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Benzodiazepines and GABAergics in Treating Severe Disabling Tinnitus of Predominantly Cochlear Origin

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Abstract: Severe disabling tinnitus (SDT) refers to a symptom severe enough to disrupt affected patients' routine and keep them from performing their daily activities. SDT of a predominantly central origin has been treated successfully with benzodiazepines and GABAergic drugs. Our aim was to test the control of SDT of predominantly cochlear origin by benzodiazepines and GABAergic drugs. We followed the format of a prospective, randomized, single-blind clinical trial at an academic tertiary-care hospital. We studied 30 patients, all with SDT of clear cochlear origin. We treated 10 patients with placebo (group 1), 10 with benzodiazepine drugs (group 2), and 10 with benzodiazepine and GABAergic drugs (group 3). We recorded a decrease in the annoyance and intensity of SDT as measured by a visual analog scale ranging from 1 (negligible) to 10 (unbearable). We found statistically significant improvement in comparing groups 2 and 3 with group 1 but found no significant difference when groups 2 and 3 were compared. Addition of GABAergic to benzodiazepine drugs does not modify the treatment results in SDT of a predominantly cochlear origin.

Key Words: benzodiazepine drugs; GABAergic; severe disabling tinnitus

In 2000, using single-photon emission computed tomography (SPECT) and the benzodiazepine radioligand ^{123}I lomazenil, Shulman et al. [1] found diminished benzodiazepine binding sites in the medial temporal lobe cortex of six patients with severe disabling tinnitus (SDT) of a predominantly central origin. This finding was consistent with the implication of GABAergic mechanisms in the genesis of SDT of a predominantly central origin. A rationale for the treatment of the symptom with benzodiazepines and GABAergic drugs was based on these results. Abnormalities of benzodiazepine receptors have been demonstrated in Alzheimer's disease, Huntington's chorea, schizophrenia, and stress [2–6].

In a 2002 retrospective study, Ganança [7] found that clonazepam was very effective and safe in the treatment of SDT. In 2002, Shulman et al. [8] proposed the treatment of SDT of a predominantly central origin with a combination of a benzodiazepine drug (clonazepam) and a GABAergic (gabapentin) drug. He treated 30 patients, all having SDT with a predominantly central origin and showing perfusion changes in areas of interest in the brain as documented by SPECT. Twenty-one patients completed the trial and, of these, 19 had significant improvement of the symptom and increased brain perfusion, documented by SPECT, after the treatment.

Generally accepted today is that SDT of cochlear origin always has a central component that keeps the symptom active, even after deafferentation [9]. This prompted us to test the treatment with benzodiazepines and GABAergic drugs in SDT of predominantly cochlear origin following a prospective, randomized, single-blind protocol.

PATIENTS AND METHODS

We prospectively selected 36 patients with SDT of cochlear origin. We defined them as patients who had a 7 or higher score in a visual analog scale (VAS) ranging

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Table 1. Otological Diagnosis

Diagnosis	No. of Patients	Percentage
Group 1		
Presbycusis	4	40
Noise-induced	2	20
Otosclerosis	1	10
Ménière's disease	1	10
Idiopathic	1	10
Sudden deafness	1	10
Group 2		
Presbycusis	5	50
Noise-induced	2	20
Otosclerosis	1	10
Ménière's disease	1	10
Ototoxicity	1	10
Group 3		
Presbycusis	5	50
Noise-induced	3	30
Otosclerosis	1	10
Ménière's disease	1	10

from 1 (negligible intensity and annoyance) to 10 (unbearable intensity and annoyance). These patients had tinnitus of the severe disabling type for at least 6 months and, in them, treatment with the usual drugs used for tinnitus control had failed. Patients who had tinnitus as a consequence of otological surgery, who had chronic otitis media, or who had medical contraindications for the use of benzodiazepines and GABAergic drugs were excluded. All of them had an otological diagnosis associated with SDT (Table 1).

We used the VAS to measure the degrees of intensity and annoyance before and after the drug treatment. The patients were randomly assigned to three groups: group 1 was treated with placebo, group 2 with clonazepam, and group 3 with clonazepam and GABAergic drugs. The treatment duration was 6 weeks.

The doses of the drugs were as follows: Clonazepam doses were started at 0.5 mg and increased up to 2 mg/day according to the tinnitus evolution along the 6 weeks of treatment. Gabapentin was started at 300 mg and increased up to 900 mg/day following the same guidelines.

After 6 weeks of treatment, the degrees of intensity and annoyance of tinnitus were again measured via the VAS. Patients kept a detailed record of drug intake during the 6 weeks. We analyzed the results using the SPSS software version 13.0 (SPSS Inc., Chicago, IL)

Table 2. Demographics

Group	Gender	Mean Age (yr)
1	6 female, 4 male	49.9
2	5 female, 5 male	48.9
3	5 female, 5 male	48

Table 3. Hearing Status

	Normal Hearing		High-Frequency SNHL		Hearing Loss	
	No. Patients	% Patients	No. Patients	% Patients	No. Patients	% Patients
Group 1	5	50	4	40	1 (conductive)	10
Group 2	4	40	6	60	—	—
Group 3	5		4		1 (mixed)	10

SNHL = sensorineural hearing loss.

using the χ^2 test and variance analysis. The dosage schedule was that used by Shulman et al. in their 2002 study [8].

RESULTS

Thirty patients completed the study. (Six were excluded because they did not follow the protocol adequately.) The three groups were similar in age and gender status (Table 2). Otological diagnosis and hearing status were also very similar in the three groups (see Tables 2, 3).

SDT intensity and annoyance were significantly decreased in groups 1 and 3 as compared to group 1, but no statistically significant difference was detected between groups 2 and 3 (Tables 4–12). Two patients in group 1 experienced an increase in tinnitus intensity (see Table 4).

Four patients in group 2 experienced drowsiness and nausea, and two patients had sexual dysfunction (clonazepam). Five patients in group 3 reported drowsiness and nausea, and two noticed interference with cognition (clonazepam and gabapentin).

Tables 7–12 show the statistical analyses of the results using the SSPS version 13 software (SPSS Inc.), and Figure 1 summarizes the results in the three groups. Both annoyance and intensity decreased significantly in

Table 4. Visual Analog Scale Variation, Group 1

Age	Gender	Score Before Treatment	Score After Treatment	Variation
48	F	7	8	+1
54	F	8	8	0
37	F	7	5	−2
69	M	8	9	+1
46	F	10	10	0
38	M	9	7	−2
56	F	10	7	−3
40	F	7	7	0
60	M	8	7	−1
51	M	9	9	0

Table 5. Visual Analog Scale Variation, Group 2

Age	Gender	Score Before Treatment	Score After Treatment	Variation
54	F	8	6	−2
37	M	10	5	−5
48	M	8	5	−3
47	F	10	7	−3
43	F	10	4	−6
70	M	8	4	−4
40	M	7	7	0
69	F	8	5	−3
36	F	7	2	−5
45	M	9	3	−6

Table 6. Visual Analog Scale Variation, Group 3

Age	Gender	Score Before Treatment	Score After Treatment	Variation
69	F	7	4	−3
43	M	8	5	−3
38	M	10	3	−7
40	M	7	5	−2
56	M	10	3	−7
41	F	7	7	0
64	M	7	7	0
55	F	8	5	−3
44	F	9	5	−4
30	F	10	5	−5

groups 2 and 3 as compared to group 1, but no significant difference between groups 2 and 3 was found.

DISCUSSION

Shulman et al. [8] selected patients with SDT and brain perfusion changes detected by SPECT. They did not mention any otological disease affecting their patients. Our patients had SDT associated with otological diseases that are known to produce tinnitus. Therefore, it is reasonable to say that their symptom was of a predominantly cochlear origin. Another major difference between our patients and those of Shulman et al. [8] is the fact that almost all their patients had psychiatric problems (e.g., depression, anxiety, and fear severe enough to require specialized medical care). None of our patients needed psychiatric treatment.

Shulman et al. [8] selected patients with SDT "predominantly central in origin" and showed the positive effect of treatment with benzodiazepines (clonazepam) and GABAergic (gabapentin) drugs, as seen both in the reduction of SDT and on the SPECT results: The brain perfusion was enhanced after treatment. We selected SDT patients with tinnitus of a predominantly cochlear origin; we compared the effect of placebo, benzodiazepines alone, and benzodiazepines combined with a GABAergic drug; and we found that the addition of

Table 7. Groups 1 and 2, Intensity Variation (Visual Analog Scale): Independent Samples Test*

	Levene's Test for Equality of Variance		*t*-Test for Equality of Means						
								95% CI of Difference	
	F	Sig.	*t*	*df*	Sig. (two-tailed)	Mean Difference	SED	Lower	Upper
Intensity, equal variances assumed	1.632	0.218	3.585	18	0.002	2.9000	0.8090	1.2004	4.5996
Intensity, equal variances not assumed			3.585	15.636	0.003	2.9000	0.8090	1.1818	4.6182

CI = confidence interval; SED = standard error of the difference.
* Group statistics for these tests are as follows:
Group 1 (n = 10): Mean, −1.0000; SD, 1.4142; SEM, 0.4472.
Group 2 (n = 10): Mean, −3.9000; SD, 2.1318; SEM, 0.6741.

Table 8. Groups 1 and 2, Annoyance Variation (Visual Analog Scale): Independent Samples Test*

	Levene's Test for Equality of Variance		*t*-Test for Equality of Means						
								95% CI of Difference	
	F	Sig.	*t*	*df*	Sig. (two-tailed)	Mean Difference	SED	Lower	Upper
Annoyance, equal variances assumed	1.149	0.298	3.825	18	0.001	3.2000	0.8367	1.4422	4.9578
Annoyance, equal variances not assumed			3.825	16.528	0.001	3.2000	0.8367	1.4310	4.9690

CI = confidence interval; SED = standard error of the difference.
* Group statistics for these tests are as follows:
Group 1 (n = 10): Mean, −0.7000; SD, 1.5670; SEM, 0.4955.
Group 2 (n = 10): Mean, −3.9000; SD, 2.1318; SEM, 0.6741.

Table 9. Groups 2 and 3, Intensity Variation (Visual Analog Scale): Independent Samples Test*

	t-Test for Equality of Means			
	t	*df*	Sig. (two-tailed)	Mean Difference
Intensity, equal variances assumed	−0.486	18	0.633	−0.5000
Intensity, equal variances not assumed	−0.486	17.646	0.633	−0.5000

* Group statistics for these tests are as follows:
Group 2 (n = 10): Mean, −3.9000; SD, 2.1318; SEM, 0.6741.
Group 3 (n = 10): Mean, −3.4000; SD, 2.4585; SEM, 0.7775.

Table 10. Groups 2 and 3, Annoyance Variation (Visual Analog Scale): Independent Samples Test (*t*-test)*

	t-Test for Equality of Means			
	t	*df*	Sig. (two-tailed)	Mean Difference
Annoyance, equal variances assumed	−0.486	18	0.633	−0.5000
Annoyance, equal variances not assumed	−0.486	17.646	0.633	−0.5000

* Group statistics for these tests are as follows:
Group 2 (n = 10): Mean, −3.9000; SD, 2.1318; SEM, 0.6741.
Group 3 (n = 10): Mean, −3.4000; SD, 2.4585; SEM, 0.7775.

Table 11. Groups 1 and 3, Intensity Variation (Visual Analog Scale): Independent Samples Test (*t*-test)*

	t-Test for Equality of Means			
	t	*df*	Sig. (two-tailed)	Mean Difference
Intensity, equal variances assumed	2.676	18	0.015	2.4000
Intensity, equal variances not assumed	2.676	14.368	0.018	2.4000

* Group statistics for these tests are as follows:
Group 1 (n = 10): Mean, −1.000; SD, 1.4142; SEM, 0.4472.
Group 3 (n = 10): Mean, −3.4000; SD, 2.4585; SEM, 0.7775.

GABAergic drugs does not enhance the results obtained with benzodiazepine drugs alone.

The discrepancy between Shulman's results and ours may be due to the different patient populations but, to be sure about that, it is necessary to study patients with SDT of a predominantly central origin, comparing the results of placebo, benzodiazepines alone, and benzodiazepines combined with GABAergic drugs. This would be important to clarify the following question: Are we dealing with two different populations of SDT patients or do all SDT patients, regardless of the tinnitus's origin (cochlear or central), have a common central pathophysiology?

Table 12. Groups 1 and 3, Annoyance Variation (Visual Analog Scale): Independent Samples Test (*t*-test)*

	t-Test for Equality of Means			
	t	*df*	Sig. (two-tailed)	Mean Difference
Annoyance, equal variances assumed	2.929	18	0.009	2.7000
Annoyance, equal variances not assumed	2.929	15.277	0.010	2.7000

* Group statistics for these tests are as follows:
Group 1 (n = 10): Mean, −0.7000; SD, 1.5670; SEM, 0.4955.
Group 3 (n = 10): Mean, −3.4000; SD, 2.4585; SEM, 0.7775.

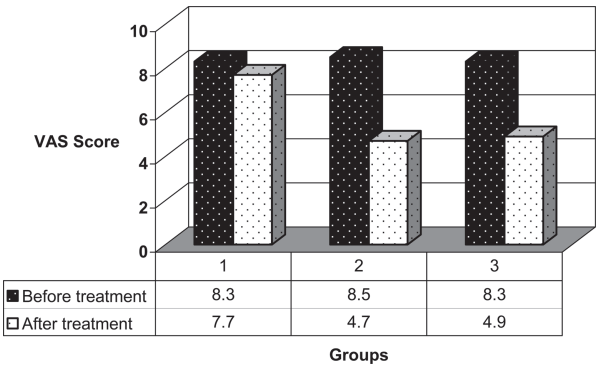

Figure 1. Tinnitus intensity average (*VAS*, visual analog scale).

CONCLUSIONS

The addition of GABAergic drugs to benzodiazepines does not modify the results of the treatment of SDT of predominantly cochlear origin. In our patients, the annoyance and intensity degrees were no different in the VAS. The same was true for Shulman et al. [8]. The VAS alone may not be able to distinguish between sensory (intensity) and affect (annoyance) components of SDT. Validated tinnitus outcome questionnaires may help to do so.

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