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$GABA_A$–Benzodiazepine–Chloride Receptor–Targeted Therapy for Tinnitus Control: Preliminary Report

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Abstract: Our goal was to attempt to establish neuropharmacological tinnitus control (i.e., relief) with medication directed to restoration of a deficiency in the γ-aminobutyric acid–benzodiazepine–chloride receptor in tinnitus patients with a diagnosis of a predominantly central type tinnitus. Thirty tinnitus patients completed a medical audiological tinnitus patient protocol and brain magnetic resonance imaging and single-photon emission computed tomography of brain. Treatment with GABAergic and benzodiazepine medication continued for 4–6 weeks. A maintenance dose was continued when tinnitus control was positive. Intake and outcome questionnaires were completed. Of 30 patients, 21 completed the trial (70%). Tinnitus control lasting from 4–6 weeks to 3 years was reported by 19 of the 21 (90%). The trial was not completed by 9 of the 30 (30%). No patient experienced an increase in tinnitus intensity or annoyance. Sequential brain single-photon emission computed tomography in 10 patients revealed objective evidence of increased brain perfusion. Patients with a predominantly central type tinnitus experience significant tinnitus control with medication directed to the γ-aminobutyric acid–benzodiazepine–chloride receptor.

Key Words: benzodiazepine receptor; gabapentin; gamma aminobutyric acid (GABA); Klonopin; receptor-targeted therapy; tinnitus control

This preliminary report outlines a receptor-targeted therapy (RTT) directed to the γ-aminobutyric acid–benzodiazepine–chloride receptor (GABA/BZ/Cl) and aimed at tinnitus control (TC)—that is, relief for patients with diagnosed severe, disabling, predominantly central type tinnitus. The RTT directed to GABA/BZ/Cl (RTT-GABA) for TC is based on the hypothesis that a GABAergic mechanism is involved in the pathophysiology of some clinical types of tinnitus [1, 2]. Preliminary investigation with single-photon emission computed tomography (SPECT) of the brain with the radionucleopharmaceutical ^{99}Tc-HMPAO has demonstrated perfusion asymmetries in multiple regions of interest in the brain, highlighted by the cortex of the medial temporal lobe system (MTLS) [3]. Brain SPECT with ^{123}I-iomazenil, an iodine containing a radionucleopharmaceutical specific for attachment to the BZ-binding sites in the GABA receptor, demonstrated diminished binding sites in multiple regions of interest in the brain, highlighted by the cortex of the MTLS, consistent with the hypothesis implicating GABAergic mechanisms in the pathophysiology of the tinnitus disorder [1; JP Seibyl, personal communication, 2001]. These SPECT findings have provided the basis for proposals of a neurochemical basis for TC directed to treatment of the GABA-BZ-Cl receptor, specifically a GABAergic drug (e.g., gabapentin [Neurontin]) in combination with a benzodiazepine (BZ) (e.g., clonazepam [Klonopin]) [4]. It is hypothesized that the deficiency in the GABA/BZ/Cl receptor is directly related to the significant deterioration in the affective component of tinnitus, which is marked by the clinical manifestations of increased emotional difficulty, anxiety, stress, depression, and fear [2].

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The diagnosis of a predominantly central, severe, and disabling tinnitus in the patients in our study was established by completion of a medical audiological tinnitus patient protocol (MATPP) [5, 6], which identified positive central cochleovestibular test findings and abnormalities in brain perfusion as identified on brain SPECT both at baseline and after acetazolamide (Diamox). Such patients with clinically recognized tinnitus were advised to undergo RTT-GABA.

RTT tinnitus therapy using such pharmacotherapeutic agents as are indicated for neuroprotection and that have antiseizure and anxiolytic actions directed to modulation of inhibition in brain is clinically considered to be supported by findings of GABA function in normal physiological processes (e.g., learning and memory), in pathological states of brain function (i.e., epilepsy, Alzheimer's disease, Huntington's or Parkinson's disease), and in neuropsychiatric disorders (e.g., anxiety, depression) [7]. Both gabapentin and clonazepam are drugs that have been selected to attempt to enhance the inhibitory activity of the GABA/BZ/Cl receptor for TC. The medication prescribed has been approved by the U.S. Food and Drug Administration for indications other than tinnitus and is not considered specific for the symptom of tinnitus. All patients in this report had been under the care of a psychiatrist for anxiety or depression (or both).

The structural heterogeneity of the GABA/BZ/Cl receptor provides an understanding of the complexity in the underlying pathophysiology and neurobiochemistry associated with the symptom of tinnitus and of attempts at its control [1]. The inhibitory neurotransmitter of the central nervous system (CNS) is GABA. Synaptic inhibition in the mammalian brain results largely from binding of the small–amino acid GABA to its receptors [8]. Approximately 17% of the synapses in the mammalian cerebral cortex have been estimated to be GABAergic [9]. The function of the $GABA_A$ receptor is primarily inhibitory and controls the chloride flux. The elements of the $GABA_A$ receptor are GABA and the attachments of the BZ and steroid molecules. The degree or extent of attachment determines chloride flux, which controls the degree of inhibition [10]. GABA is quantitatively one of the most important inhibitory transmitters in the CNS. Approximately 30% of all central synapses use GABA as their neurotransmitter. Regional specificity differences have been demonstrated for different BZs (e.g., lorazepam in cortex, hypothalamus, and hippocampus). Alprazolam occurred only in cortex and hypothalamus [11]. GABA activates two qualitatively different inhibitory mechanisms through $GABA_A$ and $GABA_B$ receptors [12].

GABA is classified into two main categories: $GABA_A$ and $GABA_B$. $GABA_A$ and $GABA_B$ are widespread throughout both the rodent and the human CNS [13]. GABA receptors are a class of cell-surface molecules that bind to sedating drugs (e.g., diazepam [Valium]), anesthetic agents (e.g., lidocaine [Xylocaine]), and steroids. Our focus has been on $GABA_A$. The neurochemistry of the $GABA_A$ receptor is complex. Its structural heterogeneity includes 5 types and 16 subtypes and is controlled or modulated by at least 20 genes [14]. This structural heterogeneity is reflected in specificity of both pharmacokinetic and pharmacological actions and in site specificity.

Significant for tinnitus are reports of involvement of GABA with physiological processes, including network synchronization and theta and gamma rhythms in brain, both considered to be associated with cognitive functions [8, 15]. Impairment of GABAergic function has been implicated in neuropsychiatric disorders of epilepsy and anxiety [16].

Gabapentin is a selected agonist for the $GABA_A$ receptor, and baclofen is a selective agonist for the $GABA_B$ receptor. High levels of the $GABA_B$ protein molecular structure have a demonstrated similarity to the metabotropic glutamate receptors (CmGluRs) and $GABA_{B_{(1)}}$ [13]. $GABA_{B_{(1)}}$ heterodimerizes with $GABA_{B_{(2)}}$ to form a functional G protein–coupled receptor (GPCR). Clinically, pharmacological application of such subtypes is suggested to be of therapeutic value in treating epilepsy, pain, and drug addiction. Impairment of GABA-mediated inhibition has been considered to lead to convulsions [17], a finding that provides clinical support for the concept of tinnitogenesis, an epileptiform auditory phenomenon.

This preliminary report of RTT-GABA for attempted TC presents the method of patient selection, the establishment of a titration schedule for both initial and long-term gabapentin and clonazepam therapy, and a discussion of the neuropharmacological issues involved for patients with diagnosed severe, disabling, predominantly central tinnitus.

METHODS

Patients suffering from severe, disabling, predominantly central type tinnitus with a duration equal to or greater than 1 year were selected for RTT-GABA. The goal of therapy was to achieve a level of tinnitus relief considered to be "significant" for each patient and with TC reaching a level of satisfaction desired by the patient (i.e., so that no additional TC was requested). The tinnitus diagnosis for the clinical type of tinnitus was established by completion of a MATPP [5, 6, 18]. The tinnitus evaluation included an electrodiagnostic cochleovestibular test battery that identified clinical cochleoves-

tibular correlates for tinnitus. Brain MRI at baseline and after gadolinium enhancement revealed no CNS pathology. Brain SPECT, both at baseline and after acetazolamide administration, revealed abnormal perfusion asymmetries of both hypoperfusion and hyperperfusion in multiple regions of interest highlighted by the cortex of the MTLS.

Treatment options were presented to patients prior to RTT and included instrumentation; medication (e.g., pentoxifylline); treatment of factors known to be identified with development or continuation of severe disabling tinnitus (i.e., fluctuation in aeration of the middle ears bilaterally; secondary endolymphatic hydrops); and control of noise exposure.

A trial of medication either alone or in combination with instrumentation was the initial therapy for attempting TC. Examination of the CNS, including brain SPECT and brain and internal auditory canal MRI with gadolinium, was recommended if the severe disabling tinnitus symptom was unchanged after an initial trial of combined instrumentation and medication. The brain MRI was not repeated prior to RTT if patients reported a brain MRI to be normal within 6 months of consultation.

Intake outcome questionnaires were completed by each tinnitus patient both prior to the initial consultation and at the time of each follow-up visit. Interval follow-up visits were determined by patients' clinical course and by their report of the degree of TC, which was individual and varied from biweekly to every 6 months.

Outcome questionnaires were completed by each patient for intensity, annoyance, handicap, depression, and stress. Scores were compared at the initial and at the last date of examination for the period being reported (i.e., October 1996–December 2000). A visual analog scale scoring 0–7, wherein 0 equals absence of tinnitus and 7 equals the worst tinnitus that the patient may experience, were completed for both tinnitus intensity (tinnitus intensity index [TII]) and annoyance (tinnitus annoyance index [TAI]). Additional outcome questionnaires included the tinnitus handicap inventory, the Zung depression score, and the stress questionnaire. This report focuses on the TII and the TAI.

The criteria for success of RTT for this report are as follows:

- TII: a unit reduction of 1–4
- TAI: a unit reduction of 1–4
- Positive answer to the question of whether RTT has produced significant tinnitus relief
- Patients' evaluation of overall TC (increased from original tinnitus of ≥20%)
- Audiogram: unchanged
- TII and TAI: improved or unchanged
- Brain SPECT at baseline and after acetazolamide (prior to RTT and compared to post-RTT): demonstration of objective improvement in perfusion, with particular focus on the MTLS of brain after RTT

In general, the dosage for each medication was differentiated on the basis of the sensory and affective components of the tinnitus symptom. Gabapentin was prescribed for the sensory component, and clonazepam was prescribed for the affective component. We explained to each patient that neither medication is specific for attempting to provide TC for a predominantly central type tinnitus.

The medication titration schedules for both gabapentin and clonazepam followed the pharmacological principle of using the lowest dose of each preparation to achieve the maximal desired effect and "to do no harm." The dosage of each was increased or decreased on the basis of reported unit change of the TII and TAI, respectively. We recommended a duration of therapy of at least 4–6 weeks and that therapy be continued with a maintenance dose to be determined for each medication so as to maintain an acceptable level of TC individualized for each patient.

Recommended Dosage Schedule

Neurontin (Gabapentin)

Our dosage titration schedule for gabapentin was based on the reported tinnitus intensity response to one tablet (100 mg) of gabapentin (Neurontin). Dosage was increased until patients reported an acceptable, significant degree of relief for the parameter of tinnitus intensity (i.e., the sensory tinnitus component). The range of dosage was individualized, with a range of 100–2,700 mg/day in divided doses (e.g., three tablets three times daily, for a total of 900 mg).

Klonopin (Clonazepam)

All patients were asked to begin taking clonazepam (Klonopin), 0.25 mg, at bedtime for the tinnitus affective component. The total clonazepam dose per day was not to exceed 1 mg/day, (i.e., two 0.5-mg tablets for the initial 4–6 weeks). The initial clonazepam dose of 0.25 mg at bedtime was maintained for 2 weeks. If TC was not achieved when combined with gabapentin, patients were instructed to add a supplemental dose of clonazepam.

Supplemental clonazepam therapy (0.25 mg) was recommended if the TII or the TAI was at a unit level of at least 5 for more than 1 hour. The total supplemental

clonazepam dose was not to exceed two additional 0.25-mg tablets in a 24-hour period, these tablets to be taken no sooner than 4 hours apart.

Psychiatric Consultation

Psychiatric consultation was advised if it was not already in place and ongoing. Psychiatric therapy attempts to treat with anxiolytic or antidepressant medication the affective component, highlighted by anxiety or depression (or both). Such treatment should be continued in an attempt to establish or maintain a stable personality. All patients in this report were considered stable by their psychiatrist and had received prior medication other than RTT GABA with no reported TC.

Follow-Up: SPECT of Brain

Brain SPECT, both at baseline and after acetazolamide administration, is recommended between 6 months and 1 year in an attempt to monitor the efficacy of RTT, to adjust dosage, and to improve the accuracy of the tinnitus diagnosis.

Complications

Complications to the prescribed medication, which may be expected, were explained to the patient. They include (for gabapentin) drowsiness or nausea, visual disturbance, vertigo, headache, or interference in cognition and memory. For clonazepam, they include drowsiness, headache, vertigo, interference in cognition, agitation, and memory loss. Occasional complaints were drowsiness and vertigo.

The parameters of tinnitus identification as regards quality, location, and masking curve were established for each patient. The initial tinnitus evaluation in the MATPP included site-of-lesion audiometric testing. A pure-tone screening audiogram was performed at the time of each follow-up visit.

RESULTS

The results of TC with RTT-GABA are reported for 30 patients, divided into two groups and all suffering from severe, disabling, predominantly central type tinnitus treated over the period October 1996–December 2000. In group I, RTT-GABA was incomplete for 4–6 weeks in 9 of 30 (30%). In group II, 19 of 21 (70%) completed the trial period and established a maintenance dose of both medications for TC. Group I patients did not complete the trial of RTT therapy, owing to reported single complaints of side effects from medication (i.e., nausea, headache, vertigo, drowsiness, and blurring of vision). No patient declined therapy because of a reported increase in intensity or annoyance (or both) after RTT, as reflected and recorded on the TII and TAI.

Table 1. Group I and II Age and Gender Distribution (N = 30)

Gender	Number	Age (avg.)
Group I		
Male	4	57.8
Female	5	80.2
Group II		
Male	14	53.0
Female	7	50.0

The gender distribution was 19 males and 11 females (Table 1). Ages ranged from 32 to 84 years. The group I male average was 57.8; the female average was 80.2. The group II male average was 53; the female average was 50.

Group II patients reported TC of 90% (19 of 21). Tinnitus was reported as unchanged in 9.5% (2 of 21). No increase in tinnitus intensity or annoyance was reported by any patient. The parameter of tinnitus identification for quality for those in group II (19 of 21) included tone (5 patients), noise (8), and tone-noise (8). Location included right ear (3 patients), left ear (2), both ears (8), head and both ears (5), and head (1). Masking curves included type I (6 patients) and type IV (15). Group I quality included noise (6 patients) and tone-

	Group II Unit Reduction						
	1.0	1.5	2.0	2.5	3.0	>4	Average
TII	3	3	4	1	4	4	2.42
TAI	1	2	6	0	3	7	2.78

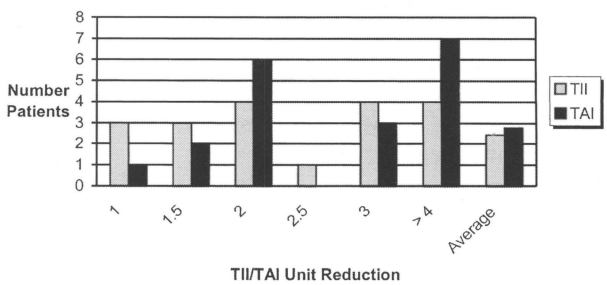

Figure 1. Group II unit reduction in 19 of 21 patients (90%). The patient-estimated percent improvement from the start of receptor-targeted therapy was 36.8%. The overall unit reduction average totaled 2.60. A Wilcoxon signed rank test of the null hypothesis that the median change score is zero was rejected at the 0.0001 level. *TAI* = tinnitus annoyance index; *TII* = tinnitus intensity index.

Table 2. Group II Statistical Analysis TII/TAI Unit Change 2 (19/21)

Unit Change 2	<2	2	>2	Total
TII	8	5	8	21
TAI	5	5	11	21

Intensity	*p* Value	Point Estimate	95% CI
≥2	0.275	(13/21) 62%	38%, 82%
>2	1.000	(8/21) 38%	18%, 62%
Annoyance			
≥2	0.016	(16/21) 76%	53%, 92%
>2	1.000	(11/21) 52%	30%, 74%

CI = confidence interval; *TAI* = tinnitus annoyance index; *TII* = tinnitus intensity index.
Notes: Statistical significance for unit change ≥2 for annoyance relief (p = .016); and approaching statistical significance for intensity relief (p = .275). Proportion of patients with improvement 90% (19/21). Exact 95% confidence interval 70–99%; p = .0002, exact test.

noise (3). Location included head (1 patient), right ear (1), left ear (1), both ears (2), and head and ear (4). Masking curves included type I (3 patients) and type IV (6).

The overall significance of the TC as reported by the patients was 84.3% (16 of 19). The number of patients who experienced tinnitus relief of a unit reduction of 2 or more on the TII and TAI scales but considered the tinnitus relief to be nonsignificant was 3 of 19 (15.7%). Sequential brain SPECT studies, both at baseline and after acetazolamide administration, were obtained in 10 of 19 patients, all of whom revealed improvement highlighted by increased perfusion in the MTLS.

The outcome questionnaires for TII and TAI reported at this time showed a 90% unit reduction average for TII and TAI in group II (19 of 21; Fig. 1). The average TII was 2.42, and the average TAI was 2.78. The overall patient estimated subjective improvement for TC from the start of RTT was 36.8%. The overall unit reduction averaged 2.60. For both scales (TII and TAI), a Wilcoxon signed rank test of the null hypothesis that the median change score is zero was rejected at the 0.0001 level [J Weedon, Academic Science Computing Center of the State University of New York, personal communication, 2001].

A statistical analysis of TC, based on TII and TAI score of a unit change of 2, was completed (Table 2).

Table 3. Duration of Tinnitus Control by Receptor-Targeted Therapy in Group II (19/21)

Duration	1–1.5 mo	3 mo	6–12 mo	1 yr	1–1.5 yr	1.5–2 yr	2 yr	3 yr
No. of patients	1	3	5	1	3	1	2	3

The proportion of patients showing improvement was 90% (19 of 21). An exact 95% confidence interval was 70,90%. The null hypothesis that this proportion is as low as 50% can be rejected (p = .0002, exact test) [J Weedon, personal communication, 2001].

Significant reduction in the associated complaint of vertigo was reported by 10 patients, and cognitive function improvement was reported by 4 patients. A decrease in the associated complaint of hyperacusis was reported by 10 patients. These gains were individual and were not limited to the geriatric patients in this report.

The duration of tinnitus relief in group II patients ranged from 4–6 weeks to 3 or more years (Table 3). TC equal to or greater than 1 year was reported by 10 of 19 (52.6%). Tinnitus relief of 1–12 months was experienced by 9 of 19 (47.3%).

Sequential brain SPECT, both at baseline and after acetazolamide administration, with radioisotope ^{99}Tc-HMPAO was completed for 10 of 19 group II patients. All have revealed improvement in perfusion highlighted by the MTLS. Correlation with outcome questionnaires for TII and TAI was positive in all patients (10 of 10).

COMPLICATIONS OF RTT–GABA

All patients were cautioned to observe and report complaints highlighted by headache, nausea, vertigo, increased hearing loss, tinnitus, ear blockage (occurring alone or in combination), excitability, interference in cognitive function, blurring of vision, or possible seizure. In group I, transient vertigo was reported by three patients, and drowsiness was reported by four patients. Two of nine patients were not interested in attempting the RTT trial. In group II, significantly, improvement in cognitive function was reported by 4 patients, and 10 patients cited reduction of vertigo. Also, drowsiness was reported by three patients; however, it was not sufficiently significant to interfere with continuation of RTT.

DISCUSSION

The criteria established for success for TC after RTT-GABA are clinically interpreted to be significant on the basis of reported results at this time. Particularly significant is the long-term TC achieved with long-term maintenance RTT-GABA. No patient reported an increase in either intensity or annoyance with long-term therapy. TC was focused primarily on intensity and annoyance, both of which demonstrated fluctuation with overall reduction (see Fig. 1). The fluctuation in TC was influenced by noise exposure and stress. Additional manifestations of TC were seen in reported changes in quality and in location of the tinnitus. Three

patients reported a change from a high to a lower frequency; four patients reported a location change from head to ears.

Outcome questionnaires based on the TII and TAI identified and demonstrated the individuality of the tinnitus symptom by the distribution of unit change in visual analog scales and by the significant relief reported by unit changes of less than 2 (see Fig. 1). The overall TC unit reduction for both scales (TII and TAI), with a confidence interval for 19 of 21 in group II of 90% ($p < .0001$), is considered statistically significant. The averaged values reported at this time are valid for the small sample of tinnitus patients reported; however, the values may not be valid for examination of a larger tinnitus population (see Fig. 1).

We completed the statistical analysis of groups I and II for unit change in TII and TAI on the basis of a goal of less than 2, 2, or greater than 2 (see Table 2). Such an analysis suggests that a statistically significant value for achieving TC can be expected on the basis of a unit reduction for annoyance of equal to or greater than 2 and a possible similar result for intensity. It provides an estimate of the proportions of patients who will show a tendency for TC involving both intensity and annoyance.

Whether the statistically significant result for annoyance on the TAI scale is the underlying basis for the TC reported by patients with RTT must be considered (see Table 2). The brain SPECT confirmation findings of subjective TC in 10 patients may not be a primary reflection of tinnitus but may be an epiphenomenon reflecting stress and its clinical manifestations of anxiety, depression, and the like.

Projection of the results of this report for future populations who plan to be treated with RTT-GABA will serve as a point and confidence level estimate of what may be expected from RTT-GABA in the selected tinnitus population (i.e., severe, disabling, predominantly central type tinnitus). The clinical results reported at this time for TC with RTT-GABA are considered additional clinical support for the hypothesis of a GABAergic mechanism involvement in the pathophysiology of some clinical types of tinnitus, one clinical manifestation of which may be a BZ deficiency [1]. The symptom of tinnitus, particularly a predominantly central type, may be a clinical manifestation of a BZ deficiency syndrome with associated complaints, highlighted by interference in memory, speech expression, and cognitive function. The complexity of the structural heterogeneity of the $GABA_A$ receptor and its specificity for both pharmacological and pharmacokinetic activity and the site of action suggest the complexity involved in underlying mechanisms of tinnitus production and in attempts at TC.

The BZ receptor and its relationship to $GABA_A$ are significant in the transition of the sensory to the affective components of tinnitus. This is hypothesized in the concept of the final common pathway for all clinical types of tinnitus and the stress diathesis model for tinnitus [19, 20]. The role of BZ, particularly with respect to the $GABA_A$ receptor and modulation of the $GABA_A$ BZ receptor by cortisol (especially under stress), is considered significant in the clinical course of patients affected by severe disabling tinnitus [1]. This study provides clinical support for the role of the $GABA_A$ receptor as a biochemical marker for tinnitus.

The sequential brain SPECT findings of improved perfusion are significant. They provide objective evidence that supports the subjective reduction in tinnitus as reported by the patient for TC. This reduction raises questions of the true effect of RTT-$GABA_A$. Is the action on the predominantly sensory component (i.e., intensity of tinnitus) or the affective component (i.e., behavioral response of the patient) or both? Is the finding of perfusion improvement highlighted by the MTLS an epiphenomenon, reflecting improvement in anxiety or depression associated with severe disabling tinnitus? Is the RTT-$GABA_A$ directed to the biochemical change of stress associated with tinnitus? Is this treatment another method directed to factors that have been identified to influence the clinical course of tinnitus (e.g., stress)?

At this time, in answer to the foregoing questions, we considered as most significant the reports of TC cited by a significant number of tinnitus patients (19 of 21; 90%). Additionally, the response to RTT-$GABA_A$ supports the concept of the final common pathway for all clinical types of tinnitus and the stress diathesis model of tinnitus. Further, the brain SPECT alterations in perfusion, particularly in the MTLS, provide a monitoring system for the sensory-affect transformation in tinnitus patients and an objective measure of the severity of some clinical types and subtypes of tinnitus.

The interesting questions raised by our initial study with the BZ radioligand ^{123}I-iomazenil are considered to be reinforced by the results of this study [1]. Particularly significant is the question of the effect of prolonged occupancy of $GABA_A$ receptors on the clinical course of tinnitus by such ligands as GABA and BZ agonists, a condition known as *use-dependent regulation* of $GABA_A$ receptors (i.e., the issue of drug tolerance). The reader is referred for details to discussion in our previous publication [1].

This report supports RTT-GABA as one additional method to be considered in the attempt at TC of a predominantly central type tinnitus. Future implications for TC include the development of an expanding combined neuropharmacology for all clinical types and subtypes of tinnitus directed to multiple neurotransmitter receptors (i.e., a combined RTT).

CONCLUSIONS

RTT-GABA has resulted in significant long-term maintenance relief in patients suffering from severe, predominantly central tinnitus (19 of 21; 90%). Sequential brain SPECT studies support the clinical impression of a BZ deficiency syndrome. We posit that a GABAergic mechanism is involved in the clinical course of severe, disabling, predominantly central tinnitus and in its control (i.e., relief). The GABA-BZ-Cl receptor has been revealed as a biochemical marker for tinnitus. The structural heterogeneity of the $GABA_A$/BZ/Cl receptor highlights the complexity of the underlying pathophysiology and neurobiochemistry associated with tinnitus. It also points the way to a neuropharmacological treatment method for severe, disabling, predominantly central type tinnitus.

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