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Review

Effect of melatonin supplementation on tinnitus: Systematic literature review and meta-analysis

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Abstract. *Background and aim.* Because melatonin exerts a number of otoprotective effects, we planned a systematic literature review and meta-analysis to determine the potential effect of melatonin supplementation in reducing the severity of tinnitus disability. *Methods:* An electronic search of Scopus and Medline (PubMed interface) was performed using the keywords "tinnitus" AND "melatonin" without language or time restrictions. All clinical trials that examined the effect of melatonin supplementation on perceived severity of disability in tinnitus patients were identified. We finally included interventional, prospective studies that used the validated Tinnitus Handicap Inventory (THI) to assess disability. *Results:* The digital search yielded 104 articles, of which 98 were excluded because they did not meet inclusion criteria. Six studies (n=176 patients) were ultimately included in our analysis. In all studies, the weighted mean difference (WMD) of THI after melatonin supplementation was negative, with mean THI changes ranging from –2.5 to –19.5. The WMD of THI was –12.5 (95%CI, from –18.5 to –6.5; p=0.005; I^2=71%). *Conclusions*: The findings of this comprehensive review and meta-analysis reveal that melatonin supplementation may have a positive influence on tinnitus disability and overall quality of life. (www.actabiomedica.it)

Key words: tinnitus, hearing loss, melatonin, meta-analysis

Introduction

Tinnitus is a highly disabling condition with an estimated pooled prevalence of approximately 15%, increasing with age to approximately 24% in persons aged 65 years or older (1). Recent evidence also suggests that coronavirus disease 2019 (COVID-19) may have contributed to further increasing the burden of tinnitus in the general population, both during acute infection and particularly as a post-infection complication reported in a substantial number of patients with long-COVID (2,3).

Identifying effective and safe treatments for tinnitus is a public health priority, given the degree of physical and psychological impairment experienced by sufferers and the direct and indirect costs attributable to the health care system (4). Melatonin (N-acetyl-5-methoxy-tryptamine) is an endogenous, natural compound produced by many different organisms, including bacteria and eukaryotes, that exerts a kaleidoscope of positive functions in humans, apart from its well-known activity in regulating the sleep-wake cycle and circadian rhythm (5). There are several lines of evidence that this natural hormone, produced by the pineal gland, plays an important role in maintaining the function of hearing and thus exerting a number of otoprotective effects (6). To this end, we planned a systematic literature review and meta-analysis to determine the potential effect of melatonin supplementation in reducing the severity of tinnitus disability.

Materials and Methods

An electronic search of Scopus and Medline (PubMed interface) was performed using the keywords "tinnitus" AND "melatonin" in the fields [Article Title] OR [Abstract] OR [Keywords], without language or time restrictions (i.e., through July 2023), identifying all clinical trials that examined the effect of melatonin supplementation on severity of perceived disability in patients with tinnitus. We included only interventional, prospective studies in which the validated Tinnitus Handicap Inventory (THI) was used as a self-report measure to assess disability severity. Two authors (C.M. and G.L.) reviewed all potential articles by title, abstract, and full text and selected those that had THI scores (reported as or converted to mean and standard deviation) before and after melatonin supplementation. The reference list of all articles was also screened for detecting additional eligible studies. All studies finally identified according to our search criteria were narratively described in the text, and THI data were also used to calculate the standardized weighted mean difference (WMD) and 95% confidence interval (95%CI) of THI variation after starting melatonin supplementation. The random effects model was applied to estimate the WMD irrespective of the inter-study heterogeneity, which was calculated using the χ^2 test and I^2 statistic. Funnel plot was used to assess publication bias. The statistical analysis was conducted using MetaXL, Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). This analysis was conducted in accordance with the declaration of Helsinki, within the term of local legislation, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 reporting checklist (Table S1).

Results

Study selection

The digital search performed with the above criteria allowed us to identify 104 articles after redundancy elimination between Scopus and PubMed, of which 98 had to be excluded for the following reasons: review articles (n=56), no data on melatonin supplementation (n=18), no data on tinnitus (n=14), letters/comments without original data (n=3), no THI data (n=2), journal discontinued and/or full text unavailable (n=2), article withdrawn (n=1), study with duplicate data (n=1), and melatonin used in a formulation containing many other compounds (n=1). Six studies (n=176 patients) were finally eligible for inclusion in our analysis (Table 1) (7-12). All of these studies were interventional and prospective; two were conducted

Table 1. Summary of all studies reporting the variation of the tinnitus handicap inventory (THI) score pre- and post-melatonin supplementation.

Authors	Country	Study	Population	Dosage	Duration	THI pre-	THI post-
Rosenberg et al., 1998	USA	Interventional	n=23 (65% males; mean age: 64 years)	3 mg die	30 days	33.9±21.6	26.1±17.3
Megwalu et al., 2006	USA	Interventional	n=24 (55% males; mean age: 61 years)	3 mg die	56 days	35.4±15.5	25.0±20.7
Neri et al., 2009	Italy	Interventional	n=34 (71% males; man age: 55 yrs)	3 mg die	80 days	46.3±19.0	43.8±18.6
Albu et al., 2014	Romania	Interventional	n=30 (70%males, mean age: 50 years)	3 mg die	56 days	49.5±7.2	30.0±4.5
Ferrari et al., 2015	Italy	Interventional	n=30 (60%males, mean age: 64 years)	3 mg die	80 days	37±20	21±19
Abtahi et al., 2017	Iran	Interventional	n=35 (54% males; mean age: 46 years)	3 mg die	90 days	45.0±17.7	30.3±19.6

Abbreviation: THI: Tinnitus Handicap Inventory.

in the United States, two in Italy, and one each in Romania and Iran. The sample size ranged from 23 to 35, the proportion of male participants was predominant and ranged between 54-71%, whereas the mean age was comprised between 46-64 years (Table 1). The melatonin dose used for supplementation was always 3 mg/day (usually taken in the evening), while fluctuations in THI after initiation of melatonin supplementation were estimated over a range of time periods from 30 to 90 days.

Narrative description

The first clinical trial to examine the effects of melatonin supplementation on the severity of tinnitus disability was published in 1998 by Rosenberg et al. (7). The authors administered 3 mg/day of melatonin per night to 23 subjects with subjective tinnitus over a 30-day period. The THI score decreased from 33.9 to 26.1 after melatonin supplementation, 39% of the subjects reported a subjective improvement in tinnitus after taking melatonin, and 35% also reported a decrease in loudness of tinnitus. Nearly a quarter of all subjects experienced an increase in tinnitus-free time after melatonin supplementation, and sleep quality improved in 27%.

In a subsequent trial, published in 2006 by Megwalu et al. (8), the authors administered 3 mg of melatonin daily (1 tablet per night, 1-2 hours before bedtime) to 24 tinnitus patients for 4 weeks, followed by a 4-week observation period. Mean THI score was found to have decreased significantly between week 0 (THI: 35.4) and week 4 (THI: 28.8) and 8 (THI: 25.0), respectively. The Pittsburgh Sleep Quality Index (PSQI) also decreased significantly from week 0 (PSQI: 7.9) to week 4 (PSQI: 5.0) and 8 (PSQI: 5.5).

In 2009, Neri et al. published the results of a clinical trial in which 34 tinnitus patients received 3 mg of melatonin for 80 days before bedtime (9). After melatonin supplementation, the mean THI score decreased slightly from 46.3 to 43.8, with subjective improvement noted in approximately 60% of participants. A modest improvement was also noted in acufenometry after melatonin supplementation (i.e., from 47.3 to 46.6).

Another trial was published by Albu et al., in 2004 (10). The study population consisted of 30 patients with unilateral acute idiopathic tinnitus who took a tablet containing 3 mg of melatonin 1 to 2 hours before bedtime for 8 weeks. After the intervention period, a significant reduction in THI was noted (from 49.5 to 30.0), accompanied by an improvement in sleep quality (PSQI decreased from 7.1 to 5.3). Tinnitus loudness score and tinnitus awareness score also decreased after melatonin supplementation, from 7.0 to 4.7 and from 0.66 to 0.41, respectively.

In 2015, Ferrari et al. published the results of a clinical trial in which 30 tinnitus patients received 3 mg of melatonin before bedtime for 80 days (11). At the end of melatonin supplementation, a reduction in THI was observed in 90% of participants, with the mean value decreasing from 37 to 21, accompanied by significant improvements in hearing thresholds on tone audiometry (acufenometry) at all frequencies.

The last article included in our systematic literature review was published by Abtahi et al., in 2017 (12). The study population consisted of 35 tinnitus patients who received melatonin 3 mg once daily for three months. At the end of the supplementation period, the mean THI score decreased from 45.0 to 30.3, with more than double the rate of subjects reporting mild-to-moderate tinnitus compared with the pre-treatment period (i.e., 76.5% vs. 31.4%).

Some of the studies that were excluded from our meta-analysis because they did not meet all of our inclusion criteria deserve to be briefly described. Hurtuk et al. published the results of a prospective, randomized, double-blind clinical trial of 61 patients with chronic tinnitus randomized to receive 3 mg of melatonin or placebo for 30 days before bedtime (13). Although the THI score was not examined in this trial, audiometric tinnitus matching (TM), Tinnitus Severity Index (TSI), and Self Rated Tinnitus (SRT) scores decreased in 57% of participants after melatonin supplementation, with an identical rate of patients also reporting improvement in sleep, reflected by a lower PSQI score after melatonin use. Interestingly, TM intensity and TSI score before melatonin supplementation were significantly associated with the likelihood of tinnitus improvement,

suggesting that patients with more disabling tinnitus were more likely to experience clinical benefit from supplementation.

In another clinical trial, 20 patients with tinnitus and primary insomnia were administered 3 mg of melatonin for 30 days before bedtime (14). The authors assessed subjective tinnitus perception using the Analogue Visual Scale (AVS), and found that the relative score decreased in 75% of patients after taking melatonin. Notably, all patients stated that they slept better at night after taking melatonin and that overall sleep quality improved.

Pooled analysis

The pooled analysis of the individual THI data from the six clinical trials included in our analysis is summarized in Figure 1. In all studies, the WMD of THI after melatonin supplementation was negative, with mean variations in THI value ranging from -2.5 to -19.5. The WMD of the THI score was -12.5 (95%CI, from -18.5 to -6.5; p=0.005), with moderate heterogeneity (I^2=71%). The analysis of the funnel plot of studies reporting the variation of THI score after melatonin supplementation reveals a low-to-moderate publication bias (Figure 2).

Discussion

Melatonin has a pivotal role in regulation of circadian rhythms, with its production increasing in the later hours of the day, promoting a state of sleep at night and wakefulness during the day (16). In addition to this undoubtedly important biological activity, there is recent evidence that melatonin has a number

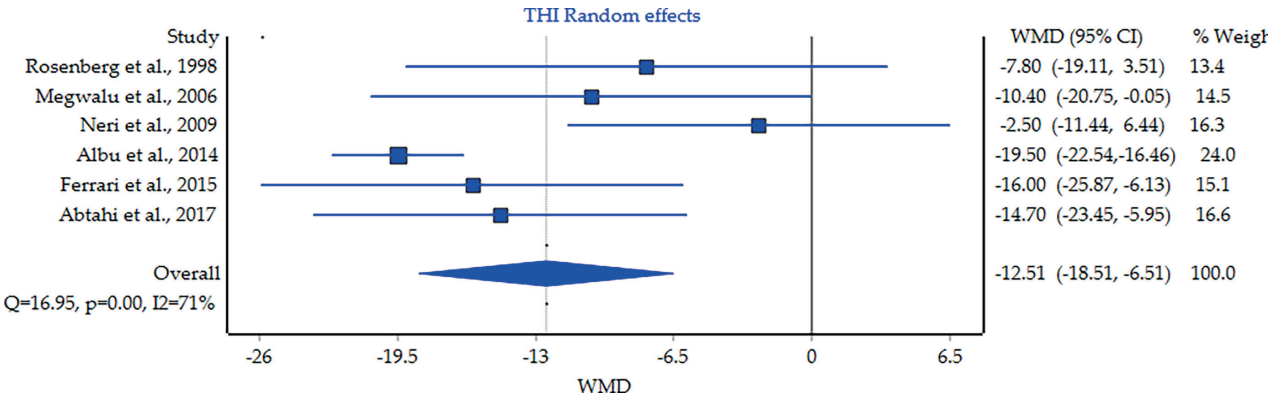

Figure 1. Pooled analysis of studies reporting the variation of the tinnitus handicap inventory (THI) score after melatonin supplementation. Pooled data are shown as weighted mean difference (WMD) and 95% confidence interval (95% CI).

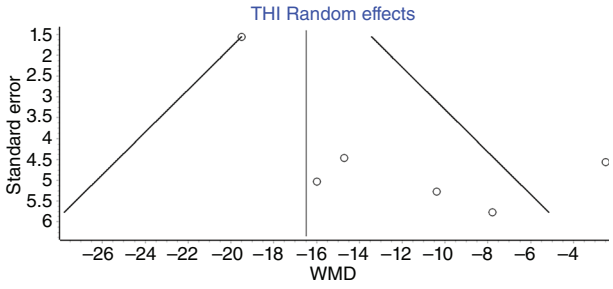

Figure 2. Funnel plot of studies reporting the variation of the tinnitus handicap inventory (THI) score after melatonin supplementation.

of additional pleiotropic effects, mainly due to its antioxidant functions and cell cycle control.

In particular, melatonin administration has been shown to significantly protect membrane lipids and nucleic acids from oxidative damage, thereby reducing the deleterious effects of free radicals on cell structure and function (17). These beneficial effects were also observed in the auditory system. A previous study has shown that melatonin supplementation helps to prevent injury to the cochlea, reducing the likelihood of developing hearing loss,

an often-irreversible condition associated with decreased hearing threshold sensitivity and speech comprehension skills (18). Because tinnitus is a common consequence of concomitant hearing loss, an investigation of the potentially beneficial role of melatonin supplementation in patients with tinnitus seems a reasonable hypothesis.

The results of this systematic literature review and meta-analysis suggest that melatonin supplementation (at a dosage of 3 mg daily) may have a beneficial effect on tinnitus disability and on overall quality of life (especially sleep) in patients with this chronic and debilitating hearing disorder. Notably, the severity of tinnitus disability was found to be reduced in all studies included in our review, with a substantial reduction in THI score (mean reduction: -12.5) in the six trials that used this subjective measure of tinnitus-related disability (Figure 1) (7-12). Nevertheless, a significant reduction in tinnitus-related disability was also observed in the two additional studies that examined tinnitus severity and quality of life using other scoring systems (13,14).

Several possible mechanisms have been proposed to explain the positive response of tinnitus patients to melatonin supplementation. Reactive oxygen/nitrogen species can be endogenously generated by different types of cochlear cells, resulting in direct damage to intracellular components and promoting apoptotic cell death (19). Degeneration of cochlear hair cells is typically followed by gradual deafferentation of auditory neurons, resulting in aberrant activity in multiple auditory areas. Thus, administration of antioxidant and anti-apoptotioc medicines like melatonin may benefit the entire hearing system, ultimately preventing or reducing the burden of hearing loss and tinnitus.

In conclusion, the findings of the clinical studies reviewed in this systematic literature review and meta-analysis of the literature support the concept that the antioxidant and anti-apoptotic effects of melatonin may interact with many intrinsic causes of tinnitus (acoustic traumas, ototoxic agents, or even simply ageing), resulting in a clinically and psychologically subjective improvement in patients suffering from this severely debilitating hearing condition (19).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: Conceptualization: RN and GL; methodology: GL and CM; writing-original draft preparation: GL; writing-review and editing: RN, BMH and CM; supervision, CM. All authors have read and agreed to the published version of the manuscript.

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Appendix–Supplementary File

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5-6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5-6
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 5-6

Section and Topic	Item #	Checklist item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7; Table 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7-9

TableS1 continues

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist *(continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Study characteristics	17	Cite each included study and present its characteristics.	Page 7-8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 1; Page 10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 7-8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-10; Figure 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10-12
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Upon request to corr. author

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/