



# Clonazepam Usage Improves Chronic Tinnitus and Sleep Quality: A Prospective Cohort Study

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## 클로나제팜의 이명 및 불면 개선 효과 분석: 전향적 코호트 연구

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**Background and Objectives** Tinnitus, although being a common chronic disease, can be an intractable disease that causes depression and insomnia. This study aimed to analyze the results of the Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index (PSQI) questionnaire surveys before and after clonazepam therapy. In addition, we analyzed the association of three pre-treatment questionnaires and evaluated whether pre-treatment factors could predict the post-treatment THI index.

**Subjects and Method** Patients were selected from those who visited a tertiary hospital from 2019 to 2021 for the treatment of chronic tinnitus they had for more than 3 months and who were over 20 years old. Patients were excluded from the study if they were diagnosed with acute sudden hearing loss, Meniere's disease, brain/internal auditory canal tumors, or muscular/vascular tinnitus. The questionnaire surveys of THI, BDI, PSQI were conducted before and after 3 months of clonazepam therapy (Rivotril [Roche Inc.] 0.25 or 0.5 mg). Questionnaire scores were compared using the paired t-test. Multiple regression analysis was used to determine the relationships among the three questionnaires.

**Results** A total of 76 patients (38 males and 38 females) with the mean age of  $57.2 \pm 9.01$  years was analyzed. The average hearing threshold was  $30.4 \pm 20.67$  dB HL on the right and  $31.7 \pm 17.06$  dB HL on the left. The pre-treatment THI, BDI, and PSQI scores were  $44.3 \pm 23.4$ ,  $7.96 \pm 2.36$ , and  $6.85 \pm 4.68$ , respectively. The relationships between the THI and BDI and the THI and PSQI were significant ( $p=0.0027$  and  $p<0.0001$ , respectively). The pre-THI score showed no significant association with age, sex, or hearing threshold ( $p=0.91$ ,  $0.85$ , and  $0.23$ , respectively). The post-treatment THI score was  $33.6 \pm 17.1$ , which was significantly lower than the pre-THI scores ( $p<0.0001$ ). Post-BDI and post-PSQI were  $7.38 \pm 2.25$  and  $4.04 \pm 3.20$ , respectively. Post-PSQI also significantly decreased compared with pre-PSQI ( $p=0.0002$ ), but post-BDI did not significantly decrease ( $p=0.1231$ ). In the THI survey, Question 7 (sleep disturbance) showed decrease the most, followed by Question 25 (unstable mood). The post-treatment THI could be predicted by using the formula,  $0.7673 + 0.6947 \times \text{pre-THI} + 0.3572 \times \text{pre-PSQI}$ .

**Conclusion** The appropriate/optional use of clonazepam at low doses (0.25–0.5 mg) can significantly improve chronic tinnitus and sleep quality. Tinnitus was significantly associated with the scores of THI, BDI, PSQI and the usage of Clonazepam significantly reduced the THI and PSQI scores. However, clonazepam did not affect the BDI score.

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## Introduction

Tinnitus is the phantom perception of sound resulting from abnormal/false activity within the auditory nervous system without any corresponding mechanical or vibratory activity from the cochlea and is not related to any external sound stimuli.<sup>1)</sup> One-third of the global population experiences tinnitus at least once in their lifetime,<sup>2)</sup> and approximately 1%–5% of individuals with tinnitus experience serious psychosocial complications that may require medication. Furthermore, recent studies have reported that patients with tinnitus are likely to have comorbid psychological disorders, including anxiety and depression, and show a high prevalence of depression.<sup>3–6)</sup> In addition, the severity of tinnitus is positively correlated with anxiety and depression levels.<sup>7)</sup>

Tinnitus is a chronic illness that has no cure. Treatments such as tinnitus retraining therapy, cognitive behavioral therapy, transcranial magnetic stimulation, electrical stimulation, and the use of masking devices and white noise machines have been studied. However, there is no definitive cure for tinnitus.<sup>8)</sup> The management of tinnitus requires a multidisciplinary approach depending on the symptoms and comorbid conditions of patients with tinnitus.<sup>9,10)</sup> Currently, there are no FDA-approved drugs for the treatment of tinnitus.<sup>11)</sup> However, clinical studies are underway to evaluate the efficacy of N-methyl-D-aspartate and dopamine D2 antagonists, selective serotonin reuptake inhibitors, and  $\gamma$ -aminobutyric acid agonists.<sup>12)</sup> Previous studies have suggested that patients with severe depression may experience improvements in tinnitus after treatment with antidepressants such as nortriptyline or sertraline.<sup>13)</sup>

Several studies have investigated the use of benzodiazepines for tinnitus treatment. Some studies have shown that clonazepam is effective for tinnitus. Clonazepam, which is sold under the brand name Rivotril, is a benzodiazepine medication that is used to prevent and treat tinnitus, seizures, panic disorder, anxiety, and movement disorders.<sup>14–16)</sup> It increases activity of GABA, and potentiates the inhibitory neurotransmission in the brain cortex. The effect of clonazepam begins within 1 h and lasts for 6–12 h. The typical side effects of clonazepam include sedation, motor impairment, and confusion. The intermittent side effects of clonazepam include irritation, psychomotor agitation, dizziness, hallucinations, memory loss, and headaches.<sup>17)</sup> Regarding long-term use, side effects such as tolerance, dependence, and withdrawal symptoms may occur.<sup>18,19)</sup> Clonazepam is a very basic drug that is widely used around the world and is also commonly used for tinnitus.<sup>20)</sup>

When clonazepam is used for tinnitus, it can easily cause various side effects;<sup>21)</sup> therefore, it is important to determine the dose of the drug for each individual. In addition, optional use is recommended after the symptoms of tinnitus have been controlled. Many studies claim that clonazepam effectively alleviates tinnitus,<sup>16)</sup> but its effects on sleep quality and depression have not been discussed.

In this study, we aimed to determine whether clonazepam at a lower dose than that used in other studies is effective in treating chronic tinnitus lasting more than 3 months. This paper will perform a comparative analysis of questionnaire scores before and after 3 months of clonazepam administration by using the Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index (PSQI), which are questionnaires that can assess the conditions of patients with tinnitus.

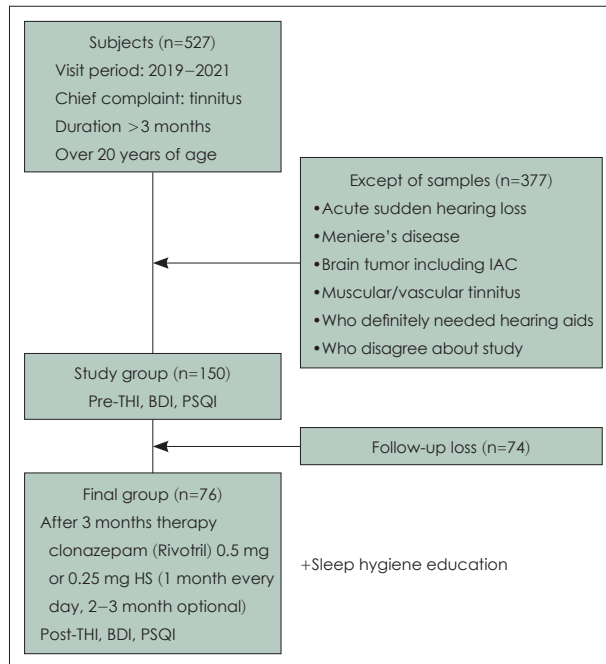
## Subjects and Methods

### Subjects

A total of 527 patients with tinnitus who visited a tertiary hospital in 2019–2021, underwent hearing and tinnitus tests, and completed a tinnitus questionnaire were considered for the study. The exclusion criteria were acute sudden hearing loss; Meniere's disease; brain tumor, including internal auditory canal schwannoma and muscular/vascular tinnitus. In addition, patients who needed hearing aids because of definite severe-to-profound hearing loss or asymmetric hearing loss and those who refused to participate in the study were excluded. The study was conducted on 150 patients who agreed to the tinnitus treatment, completed a questionnaire, and were followed up. A final analysis was performed on 76 patients who completed the questionnaire before and after treatment with clonazepam (Fig. 1).

### Treatment protocol

This study was conducted prospectively. Rivotril (Roche Inc., Morgantown, WV, USA) was to be taken as one-half to one pill (0.25–0.5 mg) before going to bed and preferably every day for the first month. Basically, 0.25 mg was taken, and 0.5 mg was taken if patients complained of severe tinnitus discomfort or sleep problems. In the second and third month, it can be taken optionally, only when the patient has trouble sleeping or severe tinnitus. This was performed to reduce the addiction caused by the drug and to establish a recommendation for effective use under autonomous management. The



**Fig. 1.** A total of 527 patients with tinnitus who visited a tertiary hospital in 2019–2021, underwent hearing and tinnitus tests, and completed a tinnitus questionnaire were considered for this study. IAC, internal auditory canal; THI, Tinnitus Handicap Inventory; BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index.

importance of ideal sleep hygiene was emphasized in patients during the treatment period for tinnitus. After taking Rivotril, it is recommended to lie down and sleep immediately without using TV, radio, cell phones, or smartphones. It is recommended to have a warm shower before going to bed. Habits such as avoiding extreme exercise 3 h before sleep, avoiding caffeine-containing and stimulating food, and drinking warm milk were encouraged.

This prospective cohort study aims to analyze the results of the THI, BDI, and PSQI questionnaire surveys before and after clonazepam usage. At the first visit, a tinnitus survey and questionnaire were administered, and tympanic membrane examination, pure tone audiometry (PTA), and tinnitogram were performed for all patients. The Institutional Review Board approved this study (Korea University College of Medicine IRB ED15142-2019).

The THI was administered to the patients to evaluate the severity of tinnitus. The Korean version of THI measures the effect of tinnitus on daily life, and its reliability and validity have been proven in a previous study.<sup>22)</sup> It contains 25 items under the following subscales: functional subscale (11 items), emotional subscale (9 items), and catastrophic subscale (5 items). Each question is rated as zero (none), two (sometimes), or four

(always). The total score is calculated in the range of 0–100.

The Korean version of BDI was used to evaluate the severity of depressive symptoms. It comprises 21 questions that include the emotional, cognitive, motive, and physiological areas of depression. Each question is rated on a scale of 0 to 3 depending on the degree of symptoms, and the total score is calculated from a range of 0 to 63. A previous study found that a BDI score of 16 or above for male and 17 or above for female was indicative of depression.<sup>23)</sup>

The Korean version of PSQI was used to assess sleep quality. It comprises 19 items that measure subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime function. Each question is rated on a scale of 0 to 3 depending on the degree of symptoms, and the total score is calculated from a range of 0 to 21. A total score of five or above indicates poor sleep quality.

## Statistical analysis

All values are presented as mean±standard deviation using SPSS 21.0 (IBM Corp., Armonk, NY, USA). A paired sample t-test was used to compare the changes in THI, BDI, and PSQI scores before and after medication use. Multiple data were analyzed using the analysis of variance. Correlation analysis was used to examine the correlation between THI/BDI and THI/PSQI. Multiple regression analysis was used to confirm the correlation between post-THI and pre-THI and BDI. A *p*-value less than 0.05 was considered statistically significant.

## Results

### Demographics of tinnitus patients

A total of 38 males and 38 females from the enrolled patients were analyzed in this study, and the average age was  $57.2 \pm 9.01$  years. The right and left PTA threshold levels were  $30.4 \pm 20.67$  dB HL and  $31.7 \pm 17.06$  dB HL, respectively. Before treatment, the THI score was  $44.3 \pm 23.4$ , the BDI score was  $7.96 \pm 2.36$ , and the PSQI score was  $6.85 \pm 4.68$ . After treatment, the THI score was  $33.6 \pm 17.1$ , the BDI score was  $7.38 \pm 2.25$ , and the PSQI score was  $4.04 \pm 3.20$ .

The initial THI score before treatment was not associated with age ( $p=0.914$ ). In addition, the right and left PTA hearing outcomes were not correlated with the initial THI scores, thus showing that age and intensity of bothersome tinnitus were not significantly related ( $p=0.101$  and  $0.549$ , respectively) (Table 1).

Fig. 2A describes the results of THI, which showed a statistically significant improvement from 44.3 before treatment to 33.6 after treatment (75.8%,  $p<0.0001$ ). Fig. 2B describes the results of BDI, which showed no significant improvement from 7.96 before treatment to 7.38 after treatment (92.7%,  $p=0.1231$ ). Fig. 2C shows the results of PSQI, which showed a statistically significant improvement from 6.85 before treatment to 4.04 after treatment (58.0%,  $p<0.001$ ).

In general, tinnitus symptoms were closely related to depression and sleep quality. THI and BDI showed a significant positive correlation ( $r=0.639$ ,  $p=0.0027$ ), and the relationship between THI and PSQI was the same ( $r=0.812$ ,  $p<0.0001$ ). On the basis of multiple regression analysis, the BDI and PSQI

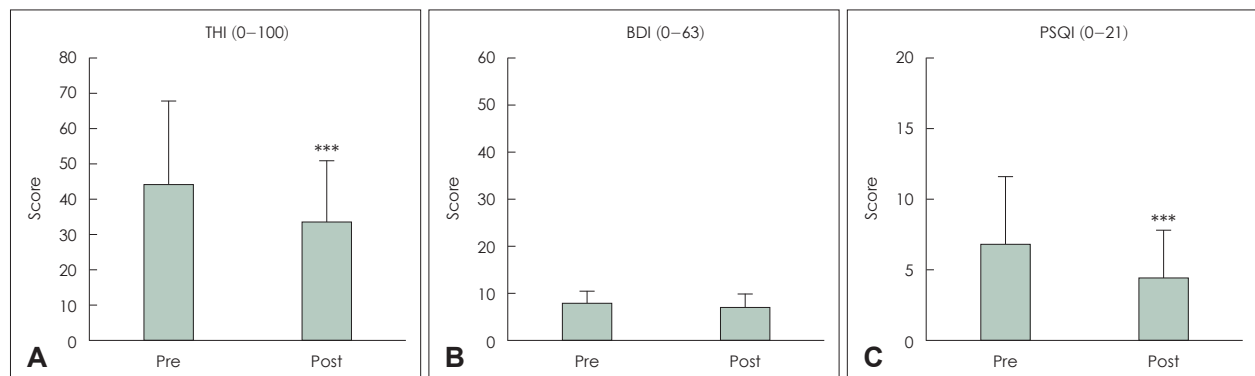
scores were found to be significantly related to the pre-treatment THI scores by 0.006 and  $<0.001$ , respectively. The initial THI score was calculated as  $\text{pre-THI} = -6.299 + 2.884 \times \text{pre-BDI} + 2.832 \times \text{pre-PSQI}$ . In addition, the change in THI after treatment could be predicted using the pre-treatment of THI and PSQI, which was calculated as  $\text{post-THI} = 0.7673 + 0.6947 \times \text{pre-THI} + 0.3572 \times \text{pre-PSQI}$  (Table 1).

Fig. 3 shows the changes in THI before and after clonazepam treatment for tinnitus. The THI items that could be improved by clonazepam were items 1, 5, 6, 7, 8, 12, 13, 14, 20, 24, and 25. Feelings of hopelessness, complaints, and irritability regarding tinnitus were also reduced. In particular, sleep quality improved at night. Work, household chores, and en-

**Table 1.** Characteristics and correlation of THI, BDI, PSQI score

	Pre-treatment	Post-treatment	p-value
Sex, M/F	38 (50)/38 (50)		
Age, yrs	57.2 ± 9.01		0.914
PTA (dB)			
Rt	30.4 ± 20.67		0.101
Lt	31.7 ± 17.06		0.549
THI	44.3 ± 23.4	33.6 ± 17.1	<0.0001***
BDI	7.96 ± 2.36	7.38 ± 2.25	0.1231
PSQI	6.85 ± 4.68	4.04 ± 3.20	0.0002***
Correlation			
Pre: THI-BDI			0.0027**
Pre: THI-PSQI			<0.0001***
Pre: THI-BDI/PSQI	$\text{Pre-THI} = -6.299 + 2.884 \times \text{pre-BDI} + 2.832 \times \text{pre-PSQI}$		<0.0001***
Post THI-THI, BDI, PSQI	$\text{Post-THI} = 0.7673 + 0.6947 \times \text{pre-THI} + 0.3572 \times \text{pre-PSQI}$		<0.0001***

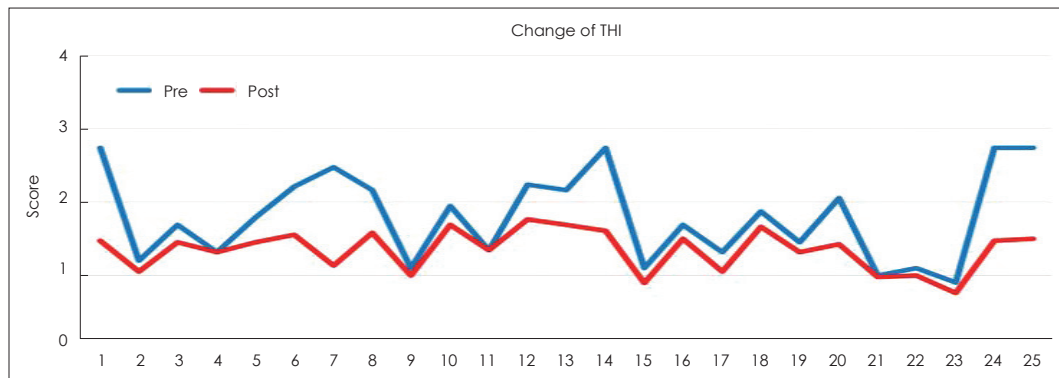
Data are presented as n (%) or mean ± standard deviation. There were 38 males and 38 females each, and the average age was 57.2 ± 9.01 years, the right PTA was 30.4 ± 20.67 dB HL, and the left was 31.7 ± 17.06 dB HL, which was almost similar. As for the score results of each questionnaire, before treatment, THI was 44.3 ± 23.4, BDI was 7.96 ± 2.36, PSQI was 6.85 ± 4.68, and after treatment, THI was 33.6 ± 17.1, BDI was 7.38 ± 2.25, PSQI was 4.04 ± 3.20. In general, the symptoms of tinnitus (THI) were closely related to depression (BDI) and sleep quality (PSQI). Initial THI score could be calculated as "pre-THI = -6.299 + 2.884 × pre-BDI + 2.832 × pre-PSQI." Also, the effect of tinnitus treatment using clonazepam could be predicted and seen as "post-THI = 0.7673 + 0.6947 × pre-THI + 0.3572 × pre-PSQI." \*\*\* $p<0.001$ ; \*\* $p<0.01$ . PTA, pure tone audiometry; THI, Tinnitus Handicap Inventory; BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index



**Fig. 2.** Changes in Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index (PSQI). A: Results of THI showed a statistically significant improvement from 44.3 before treatment to 33.6 after treatment (75.8%, \*\*\* $p<0.001$ ). B: Results of BDI showed no significant improvement from 7.96 before treatment to 7.38 after treatment (92.7%,  $p=0.1231$ ). C: Results of PSQI showed a statistically significant improvement from 6.85 before treatment to 4.04 after treatment (58.0%, \*\*\* $p<0.001$ ).

joyment of life, all of which were interrupted by tinnitus, improved. Unstable mood and fatigue caused by tinnitus were also reduced. In addition, tinnitus became less severe in stress-

ful situations. When comparing the improvement score, question 7 (i.e., “Do you have difficulties falling asleep because of your tinnitus?”) was found to have the most improvements.



**Fig. 3.** Changes by item for Tinnitus Handicap Inventory (THI) before and after clonazepam treatment for tinnitus. The items of THI that clonazepam can improve are items 1, 5, 6, 7, 8, 12, 13, 14, 20, 24, and 25.

**Table 2.** The use of benzodiazepines for tinnitus (a literature review table)

Study (year)	Nation	Design	Participants	Intervention, comparator	Outcome measure	Result	Side effect
Lectenberg and Shulman <sup>24)</sup> (1984)	New York, USA	Prospective, randomized, single-blind comparison	116 participants, 18–85 yrs, at least 1 month	Diazepam, oxazepam, clonazepam 0.5–3 mg	Self-rating scale	Diazepam: 1/15 improved Oxazepam: 12/23 Clonazepam: 18/26	Sedation Drowsiness
Johnson, et al. <sup>25)</sup> (1993)	Poland, USA	Prospective, randomized, single-blind comparison	40 participants, 21–65 yrs, at least 1 yr	Alprazolam 0.5–1.5 mg	Tinnitus loudness, VAS	Alprazolam: 13/17 improved Placebo: 1/19	
Ganancia, et al. <sup>21)</sup> (2002)	Brazil	Retrospective survey	1020 participants, 13–87 yrs	Clonazepam 0.5–1.0 mg, 60–180 days		32% improved	16.9% SE Headache Drowsiness Nightmare
Bahmad, et al. <sup>26)</sup> (2006)	Brazil	Prospective, randomized, single-blind controlled trial	36 participants, VAS score > 7, at least 6 months	Clonazepam 0.5–2 mg with gabapentin 300–900 mg or placebo	VAS	Clonazepam+placebo: decrease in tinnitus intensity & annoyance compared with placebo Clonazepam+gabapentin: no difference	Drowsiness
Jalali, et al. <sup>27)</sup> (2009)	Iran	Prospective, randomized, triple-blind, cross-over	36 participants, 21–65 yrs, at least 1 yr	Alprazolam 0.5–1.5 mg, 8 weeks	Tinnitus loudness, VAS, THI	No significant improved	Sedation Drowsiness
Han, et al. <sup>28)</sup> (2012)	Chuncheon, Korea	Prospective, randomized, open-label, cross-over comparison	38 participants, 16–80 yrs, at least 2 months	Clonazepam 0.5–2 mg Ginkgo biloba 40–160 ng, 5 weeks	Tinnitus loudness, THI, VAS	Mean THI score 61%, VAS score, tinnitus loudness 74% improved	Drowsiness (36.8%) Dizziness (5.3%)

Related studies for benzodiazepine in the treatment of tinnitus. The effectiveness of alprazolam varies from study to study. Johnson, et al.<sup>25)</sup> study showed that alprazolam improved 13 out of 17 patients with tinnitus. But the other study Jalali, et al.<sup>27)</sup> showed alprazolam cannot improved tinnitus. Unlike alprazolam, clonazepam is known to be effective in most studies. Lectenberg and Shulman's study<sup>24)</sup> showed that 18 out of 26 tinnitus improved when clonazepam 0.5–3 mg was used. Ganancia, et al.<sup>21)</sup> showed that when using clonazepam 0.5–1.0 mg for 60–180 days, 32% of tinnitus patients showed improvement. Bahmad, et al.<sup>26)</sup> showed that when using clonazepam 0.5–2 mg, VAS of tinnitus was improved. Recently, Han's study<sup>28)</sup> showed that 61% of mean THI score, VAS score, and 74% of tinnitus loudness was improved when using clonazepam 0.5–2 mg for 5 weeks. Although clonazepam was effective in the treatment of tinnitus, there were also side effects, and a common side effects during study was drowsiness, headache and sedation. VAS, visual analog scale; THI, Tinnitus Handicap Inventory; SE, side effect



This result was the same as that in the PSQI scores related to sleep. However, question 21 (i.e., “Do you feel depressed because of your tinnitus?”) showed little difference before and after treatment. Therefore, the changes in BDI before and after treatment were the same as the result that was not significant.

## Discussion

Clonazepam can improve various symptoms of tinnitus, particularly when used effectively and can improve sleep quality. The score obtained by THI, which is a tinnitus questionnaire, was significantly correlated with the scores obtained by BDI, which is a measure of depression, and PSQI, which is a measure of sleep quality. However, clonazepam did not significantly improve depression.

Many studies have investigated the use of benzodiazepine drugs for the treatment of tinnitus (Table 2), particularly alprazolam or clonazepam. The effectiveness of alprazolam varies among studies. Johnson, et al.<sup>25)</sup> showed that alprazolam improved the tinnitus of 13 out of 17 patients. However, Jalali, et al.<sup>27)</sup> showed that alprazolam did not improve tinnitus. Unlike alprazolam, clonazepam was shown to be effective in most studies. Lectenbergh and Shulman<sup>24)</sup> showed that 18 of 26 tinnitus cases improved when clonazepam 0.5–3 mg was used. Ganança, et al.<sup>21)</sup> showed that when using clonazepam 0.5–1.0 mg for 60–180 days, 32% of patients with tinnitus showed improvements. Bahmad, et al.<sup>26)</sup> showed that clonazepam 0.5–2 mg improved the visual analog scale (VAS) score for tinnitus. Recently, Han, et al.<sup>28)</sup> showed that 61% of the mean THI and VAS scores and 74% of tinnitus loudness improved when using clonazepam 0.5–2 mg for 5 weeks. Although clonazepam was effective in treating tinnitus, there were also side effects; a common side effect during the study was drowsiness, headache, and sedation.

Unlike previous studies, the current study used a low dose of clonazepam (0.25–0.5 mg) for 1 month and optionally for the next 2 months and showed improvements in tinnitus. Second, during the treatment of tinnitus using clonazepam, the THI, BDI, and PSQI scores were measured, and changes in depression and sleep disturbance were studied. In addition, the pre-THI and post-THI scores were calculated by correlating the pre-BDI and pre-PSQI scores. It is also valuable to roughly predict the post-THI score on the basis of the pre-THI and pre-PSQI scores. Therefore, it can be inferred that not only drugs but also education on sleep hygiene can be helpful in the treatment of tinnitus.

Limitation of this study was that other medications especially hypnotics and anxiolytics, and comorbidities including psychologic disorders were not considered in the current study. However, when using benzodiazepine for the treatment of tinnitus, it is important to select and use the minimum dose without side effects personally and to inform the patient that the drug will be gradually discontinued as symptoms improve.

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## Author Contribution

Conceptualization: Hyeon Geun Kim, Gi Jung Im. Data curation: Hyeon Geun Kim, Gi Jung Im. Formal analysis: Hyeon Geun Kim, Gi Jung Im. Funding acquisition: Gi Jung Im. Methodology: Hyeon Geun Kim, Gi Jung Im. Project administration: Hyeon Geun Kim, Gi Jung Im. Writing—original draft: Hyeon Geun Kim, Gi Jung Im. Writing—review & editing: all authors.

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