Tinnitus: causes and clinical management

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Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus. With prevalence ranging from 10% to 15%, tinnitus is a common disorder. Many people habituate to the phantom sound, but tinnitus severely impairs quality of life of about 1–2% of all people. Tinnitus has traditionally been regarded as an otological disorder, but advances in neuroimaging methods and development of animal models have increasingly shifted the perspective towards its neuronal correlates. Increased neuronal firing rate, enhanced neuronal synchrony, and changes in the tonotopic organisation are recorded in central auditory pathways in reaction to deprived auditory input and represent—together with changes in non-auditory brain areas—the neuronal correlate of tinnitus. Assessment of patients includes a detailed case history, measurement of hearing function, quantification of tinnitus severity, and identification of causal factors, associated symptoms, and comorbidities. Most widely used treatments for tinnitus involve counselling, and best evidence is available for cognitive behavioural therapy. New pathophysiological insights have prompted the development of innovative brain-based treatment approaches to directly target the neuronal correlates of tinnitus.

Introduction

Tinnitus is the perceived sensation of sound in the absence of a corresponding external acoustic stimulus. Unlike auditory hallucinations, which are phantom phenomena that occur mainly in people with mental disorders and manifest as the perception of voices and musical hallucinations, in which instrumental music or sound is perceived, tinnitus sensations are usually of an unformed acoustic nature such as a buzzing, hissing, or ringing. Tinnitus can be unilateral or bilateral, but can also be described to emerge within the head. The perceived sensation can be intermittent or have a pulsatile character. The matched loudness of the phantom sound ranges from a subtle noise slightly above the hearing threshold to high-intensity sounds. Tinnitus is classified as objective tinnitus or somatosound if a sound is generated in the body and is also audible by the examiner (eg, myoclonic contractions of the tensor tympani muscle or altered blood flow in vessels near the ear), or as subjective tinnitus, which is much more common, if it does not have a specific inner-body sound source.

In a large survey in Norway, 21·3% of men and 16·2% of women reported perception of tinnitus, with 4·4% of men and 2·1% of women reporting high tinnitus intensity.[1] Results of epidemiological studies show similar prevalence not only in other European countries,[2,3] the USA,[4,5] and Japan,[6] but also in low-income and middle-income countries in Africa[7,8] and Asia,[9] which indicates that the perception of phantom sounds is a global burden. Hearing impairment, increasing age, and male sex have been identified as the most relevant risk factors for tinnitus.[5] Because of demographic developments and an increase in professional and leisure noise exposure, tinnitus prevalence is expected to continue to increase.[10] Moreover, tinnitus is among the most frequent sequelae of modern warfare.[11]

Tinnitus is clinically heterogeneous in its cause, perceptual characteristics, and accompanying symptoms. Many patients with tinnitus report symptoms such as frustration, annoyance, irritability, anxiety, depression, hearing difficulties, hyperacousis, insomnia, and concentration difficulties; these symptoms are highly relevant to determine tinnitus severity.[12] Thus, tinnitus is a highly prevalent and potentially distressing condition with a wide range of symptoms that can place a huge burden on patients and substantially impair quality of life. Its socioeconomic relevance is shown by the greatly increased risk of receiving a disability pension among patients with tinnitus.[13]

Tinnitus was traditionally thought to be an otological disorder, but treatment approaches targeting the cochlea have had discouraging results.[14] With little evidence for successful therapies from randomised clinical trials, standardisation in the care of patients with tinnitus has been low,[15] with most patients left untreated. However, during the past decades advances in neuroimaging methods and the development of animal models[16] have shifted the perspective towards the neuronal correlates underlying different forms of tinnitus.[10,17] On the basis of this increased pathophysiological understanding, innovative therapeutic approaches to reduce the tinnitus signal are being developed and have had promising results. At the same time, clinical research methodology has substantially improved, providing convincing evidence for the efficacy of cognitive behaviour-based therapies to reduce tinnitus-related distress[18,19] and enabling evidence-based tinnitus treatment.[20]

Causes and pathophysiology

Tinnitus can arise from pathological changes along the entire auditory pathway. In most cases tinnitus develops as a consequence of initial cochlear lesions such as sudden hearing loss, noise trauma, presbyacusis, or administration of ototoxic drugs. These lesions can result in abnormal neuronal activity in central auditory pathways that can then be finally perceived as tinnitus. Abnormal changes to the auditory nerve (eg, microvascular compression or vestibular schwannoma) can also lead to perception of tinnitus. However, the association between hearing loss and tinnitus is not

straightforward. Not everybody with hearing loss develops tinnitus, and an abnormal audiogram is not detected in all patients with tinnitus; this finding could be explained by the fact that some forms of auditory deafferentation are not discovered by audiometry.[21] Partial cochlear nerve sections can be done without detectable changes in hearing thresholds.[22] People with tinnitus who have normal hearing thresholds frequently have cochlear dead regions[23] or outer hair cell damage[24] compared with controls. The tinnitus pitch match is associated with the frequency spectrum of hearing loss (figure 1),[25,26] indicating the relevance of hearing impairment for the generation of tinnitus; this effect is analogous to the generation of phantom perceptions as a consequence of sensory deafferentation after limb amputation.[27] Temporomandibular joint disorders and neck injuries have been associated with the development or persistence of tinnitus.[28] The underlying mechanism is probably the effect of afferent somatosensory input from the trigeminal nerve and C2 fibres on central auditory pathway activity via interaction at the dorsal cochlear nucleus at brainstem level.[10,29]

The onset of tinnitus can also be associated with emotional factors and stress.[30] In many cases tinnitus generation is multifactorial; thus, any combination of altered auditory and somatosensory inputs together with abnormal activity in central nervous structures (eg, due to traumatic or ischaemic damage or emotional factors) can be relevant for tinnitus generation, which could especially be the case in tinnitus after traumatic head injury.[31] Moreover, the factors involved in the generation of tinnitus might differ from those related to its persistence, as shown by the fact that many people perceive transient tinnitus after noise trauma but tinnitus becomes permanent only in a few of these people.[32]

A different cause is assumed in objective tinnitus, for which an internal sound source can be identified. A typical form of objective tinnitus is heartbeat-synchronous pulsatile tinnitus, which is often caused by vascular abnormalities such as arteriovenous malformation, carotid stenosis, or dissections, or by increased blood flow (eg, in anaemia). Other causes of objective tinnitus include spontaneous otoacoustic emissions and middle-ear myoclonus.

Neuronal mechanisms

Although neuroscientific research in recent decades has contributed to a substantial increase in knowledge about the neuronal mechanisms underlying phantom perceptions, the pathophysiology of the different forms of tinnitus is not fully understood. Although tinnitus is often triggered by peripheral mechanisms (eg, cochlear impairment), it usually persists after auditory nerve section,[33] underscoring the crucial involvement of central mechanisms in its pathophysiology. These changes in neuronal activity seem to arise from dysfunctional activation of neuronal plasticity induced by altered sensory input—namely, auditory deprivation in most cases.[25,34] Additionally, abnormal somatosensory afferent input from the neck and face region can affect activity in central auditory pathways and might also contribute to the generation of tinnitus.[10]

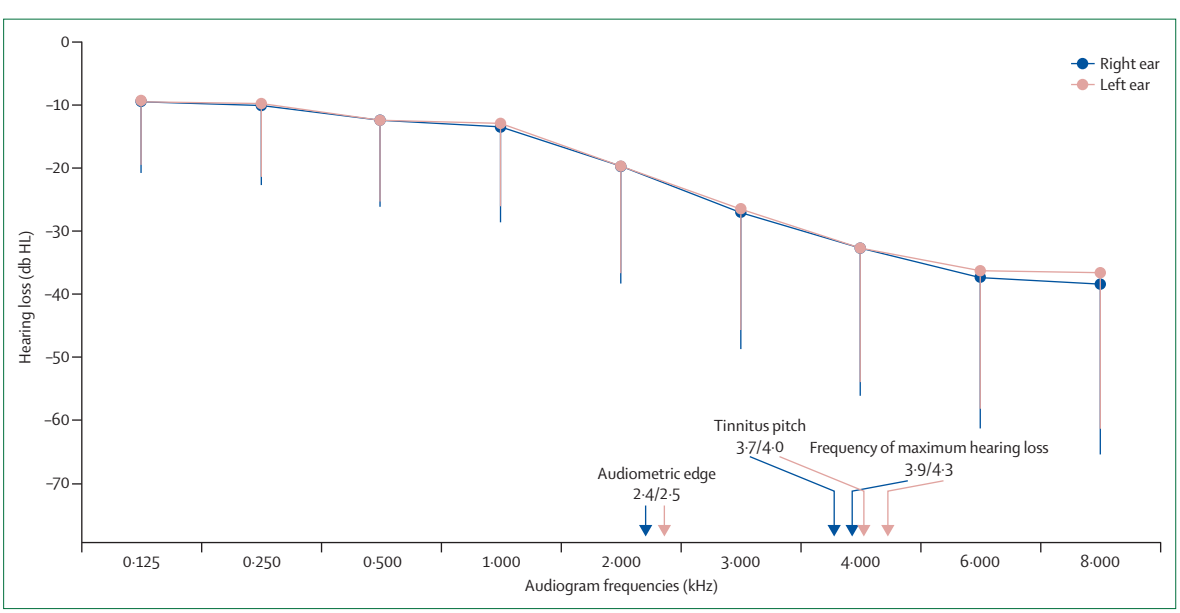

Figure 1: **Hearing loss in patients with tinnitus and the association with tinnitus pitch**
In a retrospective analysis of 286 patients with unilateral (n=117) and bilateral (n=169) tinnitus, the average audiogram in the patients with tinnitus showed hearing loss, particularly in the high frequency range. The tinnitus pitch was in the same range as the maximum hearing loss (averaged data for left-sided and right-sided tinnitus ears), suggesting that tinnitus is a fill-in phenomenon, compensating for hearing loss. Error bars indicate standard deviation. Reproduced from Schecklmann and colleagues,[26] with permission.

These neuroplastic processes can be explained by mechanisms of homoeostatic plasticity that affect neuronal activity of the auditory system at several levels along the auditory pathway to compensate for the reduced input.[35–38] At a cortical level, specific changes have been described with reduced inhibition specifically in the deafferented area,[37] and the extension of the edge region (which still receives input) into the deafferented cortical regions. Whether these distortions of the tonotopic map are the cause of tinnitus[39] or are a consequence of compensatory mechanisms is debated.[37,40] These functional changes in central auditory pathways are mediated by GABAergic, glycinergic, and glutamatergic neurotransmission.[37,41,42]

On the basis of magnetoencephalographic and electroencephalographic studies to investigate spontaneous brain activity associated with tinnitus, researchers have proposed that tinnitus is associated with γ-band activity in the auditory cortex, analogous to γ-band activity in normal auditory processing.[32,43] The emergence of γ-band activity could be enabled by the absence of inhibitory function in the auditory cortex, which in turn is shown by reduced α-band activity.[44,45]

Importantly, tinnitus-related activity changes in the CNS are not restricted to auditory pathways;[46] they can be conceived as alterations of a network involving both auditory and non-auditory structures.[27,47,48] The involvement of non-auditory brain areas could be explained by the idea that conscious auditory perception needs auditory cortex activation embedded in the coactivation of consciousness-supporting networks[49] such as the salience network comprising the anterior insula, anterior cingulate, and thalamus.[50] Moreover, pathophysiological models of tinnitus have to account for the affective component of tinnitus, which can be pronounced to different extents.[51,52] By comparison of patients with tinnitus with high and low distress, differences in neuronal activity were identified in a network of the anterior cingulate cortex, the anterior insula, and the amygdala.[48,53,54] This non-specific distress network is similarly activated in chronic pain or somatoform disorders.[27] As with chronic pain syndromes, memory mechanisms could have a role in the persistence of the phantom percept, and in the reinforcement of the associated distress.[27] In accordance with this idea, hippocampal involvement has been documented in animal models of tinnitus[55,56] and by neuroimaging in patients with tinnitus.[57] An important mutual interaction presumably exists between the different involved networks that might be relevant for the maintenance of tinnitus, even after disappearance of the initial trigger. In this context, investigators have suggested that salience-related brain circuits in the subgenual cingulate cortex or nucleus accumbens area are relevant for maintenance of tinnitus by exerting a direct effect on auditory pathways via the reticular thalamic nucleus.[58,59] Results of

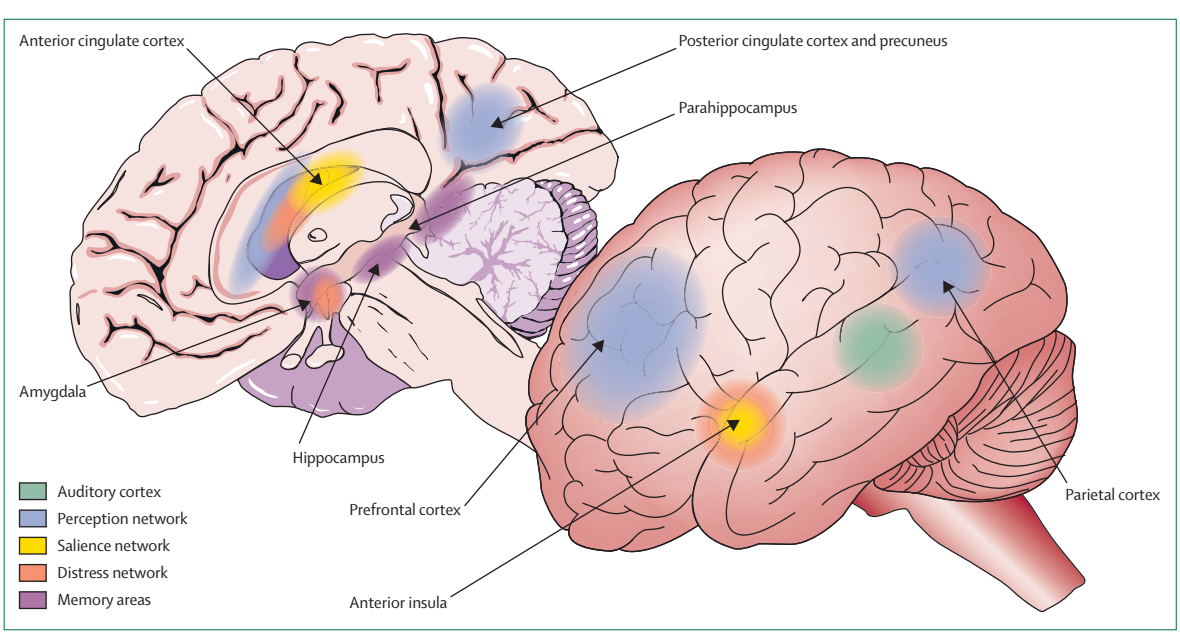

Figure 2: **Brain networks involved in phantom perception**
Increased activity in the auditory cortex (green) as a consequence of auditory deprivation is necessary, but not sufficient, for tinnitus perception. The patient becomes conscious of the stimulus if auditory activity is connected to a larger coactivated awareness network involving the subgenual and dorsal anterior cingulate cortices, posterior cingulate cortex, precuneus, parietal cortex, and prefrontal cortex (blue). Salience to the phantom percept is shown by activation of dorsal anterior cingulated cortex and anterior insula (yellow). Tinnitus annoyance is shown by coactivation of a non-specific distress network consisting of the anterior cingulate cortex (subgenual and dorsal anterior cortical cortices), anterior insula, and amygdala. Memory mechanisms involving the parahippocampal area, amygdala, and hippocampus have a role in the persistence of the phantom percept. Modified from De Ridder and colleagues,[27] by permission of the National Academy of Sciences, USA.

resting-state magnetoencephalographic[47] and electroencephalographic[60] studies have shown that tinnitus-related spontaneous activity and functional connectivity change over time. Compelling evidence exists for a dynamically changing widespread tinnitus brain network that includes sensory auditory areas and cortical regions involved in perceptual, emotional, memory, attentional, and salience functions (figure 2).[27]

Animal models

Jastreboff and colleagues[16] developed the first behavioural animal model of tinnitus in 1988. Rats were allowed to lick for water only when a sound was present in their cage. When the sound was turned off, a foot shock was administered to condition the rats to suppress licking during quiet intervals. In the testing phase the foot shocks were switched off. After induction of tinnitus in the rats by use of salicylate, they began to lick during silent intervals whereas control animals suppressed their licking. The investigators concluded that salicylate-treated rats had tinnitus and therefore could not detect silent episodes.[15] The lick–suppression paradigm has also been used to test for noise-induced tinnitus in hamsters 5 days after one ear was exposed to a 124 or 127 dB tone.[61] The hamsters all developed similar degrees of hearing loss, but not all developed tinnitus, paralleling what occurs in human beings. Research has provided a first hint as to why some animals develop tinnitus and others not.

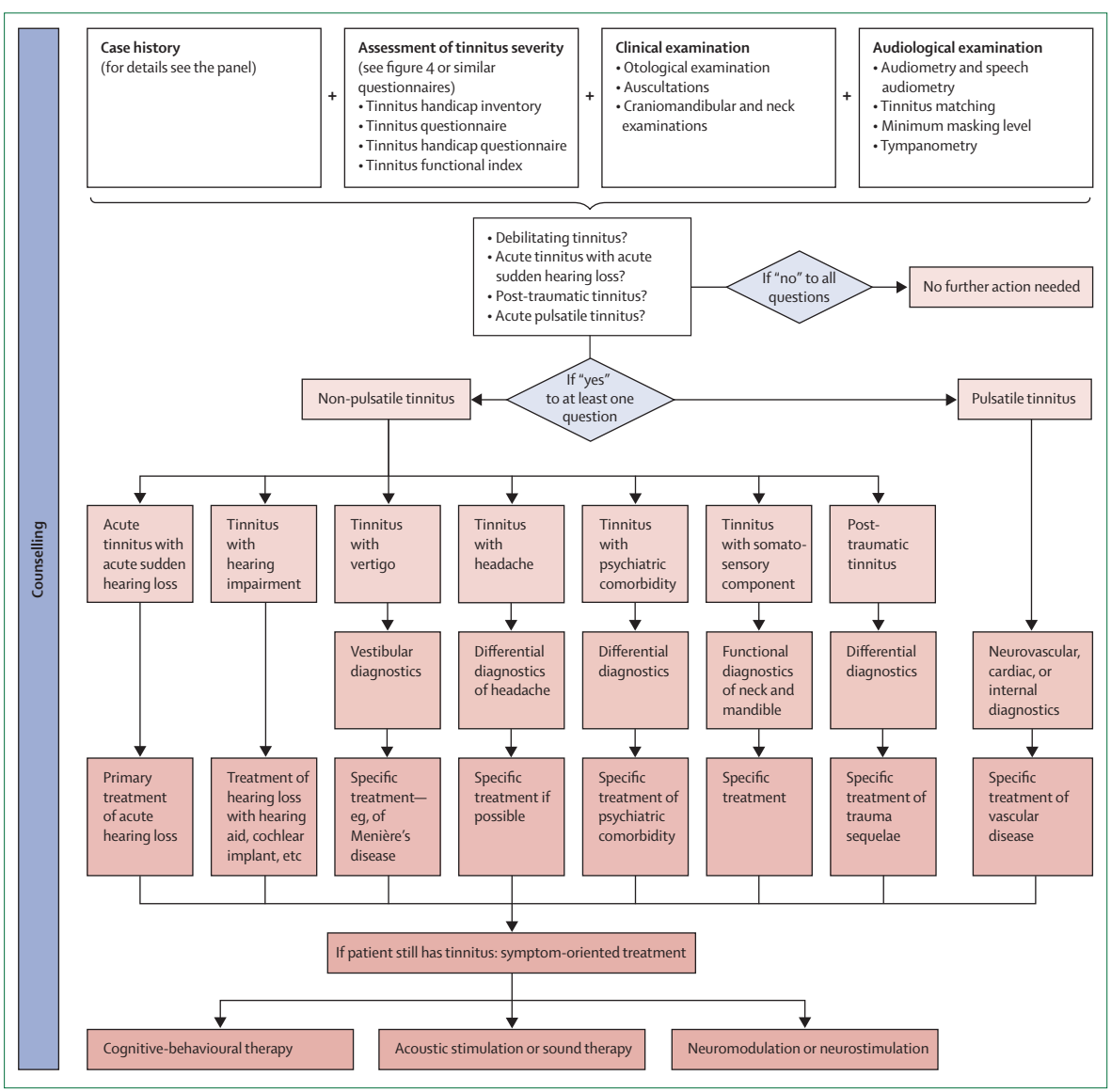

Figure 3: **Algorithm for diagnostic and therapeutic management of patients with tinnitus**
Basic diagnostic assessment should be done for all patients with tinnitus; further diagnostic and therapeutic steps are necessary only under specific conditions. All procedures should be accompanied by empathetic and insightful counselling. Modified from the Tinnitus Research initiative website, with permission.

For the **Tinnitus Research initiative website** see http:www.tinnitusresearch.org/en/projects/flowchart_en.php

Electrophysiological measurements indicate that high baseline activity together with highly functional inhibitory mechanisms in the auditory system could prevent the development of tinnitus in Mongolian gerbils.[62]

Several other behavioural techniques for the assessment of tinnitus have been developed,[63–65] but in all the animal has to be trained before tinnitus induction. The gap–startle reflex is a new method for assessment of tinnitus that does not need any training.[66] The behavioural response is a rapid body movement triggered by a brief, high-intensity noise and quantified by a sensor in the cage floor. The amplitude of the startle response can be suppressed by a warning signal that precedes the startle stimulus (pre-pulse inhibition). In the gap–startle paradigm, the warning signal is typically a 50 ms silent gap embedded in a continuous narrow band low-level noise 50 ms before the onset of the startle stimulus. The gap stimulus normally suppresses the magnitude of the startle response by at least 50–65%; this response did not occur in unilaterally noise-exposed rats, in which gap pre-pulse inhibition was greatly reduced or absent with the background noise centred at 10 kHz. On the basis of these results, the investigators concluded that the rats had tinnitus at 10 kHz, with the explanation that the internally generated tinnitus had filled the silent gap, thereby reducing pre-pulse inhibition.

Although these models provide an important opportunity to gain insight into the neuronal mechanisms of tinnitus and have shown some promise in testing of new treatment approaches,[67] they have important limitations, and which aspects of tinnitus in human beings are truly reflected by existing animal models is unclear.[68] Whether the mainly subcortically mediated behavioural responses immediately after tinnitus induction also indicate the conscious perception of tinnitus, its emotional aspects, and the transition from acute into chronic tinnitus is unknown. No animal model of tinnitus-related distress exists.

Panel: **Relevant items in the case histories of patients with tinnitus**

Background
- Age and sex
- Family history of tinnitus (parent, sibling, children)

Tinnitus history
- Duration
- Initial onset: gradual or abrupt? Associated events? Hearing change, acoustic trauma, otitis media, head trauma, whiplash, dental treatment, stress, other?
- Pattern: pulsatile? Intermittent or constant? Fluctuant or non-fluctuant? Other?
- Site: right ear? Left ear? Both ears (symmetrical)? Inside head?
- Loudness: scale 1–100. At worst and at best?
- Quality of the sound: pure tone or noise? Uncertain or polyphonic?
- Pitch: very high, high, medium, low?
- Proportion of awake time aware of tinnitus
- Proportion of awake time annoyed by tinnitus
- Previous tinnitus treatments (no, some, or many)

Modifying influences
- Natural masking? Music, everyday sounds, other sounds?
- Aggravated by loud noise?
- Altered by head and neck movement or touching of head or upper limbs?
- Effect of nocturnal sleep and daytime nap on tinnitus?
- Effect of stress?
- Effect of medications?

Related conditions
- Hearing impairment?
- Hearing aids (no, left ear, right ear, or both ears; effect on tinnitus)?
- Noise annoyance or intolerance? Noise-induced pain? Hyperacusis?
- Vertigo or dizziness?
- Temporomandibular disorder?
- Neck pain?
- Other pain syndromes?
- Under treatment for psychiatric disorder?

Modified from Langguth and colleagues.[69]

Diagnosis

Tinnitus can be a symptom of various underlying pathologies and be accompanied by many different comorbidities. Therefore, an integrated multidisciplinary approach is needed for comprehensive tinnitus diagnosis. Tinnitus can be the first sign of potentially life-threatening diseases such as carotid stenosis or vestibular schwannoma. Furthermore, rarely, undiagnosed and untreated tinnitus alone might become life-threatening if accompanied by severe depression with suicidal tendencies. Differential diagnosis of tinnitus should also focus on specific subgroups of tinnitus with defined causes that can benefit from specific treatments, such as ear wax removal in the case of obstruction of the ear canal, cochlear implants in unilateral deafness, microvascular decompression in tinnitus resulting from a microvascular conflict, and carbamazepine in typewriter tinnitus (tinnitus that sounds like a typewriter and is caused by vascular compression of the auditory nerve).

A stepwise decision-tree approach for clinical tinnitus management could be used (figure 3). Basic diagnostic steps are recommended for all patients and should include a detailed case history (panel), assessment of tinnitus severity (figure 4), clinical ear examination, and audiological measurement of tinnitus and hearing function.

For many patients these first diagnostic steps are sufficient for diagnosis, and counselling is sufficient for treatment. Further diagnostic steps are advised if the

findings of basic diagnostics indicate acute tinnitus, a potentially dangerous underlying condition (eg, carotid dissection), a possible causal treatment option, or relevant subjective impairment. Immediate action is necessary in tinnitus with sudden, acute hearing loss; in acute post-traumatic tinnitus; and in cases with concomitant suicidal tendencies.

The next step in the hierarchical diagnostic algorithm is differentiation between pulsatile and non-pulsatile tinnitus. In pulsatile tinnitus, the sound perception is heartbeat-synchronous and neurovascular examination is necessary. Diseases such as arteriovenous malformation, sinus venous thrombosis, benign intracranial hypertension, and high jugular bulb could be causes of pulsatile tinnitus. Non-pulsatile tinnitus is much more common than pulsatile tinnitus and should be differentiated according to duration, concomitant symptoms, and causal factors. In acute tinnitus accompanied by sudden hearing loss, diagnostic and therapeutic procedures will focus on the acute hearing loss and should not be postponed.

Paroxysmal tinnitus can be a symptom of auditory nerve compression, superior canal dehiscence syndrome, Ménière's disease, palatal myoclonus, migraine, or epilepsy. For differential diagnosis, MRI, auditory evoked potentials, vestibular tests, and electroencephalography could be indicated.

Constant non-pulsatile tinnitus can be accompanied by conductive or sensorineural hearing loss. Conductive hearing loss can be caused by otosclerosis, different forms of otitis, or eustachian tube dysfunction. In sensorineural hearing loss, further diagnostic procedures are indicated to identify the exact cause, including MRI and otoacoustic emissions for assessment of outer hair cell function. Tinnitus occurring together with vertigo is indicative of pathological abnormalities, such as Ménière's disease, superior canal dehiscence, or damage to the vestibulocochlear system, and needs detailed assessment of vestibular function.

If tinnitus occurs together with headache, space-occupying lesions, benign intracranial hypertension, disorders of CSF circulation, and craniocervical anomalies should be excluded by MRI. In cases of lateralised headache together with tinnitus on the same side and with a similar timecourse, trigemino-autonomal headache syndromes should be considered and, if confirmed, specifically treated.

Co-occurring psychiatric disorders, such as depression, anxiety, and insomnia, should also be investigated and specifically treated if present, because they play a major part in tinnitus-related impairment of quality of life. Hyperacusis and phonophobia frequently occur together with tinnitus and are sometimes indicative of an anxiety disorder. Immediate referral to a psychiatrist is necessary when a patient reports acute suicidal ideation.

When tinnitus is associated with neck or temporomandibular dysfunction or pain, these systems should be examined in detail by experienced dentists and physiotherapists.

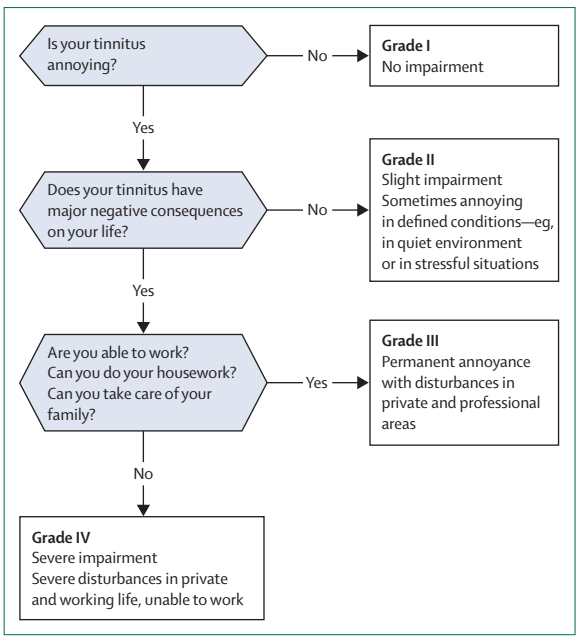

Figure 4: **Assessment of tinnitus severity**
Modified and translated from Biesinger and colleagues.[70]

Specific diagnostic tests are advised if tinnitus begins or worsens within 3 months of a traumatic event. Traumatic events can cause tinnitus in different ways. The indication for further diagnostic procedures depends on the trauma mechanism; noise, ear, head, neck, or emotional trauma, or a combination thereof (eg, in blast injuries) should be considered. In cases of post-traumatic pulsatile tinnitus, immediate diagnostic investigations for vascular pathological changes (especially carotid dissection) is mandatory.

Clinical management

Treatments for management of tinnitus in addition to specific treatment of underlying or co-occuring abnormal changes include counselling, cognitive behavioural therapy,[18,71] sound therapy,[72] hearing aids,[73] cochlear implants,[74] pharmacotherapy,[75] and brain stimulation.[76,77]

Evidence levels for most treatment strategies are low,[78] which is at least partly due to the heterogeneity of tinnitus, the difficulties in the assessment of tinnitus, substantial placebo effects, and low methodological quality of many treatment trials.[79] The need for consistency in assessment and outcome measurement is increasingly recognised as a determining factor in comparisons of treatment effectiveness.[15,69,72]

Psychological treatments

Counselling and psychoeducation

In most cases tinnitus cannot be cured, but some methods can help achieve habituation to the phantom sound.

To help people cope with tinnitus, psychoeducation—typically called counselling in the context of tinnitus treatment—is an essential component of all management options and could be deemed sufficient treatment in many cases.

Counselling comprises provision of information, advice, and empowerment of patients with tinnitus to help achieve habituation to the perception of the phantom sound, and to better cope with its potential consequences, such as emotional distress, sleep difficulties, loss of concentration, attention problems, and disruption to their personal, occupational, and social lives. By providing information, counselling aims to help individuals to understand their tinnitus, to demystify the condition, and to correct false beliefs. Finally, counselling is important to ensure compliance with treatment strategies by providing the necessary information about realistic goals of the different treatment interventions. Counselling is an essential part of the management of every patient with tinnitus, but controlled studies to estimate its efficacy are not available and are difficult to do.

Tinnitus retraining therapy

Tinnitus retraining therapy is a specific combination of counselling and sound therapy, which is founded on the assumption that the neurophysiological correlate of tinnitus is abnormal activity and connectivity of auditory and non-auditory central nervous circuits.[80] The aim of tinnitus retraining therapy is to achieve habituation by teaching or counselling for reclassification of the tinnitus signal to the category of neutral stimuli, and sound therapy to reduce the strength of the tinnitus signal. Whereas some studies suggest beneficial effects,[81,82] a Cochrane meta-analysis[83] stated that because of the absence of high-quality randomised clinical trials, no final conclusions about the efficacy of tinnitus retraining therapy can be drawn.

Cognitive-behavioural therapy

Cognitive-behavioural interventions are the best investigated psychotherapeutic strategies for coping with tinnitus. Cognitive-behavioural therapy aims to reduce the tinnitus-related handicap by altering maladaptive cognitive, emotional, and behavioural responses to tinnitus via cognitive restructuring and behavioural modification. The main components of cognitive-behavioural therapy include psychoeducation, relaxation training, mindfulness-based training, attention-control techniques, imagery training, and exposure to difficult situations, which are used to modify maladaptive behaviour. Results of a meta-analysis in which eight controlled trials involving 468 participants were assessed showed clear evidence for an improvement in quality of life and reduction of depression scores after therapy, when cognitive-behavioural therapy was compared with no treatment or another intervention, even if cognitive-behavioural therapy did not reduce tinnitus volume.[18] In a large randomised clinical trial, a multidisciplinary stepped-care approach involving counselling and elements of cognitive-behavioural therapy and tinnitus retraining therapy showed significant benefit in tinnitus severity, tinnitus impairment, and health-related quality of life compared with usual treatment.[17] There are no long-term follow-up data from controlled trials.[18]

Auditory stimulation

Sound therapy

Both environmental and custom sound generators are used in the treatment of tinnitus. Environmental sound generators are small devices that play sounds such as sea waves, creeks, waterfalls, rain, or white noise, which are intended to be relaxing and to reduce the perception of the tinnitus sound. The principle of sound generation is that the masking sound should be perceived as less disturbing than the tinnitus sound. Custom sound generators look like regular hearing aids and are worn behind the ear. They generally produce a wide band sound, the frequency composition and loudness of which can be adjusted to either partially or completely mask the tinnitus. Hearing aids with integrated sound generators are also available. Even though sound stimulation is commonly used, the evidence for its efficacy based on controlled studies is insufficient.[72,78]

Hearing aids

Hearing aids are widely used by patients with tinnitus with hearing loss (even when mild or unilateral) to compensate for the absence of auditory input in the impaired frequency range. However, amplification of sound by hearing aids is limited in the high frequency range and cannot restore auditory input in cases of complete inner hair cell loss. Results of observational studies showed a benefit of hearing aids only in patients with tinnitus at a frequency less than 6 kHz and thus in the amplification range of the hearing aids.[73,84] Evidence from controlled trials for the efficacy of hearing aids on tinnitus is still scarce.[78]

Cochlear implants

In patients with bilateral profound sensorineural hearing loss and tinnitus, a substantial suppression of tinnitus has been reported after hearing was restored by cochlear implant.[85] Cochlear implants are also beneficial in patients with unilateral profound deafness with concomitant ipsilateral incapacitating tinnitus.[74] Thus, there is increasing evidence that cochlear implants offer substantial long-term tinnitus suppression in patients with severe sensorineural hearing loss by restoration of input to the central auditory system.

Individualised sound stimulation

Three main strategies have been used in individualised sound stimulation. One approach is based on the notion that the tinnitus spectrum fills in the areas of hearing

loss,[86] and that an enriched acoustic environment that compensates for the hearing loss can remove the neural correlates of tinnitus in animals.[87] Auditory stimulation consisting of music with an individually adapted frequency spectrum to compensate for the individual hearing loss is combined with counselling in a structured rehabilitation programme in the Neuromonics Tinnitus Treatment. In initial clinical studies this treatment seems to be more effective than the combination of counselling with broad-band noise stimulation.[88] However, in a controlled study[89] music individually tailored to compensate for hearing loss did not provide any benefit, whereas overcompensation of the hearing loss worsened the tinnitus. A second individualised auditory stimulation strategy uses music stimulation with the frequency range around the tinnitus removed from the frequency spectrum.[90] A pilot study in a highly selected sample of patients with tonal tinnitus showed a small but significant reduction in tinnitus volume and auditory-evoked cortical activity after 1 year of daily stimulation with tailor-made notched music compared with a control condition.[90] A third approach has been proposed in which individualised auditory stimuli are presented as short tones above and below the tinnitus frequency as a new approach to renormalise tinnitus-related neuronal synchrony. A pilot study showed significant reductions of tinnitus volume and annoyance, and normalisation of abnormal oscillatory activity by this so-called coordinated reset stimulation compared with a control group.[91] All these approaches still have to be regarded as experimental until the preliminary results are confirmed in large randomised controlled trials.

Auditory perceptual training

Several auditory training procedures have been developed with the aim to renormalise tinnitus-related neuroplastic changes. Training procedures include frequency discrimination training, intensity discrimination training, and auditory object identification and localisation.[92] All of these training procedures have been done within and outside the tinnitus frequency region, and as active training procedures necessitating behavioural and passive responses with background sounds. Although results of these studies suggest some promise for auditory training in tinnitus treatment, final conclusions about the efficacy of auditory perceptual training are not possible because of the low methodological quality of most studies.[93]

Pharmacological treatments

Various pharmacological interventions have been investigated for the treatment of tinnitus. However, no pharmacological treatment can provide a replicable long-term reduction of tinnitus in excess of placebo effects. No drug has been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for the treatment of tinnitus.[94]

The local anaesthetic, voltage-gated sodium channel blocker lidocaine leads to a transient suppression of tinnitus in a substantial proportion of patients after intravenous application,[95] providing the proof of principle that tinnitus can be pharmacologically targeted. However, the effect of intravenous lidocaine is strictly transient, and intravenous administration of the drug has a side-effect risk that precludes it from being a long-term treatment. Many antidepressants have been studied for the treatment of tinnitus.[94,96] Whereas these compounds seem to have no direct effect on the tinnitus,[96] their use for patients with tinnitus with comorbid depressive or anxiety disorders is recommended when clinically indicated.[94] The anti-convulsant carbamazepine has been used to treat tinnitus for many years. However, controlled studies have not shown additional benefits compared with placebo.[97] Carbamazepine might have a beneficial effect at least in rare subgroups of patients with typewriter tinnitus.[98] Neither gabapentin nor lamotrigine have substantial positive effects,[97] whereas treatment with benzodiazepines has shown some beneficial effect on tinnitus distress.[99] However, in view of the adverse effects of regular benzodiazepine intake, their routine use cannot be recommended for the treatment of tinnitus.

Brain stimulation

Therapeutic brain stimulation enables focal modulation of neuronal activity and has been investigated for the normalisation of tinnitus-related abnormal neuronal activity.

Repetitive transcranial magnetic stimulation uses the rhythmic application of brief magnetic pulses delivered by a coil placed on the scalp to modulate cortical activity. Results of some, but not all, small randomised trials have shown a reduction of tinnitus severity after repetitive transcranial magnetic stimulation treatment.[77,100] However, the effect sizes are small, the interindividual variability high, and the duration of treatment effects often short, providing insufficient support for use of repetitive transcranial magnetic stimulation as a long-term tinnitus treatment in its present form.[77,100]

Epidural stimulation of the secondary auditory cortex by implanted electrodes can suppress tinnitus in a subset of patients,[76] and promising pilot data also exist that suggest an effect of deep-brain stimulation of the caudate nucleus on tinnitus.[59]

In animal models the behavioural and neurophysiological signs of acute tinnitus after noise trauma can be completely reversed by vagus nerve stimulation with paired acoustic stimulation.[67]

Conclusions and future directions

Tinnitus is a frequent and heterogeneous disorder, resulting in most cases from neuronal changes occurring in the CNS as a reaction to auditory deprivation.

A multidisciplinary approach is needed for comprehensive diagnostic assessment and therapeutic

Search strategy and selection criteria

We searched Medline to identify articles of interest. We searched for studies in English including basic science reports, neuroimaging and electrophysiological studies, randomised controlled trials, prospective and retrospective cohort studies, systematic reviews, and case reports, published between January, 1985, and January, 2013. We used the following search terms: "tinnitus AND epidemiology", "tinnitus AND pathophysiology", "tinnitus AND mechanisms", "tinnitus AND brain", "tinnitus AND animal model", "tinnitus AND diagnosis", and "tinnitus AND treatment". We reviewed the outcome of the search and included selected articles. We also searched the reference lists of articles chosen and thereby identified additional relevant references.

management. Specific treatment options exist for some subforms of tinnitus. Psychological treatment alone or in combination with sound therapy can efficiently reduce tinnitus. Moreover, the quality of life of patients with tinnitus can be improved by treatment of comorbidities such as hearing impairment, depression, anxiety, and insomnia. New therapeutic approaches targeting the neuronal correlates of tinnitus are being developed.

The management of chronic tinnitus is challenging despite the availability of various types of treatment, but therapeutic nihilism is not justified. Animal research and neuroimaging techniques have improved understanding of the pathophysiological mechanisms of the different forms of tinnitus. Alterations in several auditory and non-auditory brain networks have been identified, representing the various clinical aspects of tinnitus and the interactions among them. This knowledge has aided identification of potential therapeutic targets and innovative treatment approaches, of which many have already shown promising data in proof-of-concept studies. Further development of most of these new approaches is mandatory before they can be regarded as established treatments. Nevertheless, the increasing understanding of pathophysiological underpinnings and number of new treatments provide hope that better treatment options will soon become available.

Contributors

All authors contributed to the literature search. BL drafted the Review and all authors revised it and approved the final version.

Conflicts of interest

BL received honoraria and speakers' fee from Advanced Neuro Modulation, AstraZeneca, Autifony, Lundbeck, Merz, Magventure, Novartis, Pfizer, and Servier; research funding from the Tinnitus Research Initiative, the German Research Foundation, the German Bundesministerium für Bildung und Forschung, the American Tinnitus Association, AstraZeneca, and Cerbomed; funding for equipment from Magventure; and travel and accommodation payments from Lilly, Servier, and Pfizer. PMK received research funding from the American Tinnitus Association and Cerbomed, and travel and accommodation payments from Servier, Pfizer, Astra Zeneca, Lilly, Bristol-Myers Squibb, and Lundbeck. TK received research funding from the Tinnitus Research Initiative and the Zurich Foundation for Hearing. DDR has received speaker's fees, travel and accommodation payments, and research funding from Saint Jude Medical, and has been funded by the Tinnitus Research Initiative.

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