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Principles of Tinnitology: Tinnitus Diagnosis and Treatment A Tinnitus-Targeted Therapy

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Abstract

Objective: To provide to the tinnitus professional a rationale for establishing accuracy in tinnitus diagnosis and the selection of modalities of therapy (i.e., medication, instrumentation, and surgery) for attempting tinnitus relief for patients with tinnitus diagnosed by completion of a medical-audiological tinnitus protocol (MATPP) and clinical course and found to be subjective idiopathic tinnitus of the severe disabling type (SIT). **Background:** The completion of a MATPP has been recommended since 1977 for each tinnitus patient in an attempt to establish an accurate diagnosis. A tinnitus-targeted therapy (TTT), a combined treatment of medication and instrumentation focusing on pharmacotherapy, has evolved from our ongoing clinical experience since 1977 (now in excess of 10,000 SIT patients) [1–4]. Principles for SIT treatment have evolved from the TTT experience that provides a rationale for attempting tinnitus relief. In this report, the term tinnitus refers to SIT. **Method:** The strategies of TTT are based on the clinical translation for SIT diagnosis and treatment of (1) fundamentals of neuro-otological diagnosis; (2) fundamentals of sensory physiology; (3) extrapolation for treatment of known underlying neurochemistries from nuclear medicine imaging results e.g. single-photon emission computed tomography and positron emission tomography; (4) hypothesis of mechanism of tinnitus production , Tinnitus Dysynchrony Synchrony Theory (TDST) [5] , and hypothesis of the transformation-transition of the sensation of an aberrant auditory sensation—tinnitus (i.e., sensory component)—to one of affect (i.e., the emotional-behavioral component), Final Common Pathway of Tinnitus (FCP)[8]; and (5) innovative application of drug therapies designed for indications other than tinnitus [2,3]. **Results and Conclusion:** The ongoing clinical application of a rationale based on principles of diagnosis and treatment for SIT, which has evolved from our TTT clinical experience in SIT patients, continues to result in long-term tinnitus relief: in excess of 1 year in approximately 75% to 85% with medication and in 10% to 15% with instrumentation. SIT patients resistant to therapy persist at 10% to 15%.

Keywords: tinnitology; tinnitus-targeted therapy; subjective idiopathic tinnitus of the severe disabling type; receptor-targeted therapy

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INTRODUCTION

Clinical medicine teaches that the key to achieving positive treatment results for any diagnostic category of patient complaints is based on the clinical establishment of an accurate diagnosis.

The clinical problems presented to all tinnitus professionals attempting tinnitus treatment have been identified in our clinical experience (ongoing since 1977) to be (1) a dilemma of understanding how a sensation becomes transformed and translated into one of affect and vice versa; (2) identification of the underlying mechanism(s) of tinnitus production; and (3) difficulty in or lack of an attempt for establishing an accurate diagnosis for the tinnitus and the chronicity of the tinnitus complaint, requiring long-term treatment, individualized and variable for each patient. The term *tinnitus* in this article refers to subjective idiopathic tinnitus of the severe disabling type (SIT).

The definition of *tinnitus*, originally defined as the perception of a sound unrelated to an external source of sound stimulation (1979), is considered to be dynamic, reflecting advances in what is and is not known of the cochleovestibular system and brain function. At this time, tinnitus is considered to be an abnormal, conscious, auditory percept. It is believed to originate as an initial dyssynchrony in pre- or postsynaptic neuronal transmission within the peripheral or central nervous system (cortical or subcortical). It interferes in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neurofunction in multiple neural substrates and acts as an aberrant auditory stimulus to express this dysfunction via the auditory system [5].

We have identified since 1991 the evolution of a new discipline: tinnitology [6]. Tinnitology is an integrated multidiscipline of basic science, neuroscience, and clinical and nuclear medicine used in an attempt to understand an aberrant auditory phenomenon unrelated to an external source of sound and how it becomes transformed into one of affect.

A tinnitus-targeted therapy (TTT), a combined treatment of medication and instrumentation focusing on pharmacotherapy, has evolved from an ongoing clinical experience since 1977 (in more than 10,000 patients with SIT [1]. Principles of diagnosis and treatment for SIT have evolved from the TTT experience, which provide a rationale for attempting tinnitus relief. All patients visited the tinnitus clinic at the Downstate Medical Center at the State University of New York (DMC-SUNY) and the Martha Entenmann Tinnitus Research Center, Inc. [7,8]. Clinically, the application of these principles continues to provide significant incidences of SIT patients' reporting long-term tinnitus relief (i.e., in excess of 1 year) of all clinical types.

A previous publication, "Principles of Tinnitology," focused on both tinnitus diagnosis and treatment (i.e., their clinical application for selection of a pharmacotherapy for attempting SIT relief, 1979 to 2005) [1].

This article will update our experiences since 1977 and includes the following: (1) principles of tinnitus treatment, which have evolved from an increasing ability to provide accuracy for tinnitus diagnosis and (2) a clinical rationale for the selection of combined modalities of therapy (i.e., medication, instrumentation, and surgery) attempting tinnitus relief for tinnitus patients identified by history and clinical course to be suffering SIT.

PRINCIPLES OF TINNITOLOGY: DIAGNOSIS AND TREATMENT

History

Briefly, the identification of principles of tinnitology for diagnosis and treatment of SIT patients has evolved from our ongoing TTT experience since 1977. The clinical experience started in 1977 via translation of the goals of our otological and neuro-otological experience for sensorineural hearing loss, ear blockage, and vertigo to SIT (i.e., to establish accuracy in the neuro-otological diagnosis and to attempt to provide relief from the complaint).

The key clinical considerations included (1) that tinnitus is a neuro-otological-audiological complaint occurring alone and/or in combination with hearing loss, vertigo, ear blockage, and hyperacusis alone and/or in combination; (2) providing a standard protocol for evaluating all SIT patients by a neuro-otological-audiological team: development of a medical-audiological tinnitus patient protocol (MATPP) to be dynamic in character and reflect advances in clinical medicine, basic and neuroscience, which placed an emphasis on the clinical history, and neuro-otological examination; (3) attempting to objectivize a subjective idiopathic complaint of tinnitus, based on electrophysiological correlates of cochleovestibular function (peripheral and central); (4) translation of the principle of sensory physiology—that every sensation has three components (sensory, affect, and psychomotor)—for tinnitus diagnosis and treatment, specifically that treatment recommendations should differentiate which components of the tinnitus complaint are being targeted (i.e., sensory/affect); and (5) respect for disease of the ear and brain; interactions of ear and brain, mind and brain; and multiple brain functions of perception, consciousness, cognition, affect-emotion, behavior, attention, memory, fear, anxiety, and depression [4,5,9].

At this time, the principles of tinnitology are divided into those for diagnosis (Table 1) and treatment (Table 2). Clinically, there is an interaction between the two. Specifically, the accuracy of the diagnosis, particularly for an idiopathic symptom, will influence the efficacy of any/all modalities of therapy attempting tinnitus relief. It

Table 1. Principles of Tinnitology: Diagnosis (2010)

- Classification: objective, subjective, pulsatile, nonpulsatile
- Classification: tinnitus annoyance-ignore, cope, severe disabling type
- Category: auditory, non-auditory, clinical, subclinical
- Parameters tinnitus identification:
  - Quality-tone, noise, single, multiple
  - Location-duration-masking-rebound
- Tinnitus not a unitary symptom
- Clinical types and subtypes of tinnitus
- Components tinnitus complaint
  - Sensory-affect-psychomotor
- Medical significance: individual for each tinnitus patient
- Masking curves: individual
- GABA-A receptor— biochemical marker identified for a particular type of tinnitus, a predominantly central-type tinnitus
- Factors influencing the clinical course of tinnitus:
  - Cerumen-noise-aeration middle ear-secondary endolymphatic hydrops-stress
- Ultra-high audiometric response: can be used for identification of SIT patients who may benefit from ultra-high-frequency stimulation
- Tinnitus not a phantom phenomenon: identified electrodiagnostic, physiological, and biochemical changes significant for different clinical types of tinnitus

Table 2. Principles of Tinnitology: Treatment (2010)

- Establish accuracy for the tinnitus diagnosis.
- Attempt to establish tinnitus relief and control, as there is no cure at this time.
- General rules
  - Avoid noise; use ear protection in noisy environments.
  - Diet: eliminate stimulants.
  - Maintain stable blood pressure.
- Factors influencing the clinical course of the tinnitus (identify and treat):
  - Cerumen
  - Aeration middle ears
  - Noise
  - Stress
  - Secondary endolymphatic hydrops
  - Metabolic: sugar, hyperlipidemias, thyroid
  - Cardiovascular: hypertension, atrial fibrillation
  - Cerebrovascular: neuroprotection, neurodegeneration
  - Hematologic: anemia
- Tinnitus-targeted therapy (TTT)-combined therapy of medication and instrumentation targeting the different components of the SIT
  - Sensory-combined treatment: instrumentation, medication, surgery, alternate therapy(ies)
  –Receptor-targeted therapy (RTT-GABA)
  - Affect–behavioral evaluation treatment: stress management, anxiety, depression (psychiatry)
- Pharmacotherapeutic management
  - To do no harm
  - Drug selection: agents that have a shorter half-life to minimize the incidence and duration of side reactions.
  - Behavioral: long-term
  - Pharmacological: short-term therapy intervention
- Pharmacotherapy: innovative drug therapy(ies) based upon hypothesized underlying mechanisms of tinnitus production
  - Tinnitogenesis: anti-seizure medication
  - Stress: anxiolytics, antidepressants
  - Follow-up visit following completion of MATPP with neuro-otologist, audiologist, and physician's assistant
- Pharmacotherapeutic management
  - Multifactorial character of tinnitus
  - Single drug, multiple sites
- Combination drug strategies to increase efficacy of attempts at tinnitus relief
- Outcomes: follow-up visits

is expected that these principles will be expanded and modified to reflect future advances in tinnitology.

Our clinical experience with the MATPP has been the development of a rationale for establishing an accuracy in tinnitus diagnosis and attempting tinnitus relief [1,9]. The clinical application is resulting in a significant increase in the efficacy of modalities of therapy available for attempting tinnitus relief for all clinical types of tinnitus.

Critical for both the SIT patient and tinnitus professionals attempting tinnitus relief is to be aware of the realities of the state of the art of tinnitus diagnosis and treatment at this time. The highlights include acknowledgment that (1) there is no cure for tinnitus at this time; (2) though no cure for tinnitus exists, systems are available for attempting tinnitus relief through management; (3) tinnitus is a chronic symptom, multifactorial and heterogeneous in its etiology, clinical course, medical significance, and response to existing modalities of therapy attempting relief; (4) a limitation to advances in tinnitus diagnosis and treatment is what is and is not known of the cochleovestibular system and brain function: the dilemma of sensory physiology of how a sensory phenomenon becomes transposed or translated to one of affect and how the reverse takes place; and (5) treatment efficacy correlates with an accurate diagnosis of tinnitus [1].

Definitions in Clinical Tinnitus Therapy

The following definitions are considered significant in reporting results of modalities of tinnitus treatment and relief.

A *principle* is defined as "a fundamental truth, law, doctrine upon which others are based; an essential element; the scientific law that explains a natural action" [10]. Repetitive findings both from the clinical history and the MATPP in this combined neuro-otological-audiological approach for SIT are the basis of what we identified initially to be principles of tinnitology [1,4]; (see Tables 1 and 2). Future advances in tinnitology are expected to add to, subtract from, or modify the principles of tinnitology as set forth in this manuscript.

The *medical significance* of a symptom or disease process in a patient is defined as "a clinical manifestation of abnormal function of a living cell, tissue, organ, or organ system(s)" [4].

Treatment of a symptom or disease is "the management or care of a patient or the combating of a disease

or disorder. Active treatment is directed immediately to the cure of the disease or injury" [11]. At this time, SIT is considered a symptom, not a disease. In the future, a particular type of SIT may be identified to be a single disease entity.

Relief of a symptom or disease is "the easing of pain, discomfort, or anxiety. Anything that lessens tension or strain, or offers a pleasing change as to the mind or eye [10]. Clinically, it is a temporary interruption in the severity or clinical course of the underlying pathogenesis and/or the subjective reduction in the associated complaint(s)."

To be considered in 2010 (originally recommended in 1983) is that terminology for reporting the results of SIT treatment and used by tinnitus patients and professionals for different modalities of therapy should differentiate between (1) the terms *treatment* and *relief* for a subjective, idiopathic, aberrant, auditory percept (tinnitus), and (2) that treatment recommendations should differentiate which components of the tinnitus complaint are being targeted (i.e., sensory/affect).

Specifically, the term *treatment* should be used for recommendations attempting "cure and/or alteration in the chronicity of the complaint and the term *tinnitus relief* or *control* for modalities of therapy attempting reduction in the severity of the complaint, both for its sensory and affect components.

Chronic is defined as "conditions of long duration and/or frequent recurrence [10]. A term denoting a physical condition which persists for a long time and is associated with alteration in cellular, tissue, organ, and system level(s), becoming clinically manifest by alteration in body function(s)." The clinical recognition of SIT's chronicity persists since 1979: specifically, that SIT is a chronic complaint, symptomatic of interference in the cochleovestibular system, peripheral and/or central, and/or brain function(s); heterogeneous in its etiologies, clinical course, and response to therapy.

Tinnitogenesis is a seizure-type activity resulting in the perception of an aberrant auditory stimulus (tinnitus) [12]. Its identification provides an objective basis for an innovative anti-seizure medication attempting tinnitus relief for a predominantly central SIT. It is a mechanism, not the etiology of SIT.

Sensory physiology has identified three components of any and all sensations. They are (1) the sensory component (sensory stimulus), (2) the affect component (behavioral response to the sensory stimulus), and (3) the psychomotor component (the motor response to express the behavioral response to the sensation) [13].

The *sensory component* of tinnitus refers to the subjective perception of the sensation of the aberrant auditory stimulus—tinnitus—as described by tinnitus patients. The *affect component* of tinnitus refers to the emotional response of the patient to the sensory component. The *psychomotor component* of the tinnitus refers to a patient's motor response accompanying the emotional and subjective perception of the sensation of the aberrant auditory stimulus (tinnitus).

Behavior is defined as "the way a person behaves or acts; conduct; manners; 2) an organism's response to stimulation or environment especially those responses that can be observed" [10].

Clinical types of SIT have been identified based upon the clinical history and metabolic and electrophysiological correlates of brain activity and cochleovestibular function. SIT is not a unitary symptom [14–16].

Neurodegeneration, in this report, is a term "reflective of process(es) involved in the progressive damage or death of neurons and reflected clinically in a gradual deterioration and interference in function of the affected neural substrates of the nervous system" [17,18].

Neuroprotection refers to "processes involved in the maintenance and repair and restoration of normal neuronal function" [17–19].

The *final common pathway* (FCP) for tinnitus has been hypothesized for all clinical types of tinnitus. It is not a theory of tinnitus production. It is a hypothesis that is intended to explain the transformation-transition of the sensation of an aberrant auditory sensation (tinnitus, a sensory component)—to one of affect (i.e., the emotional-behavioral component) or, conversely, that an emotional-behavioral stimulus (affect) can result in the clinical manifestation of a sensation (a sensory stimulus). Neuroanatomical substrates that have been identified in brain contribute to an evolving pathophysiology for all clinical types of tinnitus. Understanding the pathophysiology of this transformation in brain is considered to be fundamental to diagnosing and treating tinnitus of all clinical types. When viewed in terms of sensory processing, the FCP hypothesis is considered to be expanded and broader in its application for all sensations, normal or aberrant [8,20].

The *tinnitus dyssynchrony-synchrony theory* is a hypothesis that considers tinnitus to be an abnormal, conscious, auditory percept. Tinnitus is believed to originate as an initial dyssynchrony in pre- or postsynaptic neuronal transmission within the peripheral or central nervous system (cortical or subcortical). It interferes in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neurofunction in multiple neural substrates and acts as an aberrant auditory stimulus to express this dysfunction via the auditory system [5]

TREATMENT, CONTROL, AND RELIEF

General Considerations

We present an update on TTT, a combined treatment of medication and instrumentation focusing on

pharmacotherapy [1]. All have visited the tinnitus clinic at the Downstate Medical Center of the State University of New York (DMC-SUNY) and the Martha Entenmann Tinnitus Research Center, Inc. [2–4].

The strategies of TTT are based on the clinical translation of fundamentals of sensory physiology; extrapolation of underlying neurochemistry from nuclear medicine imaging results with single-photon emission computed tomography and positron emission tomography (SPECT/PET) in SIT patients; hypotheses of mechanisms of tinnitus production; and the innovative application of drug therapies designed for indications other than tinnitus. Our clinical experiences for both tinnitus diagnosis and treatment since 1977 were summarized in 1991 and updated in 2006. Principles have evolved for both tinnitus diagnosis and treatment (see Tables 1–5). The reader is referenced to the bibliography for appropriate references [1,2,21,22].

Table 3. Principles of Tinnitology: Drug Treatment for the Sensory

Component
• Trental 400 mg tid
• Nimodopine 30 mg tid Nifedipine (Procardia) 30–60 mg/day
• Steroid: Prednisone 10–20 mg
• Cytotec (Misoprostal) 100–200 μg od–qid
• Baclofen 5–10 mg/day (40–80/day)
• Carbamazepine (Tegretal) 200–800 mg/day
• Valproic acid 15 mg/kg/day
• Dilantin 50 mg tid
• Gabatril (Tiagabine) 4 mg daily, increase to 32 mg/day
• Papaverine: 100–150 mg/day Pavabid 125 mg bid
• Furosemide 80 mg IV test dose
• Supportive therapy
Antioxidants, Multivitamins , Gingko
Vitamin E 400,000 units daily
• Memory, Cognition: Memantine 5 mg od, increased weekly to 10 mg bid
• RTT-GABA: predominantly central-type tinnitus of the severe disabling type
Gabapentin: individual, 100 mg od to 3,200 mg/day
Klonopin.25 mg hs/suppl.
• Pregabalin150 mg, individual, 150 mg od–qid

Table 4. Principles of Tinnitology: Drug Treatment for the Affect (Behavior) Component

• Nortriptyline 50–150/day
• Amitriptyline 10 mg/day
• Paroxetine(Paxil) 20 mg/day
• Fluoxetine(Prozac) 20–80 mg/day
• Sertraline (Zoloft) 25–50 mg/day
• Buproprion (Wellbutrin) 100 mg bid
• Venlafaxine (Effexor) 75–150 mg/day
• Benzodiazepines: Klonopin 5 mg hs; Xanax 5 mg hs

Tinnitus treatment efficacy is intimately related to tinnitus diagnosis. The principles of diagnosis and

Table 5. Principles of Tinnitology: Instrumentation

• Hearing aid
• Tinnitus masker
• Tinnitus instrument: combination hearing aid and masker
• Tinnitus retraining therapy
• Sound treatment systems
• Ultra-high-frequency stimulation (UltraQuiet)
• Neuromonics

treatment (see Tables 1 and 2), , and modalities of treatment available at the present time (see Tables 3–5), are presented not as menu-driven recommendations for tinnitus treatment, control, and relief but rather as a selection based on a rationale targeting hypothesized underlying biophysical processes. They have been identified as involved in sensory processing underlying cochleovestibular function (peripheral and central) and in the neuroscience of brain function.

The clinical course of tinnitus, particularly SIT, is highlighted by its individuality and chronicity. A paradigm change is recommended in clinical thinking both for the symptom itself and for the response to treatment. Specifically, the symptom should be considered not by itself classically as one in a constellation of cochleovestibular complaints (including hearing loss, vertigo, ear blockage, and hyperacusis) but in relation to multiple brain functions (e.g., perception, consciousness, cognition, affect-emotion, behavior, attention, memory, fear, anxiety, and depression).

To appreciate clinical advances that have been made for tinnitus diagnosis and treatment since 2006, it is necessary to briefly review the past.

Diagnosis

Accuracy of Tinnitus Diagnosis: Clinical Types of Tinnitus

Since 1981, our focus for treatment has been, first, to focus on establishing accuracy in the tinnitus diagnosis by integrating the clinical history with the findings on physical examination, electrophysiological correlates of cochleovestibular function, and the translation of hypothesized underlying mechanisms of tinnitus production for attempting tinnitus control (i.e., MATPP) (Figure 1). At this time, tinnitus is considered clinically to be a symptom, heterogeneous in its etiology, clinical course, and clinical manifestation as different clinical types.

Clinically, however, tinnitus is still considered by many professionals and patients to be a unitary symptom. The original concept of clinical types of tinnitus (CTT) [23] is considered to be fundamental for translation to any and all attempts for tinnitus relief. Since 1979, our team has continued to report the clinical identification of clinical types and subtypes of tinnitus, particularly for a predo-

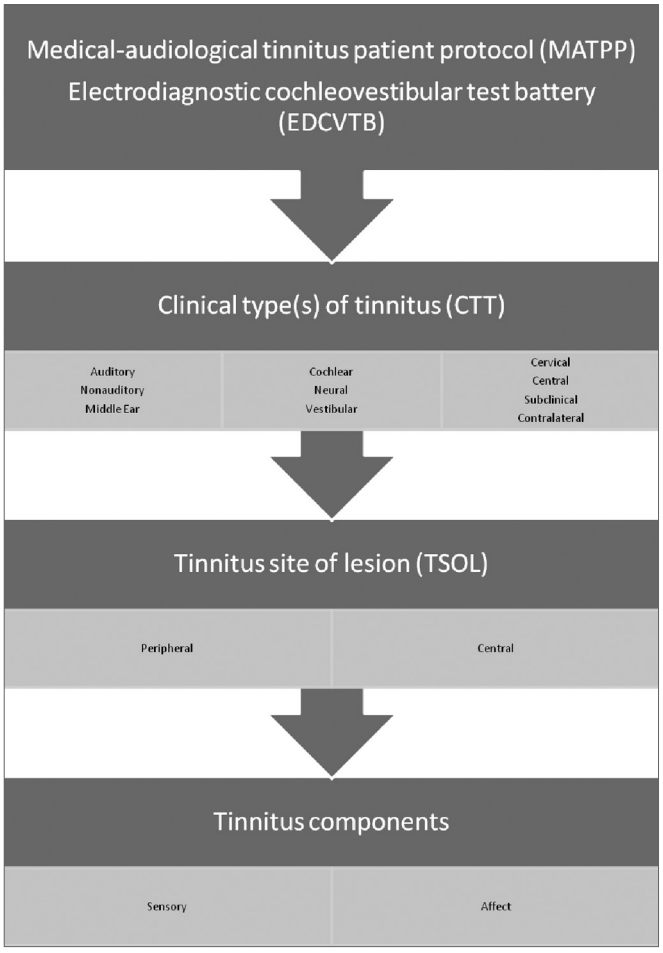

Figure 1. Algorithm for tinnitus diagnosis and treatment: the medical-audiological tinnitus patient protocol.

minantly central-type SIT. According to the definition of tinnitus, the perception of tinnitus is a central function in all CTT . The CTT are identified by the correlation of the clinical history, physical examination, electrophysiological correlates of cochleovestibular function, and an evaluation of metabolic and electrophysiological activity in brain. Critical for attempting tinnitus treatment, control, and relief for any and all clinical types and subtypes of tinnitus is the clinical establishment of accuracy for the tinnitus diagnosis [14,24]. For the future, it is hypothesized, a particular clinical type of a predominantly central tinnitus, now considered to be a symptom, will be identified to be a specific disease entity.

The recent publication of the Tinnitus Research Initiative (TRI) database has recognized the clinical reality that tinnitus is not a unitary symptom [25]! The establishment of this data base will be a significant advance for both diagnosis and translation for an increased efficacy for any and all modalities of therapy attempting tinnitus relief and control.

The recommendation for the clinical history to identify the parameters of identifying the SIT (i.e., quality, location, duration, intensity, masking, rebound, before and after treatment) is clinically valuable in understanding the subjective description of the tinnitus and in evaluating the efficacy of treatment. Two recent reports have significant clinical application for tinnitus diagnosis and its clinical course as described by patients: (1) In the rodent auditory cortex, the arrangement of relative frequency responsiveness is not preserved at a fine-scale cortical level [26] and (2) local populations in A1 were highly heterogeneous in large-scale tonotopic organization (i.e., a spatial but not action heterogeneity) [27]. These findings provide a basis for understanding the heterogeneity in the quality of the tinnitus as described by tinnitus patients and for the future potential application for attempting tinnitus control.

Cochleovestibular Testing: Tinnitus Evaluation

The classic site of lesion audiometric hearing threshold testing of 250 Hz-kHz is recommended in tinnitus patients to be extended to include the ultra-high frequencies of 10 to 20 kHz. Tinnitus patients with hearing thresholds within the range of “normal” (250 Hz–8 kHz) have been found to have elevated thresholds in excess of what is expected for their age. The ultra-high frequency findings, when positive, have clinical application for both diagnosis and treatment [28,29].

For patients with either unilateral or bilateral tinnitus and an asymmetrical sensorineural hearing loss, completion of tests of auditory brainstem response or magnetic resonance imaging (or both) of the brain and internal auditory canals with gadolinium is recommended to identify the presence or absence of acoustic tumor. The identification and removal of the acoustic tumor may be accompanied by tinnitus relief and/or exacerbation and initial onset when previously not present.

Vestibular testing is recommended in all SIT patients with or without vertigo. The cochleovestibular system is an embryological admixed system. The test results may reveal involvement of the peripheral and/or central vestibular system. Particularly significant for tinnitus is the finding of a labyrinthine asymmetry that, when correlated with the symptom of ear blockage and a positive Metz test for recruitment, provides the basis for the clinical diagnosis of a secondary endolymphatic hydrops (SEH) [30]. Visual suppression of the vestibule-ocular reflex, a sign of cerebellar dysfunction, is significant for the identification of a central component for the tinnitus and involvement of the acousticomotor system [31].

The incidence of SEH occurrence in our experience continues to be approximately 35% overall. Treatment includes diuretic/antihistamine medication, diet limitation, salt intake, and stimulants. The control of SEH

contributes to tinnitus relief by reducing recruitment and increasing the efficacy of instrumentation (e.g., hearing aid) and by stabilizing sensorineural hearing loss [30].

Evaluating tinnitus includes identifying its psychophysical and psychoacoustical characteristics, cochleovestibular testing, and masking curves [28]. The Feldman masking curves are individual for each tinnitus patient. The curves' clinical applications are identifying the clinical type of tinnitus and the advisability of recommending instrumentation (e.g., hearing aid, masker) [32].

Supplemental testing with auditory brainstem responses, nuclear medicine brain imaging with SPECT and PET, and quantitative electroencephalography (QEEG) are reserved for SIT patients resistant to conventional modalities attempting relief. These modalities are used in the attempt to improve the accuracy of the tinnitus diagnosis and provide a monitoring system for evaluating the efficacy of therapeutic modalities aimed at tinnitus, which included control of factors influencing the clinical course of the tinnitus and a previous trial of instrumentation [33,34].

Factors Influencing the Clinical Course of Tinnitus

Factors that have been identified influence the clinical course of SIT. The incidence of occurrence in our experience has been approximately 25% to 35%. These factors include cerumen in the external auditory canal with or without tympanic membrane involvement, fluctuating aeration in middle ears, SEH, noise exposure, stress, metabolic abnormalities in glucose, cholesterol, triglyceride or thyroid function, and hypertension with or without fluctuation and occurring either alone or in combination. Identification, treatment, and maintenance of normal aeration of the middle ears, when identified and treated, have resulted in tinnitus relief and control in approximately 15% of our SIT patients. The clinical significance to the patient and tinnitus clinician is that the factors (when identified and treated) provide tinnitus relief to a significant number of SIT patients and a basis for increased efficacy of treatment, relief, and control with instrumentation (e.g., hearing aid, tinnitus masker) [2,21,22].

A special clinical type of a predominantly central-type SIT has been identified in a cohort of SIT patients with cerebrovascular disease, epilepsy, and memory and cognitive disorders, reflecting neurodegenerative disease [17,18]. Identifying and treating this particular central-type SIT has been accompanied with relief. Such drugs include the vasodilator papaverine

for cerebrovascular insufficiency, clopidogrel bisulfate (Plavix) in transient ischemic attack and post-stroke patients, and anti-seizure drugs for epilepsy. For memory and cognition, we recommend the neuroprotective drugs donepezil hydrochloride (Aricept), Cognex (tacrine), memantine hydrochloride, gabapentin, and clonazepam (Klonopin). These drugs may influence the SIT by improving the underlying neuronal anatomic substrate(s) that may be contributing to SIT [1]. Again, the accuracy of the tinnitus diagnosis is the key to selecting modalities of treatment in attempting tinnitus treatment, relief, and control.

Masking

Masking is a term used to refer to the effect of one tone or one sound on another tone or sound or combinations thereof [35]. Itard [23,35] believed that utilizing external sounds to interfere with the tinnitus was the most effective relief procedure. The FCP proposes clinical consideration of auditory masking to be predominantly a brain function with peripheral and central components. The manifestation of the symptom of tinnitus is considered to be a reduction in the normal auditory masking function in the brain: The neuroanatomical substrates are hypothesized to involve the cochlea, the brainstem, the thalamus, and multiple cerebral cortices (Figure 2).

Auditory masking, the replacement of one source of acoustic stimulation by another, a "covering up" or "blockage" of one sound by another, is a normal function of the auditory system. Specific patterns of response have been identified in tinnitus and non-tinnitus patients. The Feldmann masking curves are patterns of response that are individual for each tinnitus patient.[28,32] Clinically, this is significant for tinnitus diagnosis and for suitability of recommending instrumentation to "mask" and result in tinnitus relief/control for the patient. Similarly, tinnitus relief, when reported, is clinically considered by our team to reflect a return of adequate masking.

Algorithms of the Final Common Pathway for Tinnitus

Neuroanatomical substrates of the FCP are presented as algorithms of components of a sensation (i.e., sensory, affect, and psychomotor), a translation from basic sensory physiology for tinnitus (see Figure 2) [20]. For tinnitus diagnosis, the algorithms provide the basis for an integrated theory of tinnitus and brain function, that is, tinnitus dyssynchrony-synchrony theory [5] (see Figure 2); a model for identifying underlying neurocircuitries and neurochemistries involved in brain for the sensory-affect transformation of an aberrant auditory stimulus (tinnitus); and a model for the selection-introduction of innovative therapies attempting tinnitus relief.

A significant evidence-based medicine report, considered to support the algorithms of the FCP, with emphasis on the sensory/affect interaction, and its translation for tinnitus diagnosis/treatment, is the recent report demonstrating in the ferret frontal cortex a dynamic functional connection during auditory behavior

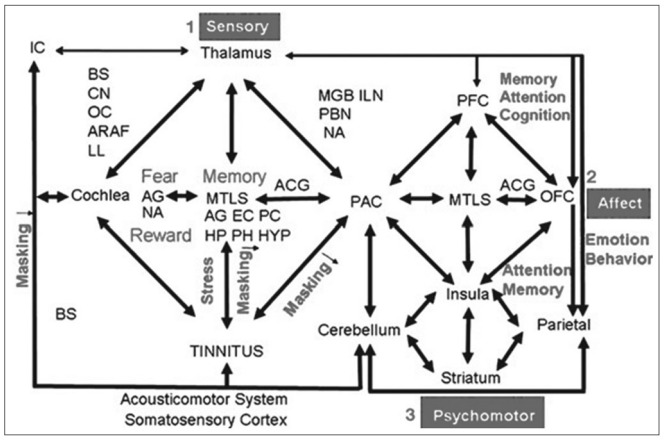

Figure 2. Algorithms of the final common pathway (sensory, affect, psychomotor components) and tinnitus treatment.
Three final common pathway algorithms reflect the neuroanatomical substrates of the sensory, affect, and psychomotor components of a sensation (i.e., the aberrant auditory sensory stimulus—tinnitus). The brain functions associated with each component of the aberrant auditory sensory stimulus (tinnitus) are integrated in each algorithm with the involved neuroanatomical substrates. The reciprocal interacting neuroanatomical substrates of the three components complete a circuit—the final common pathway sensory–affect transformation. Algorithm 1, Sensory Component: It is hypothesized that for the sensory component, the sensory information (i.e., dyssynchronous aberrant auditory signal) arising from the peripheral cochlea or central nervous system (CNS) ascends via (1) the brainstem (BS), cochlear nucleus (CN), and olivocochlear bundle (OC) to the inferior colliculus (IC) and on to the medial geniculate body (MGB), intralaminar nuclei (ILN) of the thalamus, and the parabrachial nucleus (PBN) and nucleus accumbens (NA) and (2) the primary ascending reticular activating formation (ARAF) of the lemniscal system to the thalamus—both as part of the exogenous system of the CNS [53,54] for the receipt of sensory information arising from the environment or peripheral or central nervous system that projects to the primary auditory cortex (PAC), which in turn projects to the prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate gyrus (ACG), and insula. The cerebellum, via the acousticomotor system, has reciprocal projections to and from the somatosensory cortex, IC, thalamus, PAC, and parietal lobe [18]. Hyperpolarization and depolarization of GABA-influenced thalamic neuron activity results in thalamocortical oscillations in a synchronous signal at brain cortex [204,254]. Reciprocal innervation from the thalamus to the medial temporal lobe system (MTLS), including the amygdala (AG), hippocampus (HP), paparahippocampal formation (PH), entorhinal cortex (EC), perirhinal cortex (PC), ACG, and hypothalamus (HYP), comprise an endogenous system of the CNS as hypothesized for sensory processing [53,54]. For tinnitus, the endogenous system is hypothesized to result in the establishment of a "paradoxical memory" for the aberrant auditory sensory stimulus (tinnitus) and has a reciprocal interaction with the thalamus [16]. The associated brain function processes within the neuroanatomical substrates of the sensory component include memory, stress, masking, fear, reward, and autonomic functions. Stress is considered to be a modulator of the clinical course of the tinnitus with the accompanying reduction and alteration in auditory masking [2,230–232]. Algorithm 2, Affect (Emotional-Behavioral) Component: The neuroanatomical substrates of the affect (emotional) component are highlighted by the OFC, PFC of the frontal lobe, PAC, MTLS of the temporal lobe, and insula. Reciprocal innervation is hypothesized to occur between the PAC of the sensory component and the OFC, ACG, PFC, MTLS, and insula. The insula, by its central location, is hypothesized to exert a modulating effect among the sensory, affect, and psychomotor components. The thalamic activity is ongoing with reciprocal projections to the PFC, OFC, and parietal lobe. The associated brain function processes within the neuroanatomical substrates of the affect (emotional-behavioral) component include attention and cognition (i.e., learning and memory). Algorithm 3, Psychomotor Component: The neuroanatomical substrates of the psychomotor component include the insula, parietal lobe, striatum, and cerebellum. Reciprocal interaction is hypothesized between each of the neuroanatomical substrates. The thalamic activity is ongoing with reciprocal innervation of the parietal lobe, OFC, and PFC. Significant for the sensory–affect transformation is considered to be the interaction between the striatum, parietal lobe, and OFC via the insula. The associated brain function processes within the neuroanatomical substrates of the psychomotor component include attention and cognition (i.e., learning and memory) and their influence on the affect (emotional-behavioral) component. (LL _ lateral lemniscus.) Reprinted by permission of the Martha Entenmann Tinnitus Research Center, Inc.

between A1 and the frontal lobe. Specifically, top-down signals influence the flow of sensory information, provide meaning to the sensory input, and allow direction of attention to particular features of the sensory signal (i.e., a task-related plasticity between frontal cortex and A1 [36].

Benzodiazepine Deficiency, Stress, and SIT

A benzodiazepine deficiency is hypothesized to be present in SIT patients [37]. The clinical course of SIT, a stressor, becomes clinically manifest with increased severity by a reduction in the inhibitory activity of the GABA-A receptor, which is deficient and cannot inhibit the aberrant auditory signal [7].

Treatment RATIONALE

General

All clinical types and categories of tinnitus patients are recommended to follow general rules for attempting tinnitus treatment, control, and relief : (1) Avoid loud noise; (2) use ear protection in areas of loud noise exposure; (3) avoid stimulants in diet; and (4) have complete physical examination with identification and treatment as appropriate for metabolic, cardiovascular, and cerebrovascular complaint(s).

Tinnitus-Targeted Therapy

Tinnitus treatment recommendations continue to focus on identifying the tinnitus etiology and on the conceptualization of the past that tinnitus is a unitary symptom. A menu-driven approach is that of the majority of tinnitus professionals for recommendations of instrumentation, medication, or surgery. However, this empirical approach, in our experience, has not translated to significant efficacy of tinnitus treatment/control, particularly for SIT [38,39].

Although no tinnitus cure is available in our experience for patients at this time, protocols of combined treatment modalities that are available attempt to provide accuracy in diagnosis and identifying the medical significance of the tinnitus and tinnitus treatment, relief, and control [9,40]. The MATPP has provided our team with a basis for the selection of existing modalities of treatment with resultant increased efficacy of tinnitus treatment, relief, and control, which we have called a tinnitus-targeted therapy (TTT) [1, 9]. All patients are interviewed by telephone prior to receiving the appointment and are requested to have undergone a complete physical examination within 6 months prior to neuro-otological-audiometric consultation and to provide past hearing and balance testing, imaging and pharmacological record results, and a short narrative of the clinical course of the tinnitus for review.

The neuro-otological consultation focus is on the clinical history, clinical course of the complaint, neuro-otological physical examination, and review of past medical records. A hearing screening test of 250 Hz to 20 kHz is performed. The clinical history present and past attempts to establish the tinnitus etiology; factors influencing the clinical course of the tinnitus; and the interaction/correlation among tinnitus, hearing loss, vertigo, ear blockage, and hyperacusis that, together with the neuro-otological and audiological examination and cochleovestibular testing, attempt to identify the CTT. Recommendations for additional cochleovestibular/brain testing are individualized for each tinnitus patient based on completion of the neuro-otological/audiological screening test and review of medical records. The follow-up visit with the neuro-otologist and audiologist after the initial consultation establishes an individual plan for tinnitus control (i.e., TTT for each SIT patient, consisting of a combination of instrumentation and medication. SIT patients should not be told simply to "live with it" [21].

Hypotheses of the role of biophysiological mechanisms in producing tinnitus are selected for translation to the attempt to establish accuracy for the tinnitus diagnosis and attempted treatment. We have focused on masking, glutamate neuroexcitotoxicity theory, inhibition, benzodiazepine deficiency, neurodegeneration, neuroprotection, calpain theory of apoptosis, kindling, long-term potentiation, lateral inhibition, epileptogenesis, stress, neurotransmitter action at synaptic levels of activity and alteration in the homeostasis of function between the fluid compartments of ear and brain [5,12,20-22,37, 41] For the associated compliant of hyperacusis, a plan for sound attenuation utilizing white noise is recommended.

The selection of a particular modality of treatment is individualized for each patient and differentiated between the components of the tinnitus (see Figs. 1, 2; Table 6). The reader is referred for additional details to references [1,2, 19-22,30,31,40,41]

Table 6. Drug Therapy Tinnitus Control 1977–1989 and Ongoing

- Vasodilator therapy (Arlidin) and tinnitus control 1977–
- Antihistamine therapy and tinnitus control 1977–
- Benzodiazepines and tinnitus control 1983–
- Lidocaine therapy and tinnitus control 1980–
- Blood viscosity alteration and tinnitus control 1987–
- Neurotransmitter systems identification and tinnitus control 1989–

PHARMACOTHERAPY AND INSTRUMENTATION

General

Basic pharmacotherapeutic management principles have been followed since 1979 [1] (see Table 6). The goal is pharmacological short-term tinnitus relief therapy, but planning must be made for long-term benefit. Principles mandate, first, to do no harm. Second, drug selection should take into account agents that have a short half-life so as to minimize the incidence and duration of side effects. Third, the chronicity of the SIT complaint must be considered. Plans should be made for long-term treatment, particularly for the affective behavioral component. The main clinical manifestation of tinnitus is that of multifactorial characteristics; therefore, single drugs may have multiple sites of action. We recommend a combination drug strategy to increase the efficacy of attempts at tinnitus relief. For the affect component, particular attention is directed with pharmacotherapy to avoid drug tolerance and or habituation.

Instrumentation is recommended to tinnitus patients resistant to pharmacotherapeutic modalities for attempting tinnitus relief, approximately 10% to 15% since 2000.

Strategies for Tinnitus Treatment, Control, and Relief of SIT

Combined Treatment: Sensory Component

Step 1: Completion of MATPP; history; neuro-otological physical examination; cochleovestibular evaluation; tinnitus evaluation to include masking curves; review past medical records, hearing/balance testing, pharmacology record past 1–2 years for medication prescribed for any indication; past brain and ear imaging films and reports; past attempts at tinnitus control; patient narrative of tinnitus clinical course; identification and exclusion of drug(s) associated with onset and clinical course of tinnitus; noise protection and control; stable personality (see Tables 1–5)

Step 2: Removal of keratotic debris and cerumen from external canal and tympanic membrane as appropriate.

Step 3: Maintain normal aeration of the middle

ear; medication to treat and maintain adequate aeration of the middle ear right and left.

Step 4: Treatment for the factors influencing the clinical course of the tinnitus as appropriate based on the clinical history, and the cochleovestibular/ brain test results ordered at time of initial neuro-otological consultation. For the diagnosis of SEH, diuretic therapy (i.e., Dyazide tab 1 daily is recommended if no medical contraindication; duration of therapy is individual, reflecting associated complaints of ear blockage and result of Fukuda stepping tests.

In our experience, a majority of the patients report significant tinnitus relief and control after completing steps 1 to 4 and do not require instrumentation. Instrumentation (step 5) occasionally is recommended, initially to start with a hearing aid and/or the masker or tinnitus instrument if appropriate. The clinical types of tinnitus in this group are predominantly of the middle ear and cochlea, alone or in combination. The degree of reported tinnitus relief after steps 1 to 4 determines whether additional treatment recommendations are prescribed

Category 1: Tinnitus relief significant to the patient; then conservative follow-up treatment is recommended.

Category 2: No tinnitus relief; patient resistant to attempts for tinnitus relief. If the clinical type of tinnitus is a predominantly cochlear type, intratympanic drug therapy with steroids, preceded by computed tomography of the temporal bones is recommended [43].

Category 3: No tinnitus relief; patient resistant to attempts for tinnitus relief. If the clinical type of tinnitus is a predominantly the central type, innovative drug therapies are recommended. If innovative follow-up drug therapies are declined, instrumentation is recommended, including tinnitus retraining therapy/sound treatment systems and/ or the neuromonics system (see Table 5) [35,37,40,42-47].

Step 5a: Instrumentation in collaboration with audiology [35,37,40,42-47].

Hearing loss of mixed or predominantly sensorineural type; trial amplification (i.e., hearing aid) and/ or tinnitus instrument (i.e., combination tinnitus masker and hearing aid)

Tinnitus masker: Feldman types 1 to 3

Step 5b: Tinnitus patients, predominantly central type, resistant to attempted tinnitus relief in steps 1 to 4 who agree to innovative drug therapies are recommended the following:

SPECT/PET and/or QEEG in an attempt to improve the accuracy of the tinnitus diagnosis, provide objective metabolic and electrophysiological evidence to support the clinical diagnosis of a predominantly central-type tinnitus, to establish a basis for the recommendation of a trial of innovative drug therapyies attempting tinnitus relief, and to serve as a monitor to provide objective evidence of treatment efficacy. There should be some indication of involvement of the CNS before use of an innovative application of AEDs [9,16,33,37].

Innovative receptor-targeted therapies (RTT) based on identification of the underlying neurotransmitter systems [37]. Drug selections are aimed at underlying neurotransmitter receptor systems, which are categorized into three groups at this time: (1) the glutamate system, which is that of excitation; (2) the GABA system, one of inhibition; and (3) the modulating neurotransmitter systems of dopamine and serotonin (see Tables 1–4).

RTT directed at the GABA-A–benzodiazepine–chloride receptor (RTT-GABA) [37].

We recommend an RTT-GABA for the diagnosis of a predominantly central-type tinnitus. It is an innovative application of anti-seizure (i.e., anti-epileptogenic drug medication AED) recommended for epilepsy. It consists of gabapentin and clonazepam. Other AEDs (e.g., Gabatril) can be prescribed with the understanding that not all AEDs have GABA-ergic activity (see Table 4). We recommend selection of RTT-GABA for patients with SIT of more than a year's duration and a diagnosis of a predominantly central-type tinnitus based on completion of the MATPP.

RTT-GABA: Dosage

Titration of gabapentin should begin at the lowest possible dose: The goal is to do no harm. We recommend titration of the drug starting at 100 mg/day and increased at weekly intervals by 100 mg/day in divided doses (not to exceed 2,400–2,700 mg/day). The dose titration is to be determined by the reported clinical outcome. The dose for the sensory component is based on the tinnitus intensity index (TII) and the tinnitus annoyance index (TAI), both on a scale from 0 to 7. The tinnitus is stated as unbearable at 7 and absent at 0. The benzodiazepine (Klonopin) dose recommended is 0.25 mg at bedtime and 0.25 mg one to three times daily, separated by 4-hour intervals if the TII and the TAI are maintained at a level of 5 or above. The total maximum dose of Klonopin is 1 mg/ day. Duration of treatment is individual and determined objectively by correlation of the clinical history of the tinnitus and the QEEG and/or repeat PET or computed tomography. Response to treatment is monitored by telephone communication and follow-up office visits as determined by the clinical course of the SIT [1,37].

Combined Treatment: Affect Component

A psychiatric consultation is recommended for evaluation and treatment of associated anxiety and depression or both and to consider the drug Klonopin if no medical contraindication (see Table 4).

Step 6: Tinnitus patients, predominantly central type, resistant to attempts tinnitus relief in steps 1–5 are recommended instrumentation in consultation with audiology. (see Table 5).

Results of Pharmacotherapy and Instrumentation

Since 2006, the observational results of TTT for attempting tinnitus treatment, relief, and control have been approximately the following:

Medication: 75% to 85%
Factors: 50%
Aeration: 15%
SEH: 35%
Instrumentation: 5% to 10%
Problems: 10% to 15%

ALTERNATE THERAPIES

Transcranial magnetic stimulation (TMS) research protocols have reported significant short-term tinnitus relief [48,49]. Cognitive therapy has reported tinnitus relief.[50]. Ultra-quiet therapy utilizing ultra-high-frequency stimulation has provided tinnitus relief in a particular cohort of SIT patients , however is not available at this time [47]. Biofeedback utilizing the results of QEEG for attempting to induce the alpha rhythm continues to have application in a predominantly central-type tinnitus.[33]

Surgery

In general, the results of surgery, both clinical and as research protocols for tinnitus relief, have increased since 2006. Results have been more satisfactory for objective tinnitus than for SIT.

Significant tinnitus relief with intratympanic steroid therapy has been reported for a predominantly cochlear-type tinnitus [51,52]. Tinnitus relief with auditory cortical stimulation has been reported [53] as has the surgical application of a cochlear implant in a tinnitus patient [54].

Future

We look to the future for advances in the discipline of tinnitology for tinnitus theory, diagnosis, and auditory neuroscience of sensation and brain function to provide translation for development of new and increased efficacy of existing modalities of therapy for all clinical types of tinnitus.

These advances will reinforce the alteration in the paradigm of thinking of tinnitus, as recommended in 1983, from a focus on the ear and the psychoacoustic and psychophysical characteristics of the tinnitus to that of the ear and associated multiple brain functions as reflected clinically in the heterogeneity of tinnitus at this time.

For pharmacotherapeutic approaches, we look to the development of drugs specifically targeting tinnitus (i.e., a tinnitopharmacology) . The endgame is to identify the neurobiology and pathophysiology of all clinical types of tinnitus that will provide a basis for development of a tinnitus pharmacotherapy by identification of the kinetics of gene expression in the brain of SIT patients and the specific function of the proteins involved in SIT patients with different clinical types of tinnitus (i.e., tinnitoproteogenomics).

In summary, we look forward to the pharmacological evolution of tinnitopharmaco-proteogenomics, defined as pharmacology for tinnitus based on what is known of the genetic diversity and protein functions demonstrated by tinnitus patients with different clinical types of tinnitus.

We hypothesize that future identification of epilepsy genes can provide an insight into the molecular basis of neuronal excitability and brain function, which will have application for a particular central-type tinnitus.

For instrumentation, we look forward to refinement of existing technologies and development of new devices, particularly with a focus on auditory masking, electrical stimulation, and transcortical magnetic stimulation, alone and/or in combination, transcutaneous and/or cortical in location.

For surgery, we look forward to expansion of intratympanic drug delivery systems, with a focus on hearing conservation, which we predict will result in increasing degrees of reported tinnitus relief. Cortical brain approaches with extra- or intracranial TMS (electrical stimulation), alone or in combination with drug therapies, will offer to patients with predominantly central-type tinnitus an increased degree of efficacy for tinnitus relief.

Alternate therapies will report in the future an increased significance for tinnitus relief with cognitive therapy and acupuncture as an accompaniment of anticipated advances in understanding brain function. A “cure” for tinnitus is the ultimate goal of both tinnitus patients and all professionals involved in tinnitology. It will come as an accompaniment of advances reported in auditory neuroscience and that of sensation and brain function.

CONCLUSIONS

Principles of tinnitology for diagnosis and treatment provide a “roadmap” for tinnitus theory, diagnosis, and treatment (i.e., attempting to achieve tinnitus relief).

The hypotheses of the FCP for tinnitus and tinnitus dyssynchrony/synchrony together with advances in auditory neuroscience and that of sensation provide a theoretical basis for establishment of increased clinical accuracy for tinnitus diagnosis and treatment.

Tinnitus diagnostic accuracy is essential for any and all attempts at tinnitus relief.

The reality is that no cure for tinnitus is available at this time. Protocols for tinnitus diagnosis and treatment are available to identify factors/conditions in ear/brain that, when treated, may result in tinnitus relief in a significant number of tinnitus patients.

The MATPP is presented as a dynamic neuro-otological-audiological protocol reflecting advances in tinnitology and neuroscience; it provides increased diagnostic accuracy, a monitoring system for all clinical types of tinnitus, and translation for increased efficacy of tinnitus relief.

A combined therapy of medication and instrumentation is recommended for attempting tinnitus treatment (i.e., TTT).

Tinnitus is not a unitary symptom. Clinical types and subtypes of tinnitus have been identified. Neuroanatomical substrates have been identified in tinnitus patients. Tinnitus is not a phantom symptom or phenomenon.

A paradigm switch for clinical thinking of tinnitus is recommended to concentrate on brain function responses to an aberrant dyssynchronous auditory sensory input and in particular consciousness and affect, respecting the psychophysical and psychoacoustic characteristics of the tinnitus.

A biochemical marker, the GABA-A receptor, that has been identified provides translation for treatment, called RTT-GABA, of a predominantly central-type tinnitus. It is the forerunner of others to follow.

The future is positive for both tinnitus diagnosis and treatment. Tinnitopharmacolgy and tinnitopharmacoproteogenomics is the future for pharmacotherapeutic treatment of different clinical types of tinnitus.

No longer can the patient be told to "live with it."

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