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LONG-TERM IMPACTS OF EXOGENOUS MELATONIN ADMINISTRATION IN PATIENTS: AN INTEGRATIVE REVIEW

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Abstract: Introduction: Endogenous melatonin is a hormone produced by the pineal gland and responsible for inducing sleep, regulating blood pressure, body temperature and antioxidant defense, with a reduction in serum levels during advancing age. Indeed, recent studies point to melatonin and melatonergic agents in the treatment of sleep disorders. **Goal:** The present study aims to investigate, through scientific evidence, the safety of exogenous melatonin supplementation, as well as its side effects in long-term use, in addition to better investigating its dosage. **Methodology:** A research on the platforms PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO). The descriptors used in English were: "melatonin", "long-term", "adverse effects" and "safety". Complete articles in English, Spanish or Portuguese were determined as inclusion criteria and articles that did not contain a minimum of two of the descriptors in the title were determined as exclusion criteria. Subsequently, the abstracts were read and those that answered the guiding question were selected. In total, 10 articles were selected, two of which were expanded samples. **Results:** In most articles, supplementation demonstrates short- and long-term effectiveness in children, adults and the elderly. The adverse events identified were not serious, with pubertal delay being the most significant to be analyzed and still with low evidence due to methodological limitations. The effects of withdrawal were not shown to be harmful. **Final considerations**: The exogenous use of melatonin appears safe in the long term, considering routine medical monitoring based on establishing the correct dosage, pathology and adverse events. New studies are needed to improve some results.
Keywords: Melatonin. Long-term. Adverse effects. Security. Supplementation.

INTRODUCTION

Endogenous melatonin is a hormone produced under light stimulation in the pineal gland and released by it during the night, with the main function of inducing sleep. Although the central objective of the pineal gland in humans is to convert light information into melatonin secretion for the regulation of the circadian cycle, its importance is diverse – its action interferes with prolactin secretion, puberty and also mood changes, in addition to directly or indirectly regulating blood pressure, body temperature, antioxidant defense, as well as the immune system and the level of cortisol present in the body. When exposure to light is excessive or insufficient, or there is a change in the pineal gland, altered melatonin levels can negatively interfere with these body functions, leading to serious clinical consequences. Furthermore, the body's own production of melatonin decreases over the years, which may be very low in the elderly population and is one of the causes of insomnia commonly observed in elderly patients (WADE G. ALAN, et al, 2010). In this sense, the use of exogenous melatonin has been widely investigated as a possible treatment for dysfunctions related to the pineal gland and sleep disorders.

Recent studies have highlighted the efficiency of melatonin and melatoninergic agents in the treatment of diseases and conditions that affect sleep by reducing the sleep latency period, especially in neurodivergent children and adolescents affected by Chronic Insomnia (MOON EUNSOO, et al, 2022). However, safety, drug interactions and side effects are still the subject of research in this and other populations, and safety may vary according to age and the medications already used by the patient. Furthermore, the applicability of exogenous melatonin supplementation for treatments, whether for a sleep disorder, changes in cortisol levels or systemic arterial hypertension, is widely discussed, considering that there are other already consolidated and effective treatments – such as case of cognitive behavioral therapy in the treatment of Chronic Insomnia (MANTLE D., et al, 2020).

Due to the lack of formal information about the safety of using exogenous melatonin – long or short absorption – and also the amount to be used, its use is not yet fully widespread or even permitted in certain countries. In the United States, the FDA (Food and Drug Administration), responsible for regulating the circulation of food and medications in the country, does not recognize exogenous melatonin as a medication – but rather as a supplement –, so, it is released for sale without a prescription and can be found in different dosages and formulations. Similarly, melatonin supplementation was approved in the European Union in 2007 and is freely marketed in several European countries (ZWART TOM C, 2018). In Brazil, its use was recently approved by Anvisa, in 2021, also as a supplement. However, the Brazilian prescription must only be made for patients over 19 years of age and with a maximum dosage of 0.21mg daily (DE CASTILHO, et al, 2022).

In view of the above, this work seeks to analyze and identify the safety of exogenous melatonin supplementation in scientific evidence, thoroughly investigating its side effects in short and – mainly – long-term use, the efficiency and consequences in different daily dosages and formulations. existing drugs, as well as possible drug interactions, providing a solid analysis.

METHODOLOGY

The development of this integrative review was based on articles collected in the databases of the PubMed, Latin American and Caribbean Literature in Health Sciences

(LILACS) and Scientific Electronic Library Online (SciELO) platforms.

The descriptors used for the search, in English, were: "melatonin", "long-term", "adverse effects" and "safety". The Boolean operator "AND" was used as a way to combine the data and offer a more precise search (PEREIRA; GALVÃO, 2014). The guiding question used as the basis of the research was: "Is it safe to maintain long-term exogenous melatonin supplementation in patients?"

As for the inclusion criteria, complete texts written in English, Portuguese or Spanish were considered. Regarding the exclusion criteria, duplicate articles and those that did not have a combination of at least two of the descriptors in the title were excluded. Then, the abstracts were read and those that, in a certain way, did not answer the guiding question were excluded.

In an expanded sample, the authors considered the inclusion of two articles that had not been returned in the initial search but that answered the guiding question and were relevant. These articles also passed the inclusion and exclusion criteria. It is important to highlight that the SciELO platform did not return any articles meeting the search criteria.

Through Figure 1, it is possible to understand how the research strategy and article selection were established through a flowchart. In it, it is possible to clarify that our

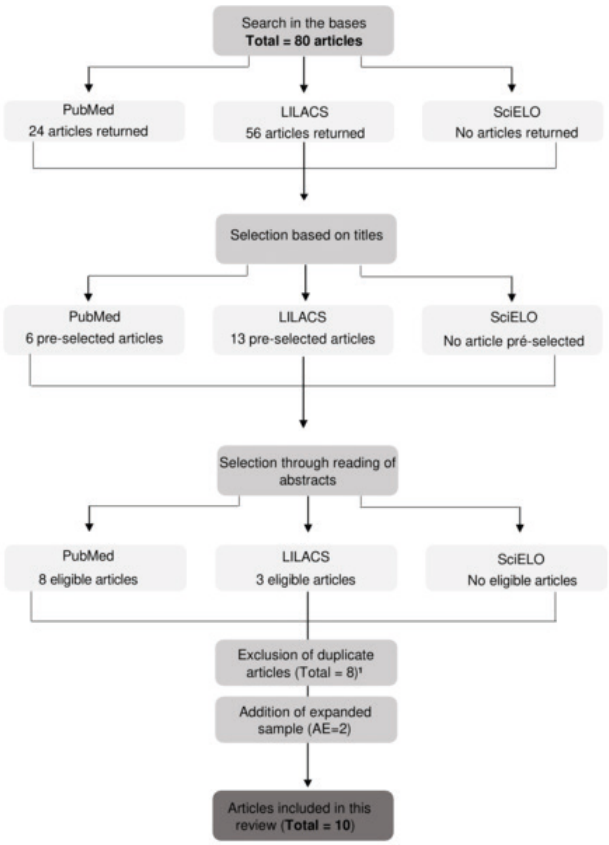

Figure 1: Identification and selection of articles on melatonin and long-term use in the PubMed, LILACS and SciELO databases.

SUBTITLE: [1] an article was subsequently excluded for presenting an extension of another existing article by the same author.

SOURCE: PACHECO, G, et al,2024.

Author/year	Population	Dosage	Duration	Long-term security
(ZWART C. TOM, *et al*, 2018)	Children aged between 6 and 12 years who suffer fromChronic Sleep Onset Insomnia (CSOI) and individuals with CSOI at a young age.	3 to 5mg/ day	9 to 12 years	The administration of exogenous melatonin wasproven to be safe in the long term after an averageof 7.1 years of treatment, based on the characteristicsof the studied population. About 75% of childrenwith Chronic Insomnia will have normal sleep without medicationafter 10 years.
(WADE G. ALAN, *et al*, 2010)	Men and women aged between 18 and 80 who suffered fromPrimary Insomnia and reported an average sleep latency of 420 minutes.	2 mg	29 weeks	Results demonstrate short- and long-term effectiveness of PRM[2] in patients with Insomnia ages 18 to 80, especiallythose aged 55 and over. PRM was well toleratedthroughout the 6-month period, without symptoms ofrebound or withdrawal after discontinuation. BiggerStudies are needed to answer the effects oflong term.
(HANDEL NICOLEMINA,*et al*, 2023)	Children and Adolescents between 2 and 18 years old	0,5 to15mg/ day	1,4 to 10,8years	The adverse events identified were not serious, but their real extent cannot yet be confirmed. There is a large gap in knowledge about the short- and long-term safety of exogenous melatonin, showing that more studies need to be done until a conclusion is faithfully established.
(JOSEPHINE ARENDT, 1997)[3]	Multiple analyzes in adolescents, adults, healthy night workers and reports of a visually impaired person.	Approx.5mg/ day (with breaks[4])	10 years[4]	The author brings multiple studies and personal observations about the use of exogenous melatonin. In his largest case report (involving a blind patient; duration of 10 years), he considers the absence of adverse effects. In his own use/ personal report (approx. 5mg, with periods of reduction), he observed benefits for Delayed Sleep Syndrome and rare adverse effects – with a morning hangover being one of these few.
(MOON EUNSOO,*et al*, 2022)	Children and Adolescents.	1 to 10mg/ day	26 weeks to 6 years	Until the date of publication of this article, prolonged use of melatonin in children and adolescents has not been related to serious adverse effects, in addition to there being no evidence of inhibition of physiological melatonin secretion. However, despite growing evidence on the safety of long-term use of melatonin in children and adolescents, the volume of studies in this age group is still small.
(MARAS ATHANASIOS,*et al*, 2018)	Children with Autism Spectrum Disorder (ASD)	2 to 5mg/day	Up to 52 weeks	Despite little research, melatonin treatment is a valid and effective option for the long-term treatment of insomnia in children with ASD.
(BUSCEMI NINA,*et al*, 2005)	Population with primary sleep disorders	Not informed	4 weeks	The safety of long-term use of exogenous melatonin (months and years) is still uncertain, requiring further studies to confirm.
(ANDERSEN H. P.LARS, *et al*, 2015)	Children, Teenagers, Adults and Elderly	1 to 10mg/ day	10 days to 24 weeks	Randomized clinical studies indicate that long-term use of melatonin induces mild adverse effects when compared to placebo treatment. Due to the lack of human studies, pregnant and lactating women must not take exogenous melatonin. Furthermore, there is still no consensus on whether prolonged administration of melatonin in children and adolescents is safe, which requires further studies within this age group.

(HOEBERTM., *et al*, 2008)	Children with Attention Deficit/ Hyperactivity Disorder (ADHD) and Chronic Sleep Onset Insomnia (ICIS)	2 to 10mg/ day	3,7 years	Exogenous melatonin treatment in children with chronic sleep onset insomnia (ICIS) is considered safe in the long term for 88% of children. Adverse events were not significant and withdrawal has a recurrence in 92% of children.
(MANTLE D., *et al*, 2020)	Children with delayed sleep-wake phase disorder, ADHD, ASD and neurogenetic disorders	3 to 6 mg/ day; 5 to 10 mg/day	4 weeks to 10.8 years	Although melatonin supplementation has been shown to be safe in shorter studies, its long-term safety is still inconclusive and needs to be further studied.

Table 1 - Presentation of research results for the review on the use of exogenous melatonin, covering details such as author/year, population, dosage, duration and considerations on safety in the long-term use of eligible studies.

SUBTILTE: [2]PRM = extended-release melatonin.[3] In this study, the author considers an extensive analysis that encompasses different populations, periods and case reports.[4] We considered the largest of the case reports, as it is the object of the question.

SOURCE: PACHECO, G., et al, 2024.

advanced search initially returned a total of 80 articles, already considering the inclusion criteria. Applying the exclusion criteria, 19 articles were selected based on the title and, subsequently, 11 articles by reading the abstracts. Finally, after excluding duplicate articles and adding the expanded sample (AE=2), 10 articles were finally selected for this review.

RESULTS

The results of this integrative review encompass 10 studies dedicated to analyzing the long-term use of exogenous melatonin, its effects and safety. These studies bring together different age groups, from children to the elderly, and considered both sexes. The supplementation protocols presented variations in terms of dose, time of use and dosage and are presented below (Table 1).

DISCUSSION

Insomnia and sleep disorders are issues closely related to mental health; The prevalence of insomnia in adolescents between 13 and 16 years old is 10.7% (MOON EUNSOO, et al, 2022), and thus concerns arise regarding treatment options. Low adherence to cognitive-behavioral therapies and side effects when using antipsychotics and antidepressants are factors that divert attention to treatments with melatonin – which raises questions about long-term administration, adverse effects, interference with pubertal development, drug interactions, formulations and discontinuity of treatment. Some of these topics are further discussed below.

LONG-TERM USE AND ADVERSE EFFECTS

Among the selected texts, 2 studies draw attention to the relationship between time, dose and effectiveness. A study that was carried out with 69 participants in a trial entitled Meldos followed the long-term effects of melatonin administration (ZWART C. TOM, et al, 2018).

Of these, 33 responded to questionnaires that assessed sleep quality using scores such as the Pittsburg Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). The dosage of melatonin used varied between 3 and 5mg, and, of the patients, 9 (27.3%) were still using exogenous melatonin in higher dosages after an average of 10.8 years. In conclusion, it was reported that the effectiveness of the treatment was 75% after 10 years.

In comparison, another randomized, double-blind, placebo-controlled study with pediatric extended-release melatonin (PedPRM) was done over 52 weeks with 125 children (MARAS ATHANASIOS, et al, 2018), of which, 72 completed the study. The doses administered were escalated from 2 to 5 mg in the initial phases and from 2 to 10 mg in the last phase of the study. In the results, individuals who received 52 weeks of medication had their total sleep increased by 62.08 minutes and those who received only 39 weeks – and originally placebo – increased by 25.6 minutes. Of these seventy-two, 76% had a satisfactory response with an average dosage of 5.3 mg and 24% an unsatisfactory response, even at doses of 10 mg.

It is possible to notice similar efficacy in the 2 studies, even at different treatment durations, with higher doses not necessarily being more effective, but rather being adjusted in terms of age, severity of the problem, total sleep time desired and type of release. of the medicine.

As for adverse events, those observed were, in general, few. For the most part, the reported manifestations were mild, easy to manage, and equivalent to those in the placebo group.

It is important to highlight that these effects varied precisely according to the dosage, administration time and treatment time, considering that, when carried out incorrectly, this therapeutic intervention can alter the natural physiology of sleep.

In research carried out by JOSEPHINE ARENDT (1997), a group of 16 young, healthy men received treatment with melatonin and placebo daily for a period of 16 days. The only adverse effect reported was headache, which affected only one of the participants. JOSEPHINE ARENDT (1997) also found that drowsiness and lack of energy in daily tasks can be a consequence of administering melatonin at the wrong time, leading to a change in the normal circadian rhythm.

Studies carried out in children and adolescents with problems such as ASD (Autism Spectrum Disorder) and ADHD (Attention Deficit Hyperactivity Disorder) also did not report serious adverse events. The most common effects were limited to fatigue, vomiting, mood changes and upper respiratory tract infections (MOON EUNSOO, et al, 2022). In another survey carried out on children with the same characteristics, events such as morning drowsiness, headache, dizziness, gastric problems and fatigue were the most reported (MOON EUNSOO, et al, 2022). To a lesser extent, there were also reports of nasopharyngitis and arthralgia, with equal prevalence between the treatment and placebo groups (WADE G. ALAN, et al, 2010).

These manifestations can be considered relatively irrelevant in special clinical conditions – in contrast to the benefits. In premature neonates and those with abnormal brain development, for example, exogenous melatonin can be of great benefit in reversing the condition (MOON EUNSOO, et al, 2022); Furthermore, melatonin has an important role in reducing free radicals, which gives it a neuroprotective character, especially in children whose levels are below expectations, thus overcoming their adverse events (MOON EUNSOO, et al, 2022).

DELAY IN PUBERTAL DEVELOPMENT

While three studies indicated no significant impacts after 2-4 years of treatment, one study suggested a potential delay at longer durations (>7 years). These results, however, require an in-depth evaluation due to methodological limitations present in the studies (ZWART C. TOM, et al, 2018).

Similarly, research carried out by ZWART C. TOM (2018) in children aged between 6 and 12 years, identified a small delay in relation to pubertal perception, with 31.3% of participants experiencing later puberty. Although an exact conclusion has not yet been established, this may be related to the influence of melatonin on sexual maturation, having an inhibitory function on the hypothalamic-pituitary-gonadal axis. Because of this possibility, many studies are required to confirm the complete safety of exogenous melatonin in children and adolescents (ANDERSEN H. P. LARS, et al, 2015).

DRUG INTERACTIONS

Cytochrome P450 1A2 (CYP1A2) is responsible for metabolizing melatonin in the liver. In this case, melatonin is transformed into 6-hydroxymelatonin and excreted. Substances that can inhibit cytochrome expression will increase the availability of melatonin in the body, just as the increase in the effectiveness of CYP1A2 will decrease its performance (MOON EUNSOO, et al, 2022). In this sense, the expression of this enzyme in children showed divergences in two articles: one of them points out around 30% of the adult level in children aged 1 to 12 months and 50% in children aged 1 to 9 years (MOON EUNSOO, et al, 2022), while the other pointed to higher clearance – advocating higher doses (MANTLE D., et al, 2020). Due to the discrepancy in both studies, further research is needed to understand the expression of the CYP1A2 enzyme in children.

When talking about interactions with melatonin clearance, two compounds draw attention because they interact directly with CYP1A2: caffeine and tobacco. Because they affect the availability of cytochrome P450 1A2, smoking and consuming caffeine during treatment will negatively interfere with the time and effectiveness of the treatment (ZWART C. TOM, et al, 2018).

EXTENDED-RELEASE AND RAPID-ABSORPTION FORMULATIONS

According to MOON EUNSOO (2022), extended-release formulations are designed to offer a gradual and constant release of melatonin over time. This format aims to imitate the natural production of melatonin in the body. This approach can be especially beneficial for those who experience difficulty maintaining a continuous sleep pattern.

On the other hand, quick-release formulations are developed to provide a more immediate effect. This variant is indicated for cases in which rapid sleep induction is a priority. According to ANDERSEN H. P. LARS (2015), generally available in tablets or capsules that dissolve quickly, rapid-release melatonin is absorbed by the body more efficiently and can be particularly useful in situations where a quick response to sleep disturbance is required.

The choice between extended-release and rapid-release formulations depends on the specific needs of the patient and the nature of the disorder. While prolonged release may be more appropriate for cases of chronic insomnia or difficulty staying asleep, rapid release may be preferable in situations that require immediate action, such as jet lag or sleep disorders related to changes in work schedules.

DISCONTINUATION OF TREATMENT

A study carried out on children with Chronic Insomnia revealed that 75% of patients will have normal sleep quality after 10 years of treatment, even without medication (ZWART C. TOM, et al, 2018).

The study called Meldos also analyzed two distinct groups: "STOP", whose participants interrupted therapy and "CONT", whose participants continued melatonin therapy. Four participants in the CONT group temporarily stopped supplementation, but restarted it. Five stopped taking it during the holidays and three stopped taking it weekly during the weekends. These participants said that the delay in their sleep rhythm on vacations and weekends, as well as the verification of the real need for therapy made them interrupt it. In the STOP group, 21 participants indicated that they had adopted a desired sleep rhythm and no longer needed melatonin to fall asleep; 2 participants reporting non-beneficial effects on sleep time and one who did not report the reason for discontinuing – which led them to leave therapy. (ZWART C. TOM, et al, 2018).

For now, the study demonstrated that the effect of withdrawal is not harmful, but the low bias of the research makes it necessary to implement additional studies.

FINAL CONSIDERATIONS

By analyzing the selected studies, we can conclude that, currently, there is no evidence that long-term supplementation of exogenous melatonin may be harmful to health or cause sleep impairment after discontinuing treatment. Although some studies have indicated the presence of adverse effects, its use can still be considered safe, given that, for the most part, the symptoms did not demonstrate clinical relevance. Furthermore, melatonin has been shown to be effective in the treatment of Chronic Insomnia, Acute (or maintenance) Insomnia and Delayed Sleep Phase Syndrome (SAFS) in different age groups and groups – such as children with Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and neurogenetic disorders. Regarding possible pubertal delay, one study suggests significant pubertal delay in children when used long-term. This study, however, has low methodological bias.

Finally, it is crucial to establish new research that discusses the issues found in this article – such as pubertal delay – in an attempt to suppress any inconclusive evidence.

Furthermore, it is up to the doctor to monitor the results and effects to individualize the treatment, given the different formulations, interactions, individual response and personal objectives – which will directly influence the success of the treatment.

This evidence-based approach will help support the use of exogenous melatonin supplementation as a safe and effective long-term treatment option in broad settings.

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