
EDITORIAL AND COMMENTARY

Gabapentin and Tinnitus Relief

This editorial and commentary was prompted by the publication of Picirillo et al.'s "Relief of idiopathic subjective tinnitus: Is gabapentin effective?" [1], which concluded that gabapentin was no more effective than a placebo in relieving tinnitus. The goal of this editorial and commentary is constructive: to provide to tinnitus patients and professionals involved with tinnitus diagnosis and treatment (1) a protocol for patient selection in considering an innovative drug application (i.e., gabapentin [GP]) for attempting tinnitus relief; (2) an assessment of the biases in the study that—though scientifically and statistically valid—have led the authors to a conclusion that is not clinically relevant; (3) an understanding of the rationale underlying our recommendation of a combined therapy *including GP*; and (4) a basic understanding of the activity of GP and the concepts of inhibition and neuroprotection.

In general, our recommendation and experience with GP has been positive for achieving tinnitus relief over the long term in a particular cohort of tinnitus patients. Specifically, selected tinnitus patients are those who have accurately diagnosed clinical, predominantly central-type severe, disabling subjective idiopathic tinnitus (SIT). GP has not been recommended as a single therapy for tinnitus patients, but as part of a combined therapy attempting tinnitus relief after identification and treatment of factors known to influence the clinical course of the SIT [2]. GP, a drug designed originally as a supplement for seizure control, was considered for those SIT patients in whom objective evidence of abnormal electrical and metabolic brain activity was identified. Initially, nuclear medicine imaging with single-photon emission computed tomography (SPECT) of the brain provided objective metabolic evidence [3]. Since 2000, quantitative electroencephalography (QEEG) has provided electrophysiological evidence [4]. Both tools have been used not only for diagnosis but as a monitor for objectively identifying the efficacy of GP and combined treatment.

In our experience, long-term tinnitus relief with GP supplemented by clonazepam (Klonopin) was reported initially at the 2001 American Academy of Otolaryngology–Head and Neck Surgery meeting and published in 2002 in the *International Tinnitus Journal* [2].

It is unfortunate that the design of the study conducted by Picirillo et al. [1] did not reflect state-of-the-art tinnitus diagnosis and treatment at this time. On

learning of this effort to establish the efficacy of GP for tinnitus relief, our team supported it and corresponded with the primary author to share our experience. Specifically, a highlight of our correspondence was to alert the primary investigator to the following: "In general, protocols of treatment, which did not differentiate between different clinical types of tinnitus, will provide conflicting results" [5]. The authors elected to disregard that alert.

Consequently, as predicted, the results and conclusions in that report are biased. The results reflect methods of patient selection and tinnitus evaluation that are not state of the art, thereby confusing tinnitus patients and professionals attempting tinnitus diagnosis and treatment in matters of GP efficacy for tinnitus relief.

BIASES IN PATIENT SELECTION AND DIAGNOSIS

General

In the foregoing publication [1], tinnitus was clinically considered to be a unitary symptom. The study reported no attempt to identify the clinical type of tinnitus or the factors outlined in the clinical history (or both), either of which could have influenced the clinical course of the tinnitus.

Critical for establishing an efficacy for existing protocols attempting tinnitus relief is the need to establish an accurate tinnitus diagnosis. Diagnosis includes the identity of the clinical type of tinnitus by correlating the clinical history with the physical neurotological examination, the establishment of electrophysiological correlates of cochleovestibular function, and tinnitus evaluation. Diagnostic tinnitus protocols must be dynamic and flexible to allow the clinical translation of advances in cochleovestibular basic science, neuroscience, and behavioral neurology into existing protocols.

In investigating tinnitus—an aberrant auditory sensory stimulus—and reporting on the efficacy of a particular treatment modality, the ongoing translation of information from basic sensory physiology has improved our understanding of tinnitus and the accuracy of the tinnitus diagnosis by differentiating between components of a sensation (i.e., sensory, affect, and psychomotor). Treatment recommendations are based on this differentiation.

Medical-Audiological Tinnitus Patient Protocol

Since 1996, GP has been, and continues to be, recommended for tinnitus patients with diagnosed predominantly central-type severe, disabling tinnitus. The diagnosis is based on such patients' completing a medical-audiological tinnitus patient protocol [6] that includes (1) patients' medical histories and their correlation with the physical neurotological examination, (2) a complete evaluation of the peripheral and central cochleovestibular system, and (3) tinnitus evaluation. Nuclear medicine imaging with SPECT of brain (initiated in 1996 and ongoing since then), combined with positron emission tomography since 2000 and with QEEG since 2000, was primarily a clinical translation from such imaging and electroencephalography of the brain to tinnitus diagnosis as a method to monitor the efficacy of treatment [4,5]. Both have provided objective evidence to support recommendations for attempting tinnitus relief with an innovative application of GP, a drug designed primarily for antiseizure control. The study in question is marked by the absence of any such technology for evaluating GP efficacy [1].

Clinical Types of Tinnitus

The aforementioned study considers tinnitus to be a unitary symptom. That clinical concept has been refuted by the heterogeneity of tinnitus [7–9] as reflected in (1) the clinical histories reported by tinnitus patients regarding the onset and clinical course of their tinnitus; (2) electrophysiological correlates of cochleovestibular function; (3) the individuality of masking characteristics of affected tinnitus patients; (4) the clinical identity of clinical types of tinnitus since 1822 [10]; and (5) the results of various modalities of therapy (i.e., medication and instrumentation) attempting tinnitus relief [11–13].

Admittedly, the publication in question selected “severely disabled tinnitus patients,” but were they all the same on the basis of correlating their clinical histories with cochleovestibular evaluation, assessing the Feldmann masking curves [14], and determining the clinical type of tinnitus? What, if any, metabolic and electrophysiological evidence was brought forward to establish abnormality within the central nervous system (CNS) and specifically at the brain cortex? Ironically, the “failures” reported for GP tinnitus relief lend support to the clinical concept of different clinical types of tinnitus. Furthermore, are the failures of GP tinnitus relief not due to a predominantly central-type severe, disabling tinnitus? Factors known to influence the clinical course of the tinnitus—not having been identified and treated—may have contributed to the failures.

Factors Known to Influence the Clinical Course of Tinnitus

In the report under discussion, no attempt was made to identify or treat the factors known to influence the clinical course of tinnitus. These factors [6,15], particularly in the peripheral cochleovestibular system (e.g., noise control, fluctuation in aeration of the middle ear(s), and secondary endolymphatic hydrops) and within the CNS (e.g., ischemia, inflammation, and neurodegeneration) were not identified. These factors are preconditions that, if not identified and treated, eliminate or reduce the possibility of efficacy for any or all recommendations of tinnitus relief with instrumentation and medication, alone or in combination. Specifically, such has been our experience before 1996 in attempting tinnitus relief with existing modalities of therapy, and we have continued with GP, a drug designed mainly for its cortical antiseizure effect on the CNS. Specifically, this clinical experience is supported by increasing numbers of tinnitus patients who visit our offices and label themselves as GP failures. In these GP failures, significant tinnitus relief has been reported with the resumption of GP therapy—individualized for each tinnitus patient—after identification and treatment of the cited factors, particularly those of noise control, stabilization and maintenance of normal aeration of the middle ear, and control of secondary endolymphatic hydrops.

CNS Function and Dysfunction

In the Picirillo et al. study [1], no attempt was made to identify or correlate the results reported with answers to questions not only of tinnitus relief but in regard to memory, concentration, communication, and speech expression—frequent associated complaints reported by patients having severe disabling-type tinnitus.

BIAS AND TREATMENT

General

Professionals involved in tinnitus diagnosis and treatment are committed to “do no harm” to the tinnitus patient. Of particular importance to this commitment is the issue of recommending innovative drug therapy in attempting tinnitus relief (GP and Klonopin). The investigation of GP for its efficacy in tinnitus relief is stated in this report to be that “tinnitus is associated with disturbances in spontaneous neural activity in the auditory system (central-origin hypothesis)” [1]. In 2007, though such data were clinically available, that publication evinced no attempt to obtain such data not only to support a “central-origin hypothesis” but, from the perspec-

tive of and significance for tinnitus patients, to support the recommendation of an innovative application of an antiseizure drug and to be consistent with the commitment to do no harm.

Clinically, for this and future projects that attempt to evaluate modalities of tinnitus therapy, our recommendations are to obtain objective metabolic and electrophysiological data before *and* after treatment, to be correlated with present outcome questionnaires to establish efficacy of the recommended therapy.

Tinnitus: Central-Origin Hypothesis

The central-origin concept was originally observed clinically with auditory brainstem response testing (1981) [9]. It was proposed by Shulman in 1984 at the Third International Tinnitus Seminar, Munster, Germany [9], and updated in 1998 to identify tinnitus production loci other than in the peripheral cochleovestibular system [16].

Our initial efforts with medication attempting tinnitus relief were directed to this concept in the 1980s and were highlighted by the activity of the drug Klonopin, a benzodiazepine with antiseizure activity reported to result in tinnitus relief in some patients [17,18]. This experience was the basis of further investigation in the 1990s with nuclear medicine imaging by SPECT of brain that identified neural substrates in tinnitus patients, a biochemical marker—the GABA_A receptor [19]—and support for the hypothesis that a deficiency in the GABA_A receptor for benzodiazepine may exist in some tinnitus patients [18].

These findings were the basis in 1996 of introducing the innovative application of the drug GP for attempting tinnitus relief. It was hypothesized that a receptor-targeted therapy (RTT) directed to the GABA_A receptor—combining GP with Klonopin (i.e., RTT-GABA_A-R)—would, by the attachment to the GABA receptor of GABA and the benzodiazepine Klonopin, result in an increase in chloride flux and, consequently, would increase inhibition [2,20]. Klonopin was recommended to supplement the predominantly antiseizure activity of GP by its influence at the GABA_A receptor (i.e., increase inhibition).

Inhibition and Neuroprotection

As regards inhibition, in the publication in question, the authors explain their rationale for selecting GP in attempting tinnitus relief as focused on “inhibition” and the underlying mechanism of GP action. Missing in that approach is any discussion of the concept of neuroprotection, the difficulties in seizure control, and ongoing pharmacological efforts to understand and identify underlying mechanisms of action of known and new antiseizure drugs [21–23].

Neuroprotection is a term applied to any physiological process involved in the maintenance or improvement (or both) of nerve function [21–23]. It would have been interesting to readers to identify the difference, if any, that could have been demonstrated in the responders and nonresponders in that study with nuclear medicine imaging or QEEG (or both) for the issue of neuroprotection [3,4].

GP and Klonopin: A Receptor-Targeted Therapy

The rationale for our innovative drug therapy of GP and Klonopin was twofold. One aspect called for providing tinnitus control by increasing inhibition of an epileptogenic focus of activity identified in brain cortex and metabolic alteration in brain function in the medial temporal lobe system of the brain, known to have a high density of GABA_A receptor (i.e., to provide an RTT). A second consideration was to provide neuroprotection to the identified abnormal neural substrates by control of its antiseizure activity.

In the publication of interest [1], GP was selected as the “next” drug in a menu-driven approach attempting tinnitus relief. Klonopin was recommended as a supplement for increasing the inhibitory effect. Patients reported improvement in sleep and also in the control of anxiety.

GP is a drug with antidepressant and antinociceptive as well as antiseizure actions. Our team recommended GP in 1996, as stated, for treatment of the sensory component of the tinnitus symptom, for its purported GABAergic inhibitory effect and reported antiseizure side effects. Klonopin was recommended for treatment of the affect component of the tinnitus symptom. The dosage of both has been reported to be individualized for each patient with diagnosed predominantly severe, disabling, central-type tinnitus. The dosage established for both is not arbitrary but based for GP on a subjective outcome report scale of tinnitus intensity and for Klonopin on a scale of tinnitus annoyance [2].

Tinnitus patients who have been selected as described for this combined treatment (ongoing since 1996; approximately in excess of 100 patients) have reported significant tinnitus relief within 2–4 weeks. It has been maintained over the long term (more than 1 year) in approximately 90%. Adverse effects have included drowsiness and unsteadiness [2,23].

Concerning the mechanism of action of GP, this is a work in progress, with a history of more than 10 years. Important is to consider the relationship between calcium channel blockade and neurotransmitter release, a common failing in discussions of the action of antiepileptic pharmacological drugs [24]. Designed as a GABA_Amimetic

to freely pass the blood-brain barrier [25], GP was subsequently reported to be without significant activity at GABA receptors; functional studies demonstrated calcium channel-blocking properties of the drug at therapeutically relevant levels [26,27]. Most recent has been the report of interaction between GP and the GABA_B receptor on glutamatergic nerve terminals in neocortical brain slices, resulting in reduction in evoked glutamate release [28]. This may explain the anticonvulsant and antinociceptive actions of GP. However, these findings are inconsistent with other reports [29,30]. Significant for tinnitus patients is the search for underlying mechanisms of GP action, that antiseizure and antinociceptive actions have been identified, and that in a selected cohort of tinnitus patients, relief has been established and maintained long term.

In the opinion of our team, the difficulty in identifying the actions of GP does not contradict our patients' reports of tinnitus relief with GP. Significant clinical subjective reports cite long-term tinnitus control in patients selected for this therapy and its correlation with objective improvement in neural substrates identified with nuclear medicine SPECT of brain and QEEG after RTT-GABA therapy.

Long-Term Tinnitus Relief

Long-term tinnitus relief (i.e., >1 year) is missing in the report in question [1]. In our experience, long-term tinnitus relief with GP supplemented with Klonopin was reported initially at the American Academy of Otolaryngology-Head and Neck Surgery meeting in 2001 and published in 2002 in the *International Tinnitus Journal* [2]. The positive subjective results of RTT-GABA therapy have been supported in selected cases by objective metabolic evidence of alteration in activity with sequential SPECT of brain: improvement in perfusion in neural substrates initially diagnosed as abnormal (the number limited by the cost of the procedures) and, more recently, with objective electrophysiological evidence using QEEG [3,4]. Significantly, tinnitus relief was seen in patients who reported such associated complaints prior to RTT-GABA therapy.

SUMMARY

Translational medicine, evidence-based medicine, and meta-analyses all are significant additions for the clinical practice of medicine for the benefit of the patient. History teaches that respect for and knowledge of the past and observation are critical for the achievement of advances in one's field or area of interest.

In our newly emerging discipline of tinnitology, clinical information is equal in importance to that reported from basic science of auditory and brain function. There

is no place for elitism. It is essential that a translation of information occur between both basic scientist and clinician for achieving the goal that all tinnitus professionals have in common: the achievement of a cure for all clinical types of tinnitus and "to do no harm."

The report under discussion is a significant addition to the tinnitus literature [1] to demonstrate that the statistical significance of data is not necessarily clinically relevant. It is unfortunate that the authors of the study under discussion did not bring to the attention of their readers reports of the GP experience published in the *International Tinnitus Journal*, an established peer-reviewed journal, and did not include in their discussion previously published results [2]. An opportunity was lost not only to "test" our reported results and conclusions and that of others [2,31,32] but to discuss a basis for the differences, one of which may have been patient selection. The readers of the *Archives of Otolaryngology* deserve and expect such completeness in all publications appearing in peer-reviewed journals.

Though no "cure" or drug is specifically available for attempting tinnitus relief, GP continues in our experience to provide safe, long-term relief to a selected cohort of tinnitus patients with diagnosed predominantly central-type severe, disabling tinnitus. The dosage is individualized and, combined with Klonopin, has increased the incidence of positive reports of tinnitus relief.

Clinical experience supports the opinion that attempts at tinnitus relief with medication for the present and immediate future will be individual and require a combined approach reflecting the known interaction of different neurotransmitter systems in brain. For tinnitus, the search for a heterogeneous symptom and clinical consideration that there might be a single drug that will provide relief to all afflicted patients is unrealistic and not supported by clinical experience or recent advances as reported in auditory and neuroscience for ear and brain function. Significant is the need for reports evaluating tinnitus therapy to specify long-term efficacy of any and all modalities attempting tinnitus relief.

CONCLUSIONS

GP is not for some tinnitus patients. An accurate diagnosis of the clinical type of tinnitus is the basis for recommending an innovative drug application for attempting tinnitus relief. If not identified and controlled, factors influencing the clinical tinnitus course interfere in the efficacy of therapy attempting tinnitus relief. GP has, from the time of our initial recommendation, been part of a combined therapy, whether with medication or instrumentation (or both).

There is no place for elitism in the discipline of tinnitology. Unfortunately for tinnitus patients and profes-

sionals attempting tinnitus diagnosis and treatment, the authors in question [1] elected to disregard our alert. Subsequently, as predicted, the results and conclusions in that report are biased, reflecting a method of patient selection and tinnitus evaluation that was not state of the art. Consequently, they confused professionals involved in tinnitus diagnosis and treatment regarding the issue of the efficacy of GP for tinnitus relief.

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