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New trends in the therapy of chronic tinnitus

Gerhard Hesse

Tinnitus-Klinik at Arolsen General Hospital, University of Witten-Herdecke, North Rhine-Westphalia, Germany

Correspondence to Gerhard Hesse, MD, Ohr – und Hörinstitut, Tinnitus-Klinik am Krankenhaus, Bad Arolsen, GroßeAllee 50, D-34454 Bad Arolsen, Germany
Tel: +49 5691 800330;
e-mail: ghesse@tinnitus-klinik.net

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Although tinnitus is mostly primarily of peripheral origin and due to damage of hair cells, suffering and annoyance derives from central cortical reactions and functional networks of cerebral plasticity. New therapeutic approaches thus try to influence these structures directly through magnetic or direct or indirect electrical stimulation. Acoustic stimulations were also presented with tones or notched music, but they must integrate the existing hearing loss. Effective habituation therapies combine hearing therapy, rehabilitation of hearing loss by hearing aids, and psychosomatic stabilization. This review presents different therapeutic approaches.

Keywords:
hearing therapy, neuromodulation, tinnitus

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Introduction

To date, a curative therapy that can extinguish the tinnitus completely is not available.

However, a number of therapeutic approaches are capable of reducing patients suffering from tinnitus or even achieve partial or complete relieve in tinnitus perception. Thus, there are possibilities to improve the individual handling of tinnitus and consecutively hearing and life quality.

Regarding generation of tinnitus in the last years, new scientific insight has emerged through animal models as well as studies with patients regarding more knowledge about central auditory processing and new therapeutic possibilities influencing cortical plasticity.

It is still a crucial point how long the tinnitus exists; in the acute phase, when it first appears, the chance of complete abolition is very high due to spontaneous cure or due to medical, normally pharmacological interventions [1].

Acute tinnitus

A suddenly emerging tinnitus is mainly accompanied by or following a sudden hearing loss. Sometimes, the basic hearing loss is subjectively not felt but can be detected in the audiological examination. More often the tinnitus emerges or is perceived after a sudden hearing loss improves, spontaneously or through therapy. That is why an acute emerging tinnitus is looked upon as an equivalent of sudden hearing loss and is treated accordingly.

In Germany, the guideline for treating sudden hearing loss, made topical 2014 [2], recommends for an acute treatment, a medication with systemic high-dosage steroids [3,4] as intravenous infusion or as oral medication [5]. Alternatively or as a salvage therapy, intratympanic application of steroids is recommended [6]. Other pharmacological or other interventions are not recommended in this German guideline because there is (weak) evidence for effects of high-dosage steroids [7], whereas there is no evidence for rheological agents and medicines to improve the blood circulation [8] nor for Ginkgo biloba [9]. A newly published USA guideline for the treatment of tinnitus also does not recommend these medications [10].

This treatment should be accompanied by a sound and empathetic counseling and should support the patient psychologically [11]. A proper audiological testing must be performed, refraining from tests with high loudness levels, such as auditory brainstem response (ABR), stapedius reflex testing, or MRI checkups in the acute phase [2].

For the extremely rare cases where tinnitus emerges completely without hearing loss (detectable through distortion product of otoacoustic emmissions (DPOAE) findings) [12], a medication is definitely obsolete. These types of tinnitus are looked upon as central overexcitation and should be treated accordingly: individual counseling and – more important – psychological support and learning of relaxation techniques. Sometimes, sedatives or anxiolytics can be prescribed, keeping in mind the highly addictive potential of these drugs [13]. Modern antidepressive drugs such as serotonin reuptake inhibitors [14] very often are a better choice.

It has to be emphasized that an exacerbation of an existing tinnitus is not equivalent to an acute tinnitus, because here the tinnitus was already pre-existing and is only perceived more strongly or more annoying through specific reactions of attraction [15].

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Chronic tinnitus

Tinnitus existing for more than 3 months, be it unilateral or bilateral, low-frequency or high-frequency, is looked upon as chronic. Although there is no curative therapy, patients and health professionals are looking for the 'lost switch'; huge efforts are undertaken to eliminate the tinnitus completely.

In this context, we have to realize why tinnitus becomes an annoying symptom and why perception becomes a dominant and major factor. Many people have tinnitus, without getting bothered or even without consciously perceiving it [16]. Only when tinnitus reaches a separate circle of valuation, it amplifies itself in a vicious circle by permanent reactions of focussing on this internal random noise. Thereafter, a subjective suffering develops and often psychosomatic comorbidity [17].

This means that, although tinnitus generates almost always from the inner ear, especially from defects of outer hair cells (after acute trauma or damage), the decisive factor whether it becomes a problem or even a disease is determined by the further processing of this signal in the central auditory pathway and its connectivity to other regions of the brain. Thereafter, it is connected to emotions, valuations, and judgements [18].

Stress as cause of hearing loss, hyperacusis, and tinnitus

Stress reactions, especially negative strain, can lead to generation of tinnitus or to a stronger perception of tinnitus. It is necessary in this context to distinguish between stress of the auditory pathway alone or stress reactions concerning the complete network of sensory integration.

Regarding the auditory pathway alone, however, the main stress factor is hearing loss.

Hearing loss induces many reactions, auditory and psychoemotionally. The reason is that normal hearing with functioning auditory signals produces a definite pattern of auditory memory in the cortex; part of this is the capability to interpret disturbing external sounds as unimportant, and thus inhibit their perception [19].

When signal processing in the inner ear is disturbed and when certain frequencies do not reach the cortex with usual strength and intensity, then the auditory cortex reacts and tries to compensate this deficit with specific reactions [20]. This happens even stronger, when the hearing loss is sudden and unforeseen, such as noise trauma or idiopathic hearing loss.

It is not astonishing that the number of patients with tinnitus increases in older age [21], because the total number of hearing impaired people increases significantly with higher age [22].

Stress reactions of the cochlea and the cortex

Sudden hearing loss induces an increase in cortisol distribution. Parallel emerging hypoxia leads to apoptosis of hair cells and increased upregulation of glutamate. This leads to an increase in free calcium, which can destroy the synapses between inner hair cell and ganglion spirale [23].

Direct stress reactions in the cortex are a fast beginning process of reorganization of the tonotopic map of the primary auditory cortex [24] and an enhancement of so-called edge frequencies – for example, frequencies close to the hearing loss [25].

Cortical inhibition is adjusted downward, which again enhances the development of maladaptive patterns [26] such as tinnitus, dysacusis, and hyperacusis.

We know from the research that Eggermont [24] performed with cats that shortly after a cochlear trauma (by noise) there is a loss of hair cells as well as a loss of ABR potentials for high frequencies.

Interestingly, this process is partially reversed, if the animals are exposed to high frequencies shortly after the trauma. Thereafter, the cochlear damage remains, but the reorganization of the cortical map is much less compared with animals that are not equally stimulated [27]. Thus, after hearing loss, especially after acute traumas, there is a reorganization of the cortical tonotopy, an increased spontaneous activity, and increased neural synchronization.

However, acoustic stimulation counteracts this process.

Influencing the central auditory pathway and the auditory cortex as a new therapeutic approach

Tinnitus is mostly a symptom of disturbed auditory perception, based on auditory deficits. However, loudness and annoyance of the tinnitus percept is determined by the cortical network and cortical plasticity, by concrete reactions of perception and focussing.

A number of studies showed this connectivity but with very different results.

A total of 105 persons were examined with functional MRI: 42 patients without and 63 patients with tinnitus. The research found an enlargement of the corpus

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callosum with tinnitus patients – for example, the connection of the auditory parts of the left and right hemisphere. This shows an enhanced excitation [28]. Another review analyzed 10 studies using PET scan. There was a description of all together 56 foci, which means that tinnitus leads to activation of a sum of 14 brain regions (but different patients show enhanced activity in different regions).

Besides the primary and secondary auditory cortex, the gyri temporalis, parahippocampus, corpus geniculatum, precuneus, cingulum, claustrum, and the gyriangularis of the temporal lobe are involved in this activation [29]. Therefore, we can demonstrate by MRI or PET scans that there are special zones of activity with tinnitus patients, but these are not unique. Furthermore, there is no clear pattern demonstrating which changes are induced by the tinnitus directly or whether they are more probably due to the coexisting hearing loss.

The same applies for the numerous electro encephalo graphic (EEG) studies regarding 'connectivity'. These studies compare EEG changes of normal hearing persons with tinnitus patients. Very often, the studies describe the coexisting hearing loss, but the change in EEG patterns is interpreted as only caused by tinnitus.

For recording EEGs, the placement of electrodes and the consecutive calculation are crucial, and this is not performed in a standardized manner.

Some studies, for example a paper from Nottingham, found enhanced δ-activities, which means an enhanced activity of slow waves with tinnitus and hearing loss, whereas the γ-activity was not different from normal persons [30].

In comparison, many studies from the Antwerpen study group (psychiatry and neurosurgery) detected multiple changes with tinnitus patients as well as from animal studies, and again the hearing loss is not taken into account. Mostly, they found an increase in γ-activity in the EEG of tinnitus patients, representing the fast waves [31].

These studies produce pictures of multiple areas of the brain that are enhanced, documented by EEG changes. However, we do not know whether this is caused by tinnitus or by hearing loss and – more important – these changes vary from patient to patient. Therefore, we cannot detect a specific region of tinnitus activity that is unique for tinnitus.

Tinnitus therapy – a promising market

Because doctors as well as patients always look for the 'switch' to definitely turn off their tinnitus, unfortunately a quite lucrative market emerged in the last years. This is emphasized by an interesting study from the USA.

Tyler [32] questioned 197 patients; 19% were willing to have a device implanted to loose their tinnitus completely and 13% if the tinnitus would be at least half as loud.

Patients would spend up to $5000, 20% of the patients more than $25 000 to reach this goal.

In a follow-up study by Engineer *et al.* [33], 439 patients were questioned again; 40% already did spend $500 to even $10 000, although with very little success. This medicoeconomic fact has to be taken into consideration regarding the numerous therapies that overwhelm the health market in waves again and again.

Neuromodulation as the most recent therapeutic approach

The headword 'neuromodulation' combines therapeutic procedures that try to influence the auditory cortex or special brain regions to stop or minimize the perception of tinnitus. Plewnia [34] introduced a review regarding different types of neuromodulation: transcranial magnetic stimulation with different pulses, ways of stimulation and fields of projection, further the transcranial electrostimulation, or even a direct cortical electrode implantation. Plewnia points out that for the moment there is very little clinical relevance for these procedures with only very small numbers of patients. The studies are mostly of poor methodology, not properly placebo-controlled, and there are no longer follow-up nor katamnesis.

Repetitive transcranial magnetic stimulation

Worldwide, but especially in Germany and also in the Middle East and Egypt, studies examined effects of this treatment.

For 192 patients, there was a significant decrease in annoyance measured by a tinnitus questionnaire directly after the stimulation with these strong magnets, but at the end the overall effect was not better than with placebo (Sham) stimulation [35]. In another study by Burger *et al.* [36], 21 (3%) of 235 patients reacted positively. This reaction lasted for 2–4 months, but after this it got worse again. In contrast, the study group from Tübingen, Germany found that, in 48 patients who were treated for 4 weeks with transcranial magnetic stimulation, there was only a slight improvement, but this was as strong as the placebo stimulation [37].

It has to be mentioned that the repetitive transcranial magnetic stimulation produces a significant noise level.

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Tringali *et al.* [38] described this fact in 2012. They found out that magnetic stimulation comes with noise levels up to 120 dB(A); mean level was 90–100 dB(A). Interestingly, the placebo coil (Sham) is 40% lower; even that questions the real placebo effect. The authors of this study presume there would be a specific cortical reaction to this noise.

Electrical transcranial and intracortical stimulation

There are some therapies that try to stimulate the auditory cortex externally with direct or alternating current [39], with hardly any effect. Very few patients were even stimulated with electric current intracortically. De Ridder and Vanneste presented a study, where he implanted electrodes into the auditory cortex in 43 tinnitus patients who had reacted positively to transcranial magnetic stimulation. Three days after the implantation, the electrodes were stimulated with 40 Hz bursts; when there was no reaction, the burst frequency was varied until there was a reaction regarding the tinnitus. Results were measured with a visual analog scale before and after treatment; there was a placebo group, but it could not be evaluated. In all, 29 of these 43 patients reacted somehow on the electrostimulation, but only eight really improved. Statistically, there was an improvement in the visual analog scale scores in 67%; 33% showed no reaction at all (tinnitus). However, there were remarkable side effects; three patients developed epileptic attacks, one patient had a cerebral hemorrhage and consecutively speech and word detection disturbances (but his tinnitus was better), and one patient developed an intracranial abscess that had to be treated surgically (his tinnitus deteriorated) [40]. The authors conclude, despite this, that intracortical stimulation might be a 'promising new therapy', but in fact this therapeutic approach is very rare, as in most countries there are ethic commissions that do not allow such studies.

Tinnitus therapy with cochlear implants

Direct electrical stimulation of the acoustic nerve by cochlear implants (CIs) up to date is only used with completely or profoundly deaf patients, lately even with unilateral hearing loss.

Experience shows that the CI has a very good influence on tinnitus in most patients. This is due to the resulting reorganization of the cortical map more than the stimulation of the acoustic nerve itself. CI missing frequencies and complex acoustic signals are presented again, which result in a decrease of spontaneous activity of the auditory pathway and a decrease in tinnitus perception in most patients [41].

Acoustic neurostimulation

A new therapy also under the headword neuromodulation that has been published beforehand with high expectations (but still without evaluated results) is the so-called acoustic neurostimulation 'CR' (coordinated reset-model). This therapy was developed in Germany (Research-center, Jülich) and was brought to the market very aggressively and in many countries. The paradigm for this therapy was that tinnitus is caused by synchronicity of auditory neurons alone. Instead of influencing these neurons directly and electrically, they should be stimulated with specially calculated low-intensity tones that were centered around the tinnitus frequency. A patent was developed for this paradigm with two tones above and two tones below the exactly diagnosed tinnitus frequency. The patient had to listen to these tones through headphone several hours a day. The device was very expensive; patients had to pay (in Germany) more than €3000 but at the moment the therapy is not available any more, as the company went bankrupt.

To date, the inventors were not able to produce one reliable study to proof this effect. After some years, they published a paper (not in an *ENT* or *Audiological Journal*), which was of very poor methodology. The placebo group was very small (five patients) and had tinnitus much longer than the others and the stimulus was much below the actual tinnitus frequency. Only 22 patients were treated with the actual method; they improved in the tinnitus questionnaire significantly, but mainly their tinnitus frequency changed to lower frequencies [42].

Mühlnickel *et al.* [43] and Flor *et al.* [44] published in 1998 and 2004 similar studies, but they left this therapy again, because there were many side effects and with many patients the tinnitus got worse. The therapy has to be criticized mainly because the stimulation is performed by the normal auditory pathway, but patients had hearing loss up to 50 dB [42]. Such a hearing loss changes the incoming signal on its way to the cortex; for the study, there had to be at least a differentiation regarding actual hearing loss. This of course was not possible with the small number of participants, but it was not even discussed.

In 2012, a high-standard study for this acoustic neurostimulation was recruited and actually completed in Nottingham University and registered under 'Clinical Trials' [45]. Meanwhile, this study is completed; results are to be presented, but the sponsoring company impedes publication of these results.

However, some facts will be presented soon.

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Stimulation of the vagal nerve to treat tinnitus

A complete new therapeutic approach uses knowledge from animal studies, where learning could be improved by simultaneous stimulation of the vagus nerve. In animal studies, electrodes were implanted on the cervical part of the vagus nerve; the rats received 300 stimuli per day combined with acoustic stimuli that were different from the tinnitus frequency. Results showed an improvement in the gap detection of these animals, corresponding to an improvement in tinnitus perception [46].

This was followed by feasible studies for humans; no major contraindications were found [47].

Recently, a clinical study started in the USA with a specially developed device. Patients are implanted with electrodes on the vagus nerve at the neck for the duration of the therapy. Through headphone, they listen to sounds and at the same time are stimulated with small electric stimuli. This should result in cortical learning to reduce tinnitus perception or to ignore this tinnitus tone. There are no results yet, but expectation is only a better habituation, not to extinguish the tinnitus.

Music therapies

Similar effects can be achieved by music therapies that are introduced as part of audiotherapy supplementing habituation therapies. There are also direct music therapies with instruments [48]. The Heidelberg tinnitus music therapy works with vocal improvisations around the tinnitus. This therapy was published with good results, but the publication was not clearly differentiating therapeutic effects. The therapy itself was combined with many other therapeutic interventions such as relaxation techniques, counseling, and psychological support. Therefore, it was not clear what amount of the effect was due to the music [49].

Pantev *et al.* [50] introduced a therapy, where patients presented their favorite music. Thereafter, the tinnitus frequency was filtered out of this music and the patients had to listen to this changed music several hours per day (a device for this 'notched music therapy' was immediately and independently sold without knowledge of the actual study group).

In the first study, 39 normal hearing tinnitus patients were divided into three groups: one group listened to the notched music, another to a different (placebo) change, the third to normal unchanged music over 12 months (1–2 h/day).

There were changes in the loudness of tinnitus; in addition, changes in magnetoencephalographic findings were detectable but only for tinnitus frequencies below 8 kHz [51]. We introduced similar therapies (1986–1995) with a device called 'Tinnicur', however, without reliable results.

All these therapies cannot prove a scientifically reliable effect, but they definitely can play a good supportive role in the sense of audiotherapy, because music definitely has a stabilizing and positive effect on the auditory system. Music helps to improve and intensify auditory perception.

In contrast, these therapies are problematic when they promise cure and at the same time are very costly for the patients.

Fitting of hearing aids as an effective acoustic stimulation

A completely different approach and much more effective is the direct acoustic stimulation of missing frequencies by hearing aids. Most of the patients perceive tinnitus in the frequency of their hearing loss. Modern insights propose fitting of a hearing aid as early as possible to prevent cortical loss and help reorganizing the tonotopic map of the auditory cortex [52]. For Germany, for example, 16 million of the inhabitants (out of 80 million) need a hearing aid, whereas only 10% are actually supplied.

At the same time, the quality of hearing aid technology has improved tremendously in the last years, especially regarding high-frequency hearing loss. In addition, through open fitting the acceptance has become much better. Noise reduction and suppression of acoustic feedback is very effective. Very often loudness of tinnitus and annoyance can be reduced significantly [53].

Hearing/audiotherapy

Therapeutic interventions directly influencing and improving central auditory processing and perception can very effectively support habituation therapies and the most efficient cognitive behavioral therapies; they influence disturbances of the hearing system with the remaining capacities of this system [54].

Rehabilitation of an existing hearing loss is an integrative part of these hearing or audiotherapy, using hearing aids or CIs. Central auditory functions are improved, such as focussing, inhibition, and reduction of random noise; patients learn to overhear their 'personal random noise', their tinnitus [55].

Conclusion

Although tinnitus almost always generates peripherally, the decisive criteria for annoyance is negative evaluation

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of tinnitus in the central auditory perception. This occurs by reorganization of the cortex after hearing loss and emergence of new patterns in the cortex.

Tinnitus and hyperacusis are always symptoms of a disturbed auditory perception.

There is no indication for pharmacological therapies with chronic tinnitus, as all of them are ineffective, especially ginkgo, betahistine, or other agents to improve blood circulation.

Central-acting agents such as neramexane, examined in very thorough and correct studies, could not prove to be effective [56]. In addition, a medication with antidepressants to treat psychosomatic comorbidity can be prescribed, although this does not treat the tinnitus but depressions or anxieties or sleeping disorders.

Possibly in the (near or far) future, an improvement by gene therapy can be expected, but this is not very imminent.

Methods such as neuromodulation and especially magnetic stimulation could not prove to be effective for tinnitus, as a new guideline emphasizes [57]. They have only limited number of patients and no lasting effects; improvement lasts only for the time of treatment.

Acoustic stimulation is very useful in the treatment of chronic tinnitus. The focus lies on a useful and necessary rehabilitation of hearing loss with hearing aids or CI. This can be supported and improved by a specific audiotherapy; some patients without hearing loss might profit from noise generators.

The strongly promoted 'CR-neurostimulation' has not been proven to be effective. Acoustic stimulation with tones or music can temporarily mask but not extinguish the tinnitus.

Therefore, acoustic stimulation has to take the existing hearing loss into consideration, because it has to pass the complete auditory pathway with all its deficits. That is why rehabilitation of an existing hearing loss and an improvement of central auditory functions by audiotherapy is crucial.

New and modern therapies for chronic tinnitus do not postulate to have found the 'switch to shut off tinnitus'; nonetheless, they can achieve very good results with a combination of neurotologic and psychosomatic therapeutic approaches.

These are based on a proper and profound audiological diagnosis, an empathetic counseling and instruction, a compensation of hearing loss by acoustic stimulation, a hearing therapy, and a necessary psychological stabilization. With these procedures, the tinnitus cannot be extinguished, but it can be replaced from perception and the annoyance can be effectively reduced.

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Conflicts of interest

There are no conflicts of interest.

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