 112. Donaldson I. Tegretol: a double blind trial in tinnitus. *J Laryngol Otol* 1981;95:947-51
 113. Hulshof JH, Vermeij P. The value of carbamazepine in the treatment of tinnitus. *ORL J Otorhinolaryngol Relat Spec* 1985;47:262-6
 114. Levine RA. Typewriter tinnitus: a carbamazepine-responsive syndrome related to auditory nerve vascular compression. *ORL J Otorhinolaryngol Relat Spec* 2006;68:43-6
 115. Bauer CA, Brozoski TJ. Effect of gabapentin on the sensation and impact of tinnitus. *Laryngoscope* 2006;116:675-81
 116. Witsell DL, Hannley MT, Stinnet S, Tucci DL. Treatment of tinnitus with gabapentin: a pilot study. *Otol Neurotol* 2007;28:11-15
 117. Bakhshae M, Ghasemi M, Azarpazhooh M, et al. Gabapentin effectiveness on the sensation of subjective idiopathic tinnitus: a pilot study. *Eur Arch Otorhinolaryngol* 2008;265:525-30
 118. Piccirillo JF, Finnell J, Vlahiotis A, et al. Relief of idiopathic subjective tinnitus: is gabapentin effective? *Arch Otolaryngol Head Neck Surg* 2007;133:390-7
 119. Dehkordi MA, Abolbashari S, Taheri R, Einolghozati S. Efficacy of gabapentin on subjective idiopathic tinnitus: a randomized, double-blind, placebo-controlled trial. *Ear Nose Throat J* 2011;90:150-8
 120. Aazh H, El RA, Humphriss R. Gabapentin for tinnitus: a systematic review. *Am J Audiol* 2011;20:151-8
 121. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain* 2009;145:69-81
 122. Montgomery SA, Herman BK, Schweizer E, Mandel FS. The efficacy of pregabalin and benzodiazepines in generalized anxiety disorder presenting with high levels of insomnia. *Int Clin Psychopharmacol* 2009;24:214-22
 123. Russell IJ, Crofford LJ, Leon T, et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. *Sleep Med* 2009;10:604-10
 124. Simpson JJ, Gilbert AM, Weiner GM, Davies WE. The assessment of lamotrigine, an antiepileptic drug, in the treatment of tinnitus. *Am J Otol* 1999;20:627-31
 125. Mansbach AL, Frey P. Tinnitus: current data and treatment with sodium valproate. *Acta Otorhinolaryngol Belg* 1983;37:697-705
 126. Menkes DB, Larson PM. Sodium valproate for tinnitus. *J Neurol Neurosurg Psychiatry* 1998;65:803
 127. Guitton MJ, Wang J, Puel JL. New pharmacological strategies to restore hearing and treat tinnitus. *Acta Otolaryngol* 2004;124:411-15
 128. Denk DM, Heinzl H, Franz P, Ehrenberger K. Caroverine in tinnitus treatment. A placebo-controlled blind study. *Acta Otolaryngol* 1997;117:825-30
 129. Domeisen H, Hotz MA, Hausler R. Caroverine in tinnitus treatment. *Acta Otolaryngol* 1998;118:606-8
 130. Ehrenberger K. Topical administration of Caroverine in somatic tinnitus treatment: proof-of-concept study. *Int Tinnitus J* 2005;11:34-7
 131. Azevedo AA, Figueiredo RR. Treatment of tinnitus with acamprosate. *Prog Brain Res* 2007;166:273-7
 132. Sharma DK, Kaur S, Singh J, Kaur I. Role of acamprosate in sensorineural tinnitus. *Indian J Pharmacol* 2012;44:93-6
 133. Accamprosate. Available from: <http://clinicaltrials.gov/ct2/show/NCT00596531> 2012
 134. Figueiredo RR, Langguth B, Mello de OP, de Azevedo AA. Tinnitus treatment with memantine. *Otolaryngol Head Neck Surg* 2008;138:492-6
 135. Plazas PV, Savino J, Kracun S, et al. Inhibition of the alpha9alpha10 nicotinic cholinergic receptor by neramexane, an open channel blocker of N-methyl-D-aspartate receptors. *Eur J Pharmacol* 2007;566:11-19
 136. Suckfuell M, Althaus M, Ellers-Lenz B, et al. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus. *BMC Ear Nose Throat Disord* 2011;11:1
 137. Neramexane: Clin Trial. Available from <http://clinicaltrials.gov/ct2/show/NCT00739635>, <http://clinicaltrials.gov/ct2/show/NCT00772980>, <http://clinicaltrials.gov/ct2/show/NCT00827008> 2011
 138. Lopez-Gonzalez MA, Santiago AM, Esteban-Ortega F. Sulpiride and melatonin decrease tinnitus perception modulating the auditolimbic dopaminergic pathway. *J Otolaryngol* 2007;36:213-19
 139. Lopez-Gonzalez MA, Moliner-Peiro F, Faro-Garcia J, Esteban-Ortega F. Sulpiride plus hydroxyzine decrease tinnitus perception. *Auris Nasus Larynx* 2007;34:23-7
 140. de Azevedo AA, Langguth B, de Oliveira PM, Rodrigues FR. Tinnitus treatment with piribedil guided by electrocochleography and acoustic otoemissions. *Otol Neurotol* 2009;30:676-80
 141. Sziklai I, Szilvassy J, Szilvassy Z. Tinnitus control by dopamine agonist pramipexole in presbycusis patients: a randomized, placebo-controlled, double-blind study. *Laryngoscope* 2011;121:888-93
 142. Szczepaniak WS, Moller AR. Effects of (-)-baclofen, clonazepam, and diazepam on

- tone exposure-induced hyperexcitability of the inferior colliculus in the rat: possible therapeutic implications for pharmacological management of tinnitus and hyperacusis. *Hear Res* 1996;97:46-53
143. Westerberg BD, Roberson JB Jr, Stach BA. A double-blind placebo-controlled trial of baclofen in the treatment of tinnitus. *Am J Otol* 1996;17:896-903
144. Zheng Y, Vagal S, McNamara E, et al. A dose-response analysis of the effects of L-baclofen on chronic tinnitus caused by acoustic trauma in rats. *Neuropharmacology* 2012;62:940-6
145. Smith PF, Zheng Y, Darlington CL. Revisiting baclofen for the treatment of severe chronic tinnitus. *Front Neurol* 2012;3:34
146. Coelho C, Figueiredo R, Frank E, et al. Reduction of tinnitus severity by the centrally acting muscle relaxant cyclobenzaprine: an open-label pilot study. *Audiol Neurootol* 2012;17:179-88
147. Vanneste S, Figueiredo R, De Ridder D. Treatment of tinnitus with cyclobenzaprine: an open-label study. *Int J Clin Pharmacol Ther* 2012;50:338-44
148. Olzowy B, Canis M, Hempel JM, et al. Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly: results of a prospective, randomized, double-blind clinical trial. *Otol Neurotol* 2007;28:455-8
149. Memin Y. Perceived efficacy of cyclandelate in the treatment of cochleovestibular and retinal disturbances related to cerebrovascular insufficiency. A study in general practice comprising 2772 patients. *Drugs* 1987;33(Suppl 2):120-4
150. Hester TO, Theilman G, Green W, Jones RO. Cyclandelate in the management of tinnitus: a randomized, placebo-controlled study. *Otolaryngol Head Neck Surg* 1998;118:329-32
151. Risey JA, Guth PS, Amedee RG. Furosemide distinguishes central and peripheral tinnitus. *Int Tinnitus J* 1995;1:99-103
152. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: double blind, placebo controlled trial. *BMJ* 2001;322:73
153. Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clin Otolaryngol Allied Sci* 2004;29:226-31
154. Rosenberg SI, Silverstein H, Rowan PT, Olds MJ. Effect of melatonin on tinnitus. *Laryngoscope* 1998;108:305-10
155. Yilmaz I, Akkuzu B, Cakmak O, Ozluoglu LN. Misoprostol in the treatment of tinnitus: a double-blind study. *Otolaryngol Head Neck Surg* 2004;130:604-10
156. Davies E, Knox E, Donaldson I. The usefulness of nimodipine, an L-calcium channel antagonist, in the treatment of tinnitus. *Br J Audiol* 1994;28:125-9
157. Mazurek B, Haupt H, Szczepek AJ, et al. Evaluation of vardenafil for the treatment of subjective tinnitus: a controlled pilot study. *J Negat Results Biomed* 2009;8:3
158. Yetiser S, Tosun F, Satar B, et al. The role of zinc in management of tinnitus. *Auris Nasus Larynx* 2002;29:329-33
159. Coelho CB, Tyler R, Hansen M. Zinc as a possible treatment for tinnitus. *Prog Brain Res* 2007;166:279-85
160. Howland RH. Serendipity and psychopharmacology. *J Psychosoc Nurs Ment Health Serv* 2010;48:9-12
161. Jastreboff PJ, Brennan JF, Coleman JK, Sasaki CT. Phantom auditory sensation in rats: an animal model for tinnitus. *Behav Neurosci* 1988;102:811-22
- **The first presentation of an animal model of tinnitus**
162. Jastreboff PJ, Brennan JF, Sasaki CT. Quinine-induced tinnitus in rats. *Arch Otolaryngol Head Neck Surg* 1991;117:1162-6
163. Lobarinas E, Sun W, Cushing R, Salvi R. A novel behavioral paradigm for assessing tinnitus using schedule-induced polydipsia avoidance conditioning (SIP-AC). *Hear Res* 2004;190:109-14
164. Bauer CA, Brozoski TJ. Assessing tinnitus and prospective tinnitus therapeutics using a psychophysical animal model. *J Assoc Res Otolaryngol* 2001;2:54-64
165. Ruttiger L, Ciuffani J, Zenner HP, Knipper M. A behavioral paradigm to judge acute sodium salicylate-induced sound experience in rats: a new approach for an animal model on tinnitus. *Hear Res* 2003;180:39-50
166. Guitton MJ, Caston J, Ruel J, et al. Salicylate induces tinnitus through activation of cochlear NMDA receptors. *J Neurosci* 2003;23:3944-52
167. Leaver AM, Renier L, Chevillet MA, et al. Dysregulation of limbic and auditory networks in tinnitus. *Neuron* 2011;69:33-43
- **This paper presents support for the relevance of the interaction between limbic and auditory areas in tinnitus pathophysiology**
168. Gullledge AT, Stuart GJ. Excitatory actions of GABA in the cortex. *Neuron* 2003;37:299-309
169. Kaufmann SH. Paul Ehrlich: founder of chemotherapy. *Nat Rev Drug Discov* 2008;7:373
170. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther* 2006;110:135-370
171. Elgoyhen AB, Langguth B, Vanneste S, De RD. Tinnitus: network pathophysiology-network pharmacology. *Front Syst Neurosci* 2012;6:1
- **In this review, the relevance of network approaches for the development of tinnitus treatments is discussed**
172. Meeus O, De RD, Van de HP. Administration of the combination clonazepam-Deanxit as treatment for tinnitus. *Otol Neurotol* 2011;32:701-9
173. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 2008;4:682-90
- **This review highlights the value of network approaches in drug development**
174. Azmi AS, Wang Z, Philip PA, et al. Proof of concept: network and systems biology approaches aid in the discovery of potent anticancer drug combinations. *Mol Cancer Ther* 2010;9:3137-44
175. Yildirim MA, Goh KI, Cusick ME, et al. Drug-target network. *Nat Biotechnol* 2007;25:1119-26

176. Lounkine E, Keiser MJ, Whitebread S, et al. Large-scale prediction and testing of drug activity on side-effect targets. *Nature* 2012;486:361-7

- **This paper indicates the value of analyzing side-effect profiles for analyzing drug characteristics**

Affiliation

Berthold Langguth^{†1,2} & Ana Belén Elgoyhen^{3,4}

[†]Author for correspondence

¹University of Regensburg,

Department of Psychiatry and Psychotherapy,
Regensburg, Germany

²University of Regensburg,

Interdisciplinary Tinnitus Clinic,
Regensburg, Germany

Tel: +49 941 941 2099;

Fax: +49 941 941 2025;

E-mail: Berthold.Langguth@medbo.de

³Instituto de Investigaciones en Ingeniería

Genética y Biología Molecular Dr Héctor

N Torres Consejo Nacional de Investigaciones

Científicas y Técnicas

⁴University of Buenos Aires,

School of Medicine,

Department of Pharmacology,

Buenos Aires, Argentina