Tinnitus

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Tinnitus is a common medical symptom that can be debilitating. Risk factors include hearing loss, ototoxic medication, head injury, and depression. At presentation, the possibilities of otological disease, anxiety, and depression should be considered. No effective drug treatments are available, although much research is underway into mechanisms and possible treatments. Surgical intervention for any otological pathology associated with tinnitus might be effective for that condition, but the tinnitus can persist. Available treatments include hearing aids when hearing loss is identified (even mild or unilateral), wide-band sound therapy, and counselling. Cognitive behavioural therapy (CBT) is indicated for some patients, but availability of tinnitus-specific CBT in the UK is poor. The evidence base is strongest for a combination of sound therapy and CBT-based counselling, although clinical trials are constrained by the heterogeneity of patients with tinnitus.

Introduction

Although much progress has been made, tinnitus remains a scientific and clinical enigma. The condition is very common, and, although many patients are not unduly troubled, others find the disorder life-changing. In this Seminar we outline current knowledge of tinnitus, and critically assess established and emerging treatment approaches.

Derived from the Latin verb *tinnire* (to ring), the term tinnitus describes the conscious perception of an auditory sensation in the absence of a corresponding external stimulus. Tinnitus can be subjective, when the experience is of the individual alone, or, less commonly, objective, when an observer can hear the tinnitus. The sensation is generally of an elementary nature—descriptions of hissing, sizzling, and ringing are common—although, in some cases, more complex sounds such as voices or music are perceived. When voices or music, or both, are heard as a form of tinnitus, the perceptions are indistinct and convey no meaning, in contrast with the auditory hallucinations that can occur with psychotic illness. Tinnitus can sometimes be a rhythmical or pulsatile sound. Pulsatile tinnitus[1] can be synchronous with the heartbeat, in which case a vascular origin is likely, or asynchronous, in which case myoclonus of middle-ear or palatal muscles is probable.[2] Tinnitus can be constant or intermittent, and many patients experience more than one sound. It can be localised to one or both ears, or centrally within the head, although some patients describe an external point of origin. The onset of tinnitus can be abrupt, but it is insidious in most cases. The perceived intensity can vary; for some people, exacerbation alongside stress arousal is clear. The heterogeneity of tinnitus experience is substantial and has hampered both basic science and treatment research.

Search strategy and selection criteria

We searched Medline, Embase, and the Cochrane database for relevant studies, including systematic reviews, randomised controlled trials, basic scientific reports, retrospective studies, prospective studies, cohort studies, and case reports published in any language between Jan 1, 1987, and Aug 31, 2012. We used the search terms "tinnitus" and "pulsatile tinnitus". We also searched the reference lists of articles identified by this search strategy and selected those that we deemed relevant. We mainly focused on publications from the past 5 years, but have included commonly referenced and highly regarded older publications.

Epidemiology

Prevalence studies of tinnitus have mostly been done in western Europe or the USA, and have methodological drawbacks, especially with production of an unambiguous definition of tinnitus and phrasing of appropriate epidemiological questions. Consequently, the scatter of prevalence estimates is wide, although most study results have shown rates of between 10% and 15% of the adult population. The largest and most scientifically reliable study was undertaken as part of the National Study of Hearing in England (n=48 313).[3] The results of the study showed a prevalence of 10·1% among adults, with the tinnitus described as moderately annoying by 2·8% of respondents, severely annoying by 1·6%, and at a level that severely affected ability to lead a normal life by 0·5%. Results from studies in Egypt,[4] Japan,[5] and Nigeria,[6] indicate tinnitus prevalence is broadly similar in these countries to in Europe and the USA.

The prevalence of troublesome tinnitus increases with age to 70 years; results of some studies show that it continues to increase thereafter, although others have shown it to diminish.[3] Prevalence in men and women is similar.[3] Prevalence in children is difficult to estimate, but results of available studies suggest that tinnitus experience is common, with figures similar to those in adults.[7] Children, however, seem less likely to be distressed by the perception.[7]

The table shows known risk factors for developing tinnitus and associated conditions. The main risk factor is hearing loss,[9] but this association is not simple or straightforward;[3] some people with troublesome tinnitus have audiometrically normal hearing and, conversely, many people with hearing loss do not report tinnitus. People who report high levels of both occupational and recreational noise exposure are more likely to have tinnitus.[9] Other factors such as obesity, smoking, alcohol

consumption, previous head injuries, history of arthritis, and hypertension have been suggested as possible risk factors,[3,9] and some results have suggested a small genetic predisposition.[10] Various drugs can trigger tinnitus, including salicylates, quinine, aminoglycoside antibiotics, and some of the antineoplastic agents, particularly the platinum-based drugs.[8] The condition can occur in association with several otological diseases, including otosclerosis, Ménière's disease, and vestibular schwannoma (acoustic neuroma). Tinnitus also has several comorbidities, particularly anxiety, depression,[11] and dysfunction of the temporomandibular joint.[12] Decreased sound tolerance (hyperacusis) is a common accompanying symptom—defined as an aversion to loud sounds, some degree of hyperacusis is noted in 40% of patients with tinnitus, and up to 86% of patients who report hyperacusis also report tinnitus.[13]

Several investigators have studied the localisation of tinnitus,[14] and the consensus is that it is perceived in both ears or centrally within the head in roughly half of patients. Among the remainder, tinnitus is more frequently left-sided than right. A few people perceive it as an external sound or have difficulty defining its location. The reason for left-sided preponderance is unknown and cannot be explained by asymmetric hearing loss.[15]

Incidence and longitudinal studies are scarce. In a study in Beaver Dam, WI, USA, for a cohort aged between 48 and 92 years, the prevalence of tinnitus at baseline was reported to be 8·2%; notably, the participants tended to show improvement rather than worsening of their tinnitus during the study.[16] The 5-year cumulative incidence of new cases of tinnitus was 5·7% and the 10-year figure was 12·7%.[16,17]

	Specific diseases or conditions
Otological, infectious	Otitis media, labyrinthitis, mastoiditis
Otological, neoplastic	Vestibular schwannoma, meningioma
Otological, labyrinthine	Sensorineural hearing loss, Ménière's disease, vestibular vertigo
Otological, other	Impacted cerumen, otosclerosis, presbyacusis, noise exposure
Neurological	Meningitis, migraine, multiple sclerosis, epilepsy
Traumatic	Head or neck injury, loss of consciousness
Orofacial	Temporomandibular joint disorder
Cardiovascular	Hypertension
Rheumatological	Rheumatoid arthritis
Immune-mediated	Systemic lupus erythematosus, systemic sclerosis
Endocrine and metabolic	Diabetes mellitus, hyperinsulinaemia, hypothyroidism, hormonal changes during pregnancy
Psychological	Anxiety, depression, emotional trauma
Ototoxic medications	Analgesics, antibiotics, antineoplastic drugs, corticosteroids, diuretics, immunosuppressive drugs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs[8]

***Table*: Known risk factors for developing tinnitus and conditions associated with tinnitus symptoms**

Pathophysiological mechanisms

Because otological conditions, especially high-frequency hearing loss, present one of the major risk factors for tinnitus, the auditory phantom sensations are often deemed to be a neuroplastic response to sensory deprivation.[18] Tinnitus is not simply a straightforward correlate of the imbalance of firing patterns across the tonotopic array of the impaired cochlea, because the sound percept can persist even when input from the ear is eradicated by cutting of the auditory nerve.[19] Although cochlear abnormalities could be the initial source of tinnitus, the subsequent cascade of neural changes in the central auditory system is more likely to maintain the condition. Much of what we know about tinnitus comes from studies of hearing loss in animals,[18,20] but many questions are unanswered and some people have questioned the validity of these animal models.[21] The current assumption is that the neural changes measured in the animal models of hearing loss are the neural correlates of the human clinical symptoms; however, this assumption has not yet been confirmed.[22]

An increased spontaneous firing rate of neurons in the central auditory system is one possibility for the neural substrate of tinnitus. Cochlear hearing loss reduces cochlear nerve activity, and this reduced activity within the affected peripheral auditory region downregulates inhibitory cortical processes. That downregulation leads to hyperexcitability within central auditory structures, including primary auditory cortex.[23] Whether increases in spontaneous firing rate are linked directly to the sensation of tinnitus is, however, unclear. Such changes take between hours and days to occur in the auditory structures, and this time course does not fit well to the perceived experience because tinnitus is often experienced immediately after noise exposure.[23]

Another possible mechanism is neural synchrony. Temporal synchrony in the firing pattern across several neurons in primary auditory cortex increases immediately after a noise-induced hearing loss, particularly for neurons representing the affected part of the tonotopic array.[23,24] Increased neural synchrony also tends to be spatially coincident with changes in the frequency tuning properties of the same affected neurons.[24] In normal-hearing animals, neurons selectively respond to characteristic frequencies, and progression of frequency tuning in bands across distinct auditory fields is orderly (tonotopicity). Hearing loss results in disturbed tonotopicity in primary auditory cortex such that neurons with characteristic frequencies within the deprived region adopt the tuning properties of their less-affected neighbours, at the edge of the hearing loss.[25] Nevertheless, one major psychoacoustic finding is inconsistent with the claim that expansion of the tonotopic map at the audiometric edge underpins the tinnitus sensation—the dominant tinnitus pitch does not generally fall at the edge of the hearing loss.[26,27] Instead, it falls somewhere within the region of hearing loss, consistent with neural temporal dynamics being the neural correlate of tinnitus.

Map reorganisation in the auditory modality after hearing loss has also been compared to map

reorganisation in the somatosensory modality after amputation.[28,29] A proposed model suggests that the tinnitus sensation might reach conscious awareness only when aberrant neuronal activity in the primary sensory cortex is connected to a broader cortical network involving frontal, parietal, and limbic brain regions.[29] Human neuroimaging evidence supports this notion by implicating not only the central auditory system, but also prefrontal and emotional centres in tinnitus.[22,30]

The heterogeneity of tinnitus in aetiology, pathophysiology, and clinical characteristics probably exacerbates the variable population response to tinnitus management.[31,32] An effective classification system informed by the pathophysiological mechanisms underlying individual tinnitus symptoms would be a ground-breaking step towards personalised rehabilitation.[32] Further basic research addressing the pathophysiology of tinnitus in animals and people therefore has an important clinical rationale.

Investigation and diagnosis

No objective test is available for most tinnitus cases, and diagnosis is made on the basis of medical history and an assessment of the effect on the patient and his or her family. Important questions include the location and character of the tinnitus, particularly whether it has a rhythmical or pulsatile component. Pulsatile tinnitus can in rare cases be objectively detected by auscultation. Important questions about tinnitus consequences include its effect on sleep and concentration. Several health questionnaires are available that assess the effects of tinnitus, of which the tinnitus handicap inventory[33] is the most commonly used in the UK,[34] although the tinnitus functional index[35] might replace it. Questionnaires to assess associated symptoms such as hyperacusis[36] and psychological distress[37] can also be helpful. Pure-tone audiometry (or age-appropriate equivalents for children) should be done, and, because many patients complain of a blocked sensation in the ears, tympanometry can be useful. Tests to match the pitch and loudness of the tinnitus are difficult, relate poorly to the patient's distress,[38] and offer little to the subsequent management plan. Patients who have asymmetric tinnitus, asymmetric hearing on pure-tone audiometry, or other associated neurological symptoms or signs need further investigation, and generally the chosen modality is MRI. Patients with heartbeat-synchronous pulsatile tinnitus need more detailed investigation by a complex algorithm that could include ultrasonography, CT, MRI, CT angiography, MR angiography, or conventional angiography.

Standard treatments

After treatable pathology associated with tinnitus has been excluded, standard care is to give an explanation of the situation (including both causation and the development of associated distress), sound therapy (either hearing aids or sound generators), and, where needed, intervention to reduce the distress (relaxation therapy or cognitive behavioural therapy [CBT] or both). In England, the Department of Health has published a good practice guide for tinnitus care,[39] which describes a stepped-care approach, with the primary-care physician offering initial reassurance and diagnosis of simple remediable causes, such as cerumen or infection, and referral to secondary care when tinnitus is severe or associated with hearing loss. At this stage, in-depth counselling and sound therapy can be undertaken. A tertiary level of care is reserved for intractable or severe tinnitus and patients with otological pathology.

The heterogeneity of the disorder and the methodological challenges of undertaking controlled trials on counselling-based therapy have meant that evidence for the efficacy of this approach is sparse. The few studies reported are generally poorly designed, and no standard outcome measure has been widely adopted.[32] The individual elements have been investigated, but again the evidence base is poor. In a systematic review, the efficacy of sound therapy approaches was inconclusive,[40] though for many clinicians the practice of fitting hearing aids for individuals with tinnitus associated with hearing loss is axiomatic.[41] The use of wideband sound therapy devices—initially used to cover the tinnitus completely, and hence called maskers—is similarly unsupported by evidence.[40] Relaxation therapy does benefit patients.[42] Formal CBT was shown to reduce tinnitus distress in systematic review and meta-analysis,[43,44] although these studies involved patients sufficiently distressed as to warrant referral to a psychologist, and therapy was undertaken by expert practitioners, which could limit applicability to a general clinic.[45]

A prescriptive treatment protocol for tinnitus called tinnitus retraining therapy (TRT)[46] includes counselling and sound-generator therapy. A systematic review showed the poor quality of research on TRT.[47] We identified one trial in this review, and that work suggested that TRT is more effective than masking.[48] A subsequent trial used TRT as a control for acceptance and commitment therapy,[49] which has developed from CBT. TRT had a small benefit in that study. The principle of TRT, which is to explain both ignition of tinnitus and development of distress, has been influential on tinnitus work internationally, but its formal use is not widespread.

A randomised controlled trial compared the benefits of the combination of counselling elements of CBT and TRT with standard care[50]—standard care being an ear, nose, and throat or audiology consultation and provision of a hearing aid or sound generator, or both, and input from a social worker. The specialised care was beneficial for quality of life and specific metrics of tinnitus distress and annoyance, irrespective of the initial severity of the tinnitus. The effect was thought to be due to reduction in the fear associated with tinnitus.

Emerging sound treatments

Several sound-based technological innovations have been commercially produced for tinnitus, with experimental

prototypes also being investigated.[51] The manufacturers claim that these devices not only mask perception of tinnitus, but also are effective through other ways. For some of these emerging sound treatments (eg, acoustic coordinated reset neuromodulation, serenade, and frequency discrimination training), the suggested target site of action is the central auditory system, with the sound individually tailored to the hearing loss and tinnitus characteristics to interrupt the maladaptive neuroplasticity driving the tinnitus sensation.[51,52] Other interventions use sound mostly as a therapeutic relaxant (eg, Widex Zen[53]), while the Neuromonics device is said to reduce emotional arousal, and target the effects of auditory deprivation through spectrally shaped sound.[54]

Typically, the commercial devices are recommended as part of a holistic audiological management programme that incorporates education and counselling. Such combined approaches complicate the process of extraction of evidence for or against the effectiveness and value of each sound treatment that is separate from any general psychological benefit of rehabilitation.[40] Few trial data are available, so we conclude that emerging sound treatments on their own are of unproven benefit to tinnitus symptom reduction.[51,55]

Complementary and alternative medicine

Many individuals with tinnitus use complementary and alternative medicine, though no method has reduced tinnitus volume or associated distress. Many such treatments induce relaxation, which could benefit an agitated person with tinnitus, but this benefit would be indirect. The general caveats of the interaction of some complementary or alternative treatments with prescribed medication apply, and a specific concern is that the practice of ear candling could cause ear and facial burns.[56]

Brain stimulation

On the basis of knowledge showing tinnitus-related abnormalities in distinct regions of the central auditory system, possibly linked to high spontaneous neuronal activity,[18,20,23] brain stimulation has been investigated as a way to decrease neuronal activity.

Repetitive transcranial magnetic stimulation uses non-invasive electromagnetic induction to generate weak electrical currents in the brain, thus reducing neural excitability. A systematic review assessed five trials that compared this technique with a control, all with non-navigated coil localisation.[57] The findings showed limited support for use of low-frequency transcranial magnetic stimulation to reduce tinnitus volume or improve quality of life. Each trial described the use of a different device that delivered different waveforms at different stimulation rates; interpretation of the findings is difficult, because the various stimulation protocols were differentially beneficial for tinnitus. No serious adverse effects were reported in any of the trials, but the long-term safety of this treatment is unknown.

In several studies patients with movement disorders and comorbid tinnitus who underwent deep brain stimulation for the movement disorder reported a reduction in tinnitus volume when the implant was switched on, without affecting hearing.[58,59] One study isolated the benefit to stimulation of area LC in the caudate nucleus.[59] This brain region is not part of the classic auditory pathway, so these preliminary observations warrant further investigation.

Drug treatments

No drugs are licensed in Europe or North America for treatment of spontaneous idiopathic tinnitus, although many have been tried. A notable exception is local anaesthetics: in 1935, Bárány noted that intravenous injection of procaine temporarily alleviated tinnitus in most patients.[60] Lidocaine[61] and bupivacaine[62] also have this effect. Subsequent work has shown that the alleviation occurs within the central auditory pathways of the brain,[63] although an additional cochlear effect cannot be excluded. However, intravenous injection of local anaesthetics carries too many risks for therapeutic use, and the alleviation has not been replicated with analogous but safer compounds,[64,65] or by other administration routes.[66]

Drugs from several broad categories have been tested for effect on tinnitus. Tricyclic antidepressants and selective serotonin-reuptake inhibitors are not effective at reducing tinnitus,[67] but they might have a role in management of any concomitant psychological distress. Favourable results have been reported from one study of the benzodiazepine alprazolam,[68] but the research quality was not sufficient for reliable conclusions to be drawn. A more robust study of the same drug showed no change in the majority of outcome measures.[69] Antispasmodic drugs[70] and drugs for neuropathic pain[71] are generally ineffective, although one trial showed a possible small effect of gabapentin in a subgroup of patients with tinnitus secondary to acoustic trauma.[72] Several anticonvulsant drugs have been tested, including amino-oxyacetic acid,[73] lamotrigine,[74] and carbamazepine,[75] without success. Glutamate is the main excitatory neurotransmitter in the auditory system; consequently, various antagonist drugs have been investigated. Studies of memantine,[76] flutirpine,[77] and neremexane[78] have not shown benefits in tinnitus treatment. Investigation of glutamate antagonists continues.

Drugs aimed at improving microcirculation in both the central and peripheral auditory systems have been assessed. Diuretics,[79] anticoagulants,[80] and vasodilators[81] have been tried without success. The drug betahistine, licensed in Europe but not the USA, is thought to help Ménière's disease by improving cochlear blood flow. However, no available robust evidence suggests that betahistine is effective in the tinnitus of Ménière's disease,[82] or supports its use in other types of tinnitus. Nevertheless, it continues to be widely prescribed.

Melatonin has been the subject of several trials, the results of which suggest it could help patients who have insomnia in association with tinnitus.[83]

Some researchers have suggested that increasing intake of various dietary components, particularly vitamin B, zinc, and magnesium, could help tinnitus. Existing evidence is of poor quality and contradictory, although magnesium and several other vitamins and minerals are being investigated as potential otoprotectants.

Laser treatment

Low-level or soft laser therapy is used in some types of chronic pain management, although the mode of action remains conjectural. On the basis of similarities between chronic pain and tinnitus, lasers have been promoted by manufacturers for use in tinnitus (though no specific mode of action is known), and several devices are commercially available. Although results of a few studies have suggested a benefit of laser therpay, most suggest that it is ineffective.[84]

Surgery for tinnitus

Surgery has a small but definite role in tinnitus management. Its place with regard to pulsatile tinnitus and that associated with specific conditions such as otosclerosis or Ménière's disease is beyond the scope of this Seminar. Initial theories of tinnitus pathogenesis focused very much on the ear; consequently, the working hypothesis was that ablation of the cochlea or section of the cochlear nerve would eradicate tinnitus, albeit at the expense of causing total deafness in the affected ear. Few studies of this treatment option have been done, and none that meet stringent scientific standards. The available data show tinnitus improvement in 45%[85] to 95% of patients,[86] but complete destruction of the hearing will always limit the applicability of this procedure.

The suggestion that some cases of tinnitus could be caused by blood vessels pressing against the auditory nerve arose from work on facial neuralgia. Surgery to decompress these neurovascular conflicts could therefore offer a resolution of the symptoms in these cases; however, the evidence so far is conflicting. Although some researchers have reported positive results,[87] these are based on small numbers of patients. This type of surgery is best thought of as a preliminary experimental technique.

Cochlear implantation is one type of tinnitus research in which good evidence supports the effect of the intervention.[88] More than 80% of patients with bilateral profound sensorineural hearing loss have tinnitus. Cochlear implantation improves or eliminates tinnitus in up to 86% of these patients, although 9% report worse postoperative tinnitus. Of patients who do not have tinnitus initially, up to 4% develop it after surgery. Cochlear implantation is also being investigated as treatment for patients with single-sided profound sensorineural hearing loss and normal or near-normal hearing in the other ear. Although this approach will probably be appropriate for only a tiny proportion of patients with tinnitus, initial reports suggest that it is very successful in this subgroup.[89]

Variations in clinical practice

The clear gaps in evidence-based practice mean that linkage of assessment and diagnosis to the most effective management strategies is difficult.[34,90] Therefore, although the epidemiology of tinnitus is broadly comparable across countries, international clinical practices differ (figure). For acute subjective tinnitus, pharmacological prescriptions are common, whereas for chronic subjective tinnitus, audiological and psychological approaches are more typical.[91] Patterns of tinnitus management are highly country-specific[91]—for example, pharmaceutical treatments are favoured over acoustic devices in Italy, but the reverse is true in the UK. Physical therapy is especially popular in France, Germany, and Italy.

Without a standard diagnostic algorithm or treatment pathway, the choice of treatment is largely up to individual clinical professionals, probably influenced by country-specific training routes and practices,[91] differences in expenditure in hearing services,[92] schemes for reimbursement from medical insurance,[93] local resource limitations,[94] and patients' preference.

The capacity for self-referral by patients and the corresponding point-of-entry into health care varies greatly between countries (figure) but primary care physicians and otolaryngology specialists have substantial roles in referral and management in most. Other specialties are involved to a greater or lesser extent; examples are audiology (UK and USA) and neurology (Germany, Italy, and Spain) (figure). In some countries—such as the UK, Scandinavia, the Netherlands, and the USA—audiology is

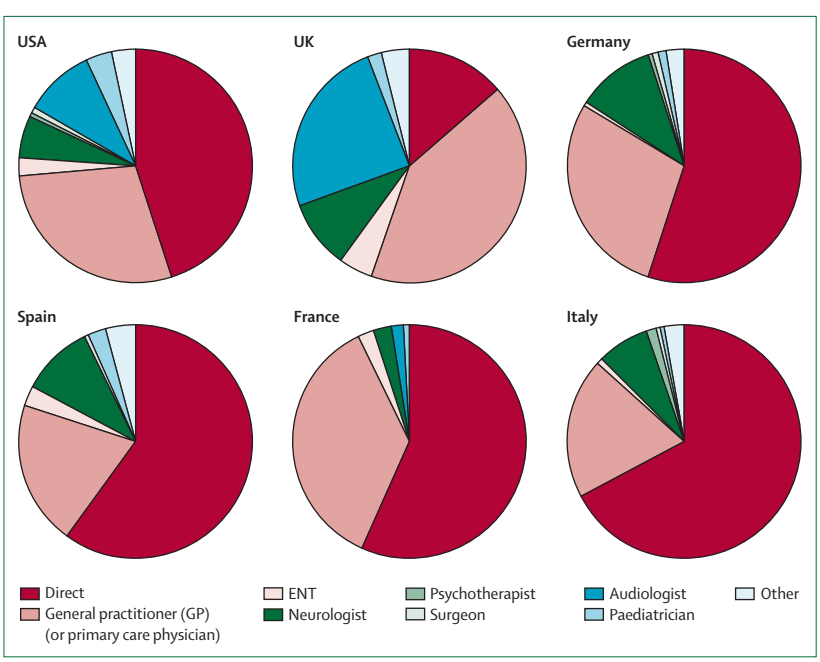

Figure: **The range of pathways for tinnitus referrals to otolaryngology (ENT) specialists**
Data taken from Hall.[91] Sizes of the segments in the chart represent the relative proportions of referrals from each specialty based on information about the last ten tinnitus patients seen by individual ENT consultants.

a recognised independent profession and practitioners provide assessment and rehabilitative health care for people with tinnitus and hearing problems.[94–96] Elsewhere in Europe, audiology, and hence tinnitus provision, is encompassed in a sub-specialty of otolaryngology (eg, in Germany[97]). Otolaryngology traditionally treats the physiological aspect of tinnitus, but audiology practice typically addresses the functional effect of the condition. Although many adults experience tinnitus-related distress sufficient to severely affect their quality of life,[3] availability of appropriate specialist psychological support varies geographically both within and between countries.[34,50]

Clinical trials in tinnitus

Many different management strategies are used in clinical practice, but individuals have highly variable responses and evidence for benefit in most cases has not yet been conclusively shown.[31,90] Although the need for effective management options for tinnitus is clear, methodological and reporting quality of clinical trials have been low. Consequently, with the exception of CBT,[43,44] evidence for the effectiveness of different treatment strategies is insufficient.[40,47,57,67,98] Investigators undertaking a UK-wide consultation of patients and clinicians made a priority list of ten unanswered questions (panel),[99,100] many of which could be addressed through high-quality randomised controlled trials.

Randomised trials are generally deemed to be the best experimental design for assessment of the efficacy of a clinical intervention. Dobie[31] reviewed 69 trials in tinnitus, but drew attention to weaknesses such as inadequate implementation of intervention, poor masking, incorrect methods of statistical analysis, absence of intention-to-treat analysis, and low consensus on an appropriate outcome measure. A systematic review of 28 trials in tinnitus pinpointed similar flaws;[98] although this search was limited to trials that used validated outcome measures, Hoare and colleagues[98] reported little evidence of masking and poor external validity—only 25% of trials estimated sample size by use of a power calculation. The conclusions that can be made from these studies, and the scope for meta-analysis of trial data, are therefore limited.

Several research groups have made suggestions for methodological standards in tinnitus trials, to stimulate debate about how to improve methods and reporting,[32,101] drawing attention to guidelines for good clinical practice and reporting (eg, CONSORT[102]).

Prevention

Exposures to cytotoxic drugs, ototoxic antibiotics, and significant noise are recognised as factors that increase the risk of developing tinnitus. These factors are known to cause death of cochlear hair cells by apoptosis rather than necrosis.[103] Apoptosis can potentially be blocked either before exposure to the injurious agent or for a short period afterwards. Research is therefore continuing to try to find agents that can block apoptosis. The action of antioxidants is attracting most attention, with D-methionine or a combination of betacarotene, vitamin C, vitamin E, and magnesium showing initial promise.[104,105] Repair of cochlear damage by use of gene therapy and stem cell therapy is also being studied.[103]

***Panel*: Top ten uncertainties relating to tinnitus assessment, diagnosis, and treatment**

Suggested questions for tinnitus research

- What management strategies are more effective than a usual model of audiological care for improvement of outcomes for people with tinnitus?
- Is cognitive behavioural therapy/psychological therapy, delivered by audiology professionals, effective for people with tinnitus? Here, comparisons might be with usual audiological care or CBT delivered by a psychologist.
- What management strategies are more effective for improving tinnitus-related insomnia than a usual model of care?
- Do any of the various available complementary therapies provide improved outcome for people with tinnitus compared with a usual model of care?
- What type of digital hearing aid or amplification strategy provides the most effective tinnitus relief?
- What is the optimum set of guidelines for assessing children with tinnitus?
- How can tinnitus be effectively managed in people who are deaf or who have a profound hearing loss?
- Do different types of tinnitus exist and can they be explained by different mechanisms in the ear or brain?
- What is the link between tinnitus and hyperacusis (over-sensitivity to sounds)?
- Which medications have been proven to be effective in tinnitus management compared with placebo?

Further details about each research question are entered under the UK Database of Uncertainties about the Effects of Treatments (DUETs).[99,100]

Conclusion

Progress of research into tinnitus is clear, including systematic reviews of treatments, basic science research on mechanisms, and development of novel approaches to treatment. Once otological pathology has been excluded or treated, the treatment of choice for tinnitus involves the interweaving of education, sound therapy, and counselling, informed by the principles of CBT.[50] Although the benefits of such treatment are small, and the perception of tinnitus does not stop, it does improve quality of life and reduce awareness of, and reaction to, tinnitus.

Contributors

DB, DM, and DH conceptualised and wrote the paper.

Conflicts of interest

DB has received fees for consultancy on tinnitus from Autifony, GlaxoSmithKline, Neuromonics, and SoundCure, and has been an expert witness on tinnitus. DM has received fees for consultancy from GlaxoSmithKline. DH has received fees for consultancy from Merz Pharmaceuticals GmbH.

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