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Effect of Melatonin on the Sleep Quality: A Systematic Review

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ABSTRACT

Introduction: Sleep is one of the most important human needs affected by many factors. Sleep disorders, such as insomnia and delayed sleep, are very common and can affect the quality and quantity of sleep. The current systematic review aimed to evaluate the evidence on the effectiveness of melatonin treatment on sleep quality.
Methods: The data on the effect of melatonin on sleep were collected using seven English databases, including Scopus, PubMed, Ovid, ProQuest, and Science Direct, as well as six Persian databases, including Iran Medex, SID, IRANDOC, Magiran, MEDLIB, and Noormags, from their inception up to the end of January 2020. English language, randomized clinical trials, human samples, and age of higher than 18 years were the main eligibility criteria. Nonrandomized clinical trials or those without a control group were excluded from the present study.
Results: Seven articles met the eligibility criteria for being included in this review. In the aforementioned studies, the effect of melatonin therapy on sleep quality was assessed in 343 subjects. The majority (86%) of the studies confirmed the effectiveness of melatonin treatment on sleep quality.
Conclusion: Melatonin as an orally administered drug had beneficial effects on sleep quality. These effects of melatonin attributed to more efficient healthier sleep, deeper sleep, longer sleep duration without causing fatigue and early morning drowsiness, and faster sleeping. One of the limitations of the present study was considered reviewing articles without the consideration of the medical conditions of the subjects. Moreover, the type of sleep disorder was not investigated in this review.

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Introduction

Sleep is an urgent need for human health and is referred to as a reversible state of reduced consciousness and response to external stimuli. Normal healthy sleep reduces the activity of the sympathetic system, decreases the heart rate, lowers the blood pressure, and increases the activity of the parasympathetic system.

Usually, sleepers pass through 5 stages, namely stages 1 (i.e., drifting from consciousness to falling asleep), 2,3,4 (i.e., nonrapid eye movement [NREM]), and 5 (i.e., rapid eye movement [REM]).Sleep starts at stage 1 and then drifts into stages 2, 3, and 4. Stages 3 and 2 are repeated prior to drifting into stage 5. Ending with time in REM sleep, the body usually returns to stage 2. These stages are repeated for 4 or 5 times during night sleep. Generally, REM sleep occurs 90 min after the onset of sleep; however, it lasts for 10-20 min. The REM and NREM stages constitute about 15-20% and 80-50% of sleep duration, respectively (1,2).

Sleep changes due to many environmental and pathogenic factors. These changes may include sleep onset, sleep duration, sleep depth, and sleep quality (3). Numerous factors, including a variety of cultural, social, psychological, behavioral, pathophysiological, and environmental ones, affect the quantity and

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quality of sleep patterns. Sleep quality refers to the wellness of a person's sleep, while sleep quantity refers to the amount of sleep per night (usually defined as 7-9 h for adults) (4). Sleep disorders not only endanger the quality of life through increasing the health risks, including hypertension, type 2 diabetes, depression, obesity, and cancer, but also reduce the efficacy (5).

Negative effects on public health, lack of satisfaction with life, mood disorders, disability in the performance of duties and personal affairs, occupational accidents caused by fatigue, job loss, and impaired sociofamily functioning are also other side effects of sleep disorders and chronic sleep deprivation.

The circadian rhythm is a 24-hour span complex system starting from the eyes and leading to the secretion of melatonin from the pineal gland (6). The suprachiasmatic nucleus in the anterior hypothalamus sets the 24-hour day-night cycle of sleep and wakefulness for the body circadian rhythms (7).

In addition to the regulation of sleep and wakefulness, the suprachiasmatic nucleus also regulates physiological and behavioral rhythms, including temperature, nutrition, 24-hour neuroendocrine, and autonomic effects (8).

Melatonin or N-acetyl-5-methoxytryptamine is a hormone released from the pineal gland in the anterior suprachiasmatic nucleus of the anterior hypothalamus and sleep-dependent nerve hormone (9).

Its highest secretion is about 2 in the morning and 10-100 times daily. In addition, melatonin levels are regulated by exposure to light (10, 11). Melatonin has hydrophilic and lipophilic properties and two major receptors in mammals, particularly humans, including methoxytryptamine 1 (MT1) and methoxytryptamine 2 (MT2).

The main site of melatonin metabolism is the liver (12). Melatonin easily crosses the blood-brain barrier via the glycoproteins of MT1 and MT2 membrane receptors and retinoid Z receptors/retinoid orphan receptors (13,14).

Both receptors are widely present in the central and peripheral nervous system and have been linked to the regulation of cell differentiation and immune response. In addition, melatonin receptors are expressed on CD4T cells, CD8T cells, and B cells. Melatonin and its metabolites also perform many physiological functions, including immunity, antioxidative activity, homeostasis, and glucose regulation (15-17).

The main function of melatonin is based on a physiological signal from peripheral darkness. Following dark signaling from the environment, the pineal gland in the suprachiasmatic nucleus stimulates and induces melatonin synthesis (8). Melatonin released from the pineal gland is distributed through the bloodstream by the MT1 and MT2 receptors. Similarly, melatonin levels rise during sleep, especially at night; however, they are suppressed during the day due to light with lower levels.

Therefore, melatonin is a chronobiotic (chronobiotics are able to alter the phase of daily timing and synchronization of short- and long-term circadian rhythms) with hypnotic properties that play an important role in initiating sleep and staying asleep (18).

In medicine, melatonin and its agonists are only used for the treatment of insomnia; however, melatonin is also commonly utilized in other sleep disorders caused by daily rhythm (11,19,20).

There are some pieces of evidence on the effect of Melatonin in the creation of a normal pattern of REM or its increased duration. It seems that Melatonin induces normal sleep (21-24). Melatonin has minimal side effects even in extremely large doses, in comparison to other sedatives and hypnotics. Moreover, it can increase the activity of T cells (25,26). In some countries, it is consumed as an over-the-counter drug. To the best of our knowledge, the results of very few studies have rejected the efficacy of melatonin on sleep quality (27).

Due to the importance of the quality of life and considering the changes in modern society that have led to increased tiredness and excessive daytime sleepiness, the assessment of the influential factors on the quality of life is highly important. The current systematic review aimed to evaluate the evidence on the effectiveness of melatonin treatment on sleep quality. In this regard, the following questions are answered in the present review:

-Does melatonin affect sleep quality?

-Is melatonin secretion effective in circadian rhythm?

-How does melatonin affect sleep quality?

Methods

This systematic review was conducted to assess melatonin therapy on sleep quality. The Cochrane Handbook guidelines were utilized to collect data through seven stages, including asking questions, determining eligibility criteria, searching process, eliminating unrelated articles, extracting data, evaluating the quality assessment, and discussing the topic.

Inclusion and Exclusion Criteria

This review included all the articles published

in English with a focus on the effect of melatonin therapy on sleep quality. All randomized clinical trials were included in the present review to assess the effect of melatonin on sleep in human samples. Nonrandomized clinical trials or those without a control group were excluded from the study.

The papers examining the samples aged less than 18 years were also excluded (age of 18 years or older as an inclusion criterion). In addition, the studies in which the patients were treated for sleep quality using other treatments except for melatonin therapy were removed from this study.

Moreover, the articles focusing on animal samples, reviews, meta-analyses, letters to the editor, case series, case reports, and experimental, qualified, narrative, and questionnaire studies were removed from the current review.

Literature search and Data extraction

In total, seven English databases, including Scopus, PubMed, Ovid, ProQuest, and Science Direct, as well as six Persian databases, including IranMedex, SID, IRANDOC, Magiran, MEDLIB, and Noormags, were searched from their inception up to January 2019.

The search process was performed using the keywords, namely "Melatonin" in combination with "Sleep", "Circadian Rhythm", and "Biological Clock". In addition, all the published data were evaluated regarding eligibility.

The Persian equivalents of the above-mentioned words were used in the Persian process. The data were gathered based on the predetermined objectives, eligibility criteria, and common findings in the literature.

Study Design

In the present review, seven English databases were searched plus six Persian databases using the selected keywords. The titles and abstracts of the identified studies were reviewed in terms of eligibility.

The reference list of all the reviewed papers was also manually searched for related papers. All the available files were also screened, and knowledgeable colleagues in the field were consulted with for further articles published outside the indexed literature.

The paper selection process (Diagram 1) was performed according to the following protocol:
1.Examination of the thematic relevance of the titles of the papers to the objectives of the study.
2.Examination of the relevance of the abstracts of the papers to the aims of the study.
3.Review the full texts of the papers and their relevance to the objectives of the study

In the first step of data collection, the studies inconsistent with the aim of the present review were removed from the study. Then, the remaining articles were obtained in full text and exactly assessed to be included in the present study. The papers with insufficient data or those that did not meet the inclusion criteria were excluded from the study. The articles were searched by two independent reviewers (two first authors).

Afterward, the reviewers screened the titles and abstracts of the papers and subsequently removed irrelevant articles. Then, the two reviewers independently studied the full texts of the articles in terms of eligibility. All the data were validated and extracted independently by the two reviewers on the basis of predefined criteria flowchart representing the study selection process (Figure 1).

Finally, the main data (i.e., time, location, sample size, age, tools, and outcomes) were extracted from the articles and recorded in a premade form in detail. All disagreements between the two reviewers were resolved through dialogue, and a third person intervention was requested if necessary. The obtained data were descriptively explained in the study, and the results were categorized based on similar concepts and the main topic, which were in agreement with the researchers' opinions.

Risk of Bias and Quality Assessment

The Jadad scoring system was used to evaluate the quality of clinical trial methodology. According to the Jadad scoring system, clinical trials are assessed on the basis of three key methodological features, including randomization, double-blindness, and sample dropout or withdrawal. Each clinical trial receives a maximum of 5 points in this scoring system. A score of 5 indicates the highest and a score of 0 demonstrates the poorest quality of clinical trials.

Clinical trials receiving a score of 2 or less based on the Jadad scoring system are considered low-quality clinical trials. The quality of the articles was blinded to the authorship or journal of publication. Seven articles were carefully reviewed in the current study.

Eight domains were assessed to determine the quality of the included studies based on the Cochrane guidelines. For the assessment of the risk of bias, the low and high risks of bias were marked as "Yes" and "No", respectively. "Unclear" was considered for the unclear or unknown risk of bias. Figure 2 illustrates the quality assessment of the selected articles.

Figure 1. Flowchart representing study selection process

Figure 2. Quality assessment of entered studies in review

Findings

Seven articles met the eligibility criteria for being included in this review. The current paper showed that most of the studies in the present review were related to sleep disorders in intensive care units (ICUs) and conducted as clinical trials.

Most articles collected data using the Pittsburgh Sleep Quality Index (PSQI) with probable variations in the content, number of questions, and scores of questions per paper. Based on the obtained results of this study, three studies were performed in the USA (43%).

Moreover, two studies were conducted in Germany and England, one in Brazil, and one in China. All the studies were focused on the effect of melatonin therapy on sleep quality.

In the aforementioned studies, the effect of melatonin therapy on sleep quality was assessed in 343 subjects. The dosage of oral melatonin was different from 2.5 to 10 mg daily.

The duration of melatonin administration was reported within 4 days to 4 weeks. The Richards-Campbell Sleep Questionnaire was used in two studies as a tool for the measurement of sleep quality (29 ,28), and the PSQI was applied in one study (30). Polysomnography and actigraphy scorings or visual scoring were used as tools for the assessment of sleep quality in three studies (32 ,31 ,27). The majority (%86) of the studies confirmed the effectiveness of melatonin therapy on sleep quality.

Table 1. Inserted studies in this review

Reference/ Domestic	Samples	Topic	Intervention and control groups	Used tools for assessment of sleep quality	Whether sleep quality statistically better than control	Main conclusion
Huang et al., China, 2014	198 subjects aged 18 years and older	Effect of oral melatonin on intensive care unit patients suffering from sleep deprivation	The intervention group received 3 mg oral melatonin. The same amount of placebo was simultaneously administered to the control group	Richards-Campbell Sleep Questionnaire	Yes	Melatonin is an effective and safe drug for sleep deprivation in intensive care unit patients.
Bourne et al., Sheffield, England, 2008	24 subjects with tracheostomy to remove them from the ventilator	Melatonin therapy for the improvement of nighttime sleep in critically ill patients	The intervention group received 10 mg oral melatonin for 4 days. The control group received the same placebo with the same conditions.	Richards-Campbell Sleep Questionnaire	Yes	In the melatonin-receiving group, sleep duration improved for 1 h.
Andrade et al., USA, 2001	33 samples	Melatonin on insomnia patients	In the intervention group, 5.4 mg oral melatonin was administered with follow-ups at the end of the 8th and 16th days. In the control group, similar conditions were applied with a placebo.	Polysomnography and actigraphy scorings	Yes	Faster sleep onset and increased sleep depth and duration were reported in the intervention group receiving melatonin.
Scheer et al., USA, 2012	16 subjects within the age range of 45-64 years	Repeated melatonin supplement improves sleep quality in patients with hypertension treated with beta blockers.	Patients in the intervention group received 2.5 mg oral melatonin overnight for 3 weeks, and the same conditions were applied with placebo in the control group.	Polysomnography and actigraphy scorings	Yes	In the intervention group, total sleep time increased by 36 min. Sleep onset latency reduced. Stage 2 of sleep increased, and the quality of sleep enhanced without resistance.

Kunzet al., Berlin, Germany, 2010	14 subjects	Effect of external melatonin on behavioral disorders of rapid eye movement sleep	In the intervention group, 3 mg of melatonin was daily administered with a 4-week follow-up. The control group received a similar amount of placebo.	Polysomnography and visual scorings	Yes	In the melatonin-receiving group, rapid eye movement sleep increased, and dysfunction decreased during the day.
Singer et al., Washington, USA, 2003	36 subjects	A multicenter trial for sleep disorders in Alzheimer's patients	In the first and second intervention groups, 2.5 and 10 mg melatonin were administered, respectively. The placebo was administered in the control group.	Polysomnography and actigraphy scorings	No	There was no significant difference between the control and intervention groups
Campos et al., Brazil, 2004	22 females within the age range of 18-60 years	Improvement of sleep in osmotic patients with melatonin	The intervention group received 3 mg of melatonin for 4 weeks. The control group received the same amount of placebo.	Pittsburg Sleep Quality Index	Yes	The administration of melatonin improved sleep quality in asthmatic patients.

Discussion

Does melatonin affect sleep quality?

The research into the effect of melatonin on sleep has a long history. Melatonin has been examined in various studies on different groups of patients in oral and exogenous doses. Multiple studies have emphasized the effect of melatonin on the improvement of sleep quality (33-35).

Some studies have shown that melatonin can enhance sleep quality by reducing sleep latency and increasing total sleep duration alone.

Many studies have demonstrated that melatonin can increase sleep duration in different groups of patients, including those with sleep deprivation (15,36). A literature review showed that most studies have indicated the effect of melatonin on sleep.

According to the literature, melatonin has been shown to improve sleep quality, decrease sleep latency, and increase sleep duration and depth of sleep in various groups of patients and healthy individuals, albeit to a small extent.

This effect of melatonin on improving sleep quality, decreasing sleep latency, as well as increasing sleep duration and depth of sleep, can be attributed to the hypnotic effect of melatonin. In addition, melatonin has different effects on sleep quality in different groups based on differences in dose and duration of intervention. Some studies have recommended the administration of the low doses of melatonin. These studies have argued that the use of low doses of melatonin not only improves sleep quality but also results in vigilance when waking up (37-39).

Huang et al. (2014) examined the effect of melatonin on 198 critically ill patients suffering from sleep deprivation and hospitalized in ICUs. The patients received oral melatonin 3 mg/day and were followed up for 4 days. The subjects were divided into experimental and placebo groups. Mental sleep quality, auditory quality of sleep, and anxiety were measured, and the obtained results showed that melatonin improved sleep quality with more efficient sleep (35).

Bourne et al. (2008) studied the effect of a -10 mg daily dose of melatonin on sleep quality in 4 days of treatment among 24 critically ill patients with tracheostomy in the ICU. The findings revealed that there was an increase in the quantity and quality of night sleep in the experimental group, and the patients in the experimental group were reported with better sleep than those in the placebo group (28).

Studies have shown that melatonin and its supplements regulate daily rhythm and are effective in the initiation of sleep, sleep duration, and improvement of sleep quality in children, adults, and even postmenopausal women (,40 41). Melatonin is also effective in vigilance after sleep and enhancement of quality of life (42). On the other hand, melatonin improves sleep without causing side effects (43).

Andrade et al. (2001) examined the effect of the administration of 5.4 mg melatonin on 33 chronic insomnia patients in the early stages of insomnia with 8 days and 16 days follow-ups. The obtained results showed that the onset of sleep was faster in the patients of the experimental group with increased sleep quality, depth, and duration without complications, such as drowsiness, symptoms of malaise, and early morning complications (44).

In a study conducted by Campos et al. (2004) on 22 patients with persistent asthma, a -3mg daily dose of melatonin was administered for 4 weeks to improve sleep quality. The findings revealed a significant increase in sleep quality among the patients of the experimental group (30).

On the other hand, some studies suggested the ineffectiveness of melatonin in sleep quality (47-45). Singer et al. (2003) studied the effect of melatonin administration on sleep disorders in Alzheimer›s disease in 36 Alzheimer›s patients who slept less than 7 h at night and woke up twice a week to evaluate the safety and efficacy of two doses of melatonin formulation.

The obtained results showed an insignificant sleep difference among the three groups of -2.5 mg melatonin, and -10mg melatonin, and placebo. Therefore, melatonin is not an effective factor in sleep quality in patients with Alzheimer›s disease (27). However, the majority of studies showed that melatonin has beneficial effects on sleep quality (48,49 ,32 ,31).

Is melatonin secretion effective in circadian rhythm?

A review has shown that most studies have linked the secretion of melatonin with darkness through the daylight suppression of melatonin secretion and darkness stimulation of melatonin secretion (50). The circadian rhythm is responsible for the regulation of melatonin secretion; therefore, any factor that disrupts circadian rhythm can also alter melatonin secretion. Disrupting the circadian rhythm can delay and decrease the release of melatonin. Decreased melatonin release causes sleep disorders (51).

Some studies have suggested that external and oral melatonin can be used for the regulation of circadian sleep rhythm and treatment of sleep disorders; however, other studies have shown that oral melatonin may have only minor effects on sleep when the circadian rhythm is disrupted (52). Some studies have demonstrated that melatonin and its derivatives can also be effective in the prevention of delirium, which is caused by sleep deprivation in ICUs (54 ,53). The reason for such arguments in these studies is that continuous illumination in ICUs causes the disturbances of circadian rhythm leading to no melatonin secretion. A lack of melatonin secretion can cause sleep disturbances in ICU patients and increase mortality. Therefore, the administration of oral melatonin to patients in ICUs may prevent circadian rhythm disorder and consequently delirium caused by sleep disorders and increased mortality. However, some other studies pointed to the ineffectiveness of melatonin in delirium-induced sleep deprivation (55).

Some studies have administered oral melatonin for the treatment of sleep disorders. The results have shown that the hypnotic effect of melatonin is insufficient; therefore, it cannot be used as a substitute for sedatives, such as benzodiazepines, and has only a modest effect on sleep duration (56). The findings also revealed that the administration of oral melatonin not only had a significant effect on primary and secondary sleep disorders but also could only be effective in the treatment of sleep latency for short periods (57,58 ,36).

How does melatonin affect sleep quality?

Studies have indicated that melatonin has an effect on fast eye movements and REM stage of sleep by the reduction of muscle tone and behavioral complications during sleep (48). Melatonin can also enhance sleep quality by increasing the inhibition of motor activity (32). Scheer et al. (2012) examined 16 patients within the age range of 64-45 years with hypertension treated with atenolol or metoprolol and -2.5mg melatonin overnight for 3 weeks. The obtained results showed that melatonin reduced sleep onset latency, increased sleep duration by 36 min and stage 2 of sleep, and improved sleep quality without drug resistance (31).

Kunz et al. (2010) studied the effect of -3mg daily oral melatonin for 4 weeks on sleep disturbances in 14 patients without specific neurological disorders with reduced sleep duration. The findings revealed that REM sleeping duration increased in the experimental group with improved dysfunction during the day. The results of the aforementioned study also indicated that melatonin, when administered at an appropriate time, is likely to normalize circadian changes in human physiology and has very strong effects on public health, especially older people and shift workers (49 ,32).

One of the limitations of the current study was considered reviewing articles without the consideration of the medical conditions of the samples. Moreover, the type of sleep disorder (i.e., primary or secondary) was not investigated

in this review. In addition, a meta-analysis could not be performed due to the inconsistency of the included study tools. Despite the aforementioned limitations, the present study had the advantage of a comprehensive literature review based on searching multiple databases in both Persian and English.Given the increasing number of sleep disorders as the roots of many health problems and side effects of medications applied for the treatment of insomnia, such as benzodiazepines, the administration of melatonin to improve sleep quality is less costly with fewer side effects. This finding also suggested the necessity of performing further studies on the effect of melatonin on sleep quality. Future studies could also investigate further effects of melatonin on primary and secondary sleep disorders.

Conclusion

Based on the obtained results of this study, although the majority of studies showed that melatonin has beneficial effects on sleep quality, there has been controversy over the effectiveness of orally administered melatonin on sleep quality.

However, all the studies emphasized the effect of melatonin secreted by the pineal gland on the body, which stimulates the circadian rhythm and leads to the regulation of the sleep cycle. Since there are different primary and secondary sleep disorders with different melatonin effects, the impact of melatonin on sleep evaluation requires conducting further studies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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