

# The Role of Melatonin in the Management of Patients with Tinnitus

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*The therapeutic approach in tinnitus is still an open subject. Perhaps, the correct approach would be the management of a patient with a chronic suffering that occurred at the active age and who, in the absence of an adequate intervention, may be incapacitated. Sound therapy, counseling and cognitive behavioral psychotherapy are the widely accepted by specialized physicians in tinnitus. Patients are still looking for medical treatment and the physician is required to integrate new drugs into his or her therapeutic arsenal. Melatonin is a relatively recently introduced substance in Romania and its primary therapeutic use is in sleep disorders. The present paper describes our experience with melatonin as treatment for selected patients with tinnitus. The melatonin treatment has shown an efficacy of 80% in our study, as secondary treatment in tinnitus after initially counseling. The obtained results can also be a prerequisite for the integrative approach of the patients with tinnitus in the context of the pathological conditions and not as an isolated clinical picture. Considering the etiopathogenetic mechanisms of tinnitus and the other therapeutic effects of melatonin (central nervous system modulator and antioxidant), more extensive and multicenter studies are needed.*

**Keywords:** melatonin, sleep disorders, tinnitus

The term *tinnitus* is used by specialists to define a symptom with a significant incidence in the population (10-15%) over 45 years. Most of the times, the various underlying medical conditions translate into tinnitus, which is associated with the modern living conditions, but especially with an inefficient strategy to cope with stress.

There are many classifications of tinnitus, depending on the criteria used by different authors. In subjective tinnitus, sounds are perceived only by the patient, as his name implies. The subjective (idiopathic) tinnitus can be classified as acute (hours, days, weeks - up to 3 months) or chronic (more than 3 months). In accordance with the bio-psycho-social etiopathogenetic model, tinnitus is associated with three causal categories that interact with each other - somatic, psychic and social. The somatic component is represented by the auditory, somatosensory or central nervous system. The psychic side includes psychological aspects (stress, personality) as well as various manifestations (anxiety or depression) that can reach psychiatric intensity. From the social point of view, the personality, the family and the workplace complete the picture of the appearance of tinnitus, to each patient. In other words, diminishing the quality of life and well-being determines the presence of tinnitus.

Causative factors have as a common denominator the increase in dopamine activity in the auditory and central nervous system. Thus, older age leads to increased dopamine activity by hypersensitivity of dopamine receptors and also by increased dopamine synthesis. The dopamine is the primary mediator of information transmitted through the auditory pathway. The modern lifestyle characterized by competitiveness, often results in high levels of stress and implicitly increased dopamine activity. Anxiety also has an increase in dopamine activity.

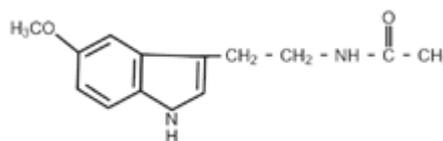


Fig. 1. Melatonin (N-acetyl-5-methoxytryptamine) - structural formula

Starting from these considerations, must be mentioned the special place of melatonin (chemical formula:  $C_{13}H_{16}N_2O_2$ ) in modulation of dopamine activity.

Melatonin is a natural hormone produced by the pineal gland and structurally related to serotonin.

At the same time, the melatonin is an important modulator of the immune system, a powerful antioxidant and plays a key role in regulation of the sleep-wake cycle. Any concentration of melatonin inhibits the effect of dopamine, suppressing the maximum response of the neurotransmitter approximately 70%. Melatonin also inhibits the stimulation of the accumulation of second messengers produced by dopamine D1 receptor agonists. Melatonin is present in the cochlea, following a circadian rhythm with higher levels at night. In addition, the cochlea generates oxygen free radicals and nitric oxide. Melatonin and its metabolites have a role as antioxidants, electron donors and free radical neutralizers. The antidopaminergic action of melatonin may be mediated by central benzodiazepine receptors through a GABAergic mechanism (gamma-Aminobutyric acid, the main inhibitory neurotransmitter in the cerebral cortex).

Synthesising the views outlined above and taking into account the significant incidence of tinnitus in the population (10-15%) over 45 years, we decided to introduce melatonin treatment in patients with tinnitus and primary insomnia.

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The present paper describes our experience with melatonin as secondary treatment in chronic idiopathic tinnitus therapy after initially counseling.

### Experimental part

Since 2008 have met all the necessary premises for setting up a functional unit for the diagnosis and treatment of sleep disorders, within the National Institute of Aeronautical and Spatial Medicine. The objective of the compartment was to provide full (medical and surgical) and multidisciplinary treatment for sleep disorders.

Insomnia is the most common reason why patients resort to the services provided by the sleep medicine unit. Our center of sleep medicine offers an integrated and multidisciplinary treatment (psychology, psychiatry, neurology and otorhinolaryngology - ENT) of patients suffering from insomnia. In this sense, patients with primary insomnia and tinnitus were introduced into the study. It should be noted that all patients were 45-65 years of age, with professional results above average and who have requested help only to eliminate *an unpleasant and constant noise*. Insomnia was considered secondary and as a consequence of tinnitus. No patient considered that he was overwhelmed by chronic exposure to high professional demands and implicitly refused any psychiatric treatment or cognitive behavioral psychotherapy to solve their problem. *We are normal people just a little tired due to the buzzing in the ears that appear especially at bedtime* - was the reason for the presentation of all patients at the somnology unit.

The initial therapeutic course for all patients was the counseling performed by various otorhinolaryngologists in different clinics.

We started from the main hypothesis that the melatonin administered in tinnitus, apart from its action on the regularization of the sleep-wake cycle, produces a decrease in the perception of tinnitus. The second hypothesis was that given the role of melatonin in regulating sleep and circadian rhythm (as well as the decline in endogenous melatonin production with aging), melatonin can effectively improve the quality of sleep, especially in patients older than 45 years, with primary insomnia.

It has been achieved a retrospective and nonrandomized study, involving 20 patients with tinnitus and primary insomnia. The study was conducted from December 2015 through December 2017, at the National Institute of Aeronautical and Spatial. Participants were followed up for 6 months.

The melatonin has no absolute contraindication but may cause drowsiness. Therefore, the medicine was used with caution if the effects of drowsiness are likely to be associated with a safety risk. In certain situations, when patients were to drive the car the next day for a long distance, they were advised not to take the tablet in the evening and not to use a double dose on the next day.

Before the start of melatonin treatment, has been achieved for each patient a detailed anamnesis, a complete tonal audiogram, tinnitus handicap inventory (with severity scale) and clinical psychological examination, in order to avoid any complications.

We used the following inclusion criteria:

- the occurrence of disease (tinnitus) in active patients ( $\geq 45$  years and  $\leq 65$  years),
- refusal of any psychiatric treatment or cognitive behavioral psychotherapy (melatonin may accentuate the sedative properties of benzodiazepine and nonbenzodiazepine hypnotics),
- unilateral / bilateral tinnitus,
- primary insomnia as coexisting condition.

The following were used as exclusion criteria:

- objective tinnitus - can be perceived, in addition to the patient, by another observer (otorhinolaryngologist), by ear or using the stethoscope,
- hyperacusia, cofosis, balance disorders, anxiety or depression,
- intolerance to excipients from the melatonin tablet.

Each patient was administered by the oral route, 3 mg of melatonin, 1 hour before bedtime, during 30 days. The arguments for choosing this posology are physiological and are the following: melatonin secretion increases shortly after dark, reaches a peak at 2-4 AM and falls in the second half of the night. Obviously, melatonin is associated with controlling circadian rhythms and maintaining the light-dark cycle. It is also associated with a hypnotic effect and an increased tendency to sleep. The predicted clearance of the active substance is up to 12 h after ingestion. Patients are forbidden to drink alcohol in the evening, before administration of melatonin, because the alcohol reduces the efficacy of melatonin on sleep.

To determine the modifications of hearing ability determined by the melatonin treatment, we have achieved pre-treatment (PRE-T) and post-treatment (POST-T) audiological examination at 30, 90 and 180 days from the start of treatment. The results were evaluated considering changes in Pure Tone Averages (PTA) at 250, 500, 1000, 2000, and 4000 Hz. All audiometric studies were performed by the same certified audiologist under standard conditions, at audiology laboratory of the National Institute of Aeronautical and Spatial Medicine. At 30, 90 and 180 days from the start of melatonin treatment, 2 questionnaires were applied: Epworth sleepiness scale and Tinnitus Handicap Inventory.

For most authors, successful treatment of tinnitus has defined arbitrarily. In the present study, we decided to consider as a positive response to treatment with melatonin, an Epworth sleepiness scale score lower than 10 units cumulative with the Analogue Visual Scale (AVS) score (increase 7-9, similar 4-6, decrease 1-3) lower than 5 units.

This protocol was approved by the Ethics Committee at the National Institute of Aeronautical and Spatial Medicine.

Regarding statistical analysis, the majority of data are presented in numeric and percent form. Due to the low number of patients in the study, the statistical tests are meaningless.

### Results and discussions

All 20 patients (14 male and 6 women) were initially treated with counseling - as primary and exclusively treatment by other doctors, in different clinics. Before melatonin treatment they have completed and signed the informed consent. All patient shave met the exclusion / inclusion criteria and agreed to participate at the study. =

The mean age was 50.46 years. Must be mentioned the higher incidence (even without statistical significance due to the small number of patients) of tinnitus in men (16 patients) in the evaluated group. The hearing loss of patients included in the study was medium. In concrete values, the mean PTA PRE-T was 45.80 dB, while the mean PTA POST-T was 45.35dB. There is no difference between the level of hearing loss recorded prior to treatment and the level recorded after treatment. To an overview of the data contained in the results table of melatonin treatment, one can easily see that the success rate of treatment according to the cumulative criteria set was of 80% (16 patients). Regarding the subjective sensation of tinnitus perception (AVS score), it is worth mentioning that 15 patients (75%) reported a decrease, while the remaining 5 patients 25(%)

PATIENTS	SEX	AGE years	PTA	PTA	EPWORTH average score	AVS average score
			PRE-T dB	POST-T dB		
1. T.V.	M	45	40	41	6	5
2. Z.A.	M	46	45	45	7	2
3. R.A.	M	57	50	48	8	3
4. I.C.	M	48	50	50	7	3
5. C.D.	F	50	60	60	6	3
6. N.D.	M	60	48	46	6	4
7. D.V.	M	45	40	40	9	6
8. F.I.	M	47	52	51	5	2
9. J.M.	F	50	35	35	8	3
10. V.V.	M	51	42	40	6	3
11. D.M.	F	57	50	52	6	3
12. G.R.	F	49	38	35	9	6
13. G.G.	M	62	55	56	9	3
14. G.I.	M	61	38	36	7	3
15. N.D.	F	48	44	45	9	2
16. B.A.	M	50	52	52	8	3
17. P.D.	M	54	54	52	6	3
18. O.S.	M	49	40	40	8	2
19. S.I.	M	58	45	45	9	5
20. T.V.	F	47	38	38	7	3

**Table 1**  
THE RESULTS OF  
MELATONIN TREATMENT IN  
THE STUDY GROUP

reported a similar level. No increase (in terms of subjective sensation of tinnitus perception) has been reported. The Epworth scale score was below 10 units for all patients, which leads to the finding that they have rested better during the night. Otherwise, all patients described the feeling of sleep better after melatonin treatment: *I fall asleep faster and I'm getting better than before after a night's sleep.*

There is no consensus on the melatonin treatment as secondary therapy in tinnitus. A brief review of medical articles / clinical guidelines on this subject, fully confirms the previous statement [1-6].

Thus, Miroddi et al, 2015, performed a review (using Pubmed, Medline, Embase, Central and Google Scholar) with the purpose to summarise, analyse and discuss the evidence provided by clinical studies evaluating effectiveness of melatonin in the cure of tinnitus. The conclusion was that the confirmation of melatonin clinical effectiveness in the treatment of tinnitus cannot be given in the light of the biases observed in the considered evidence. Melatonin seems to improve sleep disturbance linked to tinnitus [1].

Larsen et al., 2014, conducted a study (systematic literature search) on tinnitus guidelines and treatment and concluded that the antidepressants, melatonin and cognitive behavioural therapy have no effect on tinnitus, whereas sound generators, hearing aids and tinnitus retraining therapy show some but limited improvement. National recommendations are required to ensure a homogenous and optimum offer for all patients [2].

Tunkel et al., 2014, in *Clinical practice guideline: tinnitus*, have made recommendations against Ginkgo biloba, melatonin, zinc, or other dietary supplements for treating patients with persistent (bothersome) tinnitus. The purpose of this guideline was to provide evidence-based recommendations for clinicians managing patients with tinnitus [3].

Unlike this author, Hurtuk al., 2011, presented the results of his study (prospective, randomized, double-blind, crossover clinical trial in an ambulatory tertiary) on 61 patients. The first finding was that melatonin is associated with a statistically significant decrease in tinnitus intensity

and improved sleep quality in patients with chronic tinnitus. According to the second conclusion of his study, melatonin is most effective in men, those without a history of depression, those who have not undergone prior tinnitus treatments, those with more severe and bilateral tinnitus, and those with a history of noise exposure [4].

In 2009, Salvi et al., in *Pharmacological Treatments For Tinnitus: New And Old*, also shows some interesting results on this topic. The author concluded that the improvements in tinnitus have also been noted in patients taking melatonin for significant sleep disturbances. At the same time he also mentioned that one drug is unlikely to resolve tinnitus in all patients, like other complex neurological disorders and that the therapies targeting specific subgroups are likely to yield the greatest success [5].

In Romania, the recommendations for the patients with tinnitus (according to the Therapeutic Guide in Otorhinolaryngology - Head and Neck Surgery), refers to measures that are taken to preventing the progression of the disease. Therapy consists of: a) counseling - is not enough as a single therapy, b) oral medication with calcium antagonists (flunarizine), c) antiarrhythmic drugs such as lidocaine or d) anticonvulsants (carbamazepine). In the case of tinnitus worsening, procaine infusion therapy should be instituted. Acoustic therapy with hearing aid is also mentioned. The psychotherapeutic procedures that can be used are also described: autogenous training, biofeedback or behavioral therapy. In the case of severe depression or sleep disturbances, psychopharmaceuticals treatment is indicated without express reference to melatonin [6].

There are many arguments for the therapeutic use of melatonin, taking into account its antioxidant effect. Most of them come from plastic surgery research and are the result of experiments using laboratory animals [7-8].

Thus, Tunç et al, 2016, concluded that the melatonin and N-acetylcysteine are important antioxidants that can be used alone or in combination to increase flap viability and prevent distal necrosis, in rats [7].

Kerem et al, in his study, showed that the usage on different doses of melatonin could play an important role in the process of flap viability and further studies will focus on these areas of interest [8].

## Conclusions

The melatonin treatment has shown an efficacy of 80% in our study, as secondary treatment in tinnitus with primary insomnia, after initially counseling. Thus, we can assert that melatonin treatment is a viable option for this specific subgroup of patients. The obtained results can also be a prerequisite for the integrative approach of the patients with tinnitus in the context of the pathological conditions and not as an isolated clinical picture. The results from other plastic surgery research were encouraging and can open up new research paths such as the use of melatonin in the reconstructive surgery of the head and neck, because the treatment with melatonin improves the vascularization of the tissues and increase flap viability. Considering the etiopathogenetic mechanisms of tinnitus and the other therapeutic effects of melatonin (central nervous system modulator and antioxidant), more extensive and multicenter studies are needed.

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