Original Article

Impact of Acamprosate on Chronic Tinnitus: A Randomized-Controlled Trial

Annals of Otology, Rhinology & Laryngology
2020, Vol. 129(11) 1110–1119

DOI: 10.1177/0003489420930773
journals.sagepub.com/home/aor
SAGE

Mohammad Farhadi[1], Mohammad Mahdi Salem[1], Alimohamad Asghari[2], Ahmad Daneshi[1], Marjan Mirsalehi[1], and Saeid Mahmoudian[1]

Abstract

Objectives: Tinnitus is a common and distressing otologic symptom, with various probable pathophysiologic mechanisms, such as an imbalance between excitatory and inhibitory mechanisms. Acamprosate, generally used to treat alcoholism, is a glutaminergic antagonist and GABA agonist suggested for treating tinnitus. Thus, we aimed to evaluate the efficacy and safety of acamprosate in the treatment of tinnitus.

Methods: The current randomized-controlled trial study included 20 subjects with chronic tinnitus. After performing psycho-acoustic, psychometric and electrophysiological evaluations, all studied tinnitus subjects were randomly divided into two groups of acamprosate and placebo. The first group received oral acamprosate (two tablets of 333 mg/d, three times a day), whereas the second group was given placebo treatment (two tablets, three times a day). After the first 30 days, all evaluations were repeated for the studied groups just in the same manner before the study. Subsequently, the final results of each evaluation were compared together with the baseline values.

Results: Nine studied subjects randomly received acamprosate, whereas eleven others received a placebo. There was no significant improvement in the psycho-acoustic tests, except a decrease was observed in the pitch match of tinnitus ($P = .039$). For those subjects who were receiving acamprosate, a significant reduction was observed in tinnitus handicap inventory ($P = .006$), tinnitus questionnaire scores ($P = .007$), and the visual analog scores ($P = .007$) compared to the placebo group. There was a significant reduction in Action Potential latency ($P = .048$) as well as an increase in the amplitude of distortion product otoacoustic emissions at 4 kHz ($P = .048$).

Conclusions: The study results indicated a subjective relief of tinnitus as well as some degree of the electrophysiological improvement at the level of the cochlear and the distal portion of the auditory nerve among the subjects who received the acamprosate.

Clinical trial registration code: IRCT2013121115751N1

Keywords

tinnitus, acamprosate, electrocochleography, auditory brainstem response, distortion product otoacoustic emissions, randomized controlled trial

Introduction

Tinnitus is defined as the perception of a sound, without any mechanical or acoustic source.[1] The pathophysiology of this perception is complicated, and several models have been suggested to explain the mechanism of the tinnitus.[2] One probable cause is the alteration in the balance of the excitatory and inhibitory neurotransmitters.[2] Increased spontaneous neural activity in the auditory pathway occurs due to the reduction in the level of the inhibitory mechanisms, probably by the decrease in the level of the gamma-aminobutyric acid (GABA), or increased release of the excitatory neurotransmitters, such as glutamate.[2-4] Various therapeutic strategies have been applied so far, but at present, there is no universally effective treatment or established standard of care. Clinical evidence suggests that limited success has been obtained with various medications, including benzodiazepines, anticonvulsants, and antidepressants.[5]

[1]ENT and Head & Neck Research Center and Department, the Five Senses Health Institute, Iran University of Medical Sciences, Tehran, Iran
[2]Skull Base Research Center, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Corresponding Author:
Saeid Mahmoudian, PhD, Laboratory for Auditory Neuroscience, ENT and Head & Neck Research Center and Department, The Five Senses Health Institute, Iran University of Medical Sciences, Hazrat Rasoul Akram Hospital, Niayesh st, Sattarkhan Ave, Tehran, 1445613131, Iran.
Email: mahmoudian.s@iums.ac.ir

Acamprosate (calcium salt of N-acetyl homotaurine) is currently used for the treatment of alcohol dependency. The chemical structure of this drug is similar to GABA.[6] This similarity causes blockage of the pre-synaptic GABA-ergic receptors in neural networks, which enhances the release of GABA.[7] On the other hand, acamprosate decreases the glutamate release by blocking N-methyl-D-aspartate (NMDA) receptors.[8] Due to the varied function in the regulation of inhibitory and excitatory mechanisms in neural networks, acamprosate can help to balance the neurotransmitters responsible for the tinnitus. Azevedo et al reported the efficacy and safety of acamprosate in decreasing the severity of tinnitus evaluated by self-report tests within a three-month treatment period.[9,10] A similar effect of acamprosate on subjective tests and tinnitus matching in loudness was also observed by Sharma et al.[11]

The current study aimed to determine the efficacy of acamprosate treatment on the subjective and objective tests in chronic tinnitus subjects.

Methods

This double-blind, randomized controlled clinical trial (code: IRCT2013121115751N1) was conducted on adults with chronic subjective tinnitus referred to a tertiary academic referral outpatient center. All subjects gave written informed consent, and the protocol was approved by the Medical Research Ethics Committee and the Board of clinical research at our institute with reference number IR.IUMS.REC.1393.9011369004. The study was clearly described for the participants, and they signed a written informed consent form. The protocol of this study was in line with the declaration of Helsinki.

Subjects

Twenty adult subjects with a history of chronic tinnitus who admitted to our tinnitus clinic between October 2014 and January 2015 were included in this study. The inclusion criteria were: (1) definite diagnosis of chronic subjective idiopathic tinnitus (>6 months), confirmed by both an audiologist and an otorhinolaryngologist; (2) Age ≥ 18 years; (3) Normal external and middle ear function checked via otoscopy and tympanometry; (4) Behavioral pure tone audiometry threshold levels ≤ 20 dB HL in octave frequencies of 250 to 2000 Hz and not more than 40 dB HL in frequencies of 4000 and 8000 Hz; (5) ability to read, speak and write in Persian; (6) Agreement to take part in the study and complete the follow-up. The exclusion criteria were: (1) History of chronic neurological or auditory diseases; (2) Use of neurological/psychiatric medications within the past 3 months; (3) Pregnancy or breastfeeding; (4) Temporomandibular disorders; (5) Receiving treatment for tinnitus within the past 3 months; (6) Alcohol or drug abuse; (7) Head and neck disease or space-occupying lesion; (8) tinnitus secondary to a systemic disease.

Measurements and Evaluations

A thorough medical history and physical and psychological examinations were obtained for each participant. The tinnitus subjective and objective tests were conducted for all the study participants before randomization. For participants with bilateral tinnitus, the dominant side with more severe symptoms was included in the study. In the cases who complained of the same severity on both sides, the measurements for both ears were considered in the analysis.

The audiological evaluations (pure tone audiometry and tympanometry) and tinnitus psychoacoustic measurement (pitch and loudness matching) were performed for all the participants.

Tinnitus Assessment

Tinnitus identification parameters were evaluated using the Tinnitus Evaluation Device (TinnED®, designed in ENT and Head & Neck Research Center of IUMS, Tehran, Iran).[12] This device includes six channels to reconstruct the Most Troublesome Tinnitus (MTT) with a similar frequency and intensity. The assessed tinnitus parameters included Pitch Matching and Loudness Matching of Tinnitus (PMT and LMT), Minimal Masking Level (MML) and finally the Residual Inhibition (RI). The accuracy of the calibrating equipment was sufficient to determine that the TinnED® was within the tolerance limits permitted by the American Standard Specification for Audiometers, S3.6-2004.[13] Tinnitus parameters of all studied subjects were evaluated pre- and post-Acamprosate. For the tinnitus pitch-match test, we used a two-alternative forced-choice method. Different pairs of pitch sounds were generated at 11 frequencies (from 125 Hz to 12 kHz); then decreased or increased the pitch, after which the subjects were asked to identify which pitch best matched the pitch of their tinnitus. Finally, we administered an octave confusion test to more accurately determined tinnitus frequency. The tone pairs were adjusted to a loudness level equivalent to that of the tinnitus before each pair was presented. LMT was obtained at each of the test tones used in the pitch-matching procedure. Subsequently, the auditory threshold level at that specific frequency (A) was increased in 1-dB steps until the subject reported that the external tone equaled the loudness of the tinnitus (B). The sound level was then slightly raised by 1-dB increments to obtain a threshold, which was slightly louder than that of the tinnitus (C). We used the mean level of loudness between points (B) and (C) as the representative loudness of the tinnitus. The formula for the loudness (expressed as decibels of sensation level) was as follows:

$$Loudness\ of\ tinnitus\ =\ \left[\left(B+C\right)/2-A\right]\ \left(dB\ SL\right)$$

The minimal masking level (MML) was measured by narrow-band noise on the affected ear until the tinnitus was fully covered and after that residual inhibition (RI) was measured using a narrow band noise for 60 seconds when the intensity was 10 dB over MML. Following an appropriate masking stimulus, tinnitus may remain suppressed for a period. This phenomenon is known as "RI." After deactivating the stimulation, one of the following results may occur. These results include Complete Residual Inhibition (CRI), Partial Residual Inhibition (PRI), Non-Residual Inhibition (NRI) and finally Rebound Effect (facilitated tinnitus) leading to some aggravation in tinnitus loudness reported by the subjects. When tinnitus remains inaudible, even after disengaging the masking stimulus, it is called CRI. The term PRI refers to the situation in which the tinnitus is reduced but still heard by the patient. While tinnitus is remained unchanged, after switching off the masking stimulation, it is called NRI. When a degree of rising in the loudness level of tinnitus occurred following switching off the masking stimuli, it is called the rebound phenomenon.

Self-report Tinnitus Questionnaires

We used the standardized Persian version of the 52-item Tinnitus Questionnaire (P-TQ),[14,15] which was firstly developed by Hallam, to evaluate the behavioral side effects of tinnitus. The questionnaire was validated with a Cronbach's alpha of 0.95 and test-retest reliability between 0.91 and 0.94.[16] The subscales consist of auditory perceptual difficulties, intrusiveness, sleep disturbances, somatic complaints, emotional and cognitive disturbances.

The standardized Persian Version of Tinnitus Handicap Inventory (P-THI),[17-19] that was firstly designed by Newman et al, consisting of 25 items, was used to describe the functional, emotional, and catastrophic effects of tinnitus on the participant's daily life.

Visual Analogue Scale (VAS) is a psychometric response scale to evaluate the impact of tinnitus in daily life in three fields of intensity, annoyance, and awareness. When responding to VAS, participants specified the loudness, annoyance, and disturbance of tinnitus by indicating a position along a continuous line between two end-points of 0 and 10.

Electrophysiological Procedures

Electrocochleography (ECochG) was performed using the Amplaid MK12 system (Amplaid, Milan, Italy). The active surface tympanic membrane electrode (Tymptrode) was inserted into the lower posterior-inferior region of the external auditory canal at the closest point to the tympanic membrane. The acoustic stimuli were delivered monaurally by a headphone (earphone Telephonics TDH-39 with cushion MX-41/AR) to the tinnitus ear. The stimuli were alternative 0.1 ms clicks presented at a rate of 7.1 per second and a bandpass filter of 30 to 3000 Hz. The responses were recorded with 1000 sweeps. The latency of the Summating Potentials (SPs) and Action Potentials (AP) and the ratio of the SP amplitude and AP amplitude (SP/AP) were computed.

Auditory Brainstem Response (ABR) was recorded using the same setting applied for electrocochleography. The stimuli were alternate 0.1 ms clicks presented at a rate of 11.1 per second and recording bandpass filtration of 30 to 3000 Hz. The responses were accumulated 2000 times. The latencies of waves I, III, and V, were computed.

Distortion Product Otoacoustic Emissions (DPOAE) test was performed using ILO92 (Otodynamics Ltd., Hatfield, United Kingdom) with three different frequency combinations for primary tones (f1 = 818, f2 = 1001 Hz; f1 = 1636, f2 = 2002 Hz and f1 = 3281, f2 = 4004 Hz). The intensity levels were L1 = 55 and L2 = 65 dB SPL and ratios of f1/f2 = 1.22. The evoked responses for 2f1 – f2 were assessed.

Randomization and Treatment

We used a simple randomization method by a random number generating software. After performing the baseline evaluations, the studied subjects were allocated to receive either acamprosate calcium tablets (Campral®, Forest Laboratories, Inc., and New York, USA) or placebo. Two tablets of acamprosate (333 mg) were given three times a day (total dosage of 1998 mg/day) for 30 days. The placebo tablets were similar to the acamprosate tablets in appearance and consisted of inactive ingredients (mainly starch, Talc, and Magnesium stearate), and were prepared in the Incubation Center for Pharmaceutical Technologies, Tehran University of medical sciences, Tehran, Iran. The placebo group received the tablets in the same frequency and duration of the intervention group. The experiment and placebo tablets were delivered to the subjects of each group in an identical package by a secretary who was unaware of the study protocol. All the studied subjects were visited in the second week to ensure tolerance and compliance.

At the end of the treatment period, all the tinnitus assessment tests and electrophysiological procedures were repeated in the same manner, and all the participants were asked to fill in the self-report questionnaires.

Statistical Analysis

All the statistical analyses were accomplished using SPSS, version 22.0 (IBM Corp., Armonk, USA). The quantitative variables with normal distribution were summarized by

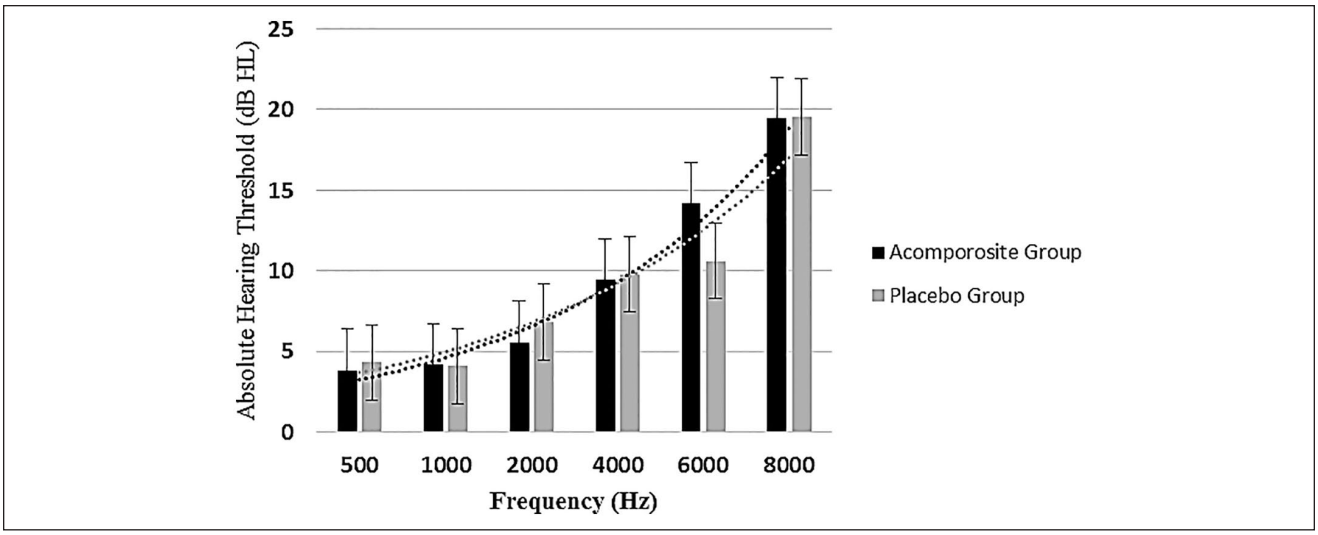

Figure 1. The comparison of means audiometric thresholds at 250 to 8000 Hz octave frequencies in decibels of hearing level (dB HL) across the two study groups.

means and standard deviations (SDs). Otherwise, they were represented as medians and interquartile ranges (IQR). The categorical variables were shown as frequency (percentage), and they were compared between the groups using the Chi-square test. The Wilcoxon signed-rank test was conducted for comparison of the variables before and after treatment. A *P*-value of $<.05$ was considered statistically significant.

Results

Population Demographics and Hearing Thresholds

Twenty-four tinnitus subjects met the study criteria and were randomized allocated into two equal groups. A preprinted pamphlet was given to all subjects with chronic tinnitus to be aware of probable medication's adverse effects. Four subjects discontinued the treatment before the end of the study due to the gastrointestinal adverse effects or loss of interest in continuing medication. There were no other notable symptoms or sensations that cause the study personnel was unblinded to the subject assignment. Finally, 20 subjects (26 ears) were able to complete the study. Among the studied subjects, nine cases allocated in the acamprosate group and the other 11 subjects allocated in the control group. The age of the participants ranged from 18 to 60 years, with an average of 40.5 ± 11.5 (41.4 ± 8.6 in the acamprosate group and 39.6 ± 13.8 years in the control group). All participants reported chronic unilateral (seven left and seven right subjects) or bilateral (both ears or in the head, six subjects) subjective idiopathic tinnitus lasting for at least 6 months (mean = 18.40; SD = 11.50 months) while they were intractable to standard treatments for tinnitus. The mean duration of tinnitus was 19.3 ± 10.2 months in the acamprosate group and 17.7 ± 12.9 in the control group. However, there was no significant difference between the groups regarding the side of involvement ($P = .538$).

Pure tone audiometry measurements showed normal to the slight sloping sensorineural hearing loss above 4 kHz for the 26 ears; the mean threshold of hearing levels at 500, 1000, 2000, and 4000 Hz frequencies were 5.4 ± 6.0, 4.2 ± 5.0, 5.2 ± 5.4, and 14.4 ± 7.2 dB HL, respectively (Figure 1). The mean pure tone average (PTA) for the mentioned frequencies was 7.3 ± 4.6 dB HL. However, the comparison of PTA values showed no statistical differences between the two studied groups from before (7.6 ± 5.3 dB HL, in acamprosate) to after treatment (7.0 ± 4.1 dB in the control group). No known major side-effect related to acamprosate occurred in the intervention group. Only a minor side effect of Acamprosate, that is, gastrointestinal problems, occurred in four studied subjects. The treatment was interrupted in three subjects due to the severity of symptoms.

Tinnitus Assessment Results

The results of the LMT, PMT, and MML measurements and their comparison between the groups before and after the intervention are shown in Table 1. No significant difference was observed before and after treatment in LMT and MML values. The mean PMT values decreased significantly after treatment with acamprosate as compared with baseline values in the intervention group.

The degree of residual inhibition responses and the related comparisons are shown in Figure 1. There was no significant improvement in RI responses between acamprosate and control group, before (*P*-value: .222) and after treatment (*P*-value: .888).

Table 1. Comparison of the Mean Values of the Tinnitus Assessment Tests, Before and After Treatment, Between the Acamprosate and the Placebo Groups.

	LMT [dB]*			PMT [kHz]*			MML [dB]*		
Groups	Before	After	*P*-value†	Before	After	*P*-value†	Before	After	*P*-value†
Acamprosate group	5.1 ± 2.9	6.9 ± 3.5	.125	5.0 ± 2.8	3.2 ± 2.9	.039*	30.3 ± 23.6	43.5 ±19.9	.145
Placebo group	8.1 ± 4.0	7.7 ± 3.1	.397	6.6 ± 2.4	6.3 ± 2.3	.167	28.5 ± 16.4	30.5 ± 16.1	.515
Intergroup comparison P-value	0.076	0.576	_	0.175	0.018	_	0.844	0.124	_

Abbreviations: LMT, Loudness Match of Tinnitus; MML, the Minimal Masking Level; PMT, Pitch Match of Tinnitus.
*The values are represented by mean ± standard deviation
†A *P*-value< .05 was considered statistically significant.

Table 2. Comparison of the P-THI and P-TQ Questionnaires Scores, Before and After Treatment, Between the Acamprosate and the Placebo Groups.

	P-THI Score*			P-TQ Score*		
Groups	Before	After	*P*-value†	Before	After	*P*-value†
Acamprosate group	50.0 [42.0, 66.0]	34 [20.0, 45.0]	.006	56.5 [42.2, 65.0]	36.7 [22.6, 55.2]	.007
Placebo group	40.0 [30.0, 60.0]	39 [28.0, 42.0]	.064	59.0 [33.8, 63.5]	48.6 [32.4, 63.5]	.619
Intergroup comparison P-value†	0.401	0.633	_	0.394	0.304	_

Note. *The values are represented by median and interquartile range.
†A *P*-value < .05 was considered statistically significant.

Table 3. Comparison of the VAS Scores in Three Subgroups of Intensity, Annoyance and Awareness, Before and After Treatment, Between the Acamprosate and the Placebo Groups.

	Intensity			Annoyance			Awareness		
Studied Groups	Before	After	*P*-value†	Before	After	*P*-value†	Before	After	*P*-value†
Acamprosate group	5.0 [4.5, 5.0]	4.0 [3.0, 4.0]	**.007**	4.0 [4.0, 5.0]	3.0 [3.0, 4.0]	**.004**	3.0 [3.0, 5.0]	3.0 [2.0, 4.0]	**.011**
Placebo group	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	.18	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	.414	4.0 [3.0, 5.0]	4.0 [3.0, 4.0]	.18
Intergroup comparison P-value†	0.063	0.744	-	0.263	0.436	-	0.602	0.137	-

Note. *The values are represented by median and interquartile range.
†A *P*-value < .05 was considered statistically significant.

Self-report Tinnitus Questionnaires

The median scores of the P-THI and P-TQ questionnaires before and after treatment in acamprosate and control groups and their corresponding level of significance are shown in Table 2. The median scores of the P-THI decreased significantly ($P = .006$) after treatment with acamprosate, and the severity of the difficulties reported by the subjects shifted from moderate to mild. There was no significant difference between the intervention and the control groups (Table 2). The P-TQ scores decreased significantly after 30 days of treatment with Acamprosate ($P = .007$).

The VAS scores in all three subgroups decreased significantly after acamprosate consumption. The scores in the control group did not change after treatment (Table 3).

Electrophysiological Procedures

Electrocochleography: There was a statistical decline in the AP latencies after treatment with Acamprosate ($P = .048$). This reduction did not meet clinical importance because of minor differences in marking latency on ECochG waves. The comparison of the SP latencies and SP/AP ratios did not reach the level of significance in the study groups Table 4).

ABR: Despite the mild decreases in the latencies of the waves I and III after treatment in both experiment and control group, these declines did not reach the significance level (Table 5). There was not a remarkable difference between wave-V latencies, before and after treatment, in experiment and control groups (Table 5). There were no significant differences between inter-peak latencies (IPL) of

Table 4. Comparing the Mean Latencies of AP and SP, and the SP/AP Ratio Obtained from the Electrocochleography, Before and After Treatment, Between the Acamprosate and the Placebo Groups.

	AP Latency [ms]*			SP Latency [ms]*			SP/AP Ratio*		
Groups	Before	After	*P*-value†	Before	After	*P*-value†	Before	After	*P*-value†
Acamprosate group	1.62 ± 0.15	1.56 ± 0.16	**.048**	1.11 ± 0.13	1.04 ± 0.18	.324	25.1 ± 4.9	25.9 ± 5.7	.702
Placebo group	1.65 ± 0.15	1.65 ± 0.15	.943	1.05 ± 0.24	1.00 ± 0.18	.267	26.3 ± 7.5	23.9 ± 6.3	.28
Intergroup comparison P-value†	0.558	0.156	-	0.402	0.528	-	0.402	0.528	-

Note. *The values are represented by mean ± standard deviation.
† A *P*-value < .05 was considered statistically significant.

Table 5. Comparison of the Mean Latencies of Waves I, III, and V Obtained from the ABR, Before and After Treatment, Between the Acamprosate and the Placebo Groups.

	Wave-I Latency [ms]*			Wave-III Latency [ms]*			Wave-V Latency [ms]*		
Group	Before	After	*P*-value†	Before	After	*P*-value†	Before	After	*P*-value†
Acamprosate group	1.72 ± 0.16	1.64 ± 0.29	.374	3.78 ± 0.26	3.61 ± 0.59	.325	5.53 ± 0.49	5.59 ± 0.56	.738
Placebo group	1.74 ± 0.29	1.60 ± 0.17	.068	3.74 ± 0.41	3.60 ± 0.37	.107	5.62 ± 0.37	5.64 ± 0.33	.491
Intergroup comparison P-value†	0.791	0.65	-	0.778	0.763	-	0.59	0.764	-

Note. *The values are represented by mean ± standard deviation.
†A *P*-value < .05 was considered statistically significant.

Table 6. Comparison of the Mean Values of Inter-peak Latencies Obtained from the ABR Recordings, Before and After treatment, in Two Studied Groups of Acamprosate and Placebo Controls.

	IPL I-III [ms]			IPL III-V [ms]			IPL I-V [ms]		
	Before	After	*P*-value	Before	After	*P*-value	Before	After	*P*-value
Acamprosate Group	2.05 ± 0.23	2.07 ± 0.15	.511	1.91 ± 0.15	1.94 ± 0.12	0.268	3.96 ± 0.23	4.01 ± 0.15	.124
Control Group	2.00 ± 0.26	2.02 ± 0.07	.316	1.88 ± 0.20	1.91 ± 0.19	0.084	3.88 ± 0.31	3.94 ± 0.27	.087
P value	0.620	0.573	-	0.638	0.693	-	0.458	0.394	-

Abbreviation: IPL, Inter-peak latency of ABR waveform.

I-III, III-V, and I-V before and after treatment in experiment and control groups (Table 6).

Distortion Product Otoacoustic Emissions (DPOAE): A comparison of the mean amplitudes before and after treatment with acamprosate represented a significant increase at 4000 Hz ($P = .048$). Nonetheless, this increase was not evident in the control group (Figure 2). There was not a significant difference between the two studied groups from before ($P = .482$) to after treatment ($P = .262$).

Discussion

Tinnitus is a pathological condition that increased spontaneous activity and neural synchrony in auditory and non-auditory areas is obvious.[20-22] GABA deficiency is a strong hypothesis for increased activity and over excitation in network activity involved in tinnitus.[23,24] Although the exact mechanism of acamprosate action is not clearly defined, this agent appears to block excitatory activity in the brain (NMDA Glutamate). It also enhances the inhibitory system (GABA) by stimulating GABAergic inhibitory neurotransmission. Thus, acamprosate enhances the number of reuptake sites for GABA and in turn improves GABAergic transmission, which inhibits the activity in the auditory pathways.[9,25] The previous study revealed evidence that the inhibitory neurotransmitter γ-aminobutyric acid (GABA) is released from some efferent olivocochlear nerve endings terminating at outer hair cells (OHCs). The previous studies revealed that the inhibitory neurotransmitter aminobutyric acid (GABA) is released from some efferent olivocochlear nerve endings terminating at outer hair cells (OHCs). These receptors are thought to allow GABA which is released

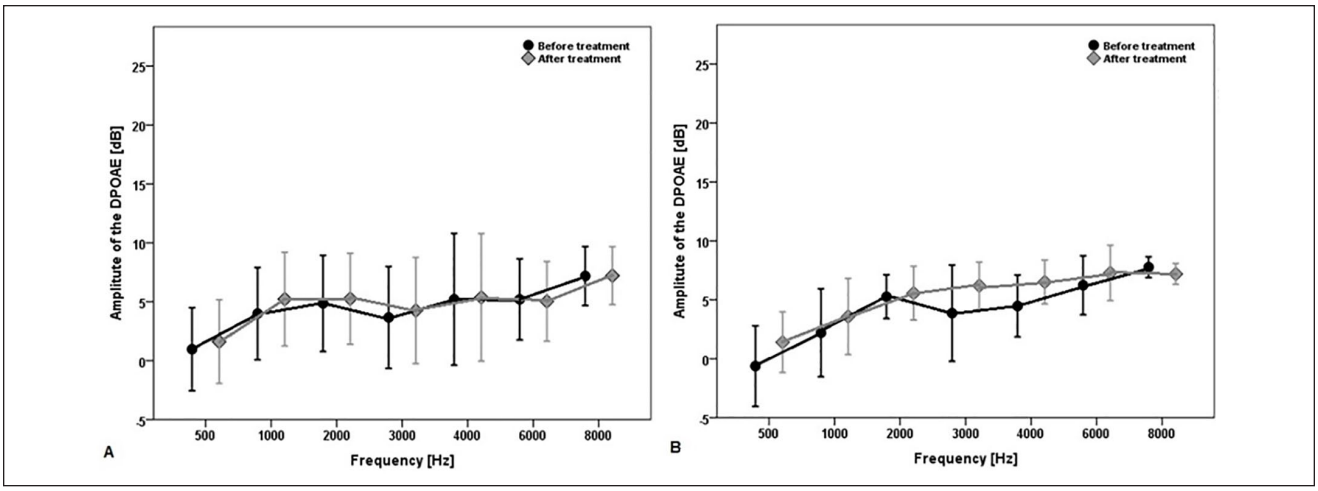

Figure 2. Mean amplitudes obtained from the DPOAE before and after treatment. The error bars represented the 95% confidence intervals. (A) Comparison of the amplitudes in the placebo group. There was not a significant difference between mean values before and after treatment in the control group. (B) Comparison of the amplitudes in the acamprosate group. There was a significant increase at 4000 Hz after treatment with acamprosate.

from efferent auditory nerve terminals to bind to the cell surface of OHCs, resulting in GABA receptor activation. This probably gates a GABA-receptor-associated chloride channel in the postsynaptic OHC membrane, allowing hyperpolarization and elongation of the cell.[26,27] The epidemiologic studies estimated that 10% to 15% of adults are suffering from tinnitus, and it affects the quality of life in 20% of these subjects.[28] Several pharmacological therapies have been introduced to improve the quality of life of the subjets.[5,29,30] These therapeutic modalities are targeting the pathophysiological aspects of tinnitus. As tinnitus may result from the disturbed balance between excitatory and inhibitory neurotransmitters, agents that regulate these mechanisms may affect the severity of symptoms.[31] The exact effect of acamprosate on neurotransmission is not completely clear because of its various effects on a different region of the brain.[32] Increased GABA binding in the hippocampus and thalamus of the alcoholized rats was observed after treatment with acamprosate.[33] However, other studies did not confirm this effect.[32,34] Antagonist activity for NMDA receptors in the cortex, hippocampus, and midbrain was reported after acamprosate treatment.[34]

On the other hand, the positive impact of acamprosate on anxiety disorders made it an option for augmentation therapy.[35] As the same disturbances in the hypothalamic-pituitary-adrenal axis were observed in tinnitus and anxiety,[36] anxiety treatments that affect this axis may be useful in tinnitus treatment. Based on the findings mentioned above, it was hypothesized that acamprosate could influence tinnitus severity. A clinical trial performed on fifty subjects with tinnitus by Azevedo and colleagues agreed with this hypothesis. The subjects were asked to score the loudness and annoyance of tinnitus using VAS and were randomized to receive receiving either acamprosate (333 mg three times a day for 90 days) or placebo. There was a significant improvement of symptoms based on VAS after 90 days in the acamprosate group (P =.004). This improvement was evident after 30 days of receiving acamprosate and increased steadily till the end of the study.[9,10] Sharma and colleagues evaluated the impact of acamprosate on tinnitus on forty subjects in a cross over trial. There was a significant improvement in QOL and VAS in subjects treated with acamprosate as compared with the placebo group. Psychoacoustic reduction in tinnitus matching for loudness was also significant in the acamprosate group.[11]

In the present study, there was a significant improvement in P-THI and P-TQ scores after treatment with acamprosate as well as the VAS scores. Evaluation of the psychoacoustic measurements revealed a significant decrease in PMT in the acamprosate group, but this reduction was not evident in LMT and MML measurements before and after treatment. As reported by Azevedo,[10] the impact of the acamprosate improves steadily after 30 days of treatment, so the short-term treatment and follow up of the current study may explain why an improvement was not demonstrated in LMT and MML tests. Although the results of the residual inhibition test did not reach the statistical significance, none of the tinnitus subjects in the acamprosate group reported any deterioration in RI. While two of seven subjects who reported NRI revealed a reasonable degree of PRI after receiving the acamprosate treatment (one improved to partial RI, and complete RI in the other). These improvements might be to make an opportunity to use tinnitus sound therapy as a management option to cope with tinnitus (Figure 3). We know that there is considerable variability amongst tinnitus subjects in the depth of RI and its duration. This issue would be an interesting topic for future

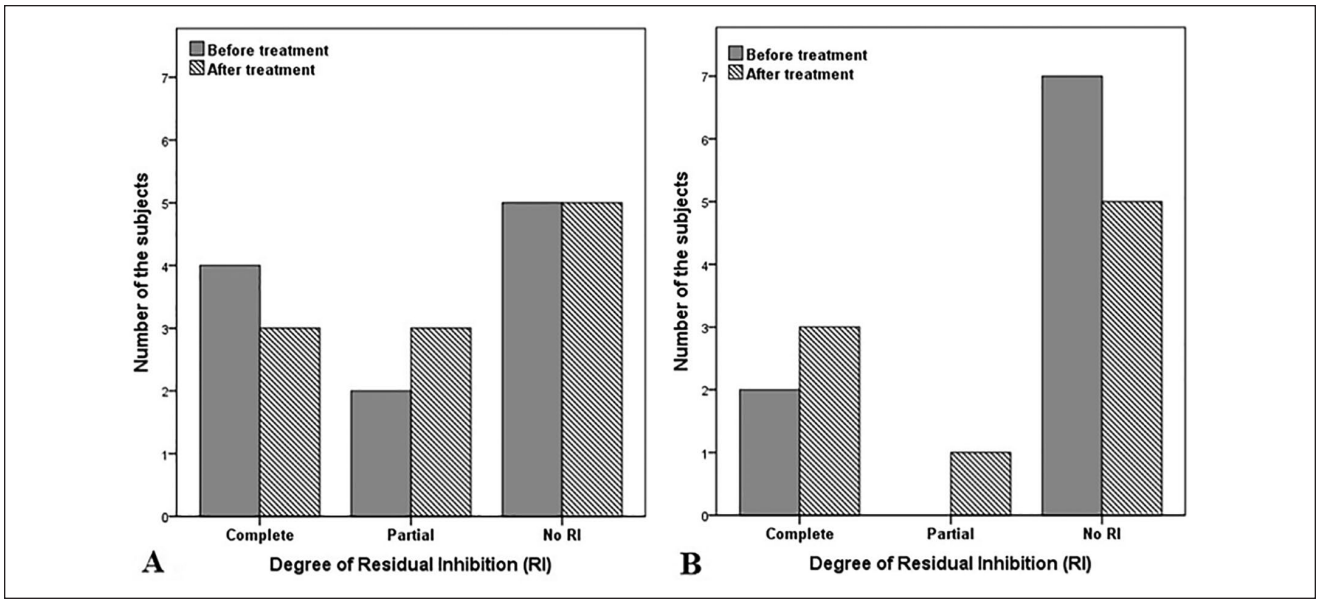

Figure 3. The degrees of residual Inhibition before and after treatment.
The gray boxes represent the responses before treatment, and the crosshatched boxes showed the responses after treatment. Panel A, indicated the degree of RI in the placebo group and panel B indicated the degree of RI in the acamprosate group. As appears in Figure 3, diagram B, despite the absence of the statistical significant findings, the depth and duration of residual inhibition was improved from before to after treatment in the acamprosate group. Also, the degree of non-residual inhibition (NRI) decreased after acamprosate treatment. However, no such result was observed in the placebo group (diagram A).

work to understand the RI mechanism. Therefore, the mentioned issue should be noticed as separate variables while conducting research. In any case, it should be noted that the mechanism involved in-depth and duration of RI remains unclear to this day.

Meikle and colleagues stated that the subjective data achieved from available self-report questionnaires are useful in diagnostic or severity assessments of tinnitus, but they are not sensitive enough for treatment-based evaluations.[37] The psychoacoustic tests are valuable in the evaluation of patient's subjective reports, but lack of a standard protocol for test conduction is a limitation in the evaluation of treatment outcomes.[38] The current study utilized the electrophysiological tests in order to evaluate the auditory system status and impact of the Acamprosate on auditory pathways. In fact, the presented primary results in this study expressed the objective interests in the Acamprosate effect by means of physiologic and electrophysiologic assessments. To the best of our knowledge, the impact of the acamprosate on electrophysiological tests has not been evaluated before. Although the electrocochleographic evaluations showed a statistical difference in the mean of AP latencies after treatment with the Acamprosate ($P = .048$), this reduction doesn't meet clinical importance because of minor differences in marking latency on ECochG waves. Changes in the SP latencies and SP/AP ratios did not reach the level of significance ($P = .324$ and .702, respectively). These findings can help to identify the site of action of acamprosate in the auditory pathway. As the compound action potential is induced by the distal part of the auditory nerve,[12] more robust and synchronized firing of the neuron fibers, can produce a wave with shortened latency.

Shulman et al demonstrated prolonged interpeak latencies of wave's I-III, III-V, and I-V in the presence of central tinnitus, and decreased by improvements of subjects' tinnitus.[39] However, the latencies of the waves I, III, and V did not change significantly after treatment with acamprosate in the current study. Thus, a study with more participants and more extended intervention is recommended to evaluate the effects of acamprosate on ABR.

Shiomi et al compared the DPOAE amplitudes in normal-hearing subjects with or without tinnitus and demonstrated a remarkable reduction of amplitudes, especially at 4 to 7 kHz frequencies.[40] A significant difference in DPOAE amplitudes at 4 to 6 kHz frequencies in the ear with tinnitus compared to the intact ear of the same subjects was reported by Park et al.[41] In the current study, the DPOAE amplitudes improved significantly at 4 kHz frequency after treatment with acamprosate. As the lack of coordination in outer hair cells and inner hair cells are considered as a possible mechanism for tinnitus,[1] the improved amplitude of DPOAE after acamprosate represented a better function of OHC, at least at 4 kHz frequency.

The concentration-dependent effect of acamprosate on NMDA receptors was demonstrated in 2004. In that study, the spontaneous neuronal activity at the level of the brainstem in neonatal rats was evaluated with acamprosate. At

30 µm, acamprosate increased the spontaneous neuronal bursts, but higher concentrations of acamprosate (100-400 µm) inhibited the NMDA-mediated neural excitation.[25] Because of this biphasic effect of acamprosate, the standard dose of acamprosate (1998 mg/day) was administered in the present study.

One of the drawbacks of the current study is the low sample size because of the interruption of treatment in four subjects. A gradual Increase of acamprosate dose may enhance the compliance of the subjects. Besides, considering crossover and washout periods in the design of the study would improve the results. It was demonstrated that the impact of acamprosate, enhanced after one-month treatment,[9,10] therefore, follow-ups longer than 30 days could improve the accuracy of the study.

Conclusion

Based on the current study, acamprosate can improve the self-report tinnitus questionnaire scores among the subjects who were complaint from tinnitus. Electrophysiological studies reported some degrees of improvement, at least at the level of the cochlea and distal of the auditory pathways. Also, investigating the validity of animal experiments is therefore essential to validate the clinical efficacy and practical feasibility of using the medication.

Acknowledgments

This study was supported by Iran University of Medical Sciences and Iran National Science Foundation (INSF), Tehran, Iran. We would also like to express our gratitude to all colleagues of the laboratory for auditory neuroscience, and ENT, Audiology and tinnitus clinic of Hazrat-e Rasool General Hospital for referring tinnitus subjects and providing equipment for performing audiological evaluations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The current study funded by a grant from the Iran National Science Foundation (INSF) (reference number: 92039381).

ORCID iDs

Alimohamad Asghari https://orcid.org/0000-0002-9107-4309
Saeid Mahmoudian https://orcid.org/0000-0002-6908-7605

References

1. Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neurosci Res*. 1990;8(4):221-254.
2. Shore SE, Roberts LE, Langguth B. Maladaptive plasticity in tinnitus—triggers, mechanisms and treatment. *Nat Rev Neurol*. 2016;12(3):150.
3. Zhao Y, Song Q, Li X, Li C. Neural hyperactivity of the central auditory system in response to peripheral damage. *Neural Plast*. 2016;2016:2162105.
4. Salvi RJ, Wang J, Ding D. Auditory plasticity and hyperactivity following cochlear damage. *Hear Res*. 2000;147(1-2):261-274.
5. Beebe Palumbo D, Joos K, De Ridder D, Vanneste S. The management and outcomes of pharmacological treatments for tinnitus. *Curr Neuropharmacol*. 2015;13(5):692-700.
6. Littleton JJA. Acamprosate in alcohol dependence: how does it work? *Addiction*. 1995;90(9):1179-1188.
7. Berton F, Francesconi WG, Madamba SG, Zieglgänsberger W, Siggins GRJAC, Research E. Acamprosate enhances N-methyl-D-apartate receptor-mediated neurotransmission but inhibits presynaptic GABA(B) receptors in nucleus accumbens neurons. *Alcohol Clin Exp Res*. 1998;22(1):183-191.
8. Zeise ML, Kasparov S, Capogna M, Zieglgänsberger W. Acamprosate (calciumacetylhomotaurinate) decreases postsynaptic potentials in the rat neocortex: possible involvement of excitatory amino acid receptors. *Eur J Pharmacol*. 1993;231(1):47-52.
9. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: double-blind study. *Braz J Otorhinolaryngol*. 2005;71(5):618-623.
10. Azevedo A, Figueiredo RR. Treatment of tinnitus with acamprosate. *Prog Brain Res*. 2007;166:273-277.
11. Sharma DK, Kaur S, Singh J, Kaur I. Role of acamprosate in sensorineural tinnitus. *Indian J Pharmacol*. 2012;44(1):93-96.
12. Mahmoudian S, Lenarz M, Esser KH, et al. Alterations in early auditory evoked potentials and brainstem transmission time associated with tinnitus residual inhibition induced by auditory electrical stimulation. *Int Tinnitus J*. 2013;18(1):63-74.
13. American National Standards Institute. *Specifications for Audiometers (ANSI S3. 6-2004)*. New York, NY: American National Standards Institute; 2004.
14. Hiller W, Goebel G. A psychometric study of complaints in chronic tinnitus. *J Psychosom Res*. 1992;36(4):337-348.
15. Hallam R. *Manual of the Tinnitus Questionnaire (TQ)*. London: Psychological Corporation; 1996.
16. Daneshi A, Mahmoudian S, Farhadi M, Hasanzadeh S, Ghalebaghi B. Auditory electrical tinnitus suppression in patients with and without implants. *Int Tinnitus J*. 2005;11(1):85-91.
17. Newman CW, Sandridge SA, Jacobson GP. Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. *J Am Acad Audiol*. 1998;9:153-160.
18. Mahmoudian S, Shahmiri E, Rouzbahani M, et al. Persian language version of the "Tinnitus Handicap Inventory": translation, standardization, validity and reliability. *Int Tinnitus J*. 2011;16(2):93-103.
19. Newman CW, Jacobson GP, Spitzer JB, Surgery N. Development of the tinnitus handicap inventory. *Arch Otolaryngol Head Neck Surg*. 1996;122(2):143-148.
20. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proc Natl Acad Sci USA*. 2011;108(20):8075-8080.

21. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. *Trends Neurosci*. 2004;27(11):676-682.
22. Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. *J Neurosci*. 2010;30(45):14972-14979.
23. Eggermont JJ, Roberts LE. Tinnitus: animal models and findings in humans. *Cell Tissue Res*. 2015;361(1):311-336.
24. Llinas R, Urbano FJ, Leznik E, Ramirez RR, van Marle HJ. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends Neurosci*. 2005;28(6):325-333.
25. Pierrefiche O, Daoust M, Naassila M. Biphasic effect of acamprosate on NMDA but not on GABAA receptors in spontaneous rhythmic activity from the isolated neonatal rat respiratory network. *Neuropharmacology*. 2004;47(1):35-45.
26. Oliver D, Klocker N, Schuck J, Baukrowitz T, Ruppersberg JP, Fakler B. Gating of Ca2+-activated K+ channels controls fast inhibitory synaptic transmission at auditory outer hair cells. *Neuron*. 2000;26(3):595-601.
27. Plinkert PK, Gitter AH, Mohler H, Zenner HP. Structure, pharmacology and function of GABA-A receptors in cochlear outer hair cells. *Eur Arch Otorhinolaryngol*. 1993;250(6):351-357.
28. Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. *J Speech Lang Hear Res*. 2005;48(5):1204-1235.
29. Langguth B, Elgoyhen AB. Current pharmacological treatments for tinnitus. *Expert Opin Pharmacother*. 2012;13(17):2495-2509.
30. Elgoyhen AB, Langguth B. Pharmacological approaches to the treatment of tinnitus. *Drug Discov Today*. 2010;15(7-8):300-305.
31. Matsui JI, Parker MA, Ryals BM, Cotanche DA. Regeneration and replacement in the vertebrate inner ear. *Drug Discov Today*. 2005;10(19):1307-1312.
32. Zornoza T, Cano MJ, Polache A, Granero L. Pharmacology of acamprosate: an overview. *CNS Drug Rev*. 2003;9(4):359-374.
33. Daoust M, Legrand E, Gewiss M, et al. Acamprosate modulates synaptosomal GABA transmission in chronically alcoholised rats. *Pharmacol Biochem Behav*. 1992;41(4):669-674.
34. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. *Br J Clin Pharmacol*. 2014;77(2):315-323.
35. Schwartz TL, Siddiqui UA, Raza S, Costello A. Acamprosate calcium as augmentation therapy for anxiety disorders. *Ann Pharmacother*. 2010;44(12):1930-1932.
36. Pattyn T, Van Den Eede F, Vanneste S, et al. Tinnitus and anxiety disorders: a review. *Hear Res*. 2016;333:255-265.
37. Meikle MB, Stewart BJ, Griest SE, et al. Assessment of tinnitus: measurement of treatment outcomes. *Prog Brain Res*. 2007;166:511-521.
38. Newman CW, Sandridge SA, Jacobson GP. Assessing outcomes of tinnitus intervention. *J Am Acad Audiol*. 2014;25(1):76-105.
39. Shulman A, Seitz MR. Central tinnitus–diagnosis and treatment. Observations simultaneous binaural auditory brain responses with monaural stimulation in the tinnitus patient. *Laryngoscope*. 1981;91(12):2025-2035.
40. Shiomi Y, Tsuji J, Naito Y, Fujiki N, Yamamoto N. Characteristics of DPOAE audiogram in tinnitus patients. *Hear Res*. 1997;108(1-2):83-88.
41. Park JP, Lim HW, Shim BS, et al. Interaural differences of distortion product otoacoustic emission amplitudes in patients with unilateral tinnitus. *Otolaryngol Head Neck Surg*. 2013;148(3):456-459.