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Pharmacotherapy for Severe, Disabling, Subjective, Idiopathic Tinnitus: 2005–2006

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Abstract: We present a tinnitus-targeted therapy (TTT), a combined treatment of medication and instrumentation focusing on pharmacotherapy [1,2]. It embodies ongoing clinical experience (since 1977) in an excess of 8,500 patients with subjective idiopathic tinnitus of the severe disabling type (SIT). All have visited the Tinnitus Clinic of the Downstate Medical Center at the State University of New York (DMC/SUNY) and the Martha Entenmann Tinnitus Research Center, Inc. [1,2].

Since 1989, as a result of our evolving experience with single-photon emission computed tomography (SPECT) of brain, we have defined tinnitus as a sensory disorder of auditory perception exhibiting an aberrant auditory signal produced by interference in the excitatory-inhibitory process or processes involved in neurotransmission [1,2]. This definition is considered to be dynamic: It embodies the integration of clinical observations and advances reported from neuroscience and nuclear medicine. These investigations have sought to identify an underlying mechanism of tinnitus production and have assisted in the establishment of the medical significance of tinnitus [1–3].

In general, the goal of tinnitus therapy in 2005–2006 is to attempt to provide tinnitus relief for all clinical types of subjective idiopathic tinnitus (SIT). Although no cure for SIT exists currently, available protocols for diagnosis and treatment increase the efficacy of therapeutic modalities for attempting tinnitus relief [1,2].

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 SPECT in SIT patients, hypotheses of mechanisms of tinnitus production, and the innovative application of drug therapies designed for indications other than tinnitus [1,2]. Such strategies have contributed to the development of a new discipline, tinnitology, an integrated multidiscipline of basic science, neuroscience, and clinical medicine attempting to understand an aberrant auditory phenomenon, unrelated to an external source of sound, and how it becomes transformed into one of affect.

The goal of increasing accuracy of the SIT diagnosis is the impetus for increased efficacy of therapeutic modalities recommended for tinnitus relief.

Key Words: GABA; receptor-targeted therapy; tinnitopharmacogenomics; tinnitus-targeted therapy

Initially, our approach for tinnitus treatment was based on the classical teaching of tinnitus as a unitary symptom investigated and reported for its psychophysical and psychoacoustic characteristics. Investigation focused on the ear and on etiology identified in the clinical history. Subjective idiopathic tinnitus (SIT) is clinically considered a symptom of neurotological disease. The evaluation of SIT and attempts for tinnitus relief require a team approach highlighted at this time by the disciplines of neurotology and audiology. The formulation of a dynamic medical-audiological tinnitus patient protocol (MATPP) that includes advances in the new tinnitology discipline has been ongoing. MATPP

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combines a neurotological clinical approach to attempting to objectify SIT for each tinnitus patient by integrating a patient's SIT history with the electrodiagnostic results of cochleovestibular testing and by correlating structure and function. MATPP has provided for each SIT patient identification of factors influencing SIT's clinical course, electrodiagnostic correlates of cochleovestibular function, the identification of clinical types of tinnitus, and a rationale for attempting tinnitus relief.

Since 1996, we have reported increased efficacy in tinnitus relief. This success is based on our clinical experience, which is teaching us that tinnitus is *not* a unitary symptom and that different clinical types and subtypes of tinnitus have been identified [1,2]. Furthermore, we have learned that it is essential to translate the basic science of sensory phenomena and neuroscience of brain function for the interpretation of MATPP results so as to establish the medical significance of tinnitus and to provide a rationale for selection and evaluation of therapeutic modalities attempting tinnitus relief.

Consultation for SIT should be preceded by a patient's complete physical examination and blood tests to focus on identifying and treating, as appropriate, any underlying systemic complaint, particularly those of cardiac, hematological, metabolic, and central nervous system (CNS) origin. The neurotological examination should exclude major diseases of the head and neck, rather focusing on cranial nerve function and extraocular eye movement disorders and identifying overall normal and abnormal cochleovestibular system function or dysfunction.

A hearing test establishes a threshold of hearing for the classical frequencies of 250–8,000 cycles. For an asymmetrical sensorineural hearing loss or unilateral SIT (or both), we recommend the completion of tests of auditory brainstem response or magnetic resonance imaging (or both) of the brain and internal auditory canals with gadolinium to identify the presence or absence of acoustic tumor. A patient's clinical history and results of the initial workup determine the extent of additional recommendations for identifying the role of the brain for SIT (i.e., SPECT and quantitative electroencephalography to improve the accuracy of the tinnitus diagnosis and to provide a monitoring system for evaluation of the efficacy of therapeutic modalities aimed at tinnitus relief). Follow-up visits with a neurotologist and an audiologist establish an individual tinnitus-targeted therapy (TTT) for each SIT patient, depending on the clinical type of tinnitus and consisting of a combination of instrumentation and medication [1,2]. SIT patients should not be told simply to "live with it."

Strategies of tinnitus relief based on underlying mechanisms hypothesized to be present for hearing and vestibular function or dysfunction were introduced in 1979. Initial treatment with instrumentation, including hearing aids and maskers, produced limited tinnitus relief reported to be approximately 25% in the long term. Identification of factors influencing the clinical course of tinnitus, including aeration in middle-ear fluctuation and secondary endolymphatic hydrops (SEH), comprised our initiation into the increased results of tinnitus relief obtained by a combination of instrumentation and medication. The clinical application of nuclear medicine imaging results—revealing perfusion asymmetries in multiple regions of the brain and the clinical translation of neuroscience to the selection of medication based on underlying neurochemistry of neurotransmitter activity in such areas—has expanded our innovative selection of medication for a predominantly central-type tinnitus. Clinical results reported with identification of epileptogenic foci with SPECT of brain, the identification of a biochemical marker for a predominantly central-type tinnitus, and the GABA-A receptor have supported the innovative application of antiexcitatory drugs (AED) for a particular type of tinnitus, predominantly the central type.

In summary, current results with medication have been and are resulting in a shortening of the interval between prescription and achieving tinnitus relief with medication, in contrast to that with instrumentation. This article summarizes TTT modalities of pharmacotherapy recommended for attempting tinnitus relief. We focus on identifying and treating factors known to influence the clinical course of SIT, identifying a biochemical marker for tinnitus—the GABA-A receptor—and a receptor-targeted therapy (RTT) directed to the GABA-A receptor. We refer the reader to appropriate references for details of instrumentation recommendations. In this report, the term *tinnitus* refers to SIT.

REALITIES AND PRINCIPLES OF SENSORY PHYSIOLOGY AND TINNITUS TREATMENT: MEDICAL SIGNIFICANCE

Realities

SIT patients and professionals involved in attempting tinnitus treatment should accept the realities of state-of-the-art tinnitus diagnosis and treatment at this time. Realities for attempting tinnitus relief in 2005–2006 include the following:

- There is no cure for tinnitus at this time.
- Treatment is based on the accuracy of tinnitus diagnosis.
- Not all tinnitus is the same. It is necessary to differentiate between patients with the symptom of SIT and those with occasional tinnitus or tinnitus that is present but not disabling.

- Tinnitus is not a unitary symptom; different types and subtypes of tinnitus exist.
- Tinnitus is chronic, multifactorial, and heterogeneous, all of which is reflected in its clinical course.
- Tinnitus has a medical significance for each patient.
- Though no cure for tinnitus exists, systems are available for attempting tinnitus relief through management.
- Treatment recommendations are based on a dilemma that continues to exist for the symptom of tinnitus and aberrant auditory phenomena unrelated to an external source of sound: How does a sensory phenomenon become transposed or translated to one of affect, and how does the reverse take place?
- The key to efficacy for tinnitus treatment depends on accuracy of tinnitus diagnosis. The completion of an MATPP with examination of the cochleovestibular system (both ear and brain) improves the accuracy of the SIT diagnosis and efficacy of any modality recommended for attempting tinnitus relief.

Principles of Sensory Physiology

Tinnitus is an aberrant auditory sensation. Recommendations for tinnitus relief should specify and differentiate among the components of the aberrant auditory sensation. Basic sensory physiology teaches that every sensation has three components: The sensory component is the sensation itself; the affect component is the behavioral response of a patient to a sensation; and the psychomotor component is the somatomotor response of the behavioral component of tinnitus. Treatment recommendations should differentiate among components of the tinnitus complaint.

In general, for the SIT sensory component, we advise a combination of instrumentation and medication. For the affect component, focusing predominantly on anxiety and depression, we recommend appropriate anxiolytic and antidepressant medication. Fear is a significant factor in new patients with SIT, and appropriate psychiatric medication or psychotherapy (or both) should be implemented. Of special consideration is that a significant number of patients, particularly those in the geriatric population, have associated complaints of interference in memory and cognition. We recommend appropriate neurodegenerative drugs or memory enhancers (or both).

Medical Significance

The medical significance of tinnitus [3] is that it is a spectrum of clinical manifestations of interference in the function of the cochlear vestibular system comprising sensory, affect, and psychomotor components. The symptom of tinnitus has a medical significance for each tinnitus patient [3]. Its identification influences treatment recommendations. The translation of known and hypothesized mechanisms underlying SIT's medical significance has been the basis for innovative selection of drugs attempting tinnitus relief (e.g., gradual, progressive sensorineural hearing loss; control of cerebrovascular disease; hypertension; metabolic factors of cardiac function; and endocrine disturbance highlighted by thyroid and sugar metabolic dysfunction).

WHAT IS KNOWN OF TINNITUS IN 2005?

By the close of 2005, certain factors were known about tinnitus. A function of the auditory system is masking, and the masking response of tinnitus patients is individual. Identification of the masking curve for a SIT patient is the basis for selecting a particular type of instrumentation, called a *hearing aid* or a *tinnitus masker*. Noise exposure increases the intensity of tinnitus, so noise control is a prerequisite for any tinnitus relief recommendation.

Hearing loss of a sensorineural type frequently accompanies the symptom of tinnitus. There is, however, no association between the severity of the hearing loss and the severity of the tinnitus. The complexities of tinnitus are reflected in difficulties in establishing an accurate diagnosis and treatment. The complexities mirror what is and is not known of the underlying anatomy, biochemistry, and physiology of the cochleovestibular system, brain function, and the mind. Tinnitus—an aberrant auditory perception—involves processes of cognition and memory. It is influenced by stress, the environment and, in particular with aging, by neurodegeneration.

A biochemical marker of a GABA-A receptor has been identified in a predominantly central-type tinnitus. We know that SIT patients examined with SPECT of brain demonstrate a significant incidence of perfusion asymmetries in multiple regions of interest in the brain, highlighted by the medial-temporal lobe system. SPECT of brain findings have been the basis underlying a hypothesis of a final common pathway for tinnitus modulated by stress, which explains the transformation of a sensation to one of affect and vice versa [4,5].

PRINCIPLES OF TINNITOLOGY

Principles of tinnitology have evolved from our clinical experience and application of the MATPP, which influences attempts for tinnitus relief. These principles are as follows [1,2]:

- Components of tinnitus have been recommended on the basis of what is known in sensory physiology for all sensations (e.g., the sensory, the affect, and the psychomotor).
- Factors have been identified that influence the clinical course of SIT and that result in significant tinnitus relief when treated.
- Secondary SEH and fluctuation in aeration of the middle ears have been diagnosed in a significant number of SIT patients. Identification and treatment result in an increased efficacy of treatment modalities attempting tinnitus relief.
- Noise is a significant etiology influencing the clinical course of tinnitus. Increasing noise exposure will result in increasing intensity of tinnitus.
- Stress exacerbates tinnitus intensity. A stress diathesis model for tinnitus has been hypothesized [4,5]. Increasing stress results in anxiety followed by depression. Tinnitus is a stressor in affected patients.
- Tinnitus has a medical significance for each patient [3].
- The masking response is different in each tinnitus patient.
- A biochemical marker—the GABA-A receptor—has been identified for a particular type of tinnitus: a predominantly central-type [6].
- An RTT directed to the GABA-A receptor has resulted in a clinical application for treatment (called *RTT-GABA*) in SIT patients with a predominantly central-type tinnitus [6,7].
- We hypothesize a final common pathway for tinnitus involving multiple regions of interest and an interneural network focused in the medial temporal lobe in the brain, wherein transformation of a sensation into one of affect takes place, modulated by stress. The primary process is considered to be the establishment of paradoxical auditory memory [4,5].
- Tinnitus is not a phantom phenomenon. Electrodiagnostic, physiological, and biochemical changes that have been identified are significant for different clinical types of tinnitus [5–7].
- The ultra-high audiometric response can be used for identifying SIT patients who may benefit from acoustic stimulation using ultra-high-frequency stimulation.
- Combined treatment (instrumentation and medication) offers the greatest success for attempting tinnitus relief [1,2,8].

FACTORS INFLUENCING THE CLINICAL COURSE OF TINNITUS

Identification and treatment of factors influencing the clinical course of tinnitus have resulted in tinnitus relief. Failure of such identification has been found to interfere in the efficacy of recommendations of medication or instrumentation (or both) attempting tinnitus relief.

SEH has been found in SIT patients with and without vertigo [9]. We recommend treatment with diuretic therapy, antihistamine, and diet-elimination stimulants. The incidence of occurrence of secondary SEH is approximately 35% in our series overall. The control of SEH indirectly contributes to tinnitus relief by increasing the efficacy of instrumentation attempting tinnitus relief and by stabilizing sensorineural hearing loss [1,2,9].

Fluctuation in aeration of the middle ear may influence tinnitus intensity. Identification of inflammatory or allergic conditions of the nose, paranasal sinuses, and throat, and secondary Eustachian tube dysfunction, and treatment with systemic antihistamine-decongestant medication and local treatment (including pneumootoscopy) have resulted in tinnitus relief in approximately 10–15% of our SIT patients.

We recommend both adequate noise protection with ear defenders and avoidance of noise. Compliance is critical for any recommendations attempting tinnitus relief.

Metabolic abnormalities in glucose, cholesterol, triglyceride, or thyroid function, either alone or in combination, may influence the clinical course of sensorineural hearing loss and SIT. Treatment involves identification and follow-up with an internist to ensure satisfactory control. A synergy that has been identified among hypertension, hyperlipidemia, and noise exposure has resulted in gradual, progressive sensorineural hearing loss.

SIT patients with hypercholesterolemia and triglyceride elevation have also reported tinnitus relief from treatment attempting to improve the oxygen-carrying capacity of blood. We recommend pentoxifylline (Trental), 40 mg, titrated to once daily or a maximum of thrice daily, if no medical contraindication exists.

Fluctuation in hypertension is, in our experience, the most frequent significant cardiovascular factor involved in the clinical course of SIT. Its identification and control are considered fundamental for any attempts at tinnitus relief. Cardiac arrhythmias, particularly auricular fibrillation with potential consequences for emboli formation, are significant. Treatment should be directed by an internist.

Identification and treatment of cerebrovascular disease, epilepsy, and memory and cognitive disorders in appropriate SIT patients have been found to accompany SIT relief. Such drugs include the vasodilator papaverine for cerebrovascular insufficiency, clopidogrel disulfate (Plavix) in transient ischemic attack and post-stroke patients, and antiseizure drugs for epilepsy. For memory and cognition, we recommend the neuroprotective drugs donepezil hydrochloride (Aricept), tacrine, memantine, gabapentin, and clonazepam (Klonopin). These drugs

attempt to improve the status of the underlying neuronal substrate that may be contributing to SIT.

When identified by integration of a patient's clinical history and tomographic examination of the temporal bones, otosclerosis is considered to be a factor influencing the clinical course of tinnitus. Recommended treatment starts with etidronate (Didronel), 400 mg once daily for 2 weeks, followed by calcium carbonate with vitamin D for 4 weeks, to be repeated every 3 months [10]. Affective disorders [1,2] highlighted by anxiety and depression are significant complaints associated with SIT. Appropriate medication for anxiety or depression (or both) may secondarily influence SIT. In general, the prevalence is 5–6 million Americans older than 65 years, and 1 in 6 suffers from depression. Between 25 and 40% of cognitively impaired nursing-home residents suffer from an underlying depression, which is frequently overlooked and untreated. Depression in the elderly is similar to depression in other age groups. Major depression is an incapacitating illness affecting 11 million more Americans each year. It is a medical syndrome associated with diabetes and other CNS diagnoses.

The stress diathesis model for depression has been translated to understand anxiety and depression associated with SIT [4,5]. Specifically, increasing stress results in the clinical manifestation of anxiety and, over time, depression. The stress diathesis theory for depression has been translated for tinnitus (i.e., stress diathesis theory for tinnitus; reference stress diathesis theory for tinnitus). The chronic nature of SIT suggests long-term treatment. Psychiatric consultation is advised to take advantage of professional experience with anxiety and depression. Drug selection is at the discretion of a psychiatrist or psychologist. Anxiolytic and antidepressant medications, when recommended, may result in tinnitus. Selection of medication involving neurotransmitter systems (other than that of the involved drug in question) are then to be used in drug selection.

Significant in the literature are reports that when anxiolytic and antidepressant medication is claimed to be associated with tinnitus production or with increased tinnitus intensity, withdrawal of the drug has resulted in elimination of the tinnitus. Treatment of the anxiety and depression is considered critical for success of any and all attempts for the sensory component.

DRUG THERAPY AND TINNITUS CONTROL

Initial Attempts at Tinnitus Control: 1977–1979

Initial attempts at tinnitus control from 1977 to 1979 [11] included primarily instrumentation and, secondarily, medical therapy. The rationale for drug selection was based on known etiologies that targeted the ear and inner-ear complaints highlighted by sensorineural hearing loss and vertigo (i.e., blood flow, infection, trauma, and allergy) and by the hypotheses of underlying mechanisms of hearing loss and vertigo at that time.

The selection of medication involved certain strategies, such as identification and treatment of underlying factors influencing the clinical course of tinnitus (i.e., fluctuation and aeration of the middle ears bilaterally and presence or absence of SEH treated as one would treat Ménière's disease).

Vasodilator therapy included the use of nylidrine (Arlidin), attempted in 1997, either alone or in combination with the antihistamines (e.g., chlorpheniramine [Chlor-Trimeton], 8 mg twice daily). Overall, this therapy was not effective. Positive reports in the literature include the use of papaverine, 100–115 mg daily, or papaverine (Pavabid), 125 mg twice daily (or both).

Benzodiazepines were recommended initially and have been continued for tinnitus control since 1983 [1,2]. Klonopin has been reported by SIT patients to be effective for sleep. Although Klonopin is not a drug specifically meant for tinnitus, some SIT patients report tinnitus relief following improved sleep. In general, in prescribing benzodiazepines, the issues of tolerance and habituation are significant. Until 1996, Klonopin, 0.25 mg at bedtime, was recommended for sleep and anxiety associated with SIT.

Lidocaine therapy in attempting tinnitus control was introduced in 1980. SIT patients reported tinnitus relief to be positive, negative, and unchanged. Lidocaine, 2–5 mg intravenously (IV), was initially injected as a test dose over a 1- to 3-minute period. If tolerated, it was followed by 100 mg in 100 ml 5% glucose in water delivered IV, and the next day by 200 mg in 250 ml 5% glucose in water. If an affected patient reported tinnitus relief, tocainide (an oral preparation), 40–600 mg four times daily, was recommended. The short duration of the tinnitus relief, the need for repeated injections, and significant side effects with the oral preparation of tocainide has limited its use. Lidocaine has been recommended since 1998 by intratympanic injection, alone or in combination with steroid, for a predominantly cochlear-type tinnitus.

Since 1987, alteration of blood viscosity has resulted in tinnitus relief with Trental, 400 mg, not to exceed one tablet thrice daily if not medically contraindicated. The rationale is to increase the oxygen-carrying capacity of the blood.

Attempted Tinnitus Relief Using Drugs for the Sensory Component of SIT, 1979–1989

A wide variety of drugs has been used to address the sensory component of SIT in an effort to attempt tinnitus relief. Among them are the following.

Trental, 400 mg tid (cochlear-type SIT)
Nimodipine, 30 mg tid
Nifedipine (Procardia), 30–60 mg/day
Steroid: prednisone 10–20 mg/day for 7–10 days
Cytotec, 100–200 μg once daily–qid (cochlear-type SIT)
Baclofen, 5–10 mg/day (40–80 mg/day)
Carbamazepine (Tegretol), 200–800 mg/day
Valproate (Depakene and Depakote), 5–10 mg/kg/day at 1-week intervals, until tinnitus is controlled or until clinical and biochemical sign(s) of toxicity appear; maximum 60 mg/kg/day divided into two to four doses; therapeutic serum levels 50–150 μg/ml; baseline liver function tests, serum amylase levels, complete blood cell and platelet counts, repeated at frequent intervals
Dilantin, 50 mg tid
Tiagabine (Gabitril), 4 mg once daily increasing to 32 mg/day (2003)
Papaverine, 100–150 mg/day
Pavabid, 1–5 mg bid
Furosemide, 80 mg IV test dose (cochlear-type SIT)
Supportive therapy (cochlear- and/or central-type SIT): antioxidants, multivitamin, vitamin E 400 mg/day
Memory and cognition: memantine, 5 mg once daily, increasing weekly to 10 mg bid (2004); *Gingko biloba*, extract 761, 60–160 mg/day

Attempted Tinnitus Relief Using Drugs for the Affect Component of SIT

The prescribing of anxiolytic and antidepressant medication in consultation with a psychiatrist or a psychologist is recommended [1,2]. Particular attention is needed for avoidance of tolerance and habituation. The use of benzodiazepines (e.g., clonazepam, alprazolam, and oxazepam) has provided substantial control of SIT in our experience when SIT is of the central type. All patients to whom such recommendation is made need to be followed by careful and accurate diagnosis of the anxiety and depression. If and when these disorders are present, the patient should be evaluated on an individual basis via an appropriate psychiatric consultation. Barbiturates generally are avoided.

Tricyclic and heterocyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors can be considered for the treatment of depression but not of tinnitus. Either tinnitus relief or exacerbation may accompany the use of such agents for depression. If an exacerbation of tinnitus occurs, we recommend withdrawing the antidepressant. The physician considering an alternate selection should avoid a drug of similar pharmacokinetic action [1,2].

Recommendations for drug selection for the affect component of SIT include the following considerations:
Nortriptyline, 50–150 mg/day; amitriptyline, 10 mg/day
Paroxetine (Paxil), 20 mg/day
Fluoxetine (Prozac), 20–80 mg/day
Sertraline (Zoloft), 25–50 mg/day
Bupropion (Wellbutrin), 100 mg twice daily
Venlafaxine (Effexor), 75–150 mg/day
Valproate (Depakene and Depakote), initial dose of 15 mg/kg/day with increases of 5–10 mg/kg/day at 1-week intervals (maximum dose, 60 mg/kg/day divided into two to four doses); therapeutic serum levels, 50–150 μg/ml

Summary, 1977–1989

Drug therapy attempting tinnitus relief was limited to control of a factor or factors identified as influencing the clinical course of tinnitus. The emphasis was on instrumentation, not medication or surgery. The complexity of the symptom of tinnitus is reflected in the multiple methods proposed for attempting tinnitus relief. The variability in tinnitus relief reported with multiple therapies is a reflection of the heterogeneity of tinnitus. Old approaches recommended a single modality of therapy that included predominantly instrumentation, occasionally medication, and rarely surgery. The new approach that is recommended is a combined therapy directed to underlying clinical types of tinnitus, any of which may exist alone or in combination.

Drug Selection Attempting Tinnitus Relief and Influencing Particular Neurotransmitter Systems, Neuroprotection, and RTTs, 1989–2006

New approaches include the concept that drug selection attempting tinnitus relief should influence the underlying neurochemistry of specific neurotransmitter systems [7, 12], as reflected by nuclear medicine imaging studies and extrapolated for brain function. Second, drugs selected for attempting tinnitus relief should be directed specifically to an underlying hypothesized mechanism of tinnitus production for a particular clinical type of SIT. Third, an RTT should focus on the GABA-A receptor to increase the inhibitory action of GABA (RTT-GABA).

TINNITUS-TARGETED THERAPY AND MEDICATION, 1989–2006

We recommend a TTT protocol for all SIT patients [1, 2,7,12]. It is a therapy combining instrumentation and medication. The increasing efficacy of drug therapy—

single or multiple agents—for tinnitus relief is reflected in a reduction in recommendations for instrumentation. TTT recognizes the principle of tinnitology: that not all modalities of tinnitus control, all neurotransmitters, and all medications are the same for all SIT patients. Drug therapies are individual for each SIT patient.

The therapeutic efficacy of a given drug is increased by accurate diagnosis of the clinical type of tinnitus. Drug recommendations need to specify the component of the SIT for which the drug is targeted (i.e., sensory and affect). An important consideration for the affect component is that different types of depression are recognized. Appropriate differentiation for selection of antidepressants must be based on such diagnosis. Consider also that the difficulty in evaluating the efficacy of various medications for SIT is the inherent inability to observe differences owing to lack of initial differentiation of the underlying clinical type or subtype of tinnitus, similar to that reported for depression.

Pharmacotherapeutic Management Principles

We recommend that pharmacotherapeutic management principles be followed. 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 must 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.

Pharmacotherapeutic Concepts and Hypotheses

The following concepts have been introduced for attempting to understand the symptom of tinnitus and for drug selection in attempting tinnitus relief.

Glutamate Neuroexcitotoxicity Theory

In general, increasing the concentrations of cytosolic calcium, initiated by glutamate, results in increasing interference in intracellular function and eventual cell death [13]. The symptomatology is seen in the involved neural substrate. The activity is hypothesized to occur in stages.

Stage 1 involves induction: Cell depth induction initiated by intracellular glutamate action on calcium receptors results in intracellular calcium overload and intracellular derangements. Stage 2 manifests amplification. Increased intracellular calcium concentration results in modulatory events that recruit additional neurons into the injury process. Stage 3 embodies expression: increased interference in cellular function and eventual cell death (i.e., apoptosis).

The Calpain Theory of Apoptosis

Calpain is a normal intracellular cytosolic protease considered to be a membrane in location [14,15]. Its activation by excessive intracellular calcium results in a cascade of changes resulting in apoptosis. The action is one of intracellular proteolysis. A final common pathway for calpain has been proposed, which is characterized by intracellular destruction and membrane protein destruction. It may or may not be the site for neuroprotective agents. A known calpain inhibitor is leupeptin. Basic science experiments have identified the neuroprotective activity of calpain for noise protection and to counter the ototoxic effects of aminoglycoside antibiotics (e.g., gentamicin).

Neuroprotection

Neuroprotection is defined as those processes involved in the maintenance and repair of normal neuronal function [12]. A neuroprotective-neurochemistry protocol has evolved for SIT and has been applied on the basis of use of neuroprotective drugs directed to pathology modification of etiologies of inflammation, trauma, ischemia, hemorrhage, neurodegeneration, and neurotrophic factors. Clinical etiologies for drug targeting include inflammation, fluctuation, aeration of the middle ear, SEH, oxidative stress, neurotrophic factors, and protein-processing modification drugs.

Benzodiazepine Deficiency, Stress, and SIT

A benzodiazepine deficiency is hypothesized to be present in SIT patients [6]. The course of SIT, a stressor, is clinically manifest in a reduction in the inhibitory activity of the GABA-A receptor, which is deficient and cannot counter the aberrant auditory signal. That lack results in SIT.

ONGOING NEW DRUG STRATEGY, 1991–2006

New neuroprotective and neurochemistry strategies of drug selection for a given type of SIT involve a sensory-modifying approach based on the underlying pathology. This memory-cognition enhancement approach is based on the presence or absence of interference in memory and cognition and an approach directed to the affect component of the tinnitus.

Receptor-Targeted Therapy

We speak of RTTs based on identification of the underlying neurotransmitter systems [7]. An RTT is defined as therapy directed at influencing the physiological and biochemical function of neurotransmitter systems at membrane receptor sites. 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.

Preliminary results with ^{123}I Iomazenil, a benzodiazepine ligand, has with SPECT of brain identified diminished benzodiazepine-binding sites in the medial temporal cortex of those with severe tinnitus. This is consistent with a hypothesis implicating GABAergic mechanisms in the pathophysiology of a tinnitus disorder.

The GABA-A benzodiazepine-chloride receptor (GABA-AR) is a functional pentameric receptor performed by five families, 27 units, and covered by 20 or more genes. The GABA-AR subtypes contain at least one each of the alpha, beta, and gamma subunits. The GABA-A receptor is the predominant CNS inhibitory neurotransmitter. The degree of inhibition is controlled by the degree of chloride flux through the GABA-A membrane receptor (GABA-AR). Attachments to the GABA-AR, in addition to GABA, can include benzodiazepines, steroids, and anesthetic agents (e.g., lidocaine). The attachment of any of these drugs increases the chloride flux, with resultant increase in inhibition. Significantly, the GABA-AR exhibits a site specificity and a pharmacokinetic specificity. The differential effects of benzodiazepines must be watched for both tolerance and habituation [16].

Region specificity clearly identifies alprazolam as resident in the cortex and hypothalamus. Lorazepam region specificity places it in the cortex, the hypothalamus, and the hippocampus. Therefore, the administration of alprazolam or lorazepam is hypothesized to be effective only in those SIT patients with a deficiency of benzodiazepine or the GABA-AR receptor in these areas. If not, the benzodiazepine will have either a lessened clinical efficacy or differential effects [17].

The turnover regulation of the GABA-A receptor dynamics involving the synthesis of the GABA-A, its degradation, and upregulation and downregulation, all have clinical application for RTT-GABA efficacy. The response of tinnitus patients to RTT-GABA receptor activity is considered to reflect the turnover regulation of the GABA-AR receptor.

Stress and RTT-GABA

Stress

Stress is significant in the clinical course of SIT. Specific chemical and biochemical alterations have been identified in the rat stress model as reported by McEwen et al. [18]. These include an increase of the glucocorticoid, an increase in *N*-methyl-D-aspartate receptors, an increase in the excitatory glutamatergic receptors, a decrease in the GABA receptors, and an increase in serotonin. A clinical consideration is the relevance of the modulating effect of stress on the final common pathway for tinnitus (SIT).

RTT Directed at the GABA-A-Benzodiazepine-Chloride Receptor

We recommend an RTT-GABA for the diagnosis of a predominantly central-type tinnitus [7]. It is an innovative application of AED medication 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 GABAergic activity.

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 or other tinnitus protocol. There should be some indication of involvement of the CNS before use of an innovative application of AEDs. We recommend this to support the clinical diagnosis of a predominantly central-type tinnitus. This may include magnetic resonance imaging of the brain with a baseline gadolinium or SPECT of brain (both baseline or after a stress Diamox test) and the auditory brainstem response for short latency responses. In our SIT series of RTT-GABA, tinnitogenesis, an epileptic focus of activity, has been identified by SPECT of brain. Patients are offered the options for instrumentation and should have already undergone treatment for factors identified as present in the clinical course of tinnitus as described earlier.

Medication for the affect component consistent with psychiatric consultation has been followed. Gabapentin has been selected and is considered to have GABAergic activity. The exact site of action is not known. Recent reports have indicated that gabapentin is a calcium channel–blocking agent. 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). The TAI is a scale from 0 to 7: The tinnitus is stated as unbearable at 7 and absent

at 0. The dose titration level is determined by the clinical TII. Some patients may achieve efficacy by once-a-day or alternative days' 100-mg dosing. The maximum dose that one patient has received has been 3,700 mg/day. The efficacy is individual. The earliest reported tinnitus relief has been within 1 week, although the majority of patients report tinnitus relief within 2–6 weeks.

The benzodiazepine (Klonopin) dose recommended is 0.25 mg at bedtime. The rationale is to augment the chloride flux by its attachment to the GABA-AR receptor. The dose per day 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. The TAI is also on a 0–7 scale, with 7 being unbearable annoyance and 0 absent annoyance.

Some patients achieve efficacy with 0.25 mg at bedtime every other night. Many patients report an improvement of sleep. On awakening, they have also reported the SIT to be relieved. We do not recommend that supplementary Klonopin dosing be exceeded based on TIA and TIA indices but rather that the dose be maintained as described earlier. Higher doses of benzodiazepines, in general, are recommended for prescription by a consulting psychiatrist as needed.

Klonopin is prescribed to potentiate the chloride flux of the GABA-AR (i.e., increased inhibition). Other GABAergic drug activities have been demonstrated with carbamazepine, 200–800 mg/day. We recommend liver and blood tests approximately every 2 weeks to test for liver or blood abnormalities (or both).

RTT-GABA therapy has resulted in significant long-term maintenance of tinnitus relief in 90–95% of SIT patients with a predominantly central-type tinnitus, in excess of the patients. Sequential SPECT brain studies support the clinical impression of a benzodiazepine deficiency syndrome in some tinnitus patients. The GABAergic mechanism is clinically thought to be involved in the clinical course of SIT of a predominantly central type and in its control (i.e., relief).

Long-term tinnitus control can now be reported to be increased to 85% with medication. The recommendation of instrumentation has been reduced but is effective in approximately 10% of affected patients. Persistent problems of 5–10% still occur.

SUMMARY: NEUROPROTECTIVE PROTOCOL AND RTT-GABA

Attempted Tinnitus Relief for the Sensory Component

The MATPP is used to identify the type of tinnitus present. In the case of a predominantly cochlear-type SIT, a trial of Cytotec or Trental is attempted for 1–3 weeks. If tinnitus relief is achieved, a maintenance dose is established. Intratympanic drug therapy with a steroid should be attempted. If no appreciable result occurs, then trial instrumentation should be used or, if such is declined by the patient, SPECT of brain is performed. If such studies prove negative, a trial of intratympanic steroid and/or trial instrumentation is recommended. If such studies prove positive, RTT-GABA therapy is undertaken for 3–6 weeks. If no tinnitus relief is achieved, then an alternate AED or instrumentation should be tried.

If the MATPP reveals a predominantly central-type SIT, the patient should be presented with options for trial instrumentation. If such is declined, then SPECT of brain is performed and, if positive, RTT/GABA is undertaken.

Attempted Tinnitus Relief for the Affect Component

A psychiatric consult and prescription of an anxiolytic or antidepressive medication is appropriate.

Surgical Therapy

In general, the results of surgery for tinnitus relief are conflicting, and there is no specific surgical procedure for the control of any clinical type of tinnitus at this time. 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 [19,20].

COMBINED METHODS OF TINNITUS CONTROL: TTT

TTT is a protocol including the combination of drugs and instrumentation targeting mechanisms hypothesized to underlie the symptom of different clinical types of tinnitus [1,2,8]. Our first-line recommendation is medication followed by instrumentation.

Available instrumentation consists of hearing aids; tinnitus masks and tinnitus instruments; tinnitus retraining therapy, including low-level noise generators; tape and compact disks of the masking or relaxation external electrical stimulation; and ultra-high-frequency stimulation [1,2,21–23]. There are many devices from which to choose, and there is a rationale for choosing a specific device. Improved instrumentation provides an increased ability to fit tinnitus patients with near-normal hearing, mild high-frequency hearing losses, hyperacusis, and high-frequency tinnitus. We refer the reader to appropriate references for specific information and recommendation of devices [1,2,21–23].

We recommend stress-managing techniques with counseling [8]. Biofeedback techniques using neurotherapy have been recommended since 2000 in an attempt to influence brain rhythm [1,2]. Cognitive therapy may provide significant support to affected patients, particularly for the control of the affect. This is strongly recommended and encouraged [1]. Alternative methods of therapy in the literature include acupuncture, psychotherapy, hypnotherapy, and use of herbal, vitamin, *Gingko biloba* extract 761, and antioxidant drugs. In general, such methods have reported conflicting tinnitus relief results.

FUTURE MODALITIES

The endgame is to identify the neurobiology of tinnitus and to identify the kinetics of gene expression in the brain of SIT patients. We must identify not only the kinetics of the genome but the specific function of the proteins involved in SIT patients with different clinical types of tinnitus (i.e., "tinnitoproteogenomics").

We define the development of drugs focusing on proteogenomics as *tinnitopharmacogenomics*. *Tinnitopharmaco-proteogenomics* is defined as a pharmacology for tinnitus based on what is known of the genetic diversity and protein functions demonstrated by patients with different diagnosed 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.

CONCLUSIONS

The accuracy of the tinnitus diagnosis is critical for the efficacy of therapy modalities attempting tinnitus relief for SIT of the severe disabling type. TTT, a combined approach of instrumentation and medication, has resulted in increasing efficacy of therapeutic modalities in attempted tinnitus relief for SIT of the severe disabling type. We have presented a pharmacotherapy for SIT based on innovative applications of drugs developed for indications other than tinnitus. We recommend specifying the component of the tinnitus to which the pharmacotherapy is directed.

An RTT directed to the GABA-AR (called RTT-GABA), a clinical application attempting tinnitus relief, is a translation of the identification of a biochemical marker—the GABA-AR—for SIT of the severe disabling type. Increasing efficacy of long-term tinnitus relief with pharmacotherapy has replaced instrumentation as a first-line recommendation attempting tinnitus relief.

Tinnitopharmacogenomics is the future for drug development for treating different clinical types of tinnitus. The identification of a biochemical marker, the GABA-AR, for SIT of the severe disabling type is a forerunner of others to follow, all of which will provide a basis for drug development. A hypothesis of a final common pathway for tinnitus provides a concept for the translational application of neuroscience reports of brain function and genomics for clinical application to improve the accuracy of tinnitus diagnosis and treatment.

The concept of tinnitus as a phantom phenomenon should be changed to keep pace with translational neuroscience, which supports its identification as a specific physiological response and not that of a phantom phenomenon. Although no cure is available for tinnitus at this time, protocols for diagnosis and treatment are available and can provide tinnitus relief. No longer should a tinnitus patient be told to "live with it."

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REFERENCES

1. Shulman A, Tonndorf J, Feldmann H, et al. *Tinnitus: Diagnosis/Treatment*. Philadelphia: Lea & Febiger, 1991.
2. Shulman A. Medical audiological evaluation of the tinnitus patient. *Semin Hear* 8(1):7–14, 1987.
3. Shulman A, Goldstein B. Medical significance of tinnitus. *Int Tinnitus J* 3(1):45–50, 1997.
4. Shulman A. Stress model for tinnitus. *Neurotol Newslett* 3(3):53–57, 1998.
5. Shulman A. A final common pathway for tinnitus—medial temporal lobe system. *Int Tinnitus J* 1:115–126, 1995.
6. Shulman A, Strashun AM, Seibyl JP, et al. Benzodiazepine receptor deficiency and tinnitus. *Int Tinnitus J* 6(2): 98–111, 2000.
7. Shulman A, Strashun AM, Goldstein BA. GABA-A–benzodiazepine–chloride-receptor-targeted therapy for tinnitus control: Preliminary report. *Int Tinnitus J* 8:30–36, 2002.
8. Kitahara M. Combined Treatment for Tinnitus. In M Kitahara (ed), *Tinnitus, Pathophysiology and Management*. Tokyo: Igaku-Shoin, 1988:107–117.
9. Shulman A. Secondary endolymphatic hydrops. *Trans Am Acad Otolaryngol Head Neck Surg* 104(1):146–147, 1991.
10. Brookler KH. Editronate for neurootologic symptoms of otosclerosis. *Ear Nose Throat J* 76(6):371–376, 2002.
11. Shulman A. Medical Methods, Drug Therapy, and Tinnitus Control Strategies. In A Shulman, J Tonndorf, H Feld-

mann, et al. (eds), *Tinnitus, Diagnosis/Treatment*. Philadelphia: Lea & Febiger, 1991:453–489.

12. Shulman A. Neuroprotective drug therapy: A medical and pharmacological treatment for tinnitus control. *Int Tinnitus J* 3(2):77–94, 1997.
13. Choi DW. Toward a new pharmacology of ischemic neuronal death. *Ann Intern Med* 110:992–1000, 1989.
14. Shulman A. Noise calpain, calpain inhibitors, and neuroprotection: A preliminary report of tinnitus control. *Int Tinnitus J* 4(2):134–140, 1998.
15. Stracher A. Calpain inhibitors as neuroprotective agents in neurodegenerative disorders. *Int Tinnitus J* 3(2):71–75, 1997.
16. Gelpirin WN, Miller LG, Green Black DJ, Shader RI. Differential effects of chronic lorazepam and alprazolam on BZ binding and GABA-A receptor function. *Br J Pharmacol* 1990.
17. Sieghart W. Differential effects of two drugs on BZ-receptor subtypes and multiplicity of GABA BZ receptors. *Trends Pharmacol Sci* 10:407–411, 1989.
18. McEwen B, Weiss J, Schwartz L. Selective retention of corticosterone by limbic structures in rat brain. *Nature* 220:911, 1968.
19. Sakata E, Itoh A, Ohtsu K, et al. Treatment of cochlear tinnitus. Effect of transtympanic infusion with dexamethasone fluid. *Audiology (Jpn)* 26:148–151, 1983.
20. Shulman A, Goldstein B. Intratympanic drug therapy with steroids for tinnitus control: A preliminary report. *Int Tinnitus J* 6(1):10–20, 2000.
21. Goldstein BA, Shulman A, Lenhardt ML, et al. Long-term inhibition of tinnitus by UltraQuiet therapy: Preliminary report. *Int Tinnitus J* 7(2):122–127, 2001.
22. Jastreboff PJ, Hazell JWP. A neurophysiological approach to tinnitus: Clinical implications. *Br J Audiol* 27:1–11, 1993.
23. Shulman A. External electrical stimulation in tinnitus control. *Am J Otol* 6:110–115, 1985.