Avenue for Future Tinnitus Treatments

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KEYWORDS

• Tinnitus • Neuromodulation • Novel approaches • Tinnitus pathophysiology
• Tinnitus models

KEY POINTS

- Current challenges in the development of new treatments for tinnitus.
- Neuromodulation approaches for tinnitus treatment.
- New drug targets for tinnitus treatment.
- The importance of clinical tinnitus databases.
- Lack of funding in tinnitus research.

INTRODUCTION

With prevalence rates of 10% to 20% of the population, tinnitus represents a major global burden.[1,2] Tinnitus prevalence grows with age and has increased in the past decades,[3] presumably owing to an increased exposure to loud sounds. Although most patients can cope adequately with their tinnitus, nearly 1 out of 10 (ie, in 2%–3% of the total population) experiences severe tinnitus[4] that can be accompanied by frustration, annoyance, anxiety, depression, cognitive dysfunction, insomnia, stress, and emotional exhaustion—all of which lead to a substantial decrease in quality of life[5,6] and an enormous socioeconomic burden.[7]

The available treatment options for tinnitus are limited. Cognitive behavioral therapy (CBT) is helpful for reducing tinnitus annoyance and tinnitus handicap, but there exists no established treatment that has shown evidence in randomized controlled studies to reduce tinnitus loudness. Thus, given the high prevalence and the enormous socioeconomic relevance, there is an urgent need to develop better treatment options for tinnitus.

This article first provides a short overview about recent advances in the understanding of the pathophysiology of tinnitus, because this provides the basis for the

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Otolaryngol Clin N Am 53 (2020) 667–683
https://doi.org/10.1016/j.otc.2020.03.013 oto.theclinics.com

development of new treatments. There exist several challenges in the development of new treatments, and how these can be addressed is discussed. Then, current research activities in neuromodulation, auditory treatments, pharmacotherapy, eHealth, and patient involvement are summarized before what might be needed to attract more private and public funding in the tinnitus field is discussed.

CURRENT KNOWLEDGE OF THE PATHOPHYSIOLOGY OF TINNITUS

In recent decades, knowledge about the pathogenesis of tinnitus has increased massively. Although there is no complete consensus among experts, the dominant opinion is that tinnitus is preceded by peripheral hearing loss. Often the affected person describes a hearing sensation that lies in a frequency range that is congruent with the frequency range of the hearing loss.[8] After peripheral hearing loss due to partial damage of the hair cells in the inner ear, the transmission of stimuli from the cochlea to the auditory cortex in the brain is interrupted.[9] Because of this sensory deprivation, an increased synchronicity of the spontaneous activity of the neurons in the auditory cortex, which represents the corresponding frequency ranges, is observed.[10] A weakening of the intracortical balance of excitation and inhibition leads to a reorganization of the architecture of the auditory cortex, resulting in new ensembles of nerve cells that have changed their frequency specificity.[11] If the synchronous activity of these nerve cell clusters continues undiminished for some time, the affected persons may perceive an ear noise with different characteristics and variable loudness and duration. Whether this maladaptive phenomenon leads to tinnitus perception at all and to what extent it is pronounced in terms of personal aversiveness, loudness, or accompanying symptoms, such as sleep disorders, anxiety, panic, and stress, depend on coactivation of nonauditory brain networks.[12,13] These networks include limbic, insular, parahippocampal, frontal, and parietal structures.[14] In the context of this more generally formulated idea on the pathogenesis of tinnitus, several models exist that give more or less weight to certain aspects of network theory.[11,15–17] These are not discussed in detail. It must be seen as a decisive moment of the modern models for the genesis of tinnitus that it is no longer the periphery with the ear structures or the auditory nerve that is in the foreground but the neuroplastic changes in central nervous structures that occur as a consequence of peripheral deafferentation. Furthermore, it has been shown that neural connections between the auditory and somatosensory systems located at the dorsal cochlear nucleus play a role in tinnitus perception as well.[18] In particular, the ability of some affected individuals to modulate the tinnitus sound through somatic maneuvers is at stake.

All these new insights have changed the focus with regard to potential therapies. For 2 decades, methods have been under discussion in research, which take into account the central aspects of tinnitus genesis, such as neuromodulation, the neural connections between the somatosensory and auditory systems, and pharmacotherapy of centrally acting neurotransmitters.

CURRENT CHALLENGES IN THE DEVELOPMENT OF NEW TREATMENTS

Based on current knowledge, that tinnitus results from functional changes of neuronal activity, there exists no reason to believe that tinnitus cannot be efficiently treated either by neuromodulation or by pharmacotherapy. But why do effective treatments for tinnitus not exist?

There are several reasons that can explain why the development of effective treatments for tinnitus is so difficult.[19]

From a historical perspective, the development of treatments for brain disorders was driven by serendipitous discoveries. Apart from lidocaine, such serendipitous discoveries are lacking in the tinnitus field, and lidocaine cannot be applied regularly because of its side effects nor can other drugs with a comparable effect be identified. Moreover, because no exact drug target is known that reliably reduces tinnitus, there also do not exist in vitro bioassays for high-throughput screening of pharmacologic compounds.[20]

Animal models have been developed but have limitations.[21] Further challenges for the development of new compounds are the heterogeneity of tinnitus and its subjective nature, which make tinnitus assessment difficult.

Limitations of Available Animal Models of Tinnitus

For the development of a valid animal model of tinnitus, it is necessary to develop methods for both reliable tinnitus induction and assessment. Two different approaches are used to generate tinnitus: first, the systemic administration of ototoxic drugs, such as salicylate or quinine; and second, the exposure to loud noise. These two methods induce tinnitus via different mechanisms, with the latter probably more similar to the clinical situation.

Assessment of tinnitus typically has been performed indirectly by measuring behavioral reactions to silence. These behavioral tests require months to train the animals and, to circumvent this problem, another animal model of tinnitus exploits the acoustic startle response, which is based on an objective reflex response that does not require lengthy training sessions.[22] The magnitude of the startle reflex in response to, for example, a loud sound, is reduced when the startling stimulus is preceded by a silent gap in an otherwise continuous acoustic background. In animals that are noise-traumatized or salicylate-treated, the inhibition of the startle reflex by the gap is reduced and this is interpreted as an indication of tinnitus. What exactly is assessed by these behavioral tests and what modulates the startle response, however, are matters of debate. The magnitude of the startle response itself can be influenced by hearing loss, hyperacusis, and anxiety. The degree of inhibition caused by gaps also varies considerably between rodent species. Nevertheless, among animals that all have been exposed to a similar noise trauma, those that demonstrate behavioral evidence of tinnitus, as assessed with the Gap-Prepulse Inhibition of the Acoustic Startle Reflex, show consistent neurophysiologic alterations compared with those that do not.[18] An additional challenge to the use of tinnitus animal models is that, in humans, the phantom sound frequently is accompanied by emotional and cognitive symptoms,[14,23] which still are not recapitulated in available animal models.[24,25]

Challenges in Translating Animal Findings to Humans

The usefulness of available animal models for testing tinnitus treatments is still a matter of debate, because some treatments, which were successful in animal studies, failed to show positive effects in humans. For instance, carbamazepine seems to be efficacious in rats[26] but not in humans,[27] and the same is true for ginkgo biloba.[28] An enriched acoustic environment seems to ameliorate tinnitus in animals[29] but not as much in humans.[30] The reported discrepancies between the results from animal models and human treatment studies do not necessarily mean that animal models of tinnitus have no predictive value, because inconsistencies also may be related to limitations in both animal and human studies (eg, methodology, outcome measure, etiology, comorbidities, time and duration of the treatment, and sample size). Caution is warranted, however, in the direct translation of tinnitus animal research to humans, especially research into novel treatments.

Tinnitus Heterogeneity

Tinnitus differs across patients in its perceptual characteristics (eg, frequency and intensity), in its time course (constant, fluctuating, and intermittent), response to interventions (eg, masking sounds and somatic maneuvers), etiologic factors, and comorbidities. This heterogeneity of tinnitus is reflected by a substantial variability in tinnitus pathophysiology.[13] This means that probably many different forms of tinnitus exist, which vary in their pathophysiology and their response to a specific treatment intervention. If patients with different subtypes are included in a clinical trial, a high variability in the treatment outcome has to be expected. Therefore, a major challenge in clinical tinnitus research is the identification of reliable subtypes or the identification of relevant criteria for subtyping patients.[31,32] One approach is the development of large clinical databases for disentangling subgroups of tinnitus.[33]

Measurement of Tinnitus in Humans

Outcome measurement in clinical trials is complicated by the fact that tinnitus is a purely subjective phenomenon, for which objective measurements are still missing.

A further difficulty is that perceptual aspects of tinnitus (eg, loudness) do not explain the subjectively perceived severity of the symptom. Thus, a comprehensive evaluation of tinnitus has to include the assessment of both perceptual aspects of tinnitus (eg, loudness and pitch) and of subjective tinnitus severity (eg, tinnitus related functional impairment or tinnitus handicap). Perceptual aspects can be assessed by psychoacoustic methods and subjective rating scales (eg, visual analog scales or numeric rating scales); tinnitus impairment can be quantified by various validated questionnaires.[34,35] Because the different measurements provide complementary information, current best practice is the use of several outcome measurements in parallel for the evaluation of treatment-induced changes.[36–38] A recent analysis revealed a high variability in the outcome instruments used in clinical trials,[35] indicating the need to standardize outcome measurement.[36,39,40] This is important particularly because regulatory agencies, such as the Food and Drug Administration (FDA) or European Medicines Agency lack standardized protocols for their approval process.

NEUROMODULATION

As a consequence of the models for the pathogenesis of tinnitus, described previously, it seems reasonable to consider a modification of neuronal activity in the areas of the brain involved in the neuronal circuits responsible for tinnitus. In this way, both auditory and nonauditory areas can be reached. Essentially, a distinction is made between invasive and noninvasive neuromodulation. The aim of any method is to normalize the tinnitus-related brain activity. The increasing improvement of structural and functional neuroimaging techniques made it possible to more precisely target those areas of the brain that are mainly responsible for tinnitus perception or the tinnitus-related distress. Over the past 2 decades, many different methods of neuromodulation have been evaluated for their effectiveness in tinnitus control. Noninvasive methods included repetitive transcranial magnetic stimulation,[41–43] transcranial electric stimulation,[44–46] transcutaneous electric nerve stimulation,[47,48] and neurofeedback.[49–51] All techniques have been tested at different institutions and with different approaches in various studies.[52] In the meantime, standardized reviews for the individual techniques are available.[45,53,54] It could be shown that the targeted neuromodulation of brain activity leads in certain cases to a reduction of tinnitus or tinnitus-related complaints.The data regarding long-term effects and complete elimination of tinnitus by noninvasive neuromodulation have not been achieved. Thus, all of these techniques are experimental at this time.[52] In this context, it seems of great importance to make further progress in the better phenotyping of tinnitus and to better understand which changes in the neuronal networks are the most important in individual cases. The general trend in noninvasive neuromodulation certainly is also in the direction of simplifying procedures. Therefore, strategies that could be carried out by those affected without dependence on complex equipment or a clinical institution, for example, at home, also are regarded as ideal procedures. First experiments with mobile electroencephalogram systems will focus on, in particular, neurofeedback or transcranial electric stimulation and transcutaneous electric nerve stimulation procedures for the future.[55,56]

Invasive neuromodulation procedures involve implanting electrodes extradurally (epidural), cortically (subdural), or for deep brain stimulation.[57] These procedures were applied experimentally in tinnitus patients, or had effects on tinnitus in patients undergoing deep brain stimulation for treatment of movement disorders (eg, Parkinson disease).[58–62] In particular, with regard to deep brain stimulation of the auditory system (inferior colliculus and medial geniculate body), animal studies currently are under way to evaluate the significance of direct electrostimulation of the structures, described previously.[63–65] Case reports exist on the use of brain stem implants in humans, suggesting a positive effect on tinnitus-related complaints.[66,67] Due to the significantly greater invasiveness, the data on invasive neuromodulation are limited.. Nevertheless, there also are reviews that attempt to evaluate the previous studies as a whole.[52,68] The quality of the studies, however, which generally do not exceed the level of case reports or case series, does not permit a final evaluation at this point in time. The significant invasiveness of the procedures, however, in conjunction with a considerable side-effect profile, suggest that such procedures will be considered for only a very small subgroup of tinnitus patients in the future, if at all.[69]

In this context of invasive neuromodulation techniques, two procedures that directly stimulate nerve structures through implanted electrodes, cochlear implantation and vagus nerve stimulation, should be discussed. In particular, cochlear implantation is a routine procedure that is used for bilateral and now also single-sided deafness. Multiple studies and reviews have shown that cochlear implantation not only improves hearing but also reduces tinnitus perception in the recipients.[70,71] The high suppression rates of tinnitus when the implant is switched on must be interpreted as an outstanding tinnitus therapy that can certainly surpass the effect of standard procedures. The indication reduced to severe hearing loss and deafness is considered a limitation. This success suggests, however, that electric stimulation of peripheral auditory structures can improve tinnitus. The exact mechanism of action has not yet been clarified. Tinnitus suppression might be discussed as a direct effect of electric stimulation or as an indirect consequence in the sense of masking with improved hearing. For future scientific approaches, this represents an approach that already has been applied in experimental form to single subjects with tinnitus who have normal hearing in the sense of stimulation of the external auditory canal, the promotorium, or the round window.[72,73] There is great potential for future studies. Because vagus nerve stimulation in tinnitus is applied in clinical studies in terms of bimodal or multimodal stimulation, it is discussed subsequently in more detail.

SOMATOSENSORY STIMULATION

An interaction between the auditory and somatosensory system has been demonstrated on different levels. Auditory and somatosensory input converges already at the level of the dorsal cochlear nucleus.[18] Further interactions occur at higher brain levels.[74] Clinical reflections of these interactions are the onset of tinnitus after neck trauma,[75] the comorbidity of tinnitus with neck pain and temporomandibular disorder,[76] and the observation that tinnitus can be modulated by head or neck movements in a majority of cases.[77]

These phenomena are summarized by the term, *somatosensory tinnitus*, but it is important to note that this term does not describe a clearly defined subtype of tinnitus but rather the degree of involvement of the somatosensory system in an individual's tinnitus. Therefore, somatosensory tinnitus should be viewed as a dimensional rather than categorical term.[78]

The involvement of the somatosensory system is the basis for several treatment approaches. First, if there exist pathologies in the neck area or in the temporomandibular system, they should be treated, because a normalization of these pathologies can improve tinnitus.[79] Second, treatments, such as transcutaneous electrical stimulation,[80] acupuncture, neural therapy, and muscle relaxation,[81] have shown promising results in subgroups of patients.

BIMODAL OR MULTIMODAL STIMULATION

Bimodal or multimodal stimulation presumably is more effective for the induction of neuroplastic effects than unimodal stimulation. Recently, different approaches of bimodal or multimodal stimulation have been proposed for the treatment of tinnitus.

A combination of auditory stimulation with vagal stimulation has demonstrated highly impressive results in an animal model of tinnitus.[82] Based on the rationale that vagal stimulation renders the simultaneously presented sounds more salient, the combined treatment almost completely reversed neurophysiologic and behavioral signs of tinnitus, which was not the case with auditory stimulation alone. In subsequent human pilot studies, the efficacy of the treatment could be confirmed albeit the effects were clearly less pronounced than in animals.[83]

Another approach explored transcranial direct current stimulation of cortical areas to facilitate the effects of masking sounds and notched music with only limited success.[84,85]

In a recent pilot study, a combination of sounds with transcutaneous electrical stimulation to the neck or the temporomandibular area yielded impressive results. The somatosensory and auditory stimuli were presented at specific intervals that were derived from basic neurophysiologic studies describing stimulus timing–dependent plasticity in the dorsal cochlear nucleus.[86]

A combined application of sounds and electrical stimulation of the tongue was investigated in 2 large trials with results not yet published.[87,88] Simultaneous application of sounds and electrical stimulation of the tongue afferents may reduce tinnitus by providing a compensatory input to the partly deafferented central auditory system.

CLINICAL DATABASES

A major limitation with regard to finding a causal therapy for tinnitus lies in the heterogeneity of the symptom.[32] Thus, the phenomenon of therapeutic procedures that help 1 person but do not work for others reflects a repeated finding. Therefore, it is a great challenge for a therapist to find out which is the most promising procedure for a specific patient. Unfortunately, there are no reliable clinical predictors for most procedures that could predict the success of a therapy from the outset. An additional complicating factor is that most studies evaluating a specific method to improve tinnitus involve only a small number of cases. The comparability between studies is hampered by different methods in tinnitus assessment and in the determination of therapy outcome. Thus, most standardized reviews come to the conclusion that a concrete statement on the value of a therapy is difficult or that the quality of the data is so limited that certain approaches cannot be recommended.[19]

In order to address these shortcomings, it makes sense that generally accepted methodological measures are taken into account in studies to improve the comparability of the studies afterward. One possibility is that there would be international databases in which both data on tinnitus assessment and data on responsiveness to certain therapies would be entered according to the same pattern. An attempt in this respect is the database of the Tinnitus Research Initiative.[33] The database is open to all interested therapists and scientists who are willing to contribute patient data according to the guidelines. After corresponding consensus conferences,[36] it was agreed that certain guidelines should be followed when entering data, such as the primary tinnitus assessment, using a standardized case report form, or a standardized recording of the success of therapy. In addition, data on hearing ability (pure tone audiometry), tinnitus matching, or tinnitus severity can be entered according to questionnaires validated in different languages. This project, established in 2008, currently comprises more than 4000 data sets on tinnitus patients from more than 10 different countries (https://www.tinnitusresearch.net/index.php/for-clinicians/database). In this way it is possible to improve the subtyping of tinnitus by cluster analyses, to identify subgroups that could respond particularly well to certain treatments, to answer epidemiologic questions, or to improve the statistical power for certain questions by pooling data. Such projects are indispensable for future genetic research. Legal and data privacy issues have to be considered in such projects. Cooperation within the framework of major research projects financed by the European Union could play an important pioneering role. In the future, it can be assumed that such database projects will represent an important step with regard to personalized medicine in the care of tinnitus patients.

eHealth (APPS AND OTHERS)

eHealth is a highly dynamic research area in medicine and refers to the use of electronic information and communication technologies for health management. In recent years, there has been an increasing interest in eHealth technologies for the support of tinnitus patients. These include tools for patient communication and information, ecological momentary assessment of tinnitus symptoms, smartphone-based auditory treatments, Internet-based CBT (iCBT), serious games, and virtual reality applications. Similar to other medical fields, within a short time a large number of electronic tools have been developed and are offered in app stores. Most of these tools, however, have no regulatory approval and a vast majority are not scientifically evaluated.

Counseling is considered the basis of every tinnitus treatment. A majority of tinnitus patients worldwide, however, do not receive structured counseling according to modern standards. Thus, information about tinnitus and counseling via the Internet or a smartphone app represents a feasible and cost-effective option to reach many tinnitus patients who currently are lacking adequate counseling. An example represents the Tinnitus E-Programme, which is an Internet-based intervention program that consists of mainly educational content (ie, about tinnitus or “the role of psychological mechanisms in tinnitus”) and relaxation-focused and attentional-focused exercises.[89] The program has been evaluated and all of the files are accessible for free on a Web site created for this intervention program [http://www.tinnituseprogramme.org/].[90] Several smartphone apps for tinnitus counseling currently are under development.

eHealth tools also have been developed for assisting diagnosis and assessment of tinnitus patients. These include Internet-based hearing tests,[91,92] tinnitus matching tools,[93,94] and tools for ecological momentary assessment.[95,96] Internet-based or app-based hearing tests and tinnitus matching tools aim at offering audiological measurements for tinnitus patients at low cost, easy availability, and sufficient quality. This approach is important especially in the context of therapeutic auditory stimulation, because many innovative auditory stimulation approaches are individualized according to a person's hearing function and tinnitus pitch.

Ecological momentary assessment in contrast opens up a new quality in tinnitus assessment, because it enables to record fluctuations in tinnitus perception and annoyance in real time.[95] This is important because the retrospective assessment of tinnitus fluctuations is only of limited reliability, for example, due to a recall bias. By assessing tinnitus by repeated assessment in normal life conditions, these ecological momentary assessment apps enable real-time assessment of tinnitus fluctuations under normal life conditions. This information can be used for diagnostic purpose, for counseling, and for CBT. Moreover, it represents the basis for the development of a closed-loop system that offers therapeutic interventions exactly at the moment when they are needed or most effective.

iCBT is an approach that delivers CBT via the Internet, either only online-based or in a blended fashion, that integrates face-to-face and online therapy. Available studies have demonstrated that its efficacy is in a similar range to that of conventional CBT. An online version of acceptance and commitment therapy (ACT) for tinnitus has been developed as well.[97] A comparison between Internet-based ACT (iACT), iCBT, and a moderated online discussion forum revealed substantial improvements for both iCBT and iACT, with no significant difference between the 2 treatments.[98]

With technological advances in the development of smartphones, sound therapy is an easily accessible treatment option. There are smartphone applications that claim to reduce tinnitus loudness by the usage of tailor-made notched music (eg, Tinnitracks [www.tinnitracks.com] or Tinnitus Pro: Music Therapy [https://tinnitus-pro-music-therapy-ios.soft112.com]).[99] One study provided the patients with tinnitus masking technologies.[100] The efficacy of none of these approaches has yet been evaluated.

Further eHealth-based approaches that have been proposed are serious games and virtual reality.[101–103]

POTENTIAL NEW DRUG TARGETS

Although many different drugs with different mechanisms of action have been investigated in the past decades, no drug target could be identified for alleviating either tinnitus loudness, tinnitus-related distress, or both. Moreover, because there are no approved drugs for the treatment of tinnitus, there also are no examples of a successful pharmacologic development program that could provide a blueprint for the development of a new compound.

Based on an increasing understanding of the pathophysiology of tinnitus, new potential target structures emerged and several candidate drugs for the treatment of tinnitus have been identified in past years.

Recent clinical research programs that targeted *N*-methyl-D-aspartate receptor (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and potassium channels are summarized.

In animal experiments NMDA receptors have been identified to pay a critical role in the development of salicylate-induced tinnitus.[104,105] These findings formed the basis for the clinical development of the NMDA receptor antagonist Keyzilen (AM-101), esketamine hydrochloride, by Auris Medical (Basel, Switzerland).

The intratympanic delivery of a gel formulation of Keyzilen (AM-101) was investigated in patients with acute tinnitus caused by acoustic trauma, idiopathic sudden sensorineural hearing loss, or otitis media.[106] This phase 2 clinical trial failed to achieve the primary endpoint of improving minimum masking level; however, statistical significant improvement was demonstrated for tinnitus loudness, annoyance, sleep difficulties, and tinnitus impact in the high-dose Keyzilen (AM-101) patient groups with tinnitus after noise trauma or otitis media.[106] Based on these findings, a phase 3 program was initiated, which unfortunately could not confirm the data from the phase 2 trial.[107,108]

Another pharmacologic compound, that has been investigated recently (2011–2012), is BGG492 (selurampanel), which is an orally active AMPA/kainate receptor antagonist.[109] The AMPA receptor has been chosen as target as the main excitatory activity in both cochlea and the central auditory pathways is AMPA mediated.[110] BGG492 was evaluated in patients with moderate to catastrophic chronic subjective tinnitus. After a 2-week treatment with BGG492, significantly greater proportion of patients showed response (improvement of $\geq$4 points from baseline in Tinnitus Beeinträchtigungs Fragebogen (TBF-12), a German short version of the Tinnitus Handicap Inventory) compared with placebo (26.7% vs 14%).[111] Due to an unfavorable side-effect profile, however, BGG492 has not been further developed.

Targeting the central nervous system also has been the focus of AUT00063, a Kv3.1 channel inhibitor. This compound has been investigated in a phase 2a study but was not superior to placebo in reducing the score of the Tinnitus Functional index.[112]

Also, Kv7.2/3, another potassium channel, has been proposed as a potential target for tinnitus treatment. It has been shown that application of the Kv7.2/3 opener retigabine prevents behavioral signs of tinnitus in mice.[113] Retigabine was approved in 2011 by the FDA as an adjunctive treatment of partial epilepsies, but the clinical use of retigabine is limited by its side effects. This may explain why this compound has not yet been investigated in a clinical trial for tinnitus. The promising findings from animal studies and its availability as an approved drug for epilepsy, however, have motivated patients to try this potassium channel modulator for tinnitus treatment. Moreover, some of the patients shared their experiences with this drug via an Internet-based tinnitus forum.[114]

An improved Kv7.2/3 activator, the compound SF0034, has been shown to act more specifically and more potently on Kv7.2/3 channels and to prevent the development of tinnitus in mice after noise trauma.[115] Because SF0034 is less toxic than retigabine, it might represent a candidate for tinnitus treatment with a more favorable side effect profile.

Thus, in summary, four different new drug targets have been explored in recent years. Two studies failed; in 1 case, the development of the compound has not been continued and a further drug has demonstrated promising results in animal studies but has not yet been investigated in humans. This illustrates the difficulty in the development of pharmacologic treatments of tinnitus. A more and more detailed knowledge about the pathophysiology of tinnitus enables the identification of new potential targets for pharmacologic treatment. With the lack of valid preclinical screening methods, however, potential new compounds still have to be tested in human pilot trials. The design of human pilot trials for screening promising compounds is not trivial. First, the definition of inclusion and exclusion criteria is of particular relevance because of the clinical heterogeneity of tinnitus. Second, the correct estimation of the dose range and the duration of the treatment is challenging, especially when knowledge about pharmacokinetics and pharmacodynamics is limited. Third, a sufficiently sensitive instrument for outcome measurement has to be chosen. Therefore, preclinical endpoints with validated translation into clinical application would be highly desirable to improve the risk/benefit balance of preclinical and clinical development of new compounds for tinnitus treatment.

In summary, despite huge advances in pathophysiologic knowledge and research methodology in the past 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.

PATIENT INVOLVEMENT

A recent development in tinnitus research is the increasing involvement of tinnitus patients. Patient representatives were critically involved in recent approaches to identify patient-relevant outcome measurements.[116]

Moreover, patient self-organization via the Internet opens up entire new possibilities compared with traditional patient organizations, because it speeds up interactions between patients, researchers, and clinicians across borders. For example, the Internet-based tinnitus forum (tinnitus talk) reaches many thousand patients; via this forum, patients are informed about newest developments in the field, but they also can contribute to research, by participating in surveys or by providing the database for trend analyses of current hot topics.

Recently, the results of a patient survey from tinnitus talk, with more than 5000 participants, provided the first empirical confirmation that there exist different tinnitus subtypes that vary in their response to different therapeutic interventions.[31]

Finally, in the competition for research money with other research areas, the close and active interaction between researchers and patients is of utmost importance, because patient involvement is an increasingly important requirement at more and more grant agencies.

GRANTS AND FUNDING

Despite the increasing incidence of hearing impairment, funding for research in this area appears to be significantly under-represented compared with other health problems of similar relevance.[117] If searching specifically for the promotion of tinnitus in the complex of hearing disorders, a further imbalance becomes apparent. Obviously, a larger part of the money is spent on research and improvement of technical approaches, such as cochlear implants and hearing aids. In relation to the large number of people affected, too little funding remains for tinnitus. This may be explained to a large extent by the fact that tinnitus is a complex disorder whose exact pathophysiology is not yet clarified in detail and for which there is no causal therapy in most cases. For the pharmaceutical industry, in particular, these facts seem to represent a too great risk for large-scale research campaigns. The few pharmaceutical studies carried out in recent years essentially have been initiated by small companies and have largely ended with a negative result without corresponding marketing approval, so that risk appetite will tend to decline. Other funding opportunities are provided by large self-help institutions, such as the American Tinnitus Association, the British Tinnitus Association, and the UK Action on Hearing Loss Campaign. In recent years, a gradual increase in funding has been recorded by these institutions. The funding provided by state institutions in Europe (German Research Foundation in Germany, Wellcome Trust in the United Kingdom, and Swiss National Science Foundation in Switzerland) appears to be lower than in the United States (eg, National Institute on Deafness and Other Communication Disorders). It can be seen, however, that in the

United States, primarily basic research projects in animal research are funded, whereas in Europe the focus is on clinical research in tinnitus.[117] Thanks to private investors (often suffering from tinnitus themselves), significant progress has been made in recent years. Specific funding programs have improved the networking and collaboration of scientists in the field of tinnitus. This has led to an enormous increase in publications in the field of tinnitus, which in turn has improved public perception by funding institutions. As a result of this development, 2 major projects on tinnitus have been funded by the European Union in recent years, with a total investment of approximately $10 million. Within the Innovative Training Networks, including the European School for Interdisciplinary Tinnitus Research (https://esit.tinnitusresearch.net)[118] and Tinnitus Assessment Causes Treatment [https://tinact.eu/]), 30 PhD students are being trained in tinnitus research. In the future, an important input into tinnitus research in general can be expected from this.

Together, the efforts of recent years have increased the funding volume in tinnitus research. In comparison to the frequency of the symptom and the amount of severely impaired individuals with resulting high socioeconomic burden, however, the investment for research still seems low.

SUMMARY

In the past decade, various efforts have been made to identify potential new targets[20] and to develop innovative auditory, behavioral, pharmacologic, and neuromodulatory interventions. Moreover, there are ongoing research efforts to refine and validate animal models further,[22,119] to develop large clinical databases to address the heterogeneity of tinnitus, and to optimize and standardize clinical trial design[39] and outcome measurement tools.[36,40] Recently the growing possibilities of eHealth have been explored for their use in tinnitus, and new media facilitate interaction between patients, researchers, and clinicians of different disciplines. With all these developments, tinnitus research has reached a state of increasing activity and diversity reflected by a growing number of publications. It is hoped that these developments soon will lead to more efficient treatment options for the many patients who currently still suffer from tinnitus.

DISCLOSURE

The authors declare that they have nothing to disclose.

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