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# Melatonin for Treatment of Sleep Disorders

Summary

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## Introduction

### Sleep Disorders

Studies suggest that sleep disorders affect 50 to 70 million Americans, representing approximately 20 percent of the population.[1] A sleep disorder exists whenever a lower quality of sleep results in impaired functioning or excessive sleepiness.[2] Insomnia, literally "inability to sleep," has various etiologies and is the most common sleep disorder, affecting between 6 to 12 percent of the adult population.[3] In addition to the adult population, difficulties initiating and maintaining sleep are very common in children, affecting about 15 to 25 percent of this population.[1]

### Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone that is primarily produced by the pineal gland, located behind the third ventricle in the brain.[4] In the synthesis of melatonin, tryptophan is hydroxylated to 5-hydroxytryptophan, which in turn is decarboxylated to 5-hydroxytryptamine (serotonin). Serotonin is converted to the melatonin precursor and metabolite N-acetylserotonin by the enzyme N-acetyl transferase.[5-7] N-acetylserotonin is methylated via the enzyme hydroxyindole-o-methyltransferase to produce melatonin.[8] Approximately 90 percent of melatonin is cleared in a single passage through the liver. A small proportion of unmetabolized melatonin is also excreted in the urine.[8] Commercially available melatonin may be isolated from the pineal glands of beef cattle[9] or chemically synthesized.

## Methods

In this report, we review the use of melatonin for the treatment of a number of categories of sleep disorders, including primary sleep disorders, secondary sleep disorders, and sleep restriction, in a number of different populations. Moreover, we review not only the safety and effectiveness of melatonin for the treatment of sleep disorders, but also the pharmacology of exogenous melatonin and the physiology of endogenous melatonin, to provide a comprehensive overview of the state of research in this area.

### Literature Review

As a first step, a number of biomedical databases were searched. Literature searches were limited to English-language reports of studies on human subjects, with no restrictions applied for age, gender, or ethnicity. We searched for reports of phase 1 and 2 clinical trials; phase 3 and 4 randomized clinical trials, quasi-randomized controlled trials, prospective cohorts, case series, registry data as well as narrative and systematic reviews. Similar searches of MEDLINE® and EMBASE were conducted periodically for more recently published studies that were potentially relevant to the review. Lastly, the reference lists of relevant articles were reviewed and abstracts of the Associated Professional Sleep Society (APSS) covering 1999 to 2003 were hand-searched.

### Inclusion Criteria

Specific inclusion criteria were developed for each question of the review. In general, only controlled clinical trials were included for each

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question of the review, except for questions pertaining to the pharmacology of exogenous melatonin and the basic mechanism by which melatonin produces sleepiness. For the latter questions, uncontrolled clinical trials, case-series, cohort, cross-sectional, and case-control studies were also included. For all questions of the review, the population of the study could include individuals of any age, gender, ethnicity, and socioeconomic status; however, these individuals were required to be free of any type of sleep disorder in the case of the question relating to the effect of melatonin on normal sleepers, and to suffer from a sleep disorder in the case of the question relating to the effect of melatonin on people with sleep disorders. For questions pertaining to the administration of exogenous melatonin to a study population, any formulation, dosage, timing, frequency, and duration of melatonin administration was acceptable; however, melatonin was required to be the primary intervention, and in the case of controlled trials, compared to placebo. In addition, a study was included for a particular question of the review, if it analyzed at least one of the predetermined outcomes relevant to that question. Only English-language reports were included in the review.

### Study Selection

The librarian removed all duplicates of the initial search results. In the first stage of study selection, the titles and abstracts of all potentially relevant articles were screened, independently, by two reviewers and classified as "relevant," "clearly irrelevant," and "unclear." A given article was considered "relevant" to the review if it was relevant to at least one question of the review. The full text of all articles deemed "relevant" or "unclear" by each reviewer was retrieved. In the second stage of screening, the reviewers independently appraised the manuscripts using predetermined inclusion criteria for each question of the review. Only studies that met all inclusion criteria for a given question of the review, as determined by both reviewers, were considered relevant to that question. Disagreements among reviewers were resolved by discussion and consensus.

### Assessment of Study Quality

For the question pertaining to the effect of melatonin on people with sleep disorders, only randomized controlled trials were used as a source of evidence. Therefore, the Jadad Scale[10] was used to assess the quality of studies relevant to this question. The concealment of allocation in the randomized-controlled trials was assessed as "adequate," "inadequate," and "unclear."[11] For all other questions of the review, which relied on evidence from studies of other designs in addition to randomized controlled trials, the Downs and Black Checklist[12] was used to assess the quality of studies relevant to these questions. Two reviewers assessed study quality, independently, and disagreements were resolved by discussion and consensus. The overall quality of the evidence regarding the safety and effectiveness of melatonin in the treatment of sleep disorders was assessed using the framework developed by the Oxford Centre for Evidence-Based Medicine.

### Data Extraction

Data were extracted from all reports of studies that were included in the review using a standardized Data Extraction Form. The type of information extracted from reports included details of study design and inclusion/exclusion criteria; details of the population such as gender, age, ethnicity, and type of sleep disorder; the number of individuals that were eligible for, and enrolled in, the study; the number of comparison groups and participants allocated to each group; the number of participants who withdrew from the study; details of the intervention such as the formulation, dosage, timing, frequency and duration of melatonin administration as well as the type and frequency of usage of concurrent medication; and results obtained for predetermined, question-specific outcomes. Additional information that was extracted from reports included the source of funding for the study and whether an intention-to-treat analysis was planned or performed. A trained reviewer extracted relevant data from a given report and a second reviewer verified the data that were extracted for that article for accuracy and completeness. Disagreements between reviewers were resolved by discussion and consensus.

## Data Analysis

Data were analyzed using a Random Effects Model. Calculations included: Relative Risk (RR) for dichotomous data and Weighted Mean Difference (WMD) or Standardized Mean Difference (SMD) for continuous data.[13] All results were reported with 95-percent confidence intervals (CIs). Sources of heterogeneity were assessed using the I-squared statistic, and publication bias was assessed by visual inspection of a funnel plot, the Rank Correlation Test,[14] the Graphical Test,[15] and the Trim and Fill Method.[16]

## Results

The following is an outline of the key observations of the literature review.

### Effectiveness of Exogenous Melatonin in Normal Sleepers

*Normal Sleepers*

- Melatonin decreased sleep onset latency (SOL) in normal sleepers (weighted mean difference (WMD): -3.9 min; 95-percent CI: -5.3 min., -2.6 min.). The magnitude of this effect appears to be clinically insignificant. There was evidence of possible publication bias in the selection of studies that were analyzed; we found a greater number of studies reporting positive results compared to negative results.
- Melatonin increased sleep efficiency in normal sleepers (WMD: 2.3 percent; 95-percent CI: 0.7 percent, 3.9 percent), and this effect was dependent on the timing of sleep, such that the effect of melatonin was greater in daytime sleepers (daytime sleep: WMD: 8.0 percent; 95-percent CI: 1.0 percent, 15.0 percent; night-time sleep: WMD: 1.2 percent; 95-percent CI: 0 percent, 2.4 percent). The magnitude of this effect appears to be clinically insignificant. There was considerable evidence of possible publication bias in the selection of studies analyzed; we found a greater number of studies reporting positive results compared to negative results.
- Overall, melatonin did not have an effect on REM latency in normal sleepers, although doses of 1 mg to 3 mg produced a significant increase in REM latency compared to placebo (WMD: 12.7 min.; 95-percent CI: 6.8 min., 18.6 min.), while both higher and lower doses did not show this effect.
- Generally, these studies were of low-to-moderate quality.

### Effectiveness of Exogenous Melatonin in People with Sleep Disorders

*People with a Primary Sleep Disorder*

- Melatonin decreased sleep onset latency in people with a primary sleep disorder (WMD: -10.7 min.; 95-percent CI: -17.6 min., -3.7 min.). SOL was decreased greatly in people with delayed sleep phase syndrome (WMD: -38.8 min.; 95-percent CI: -50.3 min., -27.3 min.). The magnitude of this effect appears to be clinically significant. SOL was decreased marginally in patients with insomnia (WMD: -4.3min.; 95-percent CI: - 8.4 min., -0.1 min.). The magnitude of this effect appears to be clinically insignificant. SOL was reduced more in children (less than age 17 years) (WMD: -17.0 min., 95-percent CI: -33.5 min, -0.5 min.) than in adults (age 18-65 years) (WMD: -11.2; 95-percent CI: -27.7 min, 5.4 min.) or elderly patients (greater than age 65 years) (WMD: -7.8 min.; 95-percent CI: -17.4 min., 1.7 min.). The effects of melatonin did not vary with dose or duration of treatment. If the analysis is approached using the Fixed Effects Model, melatonin does not have any effect on sleep onset latency in people with primary insomnia.
- Melatonin did not have an effect on sleep efficiency in people with primary sleep disorders; the effects of melatonin did not vary by age, type of primary sleep disorder, dose, or duration of treatment.
- Melatonin did not have an effect on sleep quality, wakefulness after sleep onset (WASO), total sleep time, or percent time spent in REM sleep.
- Generally, these studies were of moderate-to-high quality.

*People with a Secondary Sleep Disorder*

- Melatonin did not have an effect on sleep onset latency in people with a secondary sleep disorder; the effects of melatonin did not differ between children and adults; the effect of melatonin did not vary with dose or duration of treatment.
- Melatonin increased sleep efficiency in people with a secondary sleep disorder (WMD: 1.9 percent; 95-percent CI: 0.5 percent, 3.3 percent); the effect of melatonin did not vary by age, dose or duration of treatment. The magnitude of this effect appears to be clinically insignificant.
- Melatonin did not have an effect on WASO or percent time spent in REM sleep in people with a secondary sleep disorder, but increased total sleep time in this population
- Generally, these studies were of moderate-to-high quality.

*People Suffering from Sleep Restriction*

- Melatonin did not have an effect on sleep onset latency in people suffering from sleep restriction; the effect of melatonin did not vary by dose or type of sleep restriction disorder i.e. shift-work and jet lag
- Melatonin did not have an effect on sleep efficiency in people suffering from sleep restriction; the effect of melatonin did not vary by dose
- Melatonin did not have an effect on sleep quality, WASO and percent time spent in REM sleep in people suffering from sleep restriction, but significantly increased total sleep time in this population
- Generally, these studies were of moderate-to-high quality.

### Safety of Exogenous Melatonin

- The most commonly reported adverse effects of melatonin were nausea (incidence: ~ 1.5 percent), headache (incidence: ~ 7.8 percent), dizziness (incidence: 4.0 percent), and drowsiness (incidence: 20.33 percent); however, these effects were not significant compared to placebo. This result did not change by dose, the presence or absence of a sleep disorder, type of sleep disorder, duration of treatment, gender, age, formulation of melatonin, use of concurrent medication, study design, quality score, and allocation concealment score.
- Generally, these studies were of moderate-to-high quality.

### Formulations, Pharmacology, and Mechanism of Action of Exogenous Melatonin

- A number of different formulations of melatonin have been used in clinical trials on humans; it is unclear how these formulations differ in terms of content, quality, and effectiveness in treating sleep disorders.
- The half-life of melatonin ranged from 0.54h to 2h. The peak circulating concentration of melatonin ranged from 14.75 pg/ml to 64 730 pg/ml, reflecting a dose range of 0.003mg to 75mg. The time required to reach peak values ranged from 0.25h to 13h. There is evidence from one study that exogenous melatonin penetrates the blood-brain-barrier.
- The basic mechanism by which melatonin produces sleepiness in humans is unclear, although three main hypotheses have been proposed; the mechanism may involve a phase-shift of the endogenous circadian pacemaker, a reduction in core body temperature and/or a direct action on somnogenic structures of the brain.

### Melatonin and Other Pharmacological Treatments for Sleep Disorders

- There are no differences in the effects of melatonin and triazolam on normal sleepers; zopiclone reduced SOL to a greater extent than melatonin during particular periods of investigation of normal sleepers in one study; there were no differences in the effect of melatonin and zolpidem on alleviation of jet lag in one study; however, there were more reports of adverse effects with zolpidem than with melatonin.

### Endogenous Melatonin and Sleep and Temperature Rhythms

- There is evidence linking endogenous melatonin to the sleep cycle; manipulation of endogenous melatonin was often accompanied by changes in the sleep cycle and vice versa; an analysis of the correlation between changes in the two variables was often not conducted, and in cases where it was conducted, the results were mixed.
- There is evidence linking endogenous melatonin to the temperature rhythm. Manipulation of endogenous melatonin was often accompanied by changes in the temperature rhythm; manipulation of the temperature rhythm was accompanied by changes in endogenous melatonin in one out of two studies. An analysis of the correlation between changes in the two variables was often not conducted, and in cases where it was conducted, the results were mixed.

## Discussion

### Effectiveness of Melatonin in People with Primary Sleep Disorders

Our literature review indicated that melatonin reduced sleep onset latency to a greater extent in people with delayed sleep phase syndrome than in people with insomnia. This finding may indicate that the effects of melatonin on people with primary sleep disorders are mediated by a direct re-setting of the endogenous circadian pacemaker rather than via a direct action on somnogenic structures of the brain, given that individuals with delayed sleep phase syndrome are distinguished from individuals with insomnia by the presence of a circadian abnormality. It is also possible that melatonin may initially act on somnogenic structures of the brain to promote sleep; the reduction in sleep onset latency would decrease evening light exposure, which would in turn promote a phase-advance of the endogenous melatonin rhythm and a re-setting of the endogenous clock. The finding that melatonin had an effect on sleep onset latency, but not on sleep efficiency, in people with primary sleep disorders supports the hypothesis that melatonin exerts its effects on this population by acting as a phase re-setter rather than as a hypnotic.

### Effectiveness of Melatonin in People with Secondary Sleep Disorders

Our literature review indicated that melatonin had no effect on sleep onset latency, while increasing sleep efficiency, in people with a secondary sleep disorder. However, these summary estimates are markedly influenced by the results of a study by Shamir et al.[17] The study was unique in that polysomnography, rather than actigraphy or questionnaire/sleep diaries, was used to assess sleep outcomes, and the method of concealing treatment allocation was reported and was adequate. Additional studies that use polysomnography to assess sleep outcomes are required before it can be concluded that

melatonin does not affect sleep onset latency or that melatonin increases sleep efficiency in people with secondary sleep disorders.

### Effectiveness of Melatonin in People Suffering from Sleep Restriction

Two other systematic reviews examining the use of melatonin for the alleviation of jet lag concluded that melatonin is effective in alleviating the symptoms of jet lag.[18,19] The results of the current review suggest that melatonin does not affect either sleep onset latency or sleep efficiency in jet lag sufferers or people suffering from shift-work disorder. Taken together, the findings of the current review and those of previous reviews suggest that the effectiveness of melatonin in alleviating jet lag may not involve alleviation of the sleep disturbance, but rather, the daytime fatigue associated with jet lag.

## Safety of Melatonin

The findings of this review suggest that exogenous melatonin is a relatively safe substance when used in the short term, over a period of days or weeks, and is safe at relatively high doses and in various formulations. However, the safety of exogenous melatonin when used in the long-term, over months and years, remains unclear.

### Melatonin and Other Pharmacological Treatments for Sleep Disorders

It appears that there are no major differences in the effectiveness of melatonin and triazolam, and melatonin and zopiclone, in normal sleepers, and in the effectiveness of melatonin and zolpidem in people suffering from jet lag, although zolpidem may have more adverse effects. The adverse events associated with these treatments were not addressed in most reports, such that their relative safety is unclear.

### Clinical Significance of Observations of this Review Related to the Effectiveness of Melatonin

One cannot draw firm conclusions regarding the effectiveness of melatonin in normal sleepers due to the presence of heterogeneity and evidence of possible publication bias in the studies relevant to this area. Similarly, the presence of heterogeneity across studies related to people with primary or secondary sleep disorders prevents one from drawing firm conclusions regarding the effectiveness of melatonin in alleviating these disorders.

Despite the inability to draw firm conclusions regarding the effectiveness of melatonin in normal sleepers and people with sleep disorders, one may comment on the clinical significance of the findings of this review based on the current evidence. Indeed, the magnitude of the effects of melatonin appear to be of no clinical significance in all populations studied in this review, except for people suffering from delayed sleep phase syndrome. However, even for the latter population, one cannot definitively conclude that melatonin is effective in alleviating the sleep disturbance, since the observation of melatonin effectiveness in this population was based on only two studies with less that 25 participants. Therefore, there is evidence to suggest that melatonin is not effective in treating most primary and secondary sleep disorders, although there is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome. Moreover, there is no evidence to suggest that melatonin is effective in alleviating the sleep disturbance aspect of jet lag and shift-work disorder.

A rigorous comparison of the effectiveness of melatonin and all other treatments for sleep disorders was beyond the scope of this review, and a systematic approach is required to determine how the effects of melatonin compare to other treatments for sleep disorders. However, our literature review revealed a paucity of evidence related to how melatonin compares with other pharmacological agents for sleep disorders in its effectiveness in normal sleepers and people with sleep disorders, and in its safety.

## Future Research

In light of the substantial amount of heterogeneity across studies of melatonin for the treatment of primary and secondary sleep disorders, more studies are necessary in this area. It is necessary that the conditions of these studies be clearly defined, especially with respect to the formulation and pharmacology of the melatonin product used in these studies. For studies involving melatonin administration to normal sleepers, the presence of substantial heterogeneity and evidence of publication bias necessitates more research in this area.

In addition to the areas outlined earlier in this report, research is required in various areas within the field of melatonin and sleep disorders research. There were some aspects of some questions of this review that could not be answered by the review, due to a lack of relevant information. For example, it remains unclear how the effects of melatonin vary by age, gender, ethnicity, and co-morbid conditions of the population, as well as formulation, timing, and duration of melatonin administration. Moreover, the long-term effects of melatonin on people with primary and secondary sleep disorders, beyond 4 weeks, remains to be determined. The short- and long-term effects of melatonin on people with sleep apnea also need to be determined. The safety of melatonin in

people of different ethnicities and with different timing of administration needs to be determined, as well as the effects of long-term use of melatonin.

The mechanism by which melatonin produces sleepiness in humans is unclear as are the mechanisms by which melatonin is absorbed, distributed, metabolized, and excreted in humans, and research is in this area is required. Very few studies compare the benefits and harms of melatonin and other pharmacological treatments for sleep disorders, and more research in this area is necessary.

## Limitations of the Review

The presence of substantial heterogeneity in the conduct of and results across studies involving administration of melatonin to people with either primary or secondary sleep disorders limits one from drawing any firm conclusions regarding the effectiveness of melatonin in these populations. Similarly, the presence of substantial heterogeneity and evidence of possible publication bias across studies involving normal sleepers prevents one from drawing any firm conclusions on effectiveness of melatonin in this population. The studies did not provide any evidence surrounding the safety of long-term use of melatonin, which prevents one from drawing any conclusions regarding this aspect of its safety. Moreover, one cannot draw any firm conclusions with respect to how melatonin compares with other pharmacological agents for sleep disorders in its effectiveness and safety.

A number of gaps were identified in the area of melatonin and sleep disorders research, which prevented us from addressing certain aspects and/or entire questions of the review. Major shortcomings of the studies included in the analysis of the effectiveness of melatonin for the treatment of sleep disorders and its safety were the quality of reporting with respect to the formulation and pharmacology of the melatonin product used in the study, the details of the sleep disorder suffered by participants and the funding sources for the studies.

## Conclusions

- Evidence suggests that melatonin is not effective in treating most primary sleep disorders with short-term use, although there is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome with short-term use.
- Evidence suggests that melatonin is not effective in treating most secondary sleep disorders with short-term use.
- No evidence suggests that melatonin is effective in alleviating the sleep disturbance aspect of jet lag and shift-work disorder.
- Evidence suggests that melatonin is safe with short-term use.
- Evidence suggests that exogenous melatonin has a short half-life and it penetrates the blood-brain-barrier.
- Evidence suggests a link between endogenous melatonin and the sleep cycle.
- Evidence suggests a link between endogenous melatonin and the temperature rhythm.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Alberta Evidence-based Practice Center, under Contract No. 290-02-0023. It is expected to be available in November 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 108, *Melatonin for Treatment of Sleep Disorders*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

## Suggested Citation

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