



## Comparing the Efficacy of Amitriptyline and Melatonin on Tinnitus Treatment

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### Abstract

**Background:** Tinnitus is described as the perception of sounds occurring in one or both ears or inside the human head without external auditory stimuli.

**Objectives:** This study aimed to compare the efficacy of amitriptyline and melatonin in the treatment of tinnitus.

**Methods:** This study was a randomized double-blind clinical trial of 60 patients referred to the neurology clinics of Kashani and Al-Zahra hospitals in Isfahan, Iran in 2020. Each patient was randomly assigned 1 code. Patients first filled in the tinnitus handicap inventory (THI) and visual analogue scales (VAS) questionnaires and were given either one of the two drugs (melatonin and amitriptyline) for 6 weeks. After collecting the desired information using an independent *t* test and paired *t* test in SPSS 26 software and error level of 0.05 the results were analyzed.

**Results:** Thirty patients were in the amitriptyline group and 30 patients were in the melatonin group, of which 25 were men (41.7%) and 35 were women (58.3%) with a minimum age of 18 years and a maximum of 65 years. There was no significant difference between the reduction of tinnitus before and after taking the drugs based on VAS scale in amitriptyline and melatonin groups ( $P=0.234$ ), however there was a significant difference between the effect of two amitriptyline and melatonin drugs on the reduction of tinnitus based on the THI questionnaire ( $P=0.018$ ).

**Conclusion:** The rate of tinnitus in patients decreased for 6 weeks with the use of amitriptyline and melatonin, but amitriptyline had a better effect on reducing the complications and pain of tinnitus.

**Keywords:** Tinnitus, Melatonin, Amitriptyline

### 1. Background

Tinnitus is a Phantom auditory perception that is not caused by an external stimulus. It is a symptom experienced by about 25% of American adults, and 8% of them experience it regularly.<sup>1</sup> Hitherto, no drug approved by the Food and Drug Administration (FDA) has been explicitly proposed for the medical treatment of tinnitus.<sup>2</sup> Physio pathological and neuroimaging studies show that tinnitus is the result of dynamic interference between auditory and non-auditory pathways, and the result of this interference, especially when it is accompanied by autonomic symptoms and sleep disorders, causes discomfort for people and disrupts the quality of life and mental health of people.<sup>3</sup> Nevertheless, various factors such as structures affecting ion channels, neurotransmitters and factors affecting receptors have been proposed,<sup>4</sup> which are potentially involved in the pathophysiology of tinnitus. Therefore, there is no logical argument to believe that tinnitus cannot be treated medicinally.<sup>5</sup>

In recent studies, melatonin alone or in combination with other drugs has been proposed as a potential drug, especially in patients who have tinnitus with sleep disorders.<sup>5</sup> Few studies have been conducted on the effect of this less complicated drug on tinnitus. Rosenberg et al. in a double-blind study in 1998 on 30 patients aged 28 to 80 years with subjective tinnitus (non-psychiatric patients who reported hearing tinnitus) who were treated with melatonin for 30 days stated that the melatonin group compared to the placebo group had a significant decrease in the prevalence and severity of tinnitus.<sup>6</sup> The finding of this study was in line with several similar studies, such as Megwalu et al with 20 cases of patients with a tinnitus handicap inventory (THI) score of 25 or more in 2006 without a control group,<sup>7</sup> Neri in 2009 with 120 patients,<sup>8</sup> and Hurtuk et al in 2011 with 61 chronic tinnitus patients.<sup>9</sup> In a 2007 study, Lopez-Gonzalez et al examined four groups: a sulpiride treatment group, a melatonin group, a placebo group, and a combined group of the two drugs.

In addition to the effectiveness of melatonin in reducing symptoms, they concluded that this drug would be much more effective when combined with sulpiride.<sup>10</sup> In all the mentioned studies, melatonin has most often been used in a dose of 3 mg/d orally.

## 2. Objectives

Similarly, tricyclic antidepressants and especially amitriptyline is another drug that has been suggested for the treatment of tinnitus. However, this drug has had conflicting results in the treatment of this disease in previous studies.<sup>11,12</sup> Considering the inconsistency of the results of these studies and in order to compare these two drugs, this study was conducted to investigate the effectiveness of two drugs, melatonin and amitriptyline.

## 3. Methods

This study was a randomized double-blind clinical trial that examined 60 patients referred to neurology clinics of Kashani and Al-Zahra hospitals in Isfahan, Iran in 2019. Sixty codes (30 codes of 1 indicating the melatonin group and 30 codes of 2 indicating the amitriptyline group) were arranged randomly by SPSS software. Then, every patient who was diagnosed with tinnitus in chronological order and aged between 18 and 65 years was included in the study and received a code by the researcher. First, they filled in the THI and visual analogue scales (VAS) questionnaires, and then according to the existing code, the corresponding prescription was written by the attending physician, and the patients received one of the following two drugs for 6 weeks:

1. Melatonin tablets 3 mg every night for 6 weeks
2. Amitriptyline tablets 10-50 mg were given for 6 weeks (according to the previous studies available in the sources of the article).

At the end of the sixth week, the patients went to the clinic and were examined and visited. They completed the THI and VAS questionnaires again, and the presence of tinnitus was checked in them, and if it was effective, the drug treatment was continued. The researcher who is responsible for data collection is not aware of the code and the group and therefore the treatment of the patient. It is expected that the intensity of tinnitus will be changed by the drug during this period, otherwise the probability of responding to the drug will decrease. The dosage of amitriptyline is also different based on the physiological response of people's bodies, and according to previous studies, the dosage was considered to be 10-50 mg. Adherence to treatment and improvement of tinnitus

depends on the patient and is checked based on THI and VAS questionnaires.

After collecting the data, the desired data were analyzed using independent t and paired t statistical tests in SPSS version 26 software. The error level was considered 0.05.

## 4. Results

In the present study, there were 30 patients in the amitriptyline group and 30 patients in the melatonin group, of which 25 men (41.7%) and 35 women (58.3%) with a minimum age of 18 years and a maximum age of 65 years with an average age of  $51.82 \pm 6.89$  years. Also, the highest frequency of examined patients is in the age range of 46-55 years (45%) and the lowest frequency is in the age range of 18-45 years (21.7%).

Patients were examined in the two groups before and after the use of medicine based on two scales, VAS and THI, and as per both scales, the amount of tinnitus after using the medicine was reported to be significantly lower than before the treatment. The amount of tinnitus based on the VAS was measured before and after the drug use as  $5.92 \pm 0.979$  and  $5.48 \pm 1.186$ , respectively and the degree of improvement based on the THI scale, before and after the drug use, was reported to be  $43.70 \pm 10.465$  and  $51.40 \pm 10.595$ , respectively. In other words, the use of medicine, regardless of the type of medicine used, had a positive effect on reducing tinnitus in patients (Table 1, Figure 1).

Considering the type of drug used by the patients, no significant difference was observed between the reduction of tinnitus before and after the use of the drug based on the VAS scale in the melatonin and amitriptyline groups ( $P=0.234$ ). However, a significant difference was observed before and after the use of amitriptyline and melatonin according to the THI criteria ( $P=0.018$ ), which indicates that amitriptyline is more effective in reducing tinnitus based on the obtained numbers. In other words, amitriptyline has a better effect on reducing tinnitus in patients (Table 2, Figure 2).

## 5. Discussion

Tinnitus is one of the clinical symptoms experienced by about 51% of people in some part of their life.<sup>13,14</sup> which occurs in the form of transitions (exposure to loud noise) and severe in people.<sup>14</sup> In chronic tinnitus, spontaneous recovery is less frequent and requires treatment.<sup>15</sup> In the meantime, one of the factors that cause this condition can be due to emotional stress in people.<sup>16,17</sup> Tinnitus at a young age is mostly due to hearing loss, especially in children, but

**Table 1.** Determination of VAS and THI Scale Before and After Treatment

Scale	Number	Mean	Standard Deviation	Mean Difference	t	P Value
VAS before the drug	60	5.92	0.979			
VAS after the drug	60	5.48	1.186	0.433	4.651	0.000
THI before the drug	60	43.70	10.465			
THI after the drug	60	51.40	10.595	2.30	3.699	0.000

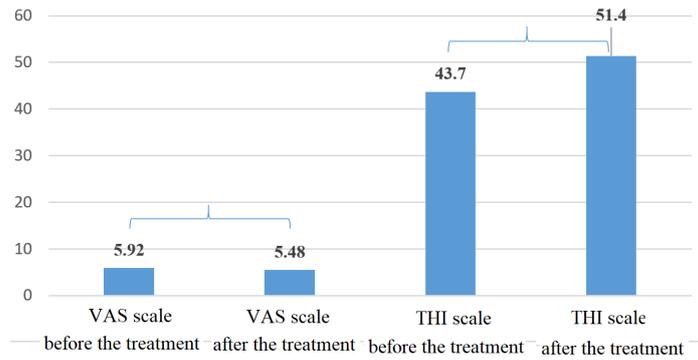


Figure 1. Determination of VAS and THI Scale Before and After the Treatment

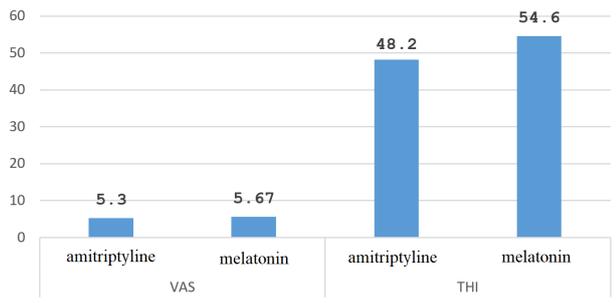


Figure 2. Investigating the Effect of Amitriptyline and Melatonin Drugs on Tinnitus in Patients

Table 2. Investigating the Effect of Amitriptyline and Melatonin Drugs on Patients' Tinnitus

Scale	Drug	Number	Mean	Standard Deviation	F	P Value
VAS	Amitriptyline	30	5.30	1.208	1.202	0.234
	Melatonin	30	5.67	1.155		
THI	Amitriptyline	30	48.20	11.601	2.435	0.018
	Melatonin	30	54.60	8.520		

with age, its rate increases due to hearing loss.<sup>18</sup>

Based on the theory that tinnitus is a seizure-type activity in the cortical and subcortical areas of the brain leading to aberrant auditory perception, the use of anticonvulsant drugs to reduce tinnitus in patients became common.<sup>19,20</sup> A variety of medications are currently used in the treatment of tinnitus, including anesthetics, antiarrhythmics, anticonvulsants, antidepressants, antihistamines, antipsychotics, anxiolytics, and calcium channel blockers, cholinergic antagonists, NMDA antagonists, muscle relaxants, vasodilators and vitamins.<sup>21</sup> In this study, two drugs, amitriptyline and melatonin, were used to reduce and treat tinnitus.

According to the results of the present study, after the use of the desired drugs for a period of 6 weeks, the amount of tinnitus was significantly decreased compared to the time before the treatment, but the greatest drug effect was related to amitriptyline, so that the amount of tinnitus after using amitriptyline significantly decreased according to the THI scale, but according to the VAS scale, no significant difference was observed between the two groups. Although the amount of tinnitus in the two investigated scales was reported to be lower in the amitriptyline group compared to melatonin, only the THI scale was statistically significant. This difference in the results obtained from the VAS scale to the THI can be due to the nature of the investigated scales, as in the THI scale, the patient gives a complete description of his mental state by answering 24 questions, but in the VAS scale only by

specifying the amount of tinnitus, it determines a number in the range of 0 to 10. Therefore, taking this issue into consideration, it can be said that prescribing amitriptyline is effective in reducing tinnitus problems.

In 2021, Chen et al<sup>22</sup> in their study examined the effectiveness of drug treatment in patients with tinnitus without a specific or treatable origin, and stated that the simultaneous use of two drug groups, including amitriptyline, acamprosate, and gabapentin and the drug group dexamethasone inside Intravenous with oral melatonin is effective in reducing tinnitus. They, of course, stated that the use of amitriptyline has a greater effect on reducing the symptoms of tinnitus. The results of this study are therefore consistent with those of the present study.

Also, in another study conducted by Kim et al<sup>21</sup> in 2021, they reviewed drug therapy for tinnitus and stated that amitriptyline and melatonin have a positive effect on reducing the problems caused by tinnitus. In 2001, Bayar et al<sup>12</sup> stated in their study that the use of amitriptyline is effective in reducing tinnitus. In their study, they investigated the effect of amitriptyline compared to the placebo group. In another study conducted in 1995 by Podoshin et al,<sup>11</sup> they stated that amitriptyline has no effect on reducing tinnitus. Therefore, in order to express the effect of amitriptyline and melatonin drugs use in reducing tinnitus, the study of Kim et al. and that of Bayar et al have a consistent relationship with the present study and a non-aligned relationship with the study of Podoshin et al.<sup>11</sup> The reason for this difference in the results can be due to the ethnic and racial differences as well as the difference in the age of the patients examined in the two studies

## Research Highlights

### What Is Already Known?

Tinnitus is a common medical symptom that can be debilitating. Risk factors include hearing loss, ototoxic medication, head injury, and depression.

### What Does This Study Add?

The amount of tinnitus in patients is reduced by taking amitriptyline and melatonin, but amitriptyline has a better effect in reducing the amount of tinnitus.

## 6. Conclusion

Based on the results, it can be stated that melatonin and amitriptyline drugs can be effective in reducing the amount of tinnitus and the inability of people to perform daily activities. But amitriptyline has a higher effect. Therefore, taking into account clinical considerations, it is better to use the mentioned drugs more carefully in reducing tinnitus. It is also suggested that due to the identification of the effectiveness of these drugs, in future research, they should be compared with intravenous lidocaine (the most effective drug for the treatment of tinnitus) in order to achieve more accurate results in this regard and in future studies, a higher dose of melatonin should be investigated in order to have a greater effect in reducing tinnitus.

### Author Contributions

AC designed the study and collected data. BRD collected data and helped with manuscript drafting. AR analyzed the data and drafted and critically revised the manuscript. All authors read and approved the final version of the manuscript.

### Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

### Ethical Approval

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ref. No: IR.MUI.MED.REC.1399.1148). This randomized clinical trial was registered at the Iranian Registry of Clinical Trial website (identifier: IRCT20200825048515N48; <http://www.irct.ir>).

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