Pharmacological approaches to the treatment of tinnitus

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Tinnitus is the conscious perception of a phantom sound in the absence of an external source. For 1 in 100 of the general population, the condition severely affects quality of life. In spite of the fact that the market for a drug indicated for tinnitus relief is huge, there are still no FDA-approved drugs, and the quest for a tinnitus-targeted compound faces important challenges. A wide variety of drugs have been used off-label to treat tinnitus sufferers, with limited but significant effects in subsets of patients. If the compounds being developed at present by the pharmaceutical industry finally reach the market, they will establish a turning point in the treatment of this pathology.

Tinnitus refers to a condition in which a patient has a conscious hearing percept that can take the form of ringing, buzzing, roaring or hissing (among others) in the absence of an external sound [1,2]. 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 spasms of the muscles in the middle ear, Eustachian tube or soft palate. Unlike subjective tinnitus, an observer, using a stethoscope, can often hear objective tinnitus. Objective tinnitus should not be mistaken with otoacoustic emissions. The latter are normal sounds generated by the inner ear that are derived from the active process of the outer hair cells and are usually not perceived by the individual [3]. 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. Some patients perceive the phantom sound as coming from inside the ear, others report that the phantom sound is located inside the head, and a few perceive the phantom sound as coming from outside the head. Some patients experience bilateral tinnitus, whereas others hear it in just one ear. Subjective tinnitus is by far more prevalent than objective tinnitus and is the subject of this review.

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Epidemiology and prevalence

Many people have experienced ringing in their ears when no external sound is present [2]. Typically, the sensation is reversible, disappears over a period of time ranging from a few seconds to a few days and can be caused by listening to loud music, fever, the use of aspirin or quinine, or transient perturbations of the middle ear. However, in 5–15% of the general population, the tinnitus sensation is unremitting [1]. It is estimated that for 1 in 100 of the general population, the condition severely affects their quality of life because it is accompanied by a variety of symptoms, which can include hyperacusis (lowered tolerance to sound), phonophobia (fear of sound), anxiety, depression, irritability, agitation, stress, depression and/or insomnia [2]. The prevalence of tinnitus steadily increases with the degree of age-related hearing loss [4]. Chronic tinnitus is more prevalent among seniors (12% after age 60) than in young adults (5% in the 20–30 age group) but can occur at any age. However, many individuals with hearing loss do not experience tinnitus, and some individuals with normal hearing experience tinnitus. Individuals who suffer from severe and disabling tinnitus often seek medical treatment from an otologist, audiologist, neurologist or psychiatrist, with the hope

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of finding a drug or surgical treatment that can completely switch off their tinnitus and bring back silence. The Royal National Institute for Deaf People, UK (http://www.rnid.org.uk) estimates that approximately 13 million people in western Europe and the USA seek medical advice for their tinnitus [5].

Noise is the greatest causative factor among the defined etiologies of tinnitus [6]. Since the industrial revolution, an increasing number of people are being exposed to extreme levels of noise [7]. Noise at levels 85 dBA and higher can lead to both mechanical and metabolic damage of the cochlea [8]. A single exposure or repeated or continuous exposure to high levels of noise can cause noise-induced hearing loss and tinnitus. In developed countries, the appetite for leisure noise among the young (e.g. attending rock concerts or discos or the use of MP3 players) is expected to have a substantial, deleterious impact on hearing loss and tinnitus incidence in older generations in the near future [5,9]. In addition, noise-induced hearing loss is one of the most important workplace hazards. Occupations such as the military, construction, mining, forestry, farming, aviation, rail and trucking report an urgent need to develop hearing conservation programs [7]. In a retrospective study of 3466 claimants who sought compensation for occupational noise-induced hearing loss, the prevalence of those reporting tinnitus as a function of hearing loss at 4 kHz ranged from 41.7% to 56.5%, regardless of the amount of hearing loss sustained [10]. These statistics indicate that tinnitus is also one of the most important workplace disabilities of modern society. The US Veterans Administration Benefits Report ranked tinnitus as the second most prevalent service-related disability. Among those who began receiving benefits in 2006, tinnitus was ranked the first service-related disability, accounting for 9.7% of the total (http://www.vba.va.gov/REPORT/abr/2006_abr.pdf). Indeed, in 2006, the annual compensation for tinnitus-related disability was $536 million. These statistics reflect not only the incidence of tinnitus but also its important burden on the health care system. The efficacy of hearing-protection devices (e.g. earplugs) and hearing-protection measures (i.e. reduced noise exposure time) could be augmented by pharmacological agents that might reduce noise-induced hearing loss and tinnitus more effectively.

A clinically unmet need

The available treatments for the management of the tinnitus patient are diverse. These include counseling and cognitive behavioral therapies; neurobiofeedback; different forms of sound therapies; methods that attempt to increase input to the auditory system, such as hearing aids and cochlear implants (for use in patients whose tinnitus is caused by the deprivation of signals to the auditory nervous system); various forms of electrical stimulation of brain structures, either through implanted electrodes or by inducing electrical current in the brain with transcranial magnetic stimulation; and drug treatments [11–18]. Although patients benefit from these therapies to some degree, a large fraction of them are left untreated and in despair with the notion that 'they have to learn to live with their tinnitus'. Thus, tinnitus today is still a clinically unmet need, and most patients would welcome a drug that could reduce or even abolish their phantom sound.

Despite the important unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market. For the majority of tinnitus sufferers that seek medical advice, the treatment goals are aimed at symptomatic relief or the management of the associated distress, which is usually justified because serious underlying pathologies are rare. More than 4 million prescriptions are written each year for tinnitus relief in Europe and the USA, but these are all off-label prescriptions of a wide variety of therapeutic drugs [5] (Box 1). Most clinicians who treat tinnitus patients would welcome a more effective drug therapy targeted at tinnitus. Thus, there is a pressing need to develop a drug targeting tinnitus relief. In some individuals, tinnitus causes irritability, agitation, stress, depression and insomnia and interferes with normal life (leading to suicidal attempts in severe cases); therefore, 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.

BOX 1

Off-label drugs investigated for the treatment of tinnitus

Antiarrythmics
Lidocaine
Tocainide
Flecainide
Mexiletine
Anticonvulsants
Carbamazepine
Gabapentine
Lamotrigine
Valproic acid
Anxiolytics
Clonazepam
Alprazolam
Diazepam
Glutamate receptor antagonists
Acamprosate
Caroverine
Memantine
Antidepressants
Amitriptyline
Trimipramine
Nortriptyline
Paroxetine
Sertraline
Fluoxetine
Others
Misoprostol
Atorvastatin
Nimodipine
Furosemide
Cyclandelate
Sulpiride
Vardenafil
Melatonin
Herbal products
Vitamins
Minerals

Tinnitus can be pharmacologically targeted

Tinnitus is a symptom that is associated with virtually all diseases and disorders affecting the auditory system and can arise from a lesion in any part of the auditory pathway. Some causes that trigger tinnitus are well known (Table 1). In particular, noise

TABLE 1

Tinnitus onset factors

Onset factor	%
Noise exposure	23.6
Head and/or neck injury	16.7
Otologic	7.0
Other illnesses	7.2
Drug medication	3.4
Stress	2.5
Surgery	1.6
Other	9.6
No related onset factor	42.6

Data from the Tinnitus Archive, Oregon Health and Science University (http://www.tinnitusarchive.org). Survey performed between 1981 and 1994 on a total of 1625 patients. Because some patients reported more than one onset factor, the total % surpasses 100.

trauma, the administration of ototoxic drugs (e.g. aminoglycosides, cisplatin and salicylates), and head and neck injuries have been associated with the development of subjective tinnitus. Interestingly, although the initial lesion might affect the peripheral organ of the auditory system, the neural correlate of the sound perceived is most probable in the central auditory circuitry [1]. A central origin of the tinnitus percept is demonstrated by the fact that the phantom sound sensation persists after the deprivation of input from the periphery via sectioning of the auditory nerve [19]. Not surprisingly, although the mechanisms of the production of tinnitus are far from being fully understood, there is growing evidence that changes in neuronal activity, neuronal synchrony, disruption of the balance between excitation and inhibition, and rearrangements of the tonotopic organization in different parts of the auditory pathway (including the dorsal cochlear nucleus, inferior colliculus, thalamus and/or auditory cortex) underlie tinnitus pathology [1,20–24]. Neuronal excitability can be modulated by different neurotransmitters, neuromodulators and voltage-gated channel acting compounds. That a local anesthetic, the voltage-gated sodium-channel blocker lidocaine, given intravenously leads to the temporary disappearance of tinnitus or a major change in the nature of the tinnitus in 70% of patients [25] indicates that activity-driven changes underlying tinnitus can be pharmacologically targeted.

Pharmacological treatment of tinnitus

There are no standardized protocols for the treatment of tinnitus patients. However, the management of tinnitus sufferers is a pressing need faced by medical doctors with different specializations. Drug therapy is one approach to the problem. The literature concerning the pharmacotherapy of tinnitus is vast. We will only focus on some of the most frequent pharmacotherapeutic treatments employed. For a comprehensive review of the literature, see Refs. [16–18,26].

Although intravenous lidocaine seems to be effective in a great number of tinnitus patients, the effect is transient and the route of administration not a practical one in a clinical setting of a chronic condition. Several other oral antiarrhythmic drugs – such tocainide, flecainide and mexiletine – have been studied for tinnitus (Box 1). None of these compounds have been demonstrated to be particularly useful, and almost all of them exhibit severe side-effects and are now in disuse [16–18].

Antidepressants are commonly used in pharmacological protocols for the management of tinnitus [16–18]. The reason for such a large use of antidepressants can be found in the well-described comorbidity between depressive disorders and tinnitus [27–29]. Among all antidepressant families that have been used for tinnitus, particular interest should be paid to the tricyclic group of drugs, mainly because of their analgesic effects [30]. This property of tricyclic antidepressants could be interesting in view of the proposed etiological similarities between tinnitus and neuropathic pain [31]. Among the tricyclic antidepressants analyzed (amitriptyline, trimipramine and nortriptyline), nortriptyline is worth mentioning. In a double-blind placebo-controlled study involving subjects with severe tinnitus and severe depression or depressive symptoms, nortriptyline significantly reduced depression scores, tinnitus disability scores and tinnitus loudness (6.4 dB reduction) relative to placebo [32]. There was a significant correlation between the reduction in tinnitus disability scores and depression scores, suggesting that nortriptyline is effective in reducing tinnitus loudness and severity in severely depressed tinnitus patients but has less benefit in non-depressed individuals [33]. Antidepressants within the serotonin reuptake inhibitors group, such as paroxetine and sertraline, have also been tested. In a randomized, double-blind placebo control study of patients without severe hearing loss but at high risk for developing severe tinnitus, sertraline was significantly more effective than placebo in reducing tinnitus loudness and tinnitus severity [34]. In a double-blind, placebo-controlled study involving chronic tinnitus patients, few of whom suffered from depression, the paroxetine group showed little difference to placebo on tinnitus loudness matching, Tinnitus Handicap Questionnaire scores and other measures; however, the paroxetine group showed a significant improvement in tinnitus aggravation compared with the control group [35]. Very little has been reported for serotonin–norepinephrine reuptake inhibitors, such as duloxetine or venlafaxine. Because activity on norepinephrine reuptake is considered necessary for an antidepressant to be effective on neuropathic pain [30], this group of drugs seems a good choice for tinnitus patients. Taken together, the results with antidepressant drugs suggest that tinnitus patients with depression might gain some benefit from these compounds [35].

Severe tinnitus can be an extremely stressful condition, heavily influencing every aspect of the patient's life. Thus, anxiolytics such as benzodiazepines have been used extensively to help patients cope with their tinnitus. In a prospective, double-blind, placebo-controlled study, alprazolam 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 [36]. Although the strong positive effects of alprazolam are encouraging, the study has been criticized because of its small sample size, drug dosing method and lack of assessment of emotional effect [17]. However, diazepam evaluated in a double-blind triple cross-over trial involving 21 tinnitus patients had no effect on tinnitus loudness [37]. In a retrospective study of medical records from more than 3000 patients taking clonazepam (0.5–1 mg/day, 60–180 days) for vestibular or cochleovestibular

disorders, 32% reported an improvement in their tinnitus [38]. However, the significance of these findings is limited by the lack of a control group. In a prospective, randomized, single-blind clinical trial involving ten patients per group, clonazepam significantly reduced tinnitus loudness and annoyance (visual analog scale) relative to the control group [39]. Additional studies are needed to evaluate the efficacy of benzodiazepines on tinnitus.

Anticonvulsants are being used increasingly in the treatment of several non-epileptic conditions, including various psychiatric disorders and pain syndromes [40]. They have been also used in tinnitus patients. Carbamazepine has long been employed; however, controlled studies have not demonstrated additional benefits compared with placebo [17]. A rare group of patients that receives a significant benefit from carbamazepine is those who have intermittent tinnitus that sounds like a typewriter, popping corn or ear clicking [41,42]. The results with gabapentin for the treatment of tinnitus are contradictory. One controlled trial has shown a significant improvement in tinnitus annoyance and loudness for a group of participants with tinnitus related to acoustic trauma [43]. A second study did not detect any improvement in tinnitus handicap but did report a significant improvement in tinnitus annoyance when compared to placebo [44]. However, a third controlled trial did not report any benefit of the compound on tinnitus annoyance or loudness [45]. Thus, although the effects of gabapentin are limited, it might benefit a subpopulation of patients in which tinnitus is associated with acoustic trauma [46]. A double-blind, placebo-controlled, cross-over clinical trial on 33 patients has shown no beneficial effect of lamotrigine [47]. Finally, although valproic acid is one of the most frequently prescribed antiepileptic drugs, only case reports have been reported for its use in tinnitus.

Glutamate receptor antagonists have been tried in tinnitus sufferers. The rationale behind their use is that imbalance between inhibitory and excitatory neurotransmission is observed in several regions of the auditory pathway [1]. Moreover, blockade of glutamatergic neurotransmission could also exert neuroprotectant effects because it is known that noise overexposure is followed by an excitotoxic injury of the hair cells. Therefore, administration of glutamate antagonists might prevent inner ear damage and, possibly, tinnitus development in the acute phase [48]. The putative non-selective N-methyl-D-aspartic acid (NMDA) receptor antagonist acamprosate has been tried in a double-blind study [49]. Patients received placebo or acamprosate (333 mg, three times per day) and rated the loudness and annoyance of their tinnitus before and at monthly intervals during treatment. 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 with 44% in the placebo group. A larger clinical trial is currently underway to analyze the encouraging results from this preliminary study (http://clinicaltrials.gov/ct2/show/NCT00596531). Treatment with intravenous caroverine, an antagonist of non-NMDA and NMDA receptors, has been analyzed, with contradictory results [50,51]. In a prospective, randomized, double-blind cross-over study using the Tinnitus Handicap Inventory to assess efficacy, 90-day treatment with the non-selective NMDA antagonist memantine was no more effective than placebo [52]. Because cochlear application of NMDA antagonists has shown positive results in animal studies, a double-blind, randomized, placebo-controlled trial with cochlear application of AM-101, an NMDA antagonist, is being carried out. The study involves patients with acute (less than three months) noise-induced tinnitus that have not responded to glucocorticoid treatment (http://www.aurismedical.com/p/therapies/am_101.php). Moreover, the memantine analog neramexane, which blocks both NMDA and α9α10 nicotinic cholinergic receptors is at phase III of a clinical trial setting (http://clinicaltrials.gov/ct2/show/NCT00405886).

Some other miscellaneous drugs have been tested, either with limited efficacy or requiring further controlled trials. These include the prostagaldin E1 analog misoprostol [53,54], the HMG-CoA reductase atorvastatin [55], the L-type calcium blocker nimodipine [56], the loop diuretic furosemide [57], the vasodilator cyclandelate [58], the dopamine D2 receptor antagonist sulpiride [59], the phosphodiesterase type 5 inhibitor vardenafil [60], melatonin [61], and some herbal products, vitamins and minerals.

From the above, it can be concluded that in an attempt to find tinnitus-relieving drugs, a wide variety of pharmacological approaches have been investigated (Box 1) and many compounds have been used off-label. Some drugs have been reported to provide moderate relief of symptoms in a subset of patients. However, no drug has yet proven sufficient effectiveness in randomized controlled clinical trials to be approved specifically for tinnitus [16–18]. Neramexane is the first compound to enter phase III trials and, thus, might become the first drug approved for the treatment of tinnitus.

The quest for a tinnitus drug: a challenging enterprise

The search for effective tinnitus therapies faces considerable challenges. First and foremost, tinnitus is only a symptom that might be the manifest of different underlying pathologies and has several etiologies and manifestations, which can include various degrees of affective disorders. Thus, heterogeneity within tinnitus patients is expected and the drug discovery endeavor faces the 'one drug won't fit all' scenario. Differential diagnosis of triggering events and temporal onset should enable a more rational and efficacious pharmacological approach and becomes a priority. That a subgroup of patients who have intermittent tinnitus that sounds like a typewriter, popping corn or ear clicking receive a significant benefit from carbamazepine [41,42] indicates that 'subtyping' tinnitus is to be highly recommended. Efforts toward establishing subgroups of tinnitus are under way [62] and will probably aid the selection of patients in future clinical trials.

Second, the current limited understanding of the neural substrates of tinnitus, together with the lack of adequate animal models that can faithfully recapitulate its pathology, hampers the screen for new molecules in preclinical studies. The basic dilemma faced by the animal researcher who wants to study tinnitus is whether the animals have tinnitus [63,64]. An additional challenge is imposed by the fact that, in humans, tinnitus is accompanied by the activation of a distress network that involves the limbic system [65], which is probably not recapitulated in the animal models. However, even in diseases in which there is a greater mechanistic understanding, there are still important disparities between the animal models used in discovery validation

and the human diseases being targeted for treatment [66]. Thus, if we look at animal models that have been developed for complex central nervous diseases such as depression or schizophrenia, they have proven useful, even if they can serve only as models of disease mechanisms and not of the disease itself. However, although a well-defined neuronal target would ease the path toward drug discovery, the empirical approach that has been used for most central nervous system disorders should not be precluded in the case of tinnitus. Thus, most central nervous system acting drugs were discovered serendipitously [67]. Therefore, the search for drugs to treat tinnitus should not wait for a deep understanding of the neural correlates of tinnitus or for the refinement of the animal models.

Finally, because the first tinnitus drugs are yet to be approved, regulatory agencies such as the FDA 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 pave the way. In addition, tinnitus being a subjective phenomenon, assessment of outcome is probably the single most important factor in conducting a clinical trial. There is widespread recognition that consistency between research centers in the ways that patients with tinnitus are assessed and how outcomes after interventions are measured would facilitate more effective co-operation and more meaningful evaluations. At the first Tinnitus Research Initiative meeting, held in Regensburg in July 2006, which gathered world-wide tinnitus experts, an attempt was made to establish a consensus both for patient assessments and for outcome measurements [68].

R&D by the pharmaceutical industry

The market for a drug indicated for tinnitus relief is huge and will grow further. The patents that have been filed world-wide on potential drugs that might offer relief are numerous. Furthermore, tinnitus can be found attached to long lists of indications in many more patents filed on molecules aimed at a range of diverse therapeutic classes. The Royal National Institute for Deaf People, UK, estimates that a novel tinnitus drug could have a product value of US$ 689 million in its first year of launch (http://www.tinnitusarchive.org/). However, there is currently no FDA-approved drug on the market, and there are very few pharmaceutical and/or biotechnology companies who have tinnitus compounds in their R&D pipeline. A search carried out in the investigational drugs databases Pharmaprojects (http://www.pharmaprojects.com), AdisInsight (http://www.adisinsight.com), Prous DDR (http://www.prous.com) and IDdb3 (http://science.thomsonreuters.com) shows that the following companies are developing a compound for tinnitus (Table 2): Merz, neramexane, an NMDA antagonist and an $\alpha 9\alpha 10$ nicotinic cholinergic receptor blocker at phase III; Epicet, a lidocaine patch at phase II; Sound Pharmaceuticals, ebselen, a glutathione peroxidase mimetic and inducer [69] at phase II; Auris Medical, AM-101, a NMDA receptor antagonist for topical administration to the inner ear at phase II, and AM-102, a compound of unidentified pharmacologic activity at the preclinical stage; GlaxoSmithKline, vestipitant, a neurokinin 1 receptor antagonist at phase II; and Ipsen, a ginkgo biloba extract at phase I.

TABLE 2

Pharmaceutical industries with tinnitus compounds in their pipeline

Company	Compound	Stage of development
Merz Pharma	Neramexane	Phase III
Epicept	Lidocaine patch	Phase II
Sound Pharma	Ebselen	Phase II
Auris Medical	AM-101 AM-102	Phase II Preclinical
GlaxoSmithKline	Vestipitant	Phase II
Ipsen	Ginkgo biloba extract	Phase I

Why is the number of companies with tinnitus compounds in their pipelines so limited, in spite of the existence of such a huge market for a clinically unmet need? The challenges described in the previous section account for this vacuum. The lack of serendipitous discoveries of effective treatments has severely limited insight into tinnitus pathology. If rational treatments for tinnitus are to be developed, its pathophysiology needs to be understood. Thus, it is the absence of fully determined neuronal correlates for tinnitus that makes research into this area potentially very high risk. However, if any of the above compounds reach the market, they will establish a turning point both in the treatment of tinnitus and in the development of future compounds that target this debilitating condition.

Concluding remarks

What does the future hold? Although we are far away from fully understanding the pathophysiology of tinnitus, the chances of treatment for tinnitus patients are much more encouraging than they were a decade ago. State-of-the-art molecular, biochemical, physiological and imaging techniques are likely to provide important insights into the underlying causes of tinnitus. The refinement of the behavioral measures of tinnitus in animals will aid the screen for new compounds. Although today, many tinnitus patients demonstrate some improvement with counseling, cognitive behavioral therapies and different forms of sound therapies, most patients would prefer a drug therapy that would rapidly lead to complete suppression of their tinnitus. Looking toward a promising future, they might finally receive encouraging news if the compounds under development by the pharmaceutical industries make it all the way to the market. If they do, they will set an important landmark in the treatment of tinnitus.

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