

Regulatory aspects and evidences of melatonin use for sleep disorders and insomnia: an integrative review

Aspectos regulatórios e evidências do uso de melatonina em distúrbio do sono e insônia: uma revisão integrativa

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ABSTRACT

Background: Insomnia is a sleep disorder characterized by difficulty of falling asleep or maintaining sleep, which affects different age groups. Currently, melatonin is used as a therapeutic treatment in cases of insomnia in children, adults, and elderly people. **Objective:** To evaluate the effectiveness of melatonin in sleep disorders, its dosage, potential adverse effects, as well as labeling laws and regulations in Brazil. **Methods:** This integrative review was carried out using the Cochrane Library, Medline (Pubmed), and Science Direct databases. Twenty-five articles and three documents available on the Brazilian Society of Endocrinology and Metabology (SBEM) and National Health Surveillance Agency (ANVISA) websites published between 2015 and 2020 were selected to be evaluated in full. **Results:** It was found that in most of the selected articles the use of melatonin reduces sleep latency. The effective melatonin doses varied according to each age group, from 0.5 to 3 mg in children, 3 to 5 mg in adolescents, 1 to 5 mg in adults, and 1 to 6 mg in elderly people. Side effects are mild when taking usual doses. In Brazil, no registered drug and current regulation on the use and marketing of melatonin has been identified. **Conclusion:** The use of melatonin is an alternative therapy that can be used for sleeping disorders. According to the evidences found, it did not demonstrate toxicity or severe side effects, nor dependence even when administered at high doses, suggesting that it is a safe medication to treat patients of different ages suffering from sleeping disorders.

Keywords: Melatonin; Sleep Wake Disorders; Pineal Gland.

RESUMO

Antecedentes: Insônia é um distúrbio do sono caracterizado por dificuldade de iniciar e manter o sono, afetando diferentes faixas etárias. Atualmente, a melatonina é utilizada no tratamento de insônia em crianças, adultos e idosos. **Objetivo:** Avaliar a eficácia da melatonina nos distúrbios do sono, posologia e potenciais efeitos adversos, bem como a regulamentação vigente no Brasil. **Métodos:** Trata-se de uma revisão integrativa, os artigos foram identificados nas bases de dados Cochrane Library, Medline (Pubmed) e *Science Direct*, totalizando 25 artigos, e foram selecionados três materiais disponíveis no site da Sociedade Brasileira de Endocrinologia e Metabologia e Agência Nacional de Vigilância Sanitária, publicados entre 2015 e 2020. **Resultados:** Verificou-se na maioria dos artigos selecionados que a melatonina reduz a latência do sono. Quanto as dosagens de melatonina identificou-se variação em cada faixa etária, para crianças de 0,5 a 3mg; adolescentes de 3 a 5mg; adultos de 1 a 5mg e idosos 1 mg a 6 mg demonstraram serem eficazes. Em doses habituais os efeitos colaterais são leves. No Brasil, não foi identificado medicamento registrado e regulamentação vigente sobre o uso e comercialização de melatonina. **Conclusão:** A utilização da melatonina é uma alternativa que pode ser utilizada em distúrbios do sono. De acordo com as evidências encontradas, não demonstrou toxicidade ou efeitos colaterais severos, nem dependência mesmo em doses elevadas, sendo, portanto, segura para tratamento de pacientes desde crianças a idosos que sofrem de distúrbios do sono.

Palavras-chave: Melatonina; Transtornos do Sono-Vigília; Glândula pineal.

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INTRODUCTION

Insomnia is a sleep disorder characterized by difficulty in falling asleep or maintaining sleep. It is defined as the persistent difficulty in falling and staying asleep, problems with sleep duration and maintenance and sleep quality¹. Insomnia occurs in different age groups and can last for weeks, months, or longer periods. In these cases, it is considered as a chronic disease when it remains for three months or more and affects the individual's occupational performance and daily routine². The prevalence of insomnia varies between 10 to 20% in the general population, and approximately 50% of these people live with this condition in a chronic way³. In China, the prevalence of insomnia is 15%⁴, followed by Spain 21.1%⁵ and Brazil, reaching above 30% of the population^{6,7} the gold standard for sleep assessment, this study aimed to describe the objective prevalence of insomnia in the São Paulo, Brazil, Epidemiologic Sleep Study cohort of 1,101 adults (20-80 years old).

Non-pharmacological treatments can help the patient in improving symptoms, including sleep hygiene, stimulus control, relaxation techniques, among other methods^{8,9}. Pharmacological treatments used to treat insomnia include selective agonists of the γ -aminobutyric acid type A (GABA-A) receptor, sedative antidepressants, melatonin and melatoninergic agonist, sedative antipsychotics, benzodiazepines, anticonvulsants, antihistamines, and herbal medicines such as *Valeriana officinalis*^{3,8,9}. Widely used, the minor tranquilizers benzodiazepines can cause tolerance, dependence, and withdrawal syndrome, as well as being considered inappropriate for elderly people due to its high risk of accidents, including falls and concomitant fractures³.

Commonly known as melatonin, n-acetyl-5-methoxytryptamine is a neurohormone, a small lipophilic molecule produced by the pineal gland. Among its functions, the chronobiotic effect is associated with the regulation of the endogenous clock in relation to the photoperiod¹⁰. A physiological function of endogenous melatonin is to reinforce the behavior related to darkness. Its production increases about two hours before bed. In addition, during the night, melatonin is responsible for transmitting information to the brain and other organs of the central nervous system about the duration of sleep, reducing the watch signal, as well as promoting fatigue and inducing sleep^{11,12}. Li *et al.*¹³ Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science reviewing exogenous melatonin as a treatment for secondary sleep disorders suggested that exogenous melatonin improves sleep quality, reduces onset latency, and increases total sleep time.

Classified as a non-prescription supplement in the United States of America, melatonin is widely used as a natural product, among all age groups, including children¹⁴. Research conducted with 31 supplements in Guelph, Ontario, Canada has showed low quality of melatonin formulations, with

high concentration variability between samples and batches and the presence of serotonin in 8 of the evaluated supplements¹⁵. In Brazil, the number of medical prescriptions for the use of melatonin to treat insomnia has increased, however their commercialization is available only in compounding pharmacies. Currently, only one supplier of pharmaceutical products is authorized to distribute melatonin in Brazil, and solely to compounding pharmacies¹⁶. Although the use of melatonin for the treatment of insomnia have expanded in recent years, information about its potential adverse effects and drug interactions are still limited. The National Health Surveillance Agency (ANVISA) newsletter (2019)¹⁶ reports that marketed medications must have proof of safety, efficacy, and quality in Brazil, but due to an injunction that allows the sale of raw materials, melatonin is available over-the-counter¹⁷. Moreover, the Brazilian Sleep Society considers that the use of melatonin to treat circadian rhythm disorders is already established, but the results for insomnia are not consistent, despite some positive results in specific populations and a good tolerability and safety profile, with few side effects¹⁸.

These results demonstrate the need for greater control over the production and marketing of melatonin supplements. It is necessary to build and develop a more effective health care and identify the best practices for health professional bodies, especially prescribers and pharmacists who work directly in the prescription and provision of this medication to patients. In this perspective, this study aimed to evaluate the effectiveness of melatonin for sleep disorders and melatonin associated symptoms, dosage, potential adverse effects, as well as the law regulations of the drug in Brazil.

METHODS

This article is an integrative review in which the six methodological steps described by Mendes, Silveira and Galvão¹⁹ were followed: (i) identification of the theme and selection of the research question to carry out the integrative review; (ii) establishment of criteria for inclusion and exclusion of studies; (iii) definition of the information to be extracted from the selected studies; (iv) evaluation of studies included in the integrative review; (v) interpretation of results; and (vi) presentation of the review.

Data collection was performed using Cochrane Library, Medline (Pubmed), and Science Direct databases. To perform the searches, Health Sciences Descriptors (Decs) were used in Portuguese and English, and the articles were selected according to the objective of the project and including the following key words: melatonin, pineal gland, sleep disorders, and insomnia. In addition, for the regulatory aspects, the Brazilian Society of Endocrinology and Metabology (SBEM) and the ANVISA websites were accessed using the descriptor "melatonin". Fifty-six documents were found using the

SBEM and two documents were selected to be evaluate in full. Thirty-four documents were identified using the ANVISA website and one document was selected to be assessed in full.

The article search using the databases was based on the following criteria: articles published between 2015 and 2020, in Portuguese or English. Articles that were not in the defined languages, did not have any descriptors of interest, or that

were outside the defined publication period were excluded. Reviews, meta-analysis, cohort studies, and randomized clinical trials were selected.

For the selection of articles, an initial search based on title and abstract was carried out in the database. Then, a new selection was made with the reading of the articles in full, according to the Figure 1.

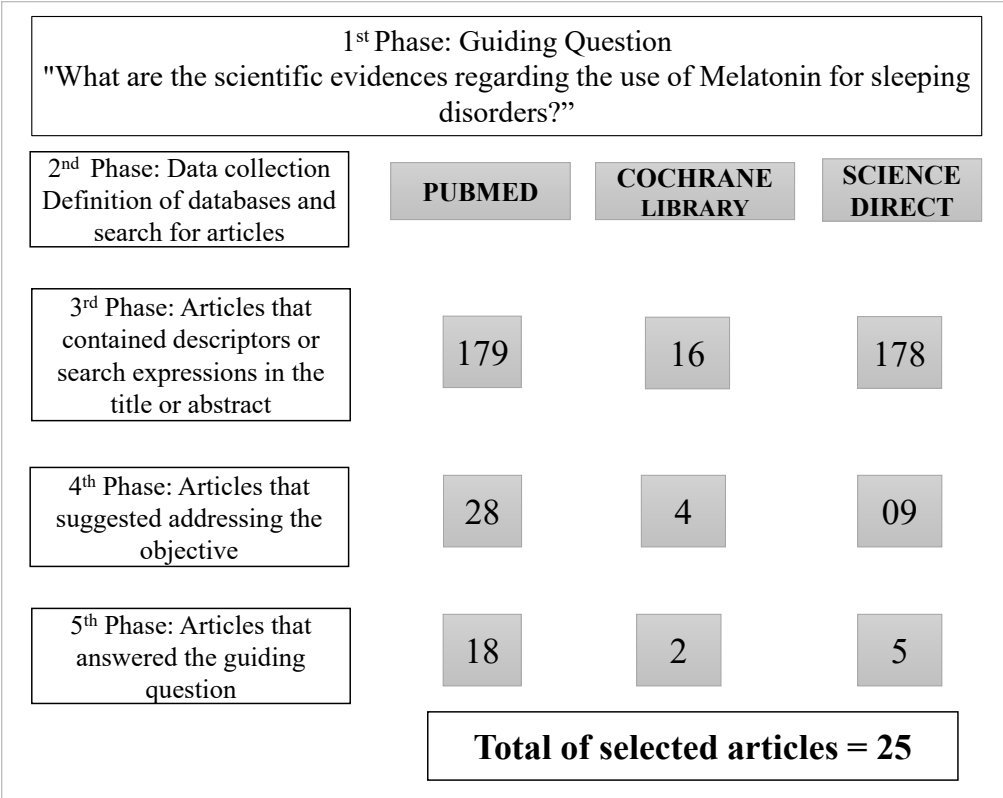


Figure 1. Summary of the article selection process.

RESULTS

The final selection consisted of 25 articles and three documents identified in the Brazilian websites. Table 1 summarizes the characteristics of the articles according to authors, year of publication, and database of publication.

No articles were identified reporting the current regulations of melatonin in Brazil. The only information found was that the commercialization of melatonin is authorized only for compounding pharmacies, and must be purchased from the Active Pharmaceutica' supplier^{16,17}. Similarly, no drug is registered with melatonin as the active ingredient. However, in Europe, a medicine registered under the trade name of Circadin' is available in the market.

Table 2 shows the characteristics of the selected articles according to the study design, population, dosage, intervention evaluation, therapeutic and adverse effects of melatonin. Of the 25 studies found, 22 showed positive results regarding the use of melatonin in insomnia disorders and three studies showed ineffective or inconclusive results.

DISCUSSION

The term circadian is derived from the Latin term *circa diem*, which means around one day. Circadian rhythms are endogenous oscillations that occur over a 24-hour period. In humans, this cycle lasts an average of 24.2 hours with individual variation of 23.7 to 25.3 hours. The waking and sleeping process is strongly influenced by the circadian system²⁴.

Currently approved by the Food and Drug Administration (FDA) for the treatment of sleep disorders in elderly people³⁵, melatonin has been used for delayed insomnia, sleep-wake cycle with periods shorter than 24 hours, sleep correction in the elderly, as an adjuvant in the treatment of autism spectrum disorder, attention deficit hyperactivity syndrome, migraine, anesthesia, metabolic diseases, and polycystic ovary syndrome²⁸. The synthetically produced melatonin can be administered exogenously and there are immediate and sustained release formulations available on the market.

Malow and collaborators⁴² report that melatonin is effective for sleep disorders in children and adolescents

Table 1. Distribution of references included in the study, according to the authors, year of publication, database and journal.

Authors	Year	Data base	Periodic
Hajak & Zisapel ²⁰	2015	PUBMED	International clinical psychopharmacology
Culpepper & Wingertzahn ²¹	2015	PUBMED	Prim Care Companion CNS Disord
Wright et al. ²²	2015	SCIENCE DIRECT	Drugs & Aging
Foley & Steel ²³	2015	SCIENCE DIRECT	Complementary Therapies in Medicine
Williams et al. ²⁴	2016	PUBMED	Pharmacotherapy
Mccleery & Sharpley ²⁵	2016	COCHRANE LIBRARY	Cochrane Database of Systematic Reviews
Cardinali et al. ²⁶	2016	SCIENCE DIRECT	Pharmacological Research
Chang et al. ²⁷	2016	PUBMED	JAMA pediatrics.
Hohl et al. ²⁸	2016	SITE SBEM	SITE SBEM
Sociedade Brasileira de Endocrinologia e Metabologia ²⁹	2016	SITE SBEM	SITE SBEM
Auld et al. ¹¹	2017	PUBMED	Sleep Medicine Reviews
Madsen et al. ³⁰	2017	PUBMED	Trials journal
Riemann et al. ⁹	2017	PUBMED	European Sleep Research Society
Abdelgadir et al. ³¹	2018	PUBMED	Archives of Disease Childhood
Maras et al. ³²	2018	PUBMED	Journal Of Child And Adolescent Psychopharmacology
Quera-Salva & Claustat ³³	2018	PUBMED	Encephale
Zwart et al. ³⁴	2018	PUBMED	Healthcare
Myers et al. ³⁵	2018	PUBMED	Journal of clinical sleep medicine
Sletten et al. ³⁶	2018	PUBMED	Public Library of Science
Lewis et al. ³⁷	2018	COCHRANE LIBRARY	Cochrane Database of Systematic Reviews
Anvisa ¹⁶	2019	SITE ANVISA	SITE ANVISA
Besag et al. ³⁸	2019	PUDMED	CNS Drugs
Schroder et al. ³⁹	2019	PUDMED	Journal of autism and developmental disorders
Lemoine; Bablon & Silva ⁴⁰	2019	PUBMED	Complementary therapies in medicine
Seiden & Shah ⁴¹	2019	PUBMED	Prim Care Companion CNS Disord
Li et al. ¹³	2019	PUBMED	Frontiers in neuroendocrinology
Malow et al. ⁴²	2020	SCIENCE DIRECT	Journal of the American Academy of Child & Adolescent Psychiatry
Low, Choo & Tan ⁴³	2020	SCIENCE DIRECT	Journal of Psychiatric Research

(2-17.5 years) with autism spectrum disorder and insomnia. According to the authors, there was an improvement in sleep quality with no changes in weight, height, body mass index, and pubertal status, and no evidence of developmental delays. Nunes et al.⁷ recommend doses of 0.5 to 3 mg for children and 3 to 5 mg for adolescents. Chang et al.²⁷ suggest that melatonin supplementation is a relatively safe and effective way to improve sleep-onset in addition to decreasing the severity of symptoms of atopic dermatitis in children, due to melatonin immunomodulatory, anti-inflammatory, and antioxidant effects, thus improving the skin and helping to maintain the epidermal barrier.

The review demonstrated that the use of melatonin is effective to treat primary and secondary insomnia at different stages of life, from children and teenagers to adults and the elderly. There was also a great diversity in the variables investigated, especially regarding the dose, time of use, and sleep outcomes. Despite of some biases, most studies

demonstrated that the use of melatonin for sleep disorders is efficient and safe.

Table 3 shows the dosages of melatonin indicated for each age group according to the publications found.

As for the use in elderly people, Culpepper et al.²¹ report that prolonged-release melatonin formulations are effective in symptoms associated with sleep-onset, however the effects may be limited to individuals over 55 years old who suffer from insomnia. Quera-Salva et al.³³ evaluated a dose of 2 mg of melatonin administered once a day for three months. The authors found that Circadin® is well tolerated, has no rebound, withdrawal or hangover effects, in addition to not causing drug interactions with antihypertensive, antidiabetic, hypolipidemic or anti-inflammatory drugs, which are the drugs most used by elderly people.

No evidence was found that the use of melatonin (up to 10 mg) assists in sleep disorders in patients with moderate to severe dementia due to Alzheimer's disease. The doses

Table 2. Effects of melatonin in insomnia.

Authors	Study type	Population	Aims	Posology	Evaluation of the intervention	Effects of melatonin in insomnia
Hajak & Zisapel ²⁰	Prospective cohort study	597 patients (210 men and 387 women)	To investigate the effects of interruption, withdrawal and rebound from Circadin®.	2 mg 2 hours before sleep for 3 weeks	Sleep quality was classified as 1 = very good, 2 = good, 3 = regular, 4 = poor and 5 = very poor. Morning alertness was classified as 1 = fully alert, 2 = alert, 3 = regular, 4 = tired and 5 = very tired. Improvement or worsening of sleep quality or morning alertness was defined as a change (decrease) of at least one point from the baseline.	75% of patients reported that sleep quality and morning alertness had improved to at least regular to good or very good. No serious adverse effects have been reported.
Culpepper & Wingertzahn ²¹	Systematic review	1344 patients aged 55 years old	To investigate the level of evidence that supports the use of over-the-counter agents: diphenhydramine, doxylamine, melatonin and valerian for occasional sleep disorders or insomnia.	5 mg daily for 8 weeks 2 mg daily for 3 weeks	Primary: sleep latency actigraphy, sleep time, awakenings, sleep efficiency Secondary: sleep diary, awakenings, alertness.	It appears to be effective for symptoms associated with onset of sleep and shows a favorable tolerability profile, but the effects may be limited to individuals over 55 years old with insomnia.
Wright et al. ²²	Systematic review and meta-analysis	322 patients with a mean age of 64 years old	To determine the effect of melatonin compared to placebo on discontinuation of benzodiazepines, in addition to determining the effect of melatonin on sleep quality in this population.	2 to 5 mg once a day before bed 4–18 weeks	Pittsburgh sleep quality score.	The effect of melatonin on sleep quality was inconsistent.
Foley & Steel ²³	Systematic review	Patients from 1 to 8 years old; 50 to 85 years old with Alzheimer's, 16–25 years old with chronic sleep problems, 3 to 16 years old with autism and sleep disorders	To explore the available clinical evidence on the safety of oral use of melatonin.	2 to 10 mg Period: 3 to 5 years old	Questionnaire applied weekly. Hematology, electrolytes, urinalysis, physical examination. Holter monitoring 24 hours by electrocardiogram. Selection of cognitive, psychomotor, dexterity and memory recall tasks. Simulated driving task, sedation scale and radioimmunoassay.	Supplementation appears to be relatively safe. Adverse events are generally minor.
Williams et al. ²⁴	Review	Patients older than 55 years old	To compare the pharmacokinetic and pharmacodynamic properties of agomelatine, prolonged release melatonin and ramelteon, to examine the impact of pharmacological properties on clinical efficacy.	2 mg day, 1–2 hours before bed for up to 13 weeks	Sleep latency, sleep onset time, number and duration of naps.	Adverse reactions: headache, nasopharyngitis, back pain, arthralgia, and potential for hepatic metabolism interaction with other drugs Pharmacokinetic parameters: Absolute bioavailability 15%, T _{1/2} average 3.5–4.0 hours, T _{max} interval, hours 0.75–3.0. In vitro protein binding: ~ 60%, mainly for albumin, α 1-acid glycoprotein and high-density lipoprotein.
Mccleery & Sharpley ²⁵	Systematic review	222 patients	To evaluate common adverse effects, compared to placebo for sleep disorders in people with dementia.	Up to 10 mg 8 to 10 weeks	Total night sleep time, proportion of day sleep to night sleep.	There is no evidence that it helped with sleep disorders in patients with moderate to severe dementia due to Alzheimer's disease.

Table 2. Cont.

Authors	Study type	Population	Aims	Posology	Evaluation of the intervention	Effects of melatonin in insomnia
Cardinali et al. ²⁶	Review	Patients aged 20 to 90 years old	To discuss the available data on the effectiveness of melatonin to reduce chronic use of benzodiazepine drugs in patients with insomnia.	1 mg, 2 mg, 3 mg, 5 mg, 10 mg 1 day - 18 months	Daily records of sleep and quality of wakefulness filled in by patients, and polysomnography.	It has a very safe profile, is well tolerated and, in some studies, has been administered to patients in very large doses and for long periods, without any potential for drug abuse. Several studies have found that more than 50% of patients treated with benzodiazepines discontinue use after treatment with melatonin. Melatonin may become the therapy of choice to reduce dependence on benzodiazepine medications.
Chang et al. ²⁷	Randomized, double-blind, placebo-controlled clinical trial.	73 children and adolescents of 1 to 18 years old with attention deficit.	To evaluate the effectiveness of melatonin supplementation to improve sleep disorders and disease severity in children with Atopic Dermatitis.	3 mg or placebo daily for 4 weeks	Actigraphy, subjective change in sleep and dermatitis, sleep variables measured by polysomnography, nocturnal urinary levels of 6-sulfatoxymelatonin and serum immunoglobulin levels.	Melatonin supplementation is a safe and effective way to improve sleep onset latency and disease severity in children with Atopic Dermatitis.
Auld et al. ¹¹	Systematic review and meta-analysis	1500 patients of 18 and 80 years old	To assess the evidence base for the therapeutic effects of exogenous melatonin in treating primary sleep disorders	0.1 a 10mg for five weeks	Sleep parameters: primary insomnia, delayed sleep phase syndrome, non 24 hours sleep wake syndrome in blind patients and REM-behaviour disorder	Reduction in the time to fall asleep between the effect on sleep onset latency for melatonin in patients with primary insomnia. Treating delayed sleep phase syndrome demonstrated an overall significant improvement in sleep onset latency compared with placebo.
Madsen et al. ³⁰	Randomized, double-blind, placebo-controlled clinical trial.	240 patients	To investigate whether prophylactic treatment with melatonin has a preventive effect on depression, depressive and anxiety symptoms, sleep and circadian disorders after Acute Coronary Syndrome.	25 mg for 12 weeks.	Actigraphy, Pittsburgh sleep diary, pain, anxiety, fatigue and general well-being measured by visual scales.	It may have advantages due to its low toxicity, as well as its proven anxiolytic and hypnotic effects.
Riemann et al. ⁹	Clinical Guideline	Different populations with insomnia, 4099 patients	To provide clinical recommendations for the management of adult patients with insomnia.	0.3 - 40 mg 12 weeks	Sleep parameters: objective and subjective, number of awakenings, sleep efficiency; sleep onset latency; total sleep time, awakenings after sleep onset.	Reduces sleep onset latency, improves sleep quality. However, the effects were small from a clinical point of view. It has been regarded as a safe medicine.
Abdelgadir et al. ³¹	Systematic review and meta-analysis	682 children aged <18 years with neurodevelopmental disorders	To determine the efficacy and safety of melatonin as therapy for sleep problems in children with neurodevelopmental disorders	0.1 - 12mg 1 a 13 weeks	Sleep parameters: total sleep time, sleep onset latency, frequency of nocturnal awakening, adverse events and child's behaviour	Melatonin improves total sleep time and sleep onset latency in children with neurodevelopmental disorders, with few adverse events related

Table 2. Cont.

Authors	Study type	Population	Aims	Posology	Evaluation of the intervention	Effects of melatonin in insomnia
Maras et al. ³²	A prospective double-blind randomized placebo-controlled	95 patients aged between 2 to 17.5 years old with Autism Spectrum Disorder.	To describe long-term efficacy and safety of pediatric-appropriate prolonged-release melatonin at the optimal daily dose and impact of the treatment on caregivers' sleep, daytime sleepiness, and quality of life.	2.5 a 10mg for 13, 39 and 52 weeks	Sleep parameters: Sleep and Nap Diary, Composite Sleep Disturbance Index, caregiver's Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and quality of life	After 52 weeks of continuous treatment subjects slept 62.08 minutes longer, fell asleep 48.6 minutes faster ($p < 0.001$), had 89.1 minutes longer uninterrupted sleep episodes e less nightly awakenings and better sleep quality compared with baseline and placebo-randomized group. The drug was generally safe; most frequent treatment-related adverse events were fatigue and mood swings.
Quera-Salva & Claustre ³³	Review	Insomnia patients aged 55 years old or older.	To provide data on the physiological and pharmacological effects of melatonin related to sleep.	2 mg for 3 months	Sleep quality, sleep latency assessed by the falling asleep score, performance the next morning assessed by the behavior score upon awakening and improvement in quality of life.	Benefits: improvement in sleep quality and latency, alertness the next day, and quality of life. Absence of rebound, abstinence or hangover effect, and without safety concerns in concomitant therapy with antihypertensive, antidiabetic, lipid-lowering or anti-inflammatory drugs.
Zwart et al. ³⁴	Cohort study	69 children	To assess the discontinuity of melatonin therapy, the time and the real quality of sleep. To investigate the occurrence of adverse events and the reasons for discontinuing the use of melatonin.	0.5 - 5 mg Average duration of treatment 7.1 years.	Pittsburgh Sleep Quality Index, subjective sleep quality, sleep duration, usual sleep efficiency, sleep disorders, use of sleeping medications and daytime dysfunction. Each item is weighted on a scale of 0 to 3.	Long-term therapy appeared to be safe after an average of 71 years of treatment. The results of this study indicate that approximately 75% of children with chronic insomnia in early sleep treated with melatonin will have normal sleep quality without medication ten years later.
Myers et al. ³⁵	Randomized, double-blind, placebo-controlled clinical trial.	13 patients aged between 2 to 50 years old.	To investigate the efficacy and safety of melatonin in the treatment of sleep disorders in patients with Dravet's Syndrome.	6 mg 30 minutes before bed for 2 weeks.	Actigraphy, average sleep latency, average sleep efficiency, frequency of seizures, caregiver's impression of clinical change and adverse events.	No significant adverse events were reported by caregivers. Although the double-blind study found no significant difference in total sleep time, the overall impression from the parents' report was that melatonin is very beneficial in some patients.
Sletten et al. ³⁶	Randomized, double-blind, placebo-controlled clinical trial.	116 patients with an average age of 29 years old of both genders.	To test the effectiveness of melatonin in patients with Delayed Sleep-Wake Phase Disorder (DSWPD)	0.5 mg for 4 weeks.	Sleep onset time, sleep efficiency.	Short-term and casual administration is an effective and safe treatment for patients with DSWPD with confirmed circadian misalignment, resulting in improvements in objective and subjective quality of sleep, daytime function, and severity of clinical symptoms.
Lewis et al. ³⁷	Systematic review	151 patients, with 16 admitted to the intensive care unit (ICU).	To assess whether the quantity and quality of sleep can be improved by administering melatonin to adults in the ICU. To assess whether melatonin improves physical and psychological results.	3 and 10 mg. Orally or enterally for a minimum of two days or until discharge from the ICU.	Sleep quantity and quality, measured by polysomnography, actigraphy, bispectral index or electroencephalogram.	Insufficient evidence was found to determine whether administration would improve the quality and quantity of sleep in ICU patients. Sparse data and differences were found in the study methodology, in the ICU sedation protocols, and in the methods used to measure and report sleep.

Table 2. Cont.

Authors	Study type	Population	Aims	Posology	Evaluation of the intervention	Effects of melatonin in insomnia
Besag et al. ³⁸	Systematic review	1625 participants between 1 and 93 years old	To assess the evidence for adverse events associated with short-term and longer-term treatment for sleep disorders	0.15 - 12 mg/day for 1 to 29 weeks	To evaluate the occurrence of adverse effects with the use of melatonin in the short and long term.	There were no serious adverse effects associated with the use of melatonin in the short term, the most frequent adverse effects were daytime sleepiness and headache. There is scarcity of data with long-term use.
Schroder et al. ³⁹	Double-blind placebo-controlled clinical trial.	125 individuals aged 2 to 17.5 years old with Autism Spectrum Disorder or Smith-Magenis syndrome.	To evaluate the efficacy and safety of prolonged-release melatonin mini-pills in improving the duration and onset of sleep in patients with Autism Spectrum Disorder or Smith-Magenis syndrome.	3-5 mg for 13 weeks.	World Health Organization Welfare Index, Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale.	The treatment improved externalizing behaviors (hyperactivity-inattention and conduct) in children and adolescents. The prolonged-release formulation was effective in improving sleep initiation and maintenance, as well as being safe.
Lemoine; Babbion & Silva ⁴⁰	Prospective Study	40 participants between 20 and 75 years old.	To investigate the effect of a combination of melatonin, vitamin B6 and medicinal plants in patients with mild to moderate sleep disorders.	1 mg of melatonin; 0.42mg of vitamin B6; 8.4 mg of California Poppy; 150 mg of passion fruit extract; 240 mg of lemon balm for 14 days.	Total sleep duration, sleep onset latency, number of nightmares per night and number of daytime naps and their duration, daytime fatigue was also subjectively assessed by participants in their sleep diary.	There was an improvement in sleep quality, latency of sleep onset, total sleep duration and daytime parameters related to sleep. No serious adverse events have been reported.
Seiden & Shah ⁴¹	Randomized clinical trial	10 patients, 4 men, 6 women aged between 18 and 40 years old.	To evaluate the pharmacokinetic and safety profile of a new melatonin of continuous release and absorption (CRA-melatonin) in comparison with the melatonin of immediate release (IR-melatonin).	5 mg. The subjects were confined to the clinic, included daytime dosing, blood collection and exposure to standard ambient light, to prevent significant endogenous production of melatonin.	For each individual, the melatonin plasma concentration time data was used to calculate the following pharmacokinetic parameters: maximum concentration, maximum time and threshold (time above the target threshold concentration).	The formulation demonstrated rapid release and then continuous release and absorption of melatonin for up to 7 hours, making it a significant advance in the pharmacokinetic release profile of exogenous melatonin delivery and therefore an important potential consideration as a therapy for sleeping disorder. Improves the quality of sleep of secondary sleep disorders.
Li et al. ¹³	Systematic review and meta-analysis.	205 patients between 29 and 41 years old.	To determine the effectiveness of melatonin versus placebo in the treatment of sleep disorders.	3 - 6 mg for 3 to 9 days.	Sleep onset latency, total sleep time and sleep efficiency.	Improves the quality of sleep of secondary sleep disorders.
Malow et al. ⁴²	Double-blind placebo-controlled clinical trial.	80 children and adolescents aged between 2 - 17.5 years old.	To report the long-term effects of prolonged-release melatonin treatment appropriate for children on sleep, growth, body mass index and pubertal development.	2.5, 10 mg daily intake for up to 104 weeks, followed by a 2-week placebo period to assess withdrawal effects.	Infant sleep was assessed at each visit during the one-year study period using the Compound Sleep Disorders Index, which scores the frequency and duration of the participant's sleep habits in the previous month (six habits: sitting at bedtime, sleep induction, waking up at night, resettlement, time of wake up, and early sleep).	It is safe and effective for long-term treatment in children and adolescents with autism spectrum disorder and insomnia. There were no detrimental effects on children's pubertal growth and development and no abstinence or safety problems related to the use or discontinuation of the medication.
Low, Choo & Tan ⁴³	Systematic review	Patients aged 18 - 65 years old.	To summarize all available systematic reviews and meta-analyses that investigate the effectiveness of melatonin and melatonin agonists in primary insomnia disorders.	0.3 - 75 mg, 3 days to 6 months	Actigraphy, waking time during sleep, awakenings, day to night sleep ratio.	There was a statistically significant improvement in latency and total sleep time, with a lack of consensus on whether these are clinically significant.

CRA-melatonin: melatonin of continuous release and absorption; DSWPD: Delayed Sleep-Wake Phase Disorder; ICU: Intensive Care Unit; IR-melatonin: melatonin of immediate release

Table 3. Melatonin dosages according to selected articles.

Population	Daily dose
Children	0.1mg – 3mg
Teenagers	3mg – 12mg
Adults	1mg – 25 mg
Elderly	1mg – 6mg

of melatonin used in these studies were equal to or higher than the doses indicated for healthy elderly people, however, the doses were lower compared to those used or studied in populations without dementia. Several different mechanisms are likely to cause sleep disorders in patients suffering from dementia, some of which may be related to circadian misalignment. Achieving full melatonin's chronobiotic effect in these circumstances can take several months. Therefore, it is possible that some patients respond after longer periods of treatment with melatonin²⁵.

Overall, no significant adverse effects were reported in most studies; however, Besag et al.³⁸ reported that daytime drowsiness and headache are among the most frequent related side effects. Similarly, Maras et al.³² stated that after 52 weeks of use of melatonin the most frequent treatment-related adverse events observed were fatigue and mood swings. Additionally, Myers et al.³⁵ in a randomized clinical study, reported that a patient had an increased serum level (within the toxic range) of valproate while using melatonin concomitantly. According to the authors, clinicians must ponder possible interactions of melatonin with antiepileptic drugs. Since melatonin is also metabolized by cytochrome P450 enzymes (CYP1A2, CYP1A1, and CYP2C19), the concomitant use of melatonin with antiepileptic and antidepressant drugs can potentially cause drug interaction. Consequently, the metabolism may be reduced leading to longer drug action time, which can cause severe sedation³⁵.

A formulation containing melatonin, vitamin B6, California poppy extract, passion fruit extract, and lemon balm extract was tested on patients of both genders between 20 and 75 years old who had moderate insomnia. There was a statistically significant improvement in sleep quality during the two-week treatment period with no serious adverse events being reported, suggesting that this combination of assets is beneficial for mild to moderate insomnia⁴⁰.

As for the doses, 0.1 to 0.5 mg is recommended for sleep-related rhythmic movement disorder, 1 to 5 mg for sleep disorders, and 3 to 10 mg for neurological diseases. These recommended doses should be taken daily, in a single dose at night, one hour before the usual bedtime. However, there is no established minimum or maximum effective dose for each use²⁹. Among the advantages of melatonin described in the included studies are its favorable safety profile, good toleration, and no addiction potential when administered for long periods²⁶. The adverse reactions commonly found in the reviewed studies included headache, nasopharyngitis, back

pain, arthralgia, nausea, dizziness, and restlessness^{20,24}. Additionally, melatonin may have advantages attributed to its anxiolytic and hypnotic effects, and low toxicity levels, as reported by Madsen et al.³⁰ while investigating the melatonin toxicity in patients with depressive, anxiety, and sleep disorder symptoms.

In Europe, the drug Circadin[®], which has a prolonged release formulation containing 2 mg of melatonin, has been marketed since 2008 as an innovative treatment for primary insomnia in patients aged 55 years and older who have sleep disorders characterized by poor quality of sleep²⁰. As a food supplement, it has not been evaluated or approved by the United States FDA to prevent or treat any diseases²⁴.

In Brazil, there is no registration of drugs with melatonin as the active ingredient, therefore, its sale is prohibited in drugstores and national websites. Although melatonin is used in some countries as an ingredient in food supplements, this substance is not authorized for use in food supplements in Brazil. Additionally, according to the rules of Ordinance SVS / MS n° 344/1998, melatonin is not an asset subject to special control, however, its commercialization is restricted to compounding pharmacists which must acquire the product from the company Active Pharmaceutica, have operation authorization granted by the ANVISA, and follow the current guidelines of Good Handling Practices. Additionally, prescription from a legally qualified professional is required, and the prescription must contain the composition, the pharmaceutical form, the dosage, and directions for use.

In this context, it is up to health professional bodies, especially doctors and pharmacists, to provide counseling to ensure the maintenance of therapy, symptom relief, functional changes, and assessment of potential adverse effects and drug interactions. These professionals must act in a multidisciplinary way, taking into account the benefit of reducing the use of benzodiazepine drugs, which can cause dependence, abuse, and contribute to higher costs of public resources resulting from the irrational use of medicines. Doctors and pharmacists can work together and offer the patient non-pharmacological and pharmacological treatments with the use of alternative, safe, and effective drugs such as melatonin.

In conclusion, it is evident from the identified studies that melatonin can be used in specific dosages according to age for sleep disorders, jet lag, insomnia in children with neurological disorders. Exogenous melatonin has emerged as an alternative therapy that can be used in sleep disorders. According to the evidence found, melatonin has not demonstrated toxicity or severe adverse effects, nor dependence even at high doses, demonstrating that its use is safe for treating young and elderly patients. However, despite the findings discussed, further investigations are needed in order to assess the dosages required for each age group, as well as dosages' safety profile.

Currently, no melatonin drug has been approved for use by regulatory bodies or legislation in Brazil, and the available

information only determines the pharmaceutical form, excipient substance, and general guidelines for melatonin handling. Guidelines addressing the accurate use of melatonin to support clinicians and pharmacists in the treatment

decision-making for sleep disorders is required. In addition, as melatonin is a relatively new drug, pharmacovigilance is essential, as it is up to health professionals to report any adverse events to the authorities.

REFERÊNCIAS

1. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014 Nov 1;146(5):1387-94. <https://doi.org/10.1378/chest.14-0970>
2. Fernandes RMF. O sono normal. *Medicina (Ribeirão Preto)*. 2006 Jun 30;39(2):157-68. <https://doi.org/10.11606/issn.2176-7262.v39i2p157-168>
3. Buysse DJ. Insomnia. *JAMA*. 2013 Feb 20;309(7):706-16. <https://doi.org/10.1001/jama.2013.193>
4. Cao X-L, Wang S-B, Zhong B-L, Zhang L, Ungvari GS, Ng CH, et al. The prevalence of insomnia in the general population in China: a meta-analysis. *PLoS One*. 2017 Feb 24;12(2):e0170772. <https://doi.org/10.1371/journal.pone.0170772>
5. Torrens I, Argüelles-Vázquez R, Lorente-Montalvo P, Molero-Alfonso C, Esteve M. Prevalencia de insomnio y características de la población insomne de una zona básica de salud de Mallorca (España). *Aten Primaria*. 2019 Dec;51(10):617-25. <https://doi.org/10.1016/j.aprim.2018.02.014>
6. Castro LS, Poyares D, Leger D, Bittencourt L, Tufik S. Objective prevalence of insomnia in the São Paulo, Brazil epidemiologic sleep study. *Ann Neurol*. 2013 Oct;74(4):537-46. <https://doi.org/10.1002/ana.23945>
7. Nunes ML, Bruni O. Insomnia in childhood and adolescence: clinical aspects, diagnosis, and therapeutic approach. *J Pediatr (Rio J)*. 2015 Nov-Dec;91(6 Suppl 1):S26-35. <https://doi.org/10.1016/j.jped.2015.08.006>
8. Ribeiro NF. Tratamento da insônia em atenção primária à saúde. *Rev Bras Med Fam Comunidade*. 2016 Jan-Dec;11(38):1-14. [https://doi.org/10.5712/rbmfc11\(38\)1271](https://doi.org/10.5712/rbmfc11(38)1271)
9. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Groselj LD, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017 Dec;26(6):675-700. <https://doi.org/10.1111/jsr.12594>
10. Vieira RB, Dantas A de A, Cayana EG. Suplementação da melatonina como alternativa terapêutica para insônia. II Congresso Brasileiro de Ciências da Saúde; 2017 Jun 14; Campina Grande, PB: Conbracis.
11. Auld F, Maschauer EL, Morrison I, Skene DJ, Riha RL. Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. *Sleep Med Rev*. 2017 Aug;34:10-22. <https://doi.org/10.1016/j.smrv.2016.06.005>
12. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br J Pharmacol*. 2018 Aug;175(16):3190-9. <https://doi.org/10.1111/bph.14116>
13. Li T, Jiang S, Han M, Yang Z, Lv J, Deng C, et al. Exogenous melatonin as a treatment for secondary sleep disorders: a systematic review and meta-analysis. *Front Neuroendocrinol*. 2019 Jan;52:22-8. <https://doi.org/10.1016/j.yfrne.2018.06.004>
14. Grigg-Damberger MM, Ianakieva D. Poor quality control of over-the-counter melatonin: what they say is often not what you get. *J Clin Sleep Med*. 2017 Feb 15;13(2):163-5. <https://doi.org/10.5664/jcsm.6434>
15. Erland LAE, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med*. 2017 Feb 15;13(2):275-81. <https://doi.org/10.5664/jcsm.6462>
16. Anvisa [Internet]. Anvisa esclarece. Brasília: Anvisa; 2020 [cited 2020 Jul 23]. Available from: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/proposta-de-consulta-publica-inclui-a-melatonina-como-constituente-autorizado/analise-da-seguranca-e-eficacia-da-melatonina-versao-para-publicacao.pdf>
17. Tribunal de Justiça de Minas Gerais. Apelação 10000190573444002 MG - Active Pharmaceutica Ltda ME. [cited 2020 Jul 21]. Available from: <https://www.jusbrasil.com.br/processos/nome/53857300/active-pharmaceutica-ltda-me>
18. Bacelar A, Pinto Jr LR. Insônia: do diagnóstico ao tratamento. São Caetano do Sul (SP): Difusão Editora; 2019. 172p.
19. Mendes KDS, Silveira RC de CP, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. *Texto Contexto Enferm*. 2008 Dec;17(4):758-64. <https://doi.org/10.1590/S0104-07072008000400018>
20. Hajak G, Lemme K, Zisapel N. Lasting treatment effects in a postmarketing surveillance study of prolonged-release melatonin. *Int Clin Psychopharmacol*. 2015 Jan;30(1):36-42. <https://doi.org/10.1097/YIC.000000000000046>
21. Culpepper L, Wingertzahn MA. Over-the-counter agents for the treatment of occasional disturbed sleep or transient insomnia: a systematic review of efficacy and safety. *Prim Care Companion CNS Disord*. 2015 Dec 31;17(6):10. <https://doi.org/10.4088/PCC.15r01798>
22. Wright A, Diebold J, Otal J, Stoneman C, Wong J, Wallace C, et al. The effect of melatonin on benzodiazepine discontinuation and sleep quality in adults attempting to discontinue benzodiazepines: a systematic review and meta-analysis. *Drugs Aging*. 2015 Dec;32(12):1009-18. <https://doi.org/10.1007/s40266-015-0322-5>
23. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: a critical systematic review of clinical evidence. *Complement Ther Med*. 2019 Feb;42:65-81. <https://doi.org/10.1016/j.ctim.2018.11.003>
24. Williams WPT, McLin DE, Dressman MA, Neubauer DN. Comparative review of approved melatonin agonists for the treatment of circadian rhythm sleep-wake disorders. *Pharmacotherapy*. 2016 Sep;36(9):1028-41. <https://doi.org/10.1002/phar.1822>
25. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database Syst Rev*. 2016 Nov 16;11(11):CD009178. <https://doi.org/10.1002/14651858.CD009178.pub3>
26. Cardinali DP, Golombok DA, Rosenstein RE, Brusco LI, Vago DE. Assessing the efficacy of melatonin to curtail benzodiazepine/Z drug abuse. *Pharmacol Res*. 2016 Jul;109:12-23. <https://doi.org/10.1016/j.phrs.2015.08.016>
27. Chang Y-S, Lin M-H, Lee J-H, Lee P-L, Dai Y-S, Chu K-H, et al. Melatonin supplementation for children with atopic dermatitis and sleep disturbance: a randomized clinical trial. *JAMA Pediatr*. 2016 Jan;170(1):35-42. <https://doi.org/10.1001/jamapediatrics.2015.3092>
28. SBEM [Internet]. Posicionamento da SBEM sobre comercialização da melatonina. São Paulo: Sociedade Brasileira de Endocrinologia e Metabologia; [cited 2020 Jul 23]. Available from: <https://www.endocrino.org.br/posicionamento-da-sbem-sobre-comercializacao-da-melatonina/>
29. Associação Médica Brasileira. Sobre o uso e comercialização da Melatonina no Brasil, a Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) esclarece. Rio de Janeiro: Sociedade Brasileira de Endocrinologia e Metabologia; 2016. [cited 2020 Jul 23]. Available from: [https://www.endocrino.org.br/media/uploads/PDFs/melatonina_sbem_2016_\(1\).pdf](https://www.endocrino.org.br/media/uploads/PDFs/melatonina_sbem_2016_(1).pdf)

30. Madsen MT, Isbrand A, Andersen UO, Andersen LJ, Taskiran M, Simonsen E, et al. The effect of Melatonin on Depressive symptoms, Anxiety, Circadian and Sleep disturbances in patients after acute coronary syndrome (MEDACIS): study protocol for a randomized controlled trial. *Trials*. 2017 Feb 23;18(1):81. <https://doi.org/10.1186/s13063-017-1806-x>
31. Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. *Arch Dis Child*. 2018 Dec;103(12):1155-62. <https://doi.org/10.1136/archdischild-2017-314181>
32. Maras A, Schroder CM, Malow BA, Findling RL, Breddy J, Nir T, et al. Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with Autism Spectrum Disorder. *J Child Adolesc Psychopharmacol*. 2018 Dec 10;28(10):699-710. <https://doi.org/10.1089/cap.2018.0020>
33. Quera-Salva M-A, Claustat B. Melatonin: physiological and pharmacological aspects related to sleep: the interest of a prolonged-release formulation (Circadin®) in insomnia. *Encephale*. 2018 Dec;44(6):548-57. <https://doi.org/10.1016/j.encep.2018.06.005>
34. Zwart TC, Smits MG, Egberts TCG, Rademaker CMA, van Geijlswijk IM. Long-term melatonin therapy for adolescents and young adults with chronic sleep onset insomnia and late melatonin onset: evaluation of sleep quality, chronotype, and lifestyle factors compared to age-related randomly selected population cohorts. *Healthcare (Basel)*. 2018 Mar 2;6(1):23. <https://doi.org/10.3390/healthcare6010023>
35. Myers KA, Davey MJ, Ching M, Ellis C, Grinton BE, Roten A, et al. Randomized controlled trial of melatonin for sleep disturbance in dravet syndrome: the DREAMS study. *J Clin Sleep Med*. 2018 Oct 15;14(10):1697-1704. <https://doi.org/10.5664/jcsm.7376>
36. Sletten TL, Magee M, Murray JM, Gordon CJ, Lovato N, Kennaway DJ, et al. Efficacy of melatonin with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder: a double-blind, randomised clinical trial. *PLoS Med*. 2018 Jun 18;15(6):e1002587. <https://doi.org/10.1371/journal.pmed.1002587>
37. Lewis SR, Pritchard MW, Schofield- Robinson OJ, Alderson P, Smith AF. Melatonin for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev*. 2018 May 10;5(5):CD012455. <https://doi.org/10.1002/14651858.CD012455.pub2>
38. Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a systematic review. *CNS Drugs*. 2019 Dec;33(12):1167-86. <https://doi.org/10.1007/s40263-019-00680-w>
39. Schroder CM, Malow BA, Maras A, Melmed RD, Findling RL, Breddy J, et al. Pediatric prolonged-release melatonin for sleep in children with Autism Spectrum Disorder: impact on child behavior and Caregiver's quality of life. *J Autism Dev Disord*. 2019 Aug 15;49(8):3218-30. <https://doi.org/10.1007/s10803-019-04046-5>
40. Lemoine P, Bablon J-C, Da Silva C. A combination of melatonin, vitamin B6 and medicinal plants in the treatment of mild-to-moderate insomnia: a prospective pilot study. *Complement Ther Med*. 2019 Aug;45:104-8. <https://doi.org/10.1016/j.ctim.2019.05.024>
41. Seiden DJ, Shah SM. A randomized, crossover, pharmacokinetics evaluation of a novel continuous release and absorption melatonin formulation. *Prim Care Companion CNS Disord*. 2019 Aug 1;21(4):19m02450. <https://doi.org/10.4088/PCC.19m02450>
42. Malow BA, Findling RL, Schroder CM, Maras A, Breddy J, Nir T, et al. Sleep, growth, and puberty after 2 years of prolonged-release melatonin in children with Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry*. 2021 Feb;60(2):252-61. <https://doi.org/10.1016/j.jaac.2019.12.007>
43. Low TL, Choo FN, Tan SM. The efficacy of melatonin and melatonin agonists in insomnia - an umbrella review. *J Psychiatr Res*. 2020 Feb;121:10-23. <https://doi.org/10.1016/j.jpsychires.2019.10.022>