An update: emerging drugs for tinnitus

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REVIEW

An update: emerging drugs for tinnitus

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**Abstract**

**Introduction**: During the last decade, a number of candidate drugs for the treatment of tinnitus have emerged with the hope of alleviating the burden of millions of sufferers with a persisting ringing in their ears. Knowledge of the pathophysiologic mechanisms has progressed remarkably in the recent years, which has led to the identification of potential new drug targets for the treatment of tinnitus. However, pharmacologic interventions are still limited.

**Areas covered**: In this editorial results from recent Phase 3 and Phase 2a trials investigating the NMDA receptor antagonist AM-101 from Auris Medical, the AMPA receptor antagonist BGG492 from Novartis and the Kv3 modulator AUT00063 from Autifony Therapeutics will be discussed. In this context, we will reevaluate the translational development approach from animal models to clinical trials and seize this opportunity to debate and improve future R&D in tinnitus pipeline.

**Expert opinion**: In spite of huge advances in pathophysiologic knowledge and research methodology in the last decades, pharmaceutical research in tinnitus still represents a high-risk field. Important research directions include the identification of potential therapeutic targets and the development of objective outcome measurements to facilitate translational research.

1. **Background**

Subjective tinnitus is the phantom perception of sounds in the absence of an external physical source. Often compared to phantom limb perception, tinnitus is thought to arise from a maladaptive process to sensory deprivation [1]. Hearing loss represents the most important etiologic factor [2], but abnormal somatosensory nerve input from the face or the neck can also contribute to tinnitus [1].

This auditory condition is experienced by a large proportion of the population and affects more than 10% of the population worldwide (estimated 70 million people in Europe) [3]. For near 3% of the population, tinnitus becomes a chronic bothersome and incapacitating symptom [4,5]. Severe tinnitus interferes with sleep, mood, and concentration [6] and thus impacts life quality, ultimately leading to sick leave and disability pension [7]. A high cost to society has been reported [8-10], and since the prevalence of tinnitus has been predicted to double in Europe by 2050 [11], there is an urgent need to develop treatment to alleviate the burden of tinnitus sufferers [12]. Seven years ago, we reviewed the emerging pharmacotherapeutic routes for tinnitus [13]. Here, we present an update of recent Phase 2a and Phase 3 trials and discuss potential barriers to overcome in future drug trials.

2. **Medical need**

With a prevalence rate of over 10% tinnitus is a very frequent disorder and the prevalence is expected to increase due to the demographic development and increasing noise exposition. More than 10 years ago the ‘Action on Hearing Loss’ in the UK estimated that a tinnitus drug could have a product value of US $689 million within the first year of launch [14]. Thus, even a drug that would have a small effect in a subgroup of tinnitus patients would still have a huge impact. Moreover, within the last 7 years, hearing loss, which is the most important risk factor for tinnitus [2], came from the 11th position to the 4th in the leading causes of life with disability [15,16]. In spite of the fact that the hearing field is being increasingly recognized by big pharma companies as a huge and still untapped market, research investments in the hearing field are still relatively low [12].

3. **Existing treatment**

In spite of the high clinical demand, attempts to treat tinnitus by various means have failed. Meta-analyses of auditory stimulation (e.g. hearing aids [17] or sound maskers [18]), medication (e.g. anticonvulsants, antidepressants, nootropics) [19-21], or other approaches such as hyperbaric oxygen therapy [22], acupuncture [23], neuromodulation [24] and cognitive behavioral therapy [25] – have failed to show clear evidence for an unequivocally efficacious in reducing tinnitus loudness. Currently no drug is approved for the treatment of tinnitus by the FDA or the EMA. However, cognitive behavioral therapy (CBT), appears to have a beneficial effect on the quality of life of patients with tinnitus [25], indicating that the effect of an intervention on tinnitus loudness and interventions concerning its impact on life quality are, at least in part, dissociable.
4. Market review

Despite the absence of approved tinnitus drugs on the market, pharmacologic treatments are widely used, with over 4 million off-label prescriptions written each year for tinnitus relief in Europe and the US [14,26]. Although the application of the currently available psychologic therapies can provide relief [27,28], such treatments are not yet offered to patients routinely [26,29]. Therefore, tinnitus remains today an unmet clinical need and many patients would welcome a drug abolishing or even reducing their phantom sound.

5. Current research goals

The primary research goal of pharmacologic tinnitus research is the identification of a compound that alleviates either tinnitus loudness or tinnitus related distress or both. Moreover, as there are no approved drugs for the treatment of tinnitus, there are also no examples of a successful pharmacologic development program that could provide a blueprint for the development of a new compound. This situation results in various additional challenges, such as the uncertainty about targets for pharmacologic treatments, the validation of the predictive value of animal models of tinnitus or the identification of trial designs and outcome measurement tools that are sensitive for detecting therapeutic effects. In the last decade, various efforts have been made to identify potential pharmacologic targets [30], to further develop and validate animal models [31,32] and to refine and standardize clinical trial design [33] and outcome measurement tools [34,35].

6. Scientific rationale

The knowledge of the pathophysiology of tinnitus has been built on a growing number of experimental studies in animals that offer a more homogeneous context to work with than with human studies. Most animal studies have been performed in mice, rats, and guinea pigs and have used either noise overexposure or drugs to induce presumptive tinnitus, either temporarily or permanently [36,37]. Behavioral assays, either using conditioning or reflex responses, provide read-outs for evaluating tinnitus associated deficits, and other tools such as implanted electrode recordings to investigate the complex underlying neurologic networks believed to be involved are also becoming standard in the pre-clinical field [36,37]. Translating and comparing animal model findings to the clinical setting however remains a challenge due to the sparse number of common methods and measures. Moreover, several clinically highly relevant aspects of tinnitus, such as the heterogeneity in perceptual quality, etiology and co-morbidities, the related emotional and cognitive impairment or the impact of chronicity are all not sufficiently reflected in currently available animal models. Finally, it is not trivial to differentiate whether findings in animal models of tinnitus do really reflect the neuronal correlates or whether they are just a consequence of the induced hearing loss or a correlate of co-occurring symptoms (e.g. hyperacusis). Therefore there is an ongoing debate to which extent animal models reflect the clinical situation [38], which has to be taken into consideration in the interpretation of their results.

It is therefore essential that the knowledge acquired from animal research is complemented by clinical research. In the last decades, important insights could be gained by imaging studies using functional magnetic resonance tomography, positron emission tomography, electroencephalography and magnetoencephalography [39]. Furthermore, there is an increasing amount of research focusing on clinical aspects of tinnitus and particularly on its heterogeneity aiming at identifying relevant features for subtyping of tinnitus (e.g., temporal features, accompanying emotional disorders as well as drug side effects, etiology, co-morbidities, prevalence according to geographic and genetic background, among others [40,41].

The current models stipulate that tinnitus mimics the processes of phantom limb perception [42], whereby the loss of sensory input (most often by sensory deafferentation) leads to compensation mechanisms in the brain. This phenomenon of maladaptive plasticity in presence of deafferentation appears as a common denominator of most forms of phantom percepts in the absence of sensory stimuli [43]. Whether these compensation mechanisms are directly causing the false sensation of a missing limb or sounds [44] or whether tinnitus occurs when the compensation mechanisms come to their limits and do not suffice any more [45] still remains to be clarified. However, there is clear evidence that tinnitus related alterations involve both auditory and non-auditory brain networks [1,39]. Peripheral dysfunctions lead to changes in central excitability and activity along the auditory pathway such as an increase in spontaneous activity and an increase in cross-fiber correlation [46]. More severe deafferentation may also cause alterations in memory related brain networks, as the brain might try to replace missing sensory information by accessing memory [42,45,47]. But also salience-, emotion- and attention-related networks involving frontal cortex, insula, hippocampus, amygdala and the limbic system might be involved in the generation of tinnitus [48,49], its distress and possibly its persistence and intensity [50,51].

7. Competitive environment

Based on knowledge obtained in preclinical models, strategies aiming at treating peripheral or central dysfunctions presumably involved in tinnitus generation and persistence have emerged (Table 1). According to our knowledge three clinical research programs were performed in the last years targeting N-methyl-D-aspartate receptor (NMDA) receptors (AM-101, Auris Medical), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (BGG492; Novartis) and potassium channels (AUT00063; Autifony), respectively. Here, we will summarize the results from these research programs. The use of NMDA receptor antagonists has been investigated in depth by the group of Jean-Luc Puel. They demonstrated a role of cochlear NMDA receptors in the development of salicylate-induced tinnitus by means of pharmacology, behavioral assays and electrophysiologic approaches in rats [52,53]. NMDA receptors, which are glutamate receptors expressed in the inner hair cell – afferent synapse [53], had long escaped attention...
Table 1. Competitive environment table.

<table>
<thead>
<tr>
<th>Name</th>
<th>Company/Entity</th>
<th>Compound</th>
<th>Stage of Development</th>
<th>Mechanism of action</th>
<th>Administration route</th>
<th>Clinical Trial.org #</th>
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<td></td>
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<td>Sodium channel blocker</td>
<td>Patch</td>
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<td>S-ketamine hydrochloride</td>
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<td>Trans-typanic</td>
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<td>NCT01803646</td>
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<tr>
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<td>Merz Pharmaceuticals GmbH</td>
<td>Neramexane mesylate</td>
<td>Phase 3 (Failed)</td>
<td>NMDA and alpha9/alpha10 nACh receptor antagonist</td>
<td>Oral</td>
<td>NCT00739635/</td>
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<td>Autifony</td>
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<tr>
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<td>Selurampanel</td>
<td>Phase 2 (recruitment completed)</td>
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<td>Phase 2</td>
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<td>NMDAR-antagonist</td>
<td>Trans-typanic</td>
<td>NCT00957788</td>
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<td>N-acetyl homotaurine</td>
<td>Phase 1</td>
<td>NMDAR antagonist/GABAAR positive allosteric modulator</td>
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<td>Flupentixol/Meltracen</td>
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<td>n.p.</td>
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<td>D2 and D3 receptor agonist</td>
<td>Oral</td>
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<td>Syntocinon</td>
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</tbody>
</table>

Completed and on-going drug trials for tinnitus therapy collected from ClinicalTrial.org. Phytochemicals have been excluded as well as those where tinnitus is not a primary condition. NA = not applicable; n.p. = not provided.
because of the lack of apparent role during normal hearing [54]. However, a contribution for NMDA receptors in cochlear excitotoxicity became apparent through a large number of studies where its role in triggering hearing pathophysiologies including tinnitus [52,53,55] and ototoxicity [56–58] was established. In tinnitus models, the first results were obtained using high doses of salicylate, an active metabolite of aspirin, which is known to cause tinnitus in patients as well. Using an active avoidance paradigm, it was shown that tinnitus associated symptoms could be prevented by the local delivery (through the round window of the cochlea) of the NMDA receptor antagonists MK-801 or 7-chlorokynureinate [52]. A follow-up study suggested that a potential underlying mechanism involved was the enhancement of the arachidonic acid cycle by salicylate, which subsequently facilitates NMDA-receptor activation by glutamate [53]. Several animal studies demonstrated a reduction of salicylate-induced tinnitus by the NMDA receptor antagonist memantine [59–61]. Guitton and Dudai could also demonstrate that NMDA receptor blockade was also effective for noise-induced tinnitus in rats but being restricted to the first 4 days after tinnitus induction [55]. In line with these findings, it was recently demonstrated that noise-induced hyperactivity in the dorsal cochlear nucleus could be prevented by pre-treatment with MK801 [62]. These findings formed the basis for the clinical development of NMDA receptor antagonists OTO-313 (Gacyclidine) by Otonomy and the more advanced Keyzilen (AM-101, Esketamine Hydrochloride) by Auris Medical. In a case series, six patients with unilateral deafness and tinnitus received gacyclidine administration near the round window niche, resulting in tinnitus relief in four of them [63]. This finding is important as – in contrast to most animal experiments, where NMDA antagonists were administered before, together or shortly after tinnitus induction – gacyclidine showed effects also in patients with chronic tinnitus.

The intratympanic delivery of a gel formulation of Keyzilen (esketamin; AM-101) in the acute phase of tinnitus (within the 3 first months after the onset of tinnitus) was investigated in tinnitus patients with either acute acoustic trauma, idiopathic sudden sensorineural hearing loss (ISSNHL) or otitis media [64]. This Phase 2 clinical trial with a total of 284 patients failed to achieve the primary endpoint of improving minimum masking level (MML), however, statistical significant improvement was demonstrated for tinnitus loudness, annoyance, sleep difficulties, and tinnitus impact in the high dose AM-101 patient groups with tinnitus after noise trauma or otitis media [64]. Near 57% of patients in the high-dose group rated their tinnitus severity to be ‘much improved’ or ‘very much improved’, compared to the low-dose and placebo groups (39% and 34%, respectively) 90 days after treatment [64]. Interestingly, the reduction in tinnitus loudness appeared more effective in patients with unilateral tinnitus, potentially suggesting a tinnitus still at a peripheral stage. Why about half of the patients did not report major improvements is unclear. In a rat model of noise-induced tinnitus, AM-101 was administered 48 h after noise trauma using similar surgical approaches as Guitton et al. [65]. From four animals with tinnitus treated with AM-101, two animals did not respond to treatment, while two others displayed a behavioral improvement, the latter of which correlated with a preservation of their synaptic ribbons [65] consistent with the hypothesis that peripheral synaptic damage may lead to tinnitus [45,66]. In spite of these early phase positive indications, Auris Medical recently announced the failure of a two Phase 3 trials [67,68] with patient reported outcomes as primary endpoints (Tinnitus loudness on a Numerical Rating Scale – TLQ NRS loudest; Tinnitus Functional Index – TFI). The results still being unpublished preempts a proper detailed interpretation of the potential factors that have led to these negative outcomes.

Another pharmacologic compound, that has been investigated recently, is BGG492 (selurampanel) which is an orally active AMPA/Kainate receptor antagonist [69]. BGG492 has been investigated for tinnitus as the main excitatory activity in both cochlea and the central auditory pathways is AMPA mediated [70]. Moreover, the AMPA receptors are over-expressed at key synapses in this pathophysiologic pathway [71].

Novartis performed a proof-of-concept study to evaluate efficacy and safety of BGG492 in patients with moderate to catastrophic chronic subjective tinnitus. Notably, there exist no published reports of an investigation of BGG492 in an animal model of tinnitus. After a 2-week treatment with BGG 492, significantly greater proportion of patients showed improvement of ≥ 4 points from baseline in TBF-12 (a short version of the THI) as compared to placebo (26.7% vs. 14%) [72].

Targeting the central nervous system has also been the focus of Autifony Pharmaceuticals, which is a spin-off from Glaxo-Smith-Kline (GSK). Taking a different preclinical approach than the one employed for glutamate receptor antagonists, Autifony developed AUT00063, a Kv3.1 channel inhibitor as a tinnitus treatment based on the ability to suppress noise-induced hyperactivity in the dorsal cochlear nucleus and inferior colliculus [73], more specifically by targeting fusiform cell activity [74]. Also for AUT00063, no published data are available from an animal model of tinnitus. In 2016, Autifony reported in a press release that the QUIET-1 study testing AUT00063 on tinnitus patients in a Phase 2a study, showed safety and tolerance however failed to achieve efficacy endpoints [69]. In this double-blind, placebo controlled, randomized study with 76 patients (at completion), a daily dose of 800 mg of AUT00063 during 28 days did not result in any change of the TFI score compared to placebo [75].

8. Potential development issues

Understanding exactly why the clinical development programs for AM 101 and AUT00063 did not deliver the awaited success is a complex question. Possibly the targets were not correct or the pharmacologic impact on the target was not sufficient. However, it is also possible that the failures in these clinical trials could be influenced by the heterogeneity of tinnitus and that a better classifications of its ‘subtypes’ and etiologies would improve the likelihood of treatment success. This is in part supported by the different subpopulation outcomes reported for the phase 2 and 3 clinical trials of AM-101 discussed above. What defines a subtype is still unclear and may depend on tinnitus characteristics [e.g. pulsatility, laterality, perception (tone, buzz, noise), duration (occasional vs constant), time since onset (acute or chronic), severity, and
accompanying psychologic or medical co-morbidities). Both the AM-101 and the QUIET1 studies were rather broad in their inclusion of subtypes. While the AM-101 studies included a wide-range of tinnitus forms and specified etiologies, the QUIET-1 study did not specify etiology. For instance, the AM-101 Phase 3 trial included participants with ‘persistent subjective peripheral tinnitus (unilateral or bilateral) following traumatic cochlear injury (acute acoustic trauma, blast trauma, middle ear surgery, inner ear barotrauma, tympanic membrane trauma) or otitis media’. In the QUIET-1 study, in brief the inclusion criteria consisted in non-pulsatile, constant tinnitus with a duration between 6 and 18 months, and stable tinnitus of a TFI score between 24 and 68 [76]. Unlike the AM-101 study, the QUIET-1 did not consider etiology in the inclusion criteria, however, subjects with clinically significant anxiety or depression, or other pathologies of the central nervous system or otologic conditions were excluded. In this context, it is interesting to note that the BGG492 trial – which revealed positive results – resembled the QUIET-1 trial in its inclusion criteria.

Although there is a careful consideration of tinnitus perception (persistent) and duration (acute <3 months for the AM-101 study, between 6–18 months in the QUIET-1 study, between 6–36 months in the BGG492 trial) in the three studies, unilateral and bilateral tinnitus may be different subtypes. Indeed, a recent large twin study has shown that bilateral tinnitus is influenced mainly by genetics up to 68% in men, and that unilateral tinnitus is much less (27%) indicating that the latter is much more influenced by environmental factors [77]. Although more research is needed to understand how different unilateral from bilateral tinnitus are one from another, these findings underline that there are potential differences in how they develop. In this regard, what is defined as acute and chronic, and how it relates to findings obtained from animal studies is also a matter of debate.

An interesting point to discuss is the relationship to noise trauma. In most animal models tinnitus is induced by acute blast trauma. But it is unclear whether noise exposure and blast trauma produce comparable changes in auditory and non-auditory brain areas. Lessons can be learned from recent interventions that have shown benefits in animals and humans. For instance, direct vagus nerve stimulation (VNS), which consists in stimulating the release of acetylcholine and norepinephrine with a high degree of temporal control to enhance neural plasticity, has been shown – when paired with tones – to decrease tinnitus perception in rats exposed to noise, while reinstating the original tonotopic map in the auditory cortex [78]. This intervention demonstrated benefits in tinnitus patients in a double-blind, randomized, controlled study on 30 patients [79,80]. The improvements correlate with reduced gamma band activity in left auditory cortex [81]. Interestingly, the treatment appeared much more effective in patients with tonal or non blast-induced tinnitus with improvements in the Tinnitus Handicap Inventory (THI) score by 34% in comparison to controls (2%), indicating that tinnitus caused by blast noise may differ from other forms of tinnitus, potentially in the way central plasticity occurs. A recent case report indeed illustrates that a blast injury caused a number of middle ear symptoms in absence of hearing loss [82]. We are aware that care has to be taken in the interpretation from post-hoc analyses, and from this result, it cannot be concluded that blast-induced tinnitus is really a distinct tinnitus subtype or not. Nevertheless, these findings illustrate the relevance of delineating tinnitus subtypes.

Contrasting the stimulation of tones paired with direct vagal nerve stimulation, two recent studies support the idea that stimulating the somatosensory system in combination with tones may provide relief in tinnitus. The Laboratory of Susan Shore established their findings on a ground work of experimental research identifying the fusiform cells of the dorsal cochlear nucleus (the same as those presumably targeted by the Kv3.1 modulator) as a center piece integrating auditory and somatosensory inputs [83]. Indeed, auditory (sound) stimulation can be used to evoke postsynaptic spikes, and somatosensory stimulation can be used to evoke presynaptic activity in fusiform cells, in such a way that paired auditory-somatosensory stimulation produces long-term changes in fusiform cell firing rates [84]. It has been suggested that it depends on the sequence and timing of the stimuli whether long-term potentiation (LTP) or long-term depression (LTD) is triggered [85]. In their recent study, Marks et al. show in guinea pigs exposed to noise that 20 minutes per day of LTD-inducing bimodal stimulation reduced neurophysiologic and behavioral correlates of tinnitus [86]. The same protocol has shown promising results in tinnitus subjects with ‘somatosensory’ tinnitus in a double-blind, sham-controlled, crossover pilot study using the TFI as an outcome measure [86]. Somatosensory tinnitus has been defined as the ability of the patients to modulate their tinnitus pitch or loudness by applying pressure or moving their head or neck [87], a phenomenon that is observed in about two thirds of all tinnitus patients [88]. In this study, the mean reduction of the TFI score during 4 weeks with daily sessions of bimodal stimulation treatment was 7 units [86]. While this result illustrates the potential of bimodal auditory and somatosensory stimulation, it has to be confirmed in further studies as there exist many examples in tinnitus research where positive findings in pilot studies could not be replicated in larger follow-up studies [89–94]. Moreover, it still remains to be determined whether the parameters used in this study are the optimal ones. Another treatment approach used bimodal stimulation by pairing auditory stimulation with synchronous electrical stimulation of the trigeminal nerve [95]. Within a follow-up study, the company Neuromod aims at improving the protocol of intervention and determining the optimal parameters for therapeutic application [96]. Importantly, both the VNS and the bimodal stimulation results illustrate the validity of the translational path from animals to humans. So how come have these AM-101 and QUIET-1 trials failed?

The results obtained with the VNS and the bimodal stimulation are quite an achievement owing to the fact that the animal and human studies used different outcome measures. In rats and guinea pigs, the measures of tinnitus consisted in objective reflex response based on gap pre-pulse inhibition of the acoustic startle (GPIAS), a behavioral approach gaining popularity in the pre-clinical field [97,98]. GPIAS however has not been optimally adapted to humans, and thus clinically objective quantifications of tinnitus frequency and intensity are still missing, which is why clinical trials have to rely on questionnaires and patient-reported outcomes. It is interesting
to note that the VNS study used both the THI and the TFI, and the greatest effects were obtained with the THI. This is a remarkable finding as the TFI was specifically designed to be sensitive for detecting treatment related changes [99]. One explanation for the higher sensitivity of the THI is that the VNS study aimed primarily at reducing the tinnitus percept, whereas cognitive behavior therapy, which was used to validate the change sensitivity of the TFI [99], aims to reduce tinnitus impact on life without changing the tinnitus percept. Thus, the TFI may not represent the most sensitive measurement tool for all therapeutic interventions as it englobes a wider range of tinnitus-related factors such as intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life and emotional all of which may stabilize in the long-term but not being obvious as immediate changes in tinnitus percepts.

The successful reduction of tinnitus after treatment with BGG492 has to be interpreted carefully, as the result comes from only one pilot study. Nevertheless, this result suggests that AMPA receptors might represent promising targets for pharmacologic treatments.

Unfortunately, the development program of BGG492 was discontinued in 2012 and 2014, for tinnitus and epilepsy respectively. The reason might have been unwanted side effects, as AMPA receptors are widely expressed in the central nervous system, causing a substantial risk for adverse effects after the systemic administration of AMPA receptor antagonists. Still, the identification of AMPA receptors as a potential target will hopefully motivate further research investigating AMPA modulating drugs. Perampanel could be a possible candidate, as it is already approved for the treatment of epilepsy. Another approved anticonvulsive, that has shown promising results in animal models [100], is the KCNQ2/3-specific potassium channel activator retigabine, for which unfortunately no systematic clinical human data are available [101]. Other approaches to identify new targets may include the exact identification of the mechanism by which lidocain suppresses tinnitus, or the identification of drug targets that are involved in the generation of tinnitus as a side effect of pharmacologic treatment [102].

Both tinnitus loudness and tinnitus distress have recently been shown to fluctuate throughout the day, being more severe at night and early morning [103]. Such phenomenon could be influenced by circadian mechanisms [104], such as those that have been evidenced in the cochlea [105] and to a lesser extent in the inferior colliculus [106]. As a consequence, collecting data on tinnitus loudness and distress at different times of the day could increase variability and cause a bias in the overall assessment. It is possible that assessing tinnitus at night or early morning may increase the dynamic range to a level sufficient to observe treatment benefits, which would have otherwise not been able to evidence. In order to account for fluctuations in tinnitus loudness and distress, Ecological momentary assessment (EMA) methods have been developed, both for characterization of tinnitus patients and for assessing efficacy of therapeutic interventions [41,107]. Another consequence of a potential circadian regulation of tinnitus [108], is chronopharmacology or the appropriate scheduling of drug administration for optimal treatment efficacy. In this regard, systemic treatment with dihydroxyflavone, a selective tropomyosin receptor kinase B (TrkB) agonist, protected from noise trauma at nighttime but not at daytime [105]. Since rodents are nocturnal animals, it is possible that the corresponding effective time of treatment in humans would be daytime. However, most pharmalogic interventions in auditory research on rodents is performed during daytime (their inactive phase), such as the pre-clinical studies mentioned above, these may not directly translate into the corresponding human biology. Consequently, since glucocorticoids and glutamate signaling are known to be circadian [108,109], failures in these clinical trials could also be due to differences in rodent versus human chronopharmacology.

9. Conclusions

Three recent drug trials have not resulted in a new compound. Two studies failed; in one case the development of the compound has not been continued. A further compound has demonstrated promising results in animal studies, but has not yet been investigated in humans. These findings illustrate quite well the specific challenges in the development of pharmacologic compounds for the treatment of tinnitus. With increasing knowledge about the pathophysiology of tinnitus, an increasing number of potential targets for pharmacologic treatment have been identified, but for none of those targets is there a clear evidence for efficacy. Similar is the situation for animal models of tinnitus, where more and more refined animal models have been developed [110–112], but evidence for their predictive validity is still scarce. Given the lack of valid preclinical screening methods, potential compounds have to be tested in human pilot trials. However, for human testing detailed knowledge about toxicology and safety is critical, limiting the scope of compounds that can be screened to those that are already marketed or at an advanced development stage.

However, the design of human pilot trials for screening promising compounds is not trivial and bears a substantial risk of false negative results. First, the definition of inclusion and exclusion criteria is of particular relevance because of the clinical heterogeneity of tinnitus. Second, the right estimation of the dose range and the duration of the treatment is challenging, especially when knowledge about pharmacokinetics and pharmacodynamics is limited. Finally, there is a need to choose a sufficiently sensitive instrument for outcome measurement. Thus preclinical endpoints with validated translation into clinical application would clearly improve the risk/benefit balance of preclinical and clinical development of new compounds for tinnitus treatment leading to higher investments of the pharmaceutical and biotech industry.

In summary in spite of huge advances in pathophysiologic knowledge and research methodology in the last decades, pharmaceutical research in tinnitus still represents a high-risk field. On the other hand, if there were a drug for which a robust effect could be demonstrated, such a drug would have a huge impact on the field, even if the effect were small and occurred only in a subgroup of tinnitus patients.

10. Expert opinion

Is it still worth to seek for a pharmacologic treatment for tinnitus, if tinnitus is so difficult to treat and what are possible strategies?
The answer to this question is a clear ‘yes.’ Firstly, tinnitus represents a huge medical need and is therefore not only a ‘high risk’ field but also a ‘high gain’ area. Secondly, tinnitus suppression by intravenously applied lidocaine provides the proof of principle that tinnitus can be pharmacologically treated.

What are the main barriers impeding the development of an effective drug treatment?

From a clinical perspective tinnitus is highly heterogeneous in its perceptual characteristics, its etiology and its comorbidities. Presumably, the different subtypes of tinnitus differ also in their pathophysiological mechanisms, which provide challenges for identifying an efficient target. In other words, tinnitus may represent a symptom resulting from various underlying conditions, which in turn differ in their pathophysiology.

A further difficulty is the sensitivity of outcome measurements. Depending on the nature of the intervention and the expected results (e.g. reduction of tinnitus loudness versus reduction of tinnitus distress versus reduction of global impact of tinnitus) different instruments might be most sensitive. In case of Phase II studies frequently, there is no detailed knowledge about the ‘profile’ of the expected therapeutic effect. In this situation, the use of a broader range of outcome measures is recommended to capture a global picture of the improvements following a specific treatment [34]. Means to visualize which instruments are sensitive for a given intervention were recently proposed by Schlee et al. [113].

In addition, the translation from animal data to clinical application is impaired by the lack of objective measurements. Therefore, larger efforts should be directed toward the development of tools to objectively quantify tinnitus loudness or severity comparatively in preclinical and clinical studies, facilitating the selection of candidate drugs with strong clinical potential as well as ensuring proper non-clinical refinement of dosing and treatment regimens using such measures. Such quantitative translational measures would enhance exploration of relationships between delays separating tinnitus onset and successful intervention, a parameter that frequently seems to differ significantly between animal models with rapid treatment interventions after onset while patients are enrolled in clinical trials with tinnitus lasting months to years before experimental treatment.

What could be promising research directions for the future?

As the exact mechanism by which lidocaine reduces tinnitus is still not completely understood, further research in this area is warranted. This would be a precondition for identifying a drug that might mimic the lidocaine effect, but has better tolerability and can be orally administered.

As long as there is still uncertainty, on which structures should be targeted to reduce tinnitus further efforts should be made to identify potential targets. The relevance of target identification is also highlighted in a recent report from AstraZeneca, in which the reason for study failures were analyzed [114]. The major reasons for Phase 2 and 3 failures are non-established target linkage to disease or no validated models available. An analysis showed that a human genetic linkage of the target to the disease indication could increase the proportion of successful Phase 2 trials from 43 to 73%, and that of Phase 3 from 29 to 82%. Thus, the hitherto largely neglected field of genetic research might help to identify potential drug target candidates, or even validate existing ones [115,116].

Recent clinical and preclinical research suggests AMPA receptors and KCNQ2/3 potassium channels as potential innovative targets, but these findings are still preliminary and need replication. The possibility of further serendipitous discoveries should not be precluded. In order to enhance the chances for further serendipitous discoveries, newly developed compounds for CNS disorders like epilepsy, migraine, schizophrenia or affective disorders should also be screened for a potential use for the treatment of tinnitus, assuming there are shared mechanisms.

Recent research in the auditory field has shown that hearing loss is not uniquely determined by hair cell loss. Instead, synaptic dysfunction might play a role as well, which opens up the possibility for pharmacologic treatments of hearing loss. One would expect that any successful improvement of hearing function may also have beneficial effects on tinnitus. Therefore, tinnitus should always be assessed as a secondary outcome measurement in any pharmacologic studies that aim at improving hearing function. In spite of the recent negative results, there are enough reasons to hope that an efficient drug for tinnitus treatment will be identified in the near future.

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Author contributions
C.R. Cederroth1 and B. Langguth performed literature search, C.R. Cederroth1, J. Dyhrljef-Johnsen and B. Langguth contributed to writing. B. Langguth was responsible for the decision to submit the final manuscript and approved the final report.

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This study identifies the first time that some forms of tinnitus are highly influenced by genetic factors, opening the possibility of discovering new drug targets by genomic studies.

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• This paper describes the first objective measure of tinnitus in animal models.


