Subjective tinnitus assessment and treatment in clinical practice: the necessity of personalized medicine

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Subjective tinnitus assessment and treatment in clinical practice: the necessity of personalized medicine.

Paul Van de Heyning, MD, PhD
Annick Gilles, MSc, PhD
Sarah Rabau, MSc
Vincent Van Rompaey, MD, PhD

University Dept. of Otorhinolaryngology and Head and Neck surgery, Antwerp University Hospital (UZA), Edegem, Belgium
Faculty of Medicine and Health Sciences, University of Antwerp, Belgium.

Corresponding author:
Prof. Dr. Paul Van de Heyning
University Dept. of Otorhinolaryngology and Head and Neck Surgery
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10, 2650 Edegem (Antwerp), Belgium
paul.van.de.heyning@uza.be
Abstract

1. **Purpose of review:** Subjective tinnitus can be caused by a variety of etiologies, and therefore tinnitus patients constitute a very heterogeneous population difficult to manage. In this article, we reviewed the current literature to present our conceptual model of the conscious auditory percept and tinnitus-based on experimental research- in order to explain the clinical approach to the individual tinnitus patient.

2. **Recent findings:** Fundamental research has provided evidence to support the neurophysiological model of tinnitus developed by Jastreboff. By manipulating the limbic, autonomic and auditory systems, tinnitus retraining therapy (TRT) aims to reduce the response to the abnormal stimulus. Evidence has confirmed the effectiveness of TRT and cognitive behavioral therapy (CBT) in reducing the negative impact of subjective tinnitus on the patients’ quality of life.

3. **Summary:** Every patient with subjective tinnitus has its unique ‘tinnitus profile’ which provides a guide to the necessary combination of therapeutic actions. Evidence suggests the multidisciplinary approach combining etiological therapy as well as TRT and CBT in specialized clinics is not only effective in reducing the patient's quality of life but also cost-effective from a health-care and societal point of view.

**Keywords**

tinnitus, diagnosis, clinical approach, model

**Key points**

- Tinnitus is a non-pathognomonic sign of involvement of the peripheral and central auditory system, necessitating a comprehensive etiological and neurophysiological assessment of each individual patient.
- A clinical working model of the conscious tinnitus percept provides insight into the mechanism(s) that play a role in the generation of tinnitus in each individual patient, enabling personalized medicine.

- Tinnitus loudness and the level of suffering are not related with the extent of lesions nor with the seriousness of the underlying condition causing secondary tinnitus.

- Specialized multidisciplinary tinnitus treatment (including tinnitus retraining therapy and cognitive behavioral therapy) has been confirmed to be cost-effective.
Introduction and defining tinnitus

Tinnitus is the medical term for the auditory perception of sounds in the absence of surrounding sounds. Tinnitus affects 10-15% of the population of which in 2-3% tinnitus severance causes health issues and decreases quality of life (QOL). [1]

Objective tinnitus is defined as sounds originating from the body itself like arterial or venous murmurs, joints or muscles. However, most often there is no sound source and the tinnitus arises from a dysfunction of the auditory and/or connected systems known as subjective tinnitus. Hyperacusis or sound and noise intolerance can accompany tinnitus, but should be considered as a separate feature as the correlation between tinnitus and hyperacusis shows quite some variability. [2, 3]

The current review describes an individualized approach in patients with subjective tinnitus and a rationale for therapy. This type of tinnitus will be simply called tinnitus further on in the present manuscript.

Tinnitus is an etiologically non-pathognomonnic sign of involvement of the peripheral and central auditory system. Due to the strong variety of etiologies, patients with tinnitus constitute a very heterogeneous population. Tinnitus can arise from underlying organic conditions such as Eustachian tube dysfunction, any middle ear or inner ear disorder, but also from cerebellopontine angle tumors or more generalized central nervous system ailments. The medical diagnosis of such conditions should be made by performing a systematic history, clinical examination, audiological assessment and MRI of the brain and cerebellopontine angle. The psycho-acoustic characteristics and the influence on health-related QOL is a compulsory, complementary assessment to establish a complete profile of the patient. [4] Extensive schematic paradigms for evaluation were reported by the Tinnitus Research Initiative (TRI) and in the most recent clinical practice guideline on tinnitus. **[5-7]

First, we will present a conceptual model of the conscious auditory percept and tinnitus - based on experimental research- in order to explain the clinical approach to the individual tinnitus patient. Later, we will discuss the systematic evaluation of the tinnitus patient. Finally, we will discuss the secondary tinnitus or etiology-specific approach and the primary tinnitus or neurophysiological model approach.
A conceptual model of the conscious auditory percept and tinnitus

Although the neural correlates of the auditory percept are not yet fully unraveled nor understood, a model is schematically depicted in figure 1 that considers the auditory percept (figure 1a) and tinnitus (figure 1b) as a multisystem network property combining perceptual and limbic characteristics. This model aims to be a backbone for getting insight into the patient’s personal pathophysiological mechanism and supporting the clinician in explaining the influences to the patient. The model does not claim to be comprehensive nor to include or explain all current neurophysiological observations. [8] There is a lot of scientific research supporting the hypothesis that a sound, in order to be perceived, enhances the resting state activity of hierarchical ascending neural networks. [6] The signal voyages via the sensory peripheral cochlea-acoustic nerve input through the brainstem and thalamic nuclei to the central auditory nervous system (CANS) comprising the primary and secondary auditory cortex. However, CANS activation does not yield the percept itself. The signal has to be distinctly noticed and brought into our attention by the salience network connecting the signal into our awareness network. Only at that point we become aware of the sound: the percept is experienced consciously. Simultaneously, the network related to the limbic system is involved and delivers emotional content to the percept. [9] This is the bottom-up part of the percept.

The top-down influence arises from the cognitive network and steers both the salience and awareness network. Moreover, there is increasing evidence that perception is an active process in which the brain searches for the information it expects to be present, suggesting that auditory perception requires the presence of both bottom-up (sensory) and top-down (prediction-driven) processing. [10] The top-down cognitive process modulates the entire auditory system down to the hair cells in the cochlea through the olivo-cochlear bundles. [11]

This model leads to a simplified version of the neurophysiological model of tinnitus developed by Jastreboff [12]. The common neurophysiologic pathway of tinnitus patients in the model depicted in Fig 2a-c consists of inappropriately linking of central auditory resting state activity and limbic activity to the awareness network without external sound trigger. This can occur due to enhanced activity of the auditory network or a decreased threshold of the salience network. [13] The result is the perception of tinnitus, linked with a mostly negative emotional feeling.
Systematic evaluation of the tinnitus patient

At the initial evaluation, conditions that may readily cause the tinnitus should be promptly identified. Only in this way an appropriate treatment can be initiated comprising the treatment of the underlying disorder - if present and detected - and the therapeutic steps towards alleviating the tinnitus annoyance. Therefore, the ENT doctor or audiologist will perform a systematic history at the specialized outpatient clinic. Tinnitus characterization includes the tinnitus type (noise – pure tone – polyphonic - pulsatile), side (unilateral – bilateral – central) and duration (in days, months or years). Potential triggers experienced by the patient are explored as well as any chronic noise exposure during the life span. Co-existent symptoms such as subjective hearing loss, decreased speech understanding, otalgia, hyperacusis and vertigo are enquired. Sleeping problems are identified which might lead to day-time concentration deficits and tinnitus worsening. [14] Stress coping capabilities are considered as well as past or active depression. Additionally, signs of bruxism, cervical tension or pain or known history of temporomandibular joint dysfunction are explored. Quantification of caffeine, and alcohol is performed and former tinnitus treatments are discussed. Factors that modulate tinnitus loudness (both in negative or positive way) are actively searched for. Special attention goes to migraine since we know that it can at least modulate the tinnitus if left untreated. [15, 16]

Besides the anamnesis it is important to quantify the psychoacoustic characteristics as well as the impact on QOL. Psychoacoustic measurements provide more information on pitch matching, loudness matching and minimal masking level. However, the perceptual characteristics do not entirely reflect the severity of the tinnitus and the clinical need. [17, 18] A reliable method to measure the loudness of tinnitus is the Visual Analogue Scale (VAS) of loudness. [19] Questionnaires are used to investigate the impact on QOL. Recently, the Tinnitus Functional Index (TFI) [20] has gained international acceptance to assess the degree of tinnitus severance and to evaluate the effect of treatment. [17] Additionally, to complete the profile, the symptoms associated with tinnitus, for example hyperacusis [21] and psychological problems such as anxiety and depression should be screened [22-24] to enclose the whole problem. Recent investigations demonstrated the higher sensitivity for change of the QOL questionnaire compared to psychoacoustic measurements, which should
be considered optionally. (18)

Along with each individual patient, we want to gain insight into the mechanism(s) that play a role in the generation of the tinnitus in order to reverse these processes. First we will discuss those mechanisms relevant to secondary tinnitus.
Secondary tinnitus: the etiology-specific approach

Is the tinnitus of cochlear origin?

Cochlear tinnitus arises when a sustained higher firing rate of the inner hair cells is present such as immediately after loud noise exposure. Experimentally, the role of cochlear N-methyl-D-aspartate (NMDA) receptor activation in tinnitus occurrence was demonstrated. [25]

In case of acute otitis- or noise-induced tinnitus, the intratympanic injection of AM-101, an NMDA receptor antagonist, represents an innovative approach to treat acute tinnitus triggered by glutamate excitotoxicity. [26] A recent double-blind, randomized, placebo-controlled phase II clinical trial reported by Van de Heyning et al. * has demonstrated a significant and dose-dependent improvement in tinnitus triggered by acute acoustic trauma or otitis media from baseline to day 90. [26, 27] If these results are confirmed in the phase III trial, this can mean a breakthrough in the management of acute otitis- or noise-induced tinnitus.

In case of anticipated noise exposure (such as in military personnel), N-acetyl-cysteine has been demonstrated to reduce irreversible noise-induced hearing loss in vitro, explained by its antioxidant capabilities. [28] However, Kopke et al. did not observe any statistically significant differences before and after weapons training. [29]

Is tinnitus related to hearing loss?

Hearing loss generally leads to a decreased peripheral output and an increased central hyperactivity or synchronicity. This type of tinnitus is described as the phantom auditory sensation, and it is associated with a reorganization of the tonotopic cortical map. Moreover, the decrease of lateral inhibitory masking is a concomitant effect of decreased cochlear output. [30]

In case of sudden SNHL, optimal and successful treatment is an important factor in obtaining favorable long-term control of tinnitus accompanied by sudden SNHL. Rah et al. * demonstrated that the group of patients satisfied with their tinnitus outcome included significantly more cases with better hearing recovery after sudden SNHL treatment than the unsatisfied group. [31] Recommendations for treatment of sudden hearing loss were already issued by the AAO-HNS in 2012. [32]
Stapes surgery in case of otosclerosis can alleviate subjective tinnitus in many cases if still in the initial reversible phase. Chang and Cheung demonstrated that in case of TFI score exceeding 15 preoperatively, the postoperative TFI dropped 20 point on average after stapes surgery. [33] They also reported a 10% risk of transient worsening in the first postoperative month, which is important for appropriate preoperative patient counseling.

Traumatic perforation of the tympanic membrane has a good prognosis since only 2% have persisting symptoms at follow-up, while 30.8% report bothersome tinnitus at onset. [34] However, tinnitus caused by blast-injury is somewhat different with 68% of new-onset or worsening of tinnitus and only 23% of spontaneous tympanic membrane healing. * [35] Co-occurrence of posttraumatic stress disorder in trauma-associated tinnitus should be taken into consideration as a complicating variable. [36]

The potential of cochlear implantation (CI) to reduce unilateral tinnitus disturbance resulting from single-sided deafness has been demonstrated several years ago by Van de Heyning et al. [37] These findings were confirmed by other clinicians’ experiences reported more recently. [37-39]

Is the tinnitus somatic?

Somatosensory modulation of the auditory system can be caused by influences especially from the jaw and masticatory muscles such as teeth clenching and nocturnal grinding, and from the upper neck region e.g. after a whiplash trauma. This is explained by somatosensory input at the level of the cochlear nuclei. Attanasio et al. demonstrated a positive effect on tinnitus loudness and handicap in temporomandibular dysfunction patients treated with a neuromuscular occlusal splint (after exclusion of any neuro-otological etiology). [40]

Is there any distinct lesion of the brainstem and central nervous system present?

Any other space occupying lesion or demyelinating disorder can interfere with connectivity within and between the networks. [41] The main reason to perform an MRI scan of the cerebellopontine angle and brain is to exclude intracranial tumors in general, and the vestibular schwannoma in particular. [42]
A controversial condition is the cochleovestibular compression syndrome (CVCS) or the neurovascular conflict. In CVCS a contact exists between the blood vessels, which are in approximation with the cochleovestibular and facial nerve. In classical CVCS the vascular conflict is in the cisternal segment of the eighth nerve, in typewriter tinnitus the conflict is located in the internal auditory canal. Medical treatment is possible with low-dose anticonvulsant drugs such as clonazepam or carbamazepine. [43] Microvascular decompression should be carefully considered since previous studies could not confirm its effectiveness [44, 45]
Primary tinnitus: the neurophysiological approach

Primary tinnitus is defined as idiopathic, therefore after formal exclusion of any apparent conditions causing secondary tinnitus, and may or may not be associated with SNHL. In this category, the continuous tinnitus is caused by dysfunction of the peripheral or central auditory system. Any permanent influence on the auditory system resulting in an increased activity of the auditory cortex or decreased awareness threshold can result in the percept of tinnitus. Some hypotheses suggest an initial reversible phase and a later more irreversible phase after two to three years due to changes in connectivity. Based on this paradigm the following mechanisms are identified in the individual patient.

Does it concern a physiological tinnitus?

If the evaluation cannot point to a specific pathologic condition we conclude to a physiological type of tinnitus and are able to reassure the patient. An example is the tinnitus heard when the person is placed in a silent booth. Figure 2a demonstrates the fluctuation of brain activity and the annoyance threshold in absence of suffering.

Annoyance, suffering, attention and distress

The amount of annoyance, suffering and distress, provoked by and accompanying the tinnitus, is assessed. Focusing decreases the awareness threshold, as depicted in figure 2b. The degree of QOL interference and annoyance is an important guide to a stepwise therapeutic approach of the tinnitus, going from explanation and psycho-education in case of mild annoyance through a comprehensive series of tinnitus retraining therapy (TRT) and cognitive behavioral therapy (CBT) when there is a severe form of tinnitus suffering caused by increase cognitive attention to the tinnitus sound. TRT and CBT focus on coping mechanisms to change the reaction towards tinnitus. Greneil et al. conclude that both therapies are as effective for tinnitus based on a systematic review. Maes et al. demonstrated the superior cost-effectiveness of specialized multidisciplinary tinnitus treatment compared to usual care (i.e. identification and management of conditions that cause secondary tinnitus, counseling, fitting of hearing aid, and/ or sound generator).
Several neuromodulation techniques, such as Transcranial Magnetic Stimulation (TMS) [55, 56], transcranial Direct Current Stimulation (tDCS) [57] and neurofeedback [58], were reported to decrease neural activity associated with tinnitus. [59] Although the neuromodulation techniques showed some promising effects, the main effect is still small and not always repeatable.

**Generalized central nervous system disorders**

A last mechanism embraces all *generalized central nervous system disorders*, enhancing the overall activity of many brain centers, among which also the auditory network (depicted in figure 2c). Diseases such as depression, burnout, generalized anxiety disorder or even conditions of fearful stress may provoke tinnitus suffering. [60] It is important to identify the patient's vulnerability to these conditions and manage them adequately. [61] Physical inactivity or hyperactivity adds often to the whole picture, as does insomnia. [14] In case of any sleeping problems, clonazepam has the most evidence to be effective, but care should be taken to its side effects. [62]
Conclusion

A combination of the different items discussed in primary and secondary tinnitus constitute the unique ‘tinnitus profile’ of a particular patient. It will provide a guide to the necessary combination of therapeutic actions. It is essential to explain to the patient which mechanism(s) cause(s) his or her tinnitus to provide reassurance. It is also emphasized that loudness and the level of suffering is not related with the extent of lesions nor with the seriousness of the underlying condition causing secondary tinnitus. Correcting the modulating factors gives the patient a sense of control over their tinnitus. This kind of specialized multidisciplinary tinnitus treatment has been confirmed to be cost-effective.
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Conflicts of interest

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Figures

**Figure 1.** Diagram of (a) conscious auditory percept and (b) tinnitus. The dashed line represents the salience line. CANS, central auditory nervous system; TMJ, temporomandibular joint.

**Figure 2.** Diagram representing the sinusoidal fluctuation of brain activity and the awareness threshold in relation to tinnitus suffering.
References


This clinical practice guideline provides useful and evidence-based recommendations for clinicians managing patients with persistent primary tinnitus, including evaluation and treatment.


The intratympanic injection of an NMDA receptor antagonist represents an innovative approach to treat acute tinnitus triggered by glutamate excitotoxicity. A phase III trial is currently ongoing.


This study has demonstrated that sudden sensorineural hearing loss should be treated adequately to improve the associated tinnitus outcome.


Tinnitus caused by blast-injury has a worse outcome in spontaneous tympanic membrane healing and tinnitus outcome than other traumatic perforations.


TRT and CBT focus on coping mechanisms to change the reaction towards tinnitus. Both cognitive behavioural therapy and tinnitus retraining therapy are effective for tinnitus, with neither therapy being demonstrably superior.


